Monographs on Fragrance Raw Materials

A Collection of Monographs originally appearing in Food and Cosmetics Toxicology

An International Journal

Edited by

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FOREWORD

Since 1973, the Research Institute for Fragrance Materials Inc. has been publishing its Monographs on Fragrance Raw Materials as a regular feature of the international journal *Food and Cosmetics Toxicology*.

Many people have expressed a desire to have these monographs all in one volume, and the present book represents a collection of them from the first issues in 1973 to the last ones in 1978. When a suitable number of additional monographs have been collected a companion volume will be issued.

A note of appreciation here must be made to Miss Charlene Letizia, my able assistant, without whose efforts these monographs would not have appeared, and to Miss Audrey Seeley, Assistant Editor of *Food and Cosmetics Toxicology*, whose editorial skills have been most helpful.

It would be negligent if I did not also express my gratitude to the successive members of the Board of Directors of RIFM who encouraged the publication of the monographs, the members of the Advisory Committee whose counsel was helpful, and the Expert Panel who sat in judgement of the toxicological aspects.

Donald L. Opdyke, Ph.D.
Englewood Cliffs. 1978

INTRODUCTION

The Research Institute for Fragrance Materials, Inc. (RIFM) was established in 1966 by the principal suppliers of raw materials to the fragrance industry. At present, RIFM is supported by 38 of these companies, representing nearly 97% of the industry in the United States and Europe. The sole purpose of RIFM is to assure the safety of perfumery raw materials.

The Board of Directors is composed of the chief executive officers of the member companies, elected at an annual meeting. In order to ensure an independent scientific status for the Institute, it is structured so that the only link between the administrative branches and the scientific arms is the President, who performs a dual role as scientist and administrator. The President has available to him the advice of a Scientific Advisory Committee composed of perfumers, research scientists and analytical chemists drawn from the fragrance industry. Judgements in matters pertaining to the evaluation of safety are made completely independently by a Panel of Experts, who are toxicologists, pharmacologists or dermatologists drawn from the academic world and have no connexion whatever with the fragrance industry.

The monographs on fragrance materials have been prepared by the Institute as part of its programme to evaluate the safety of the raw materials used in perfumery and cosmetics. They will appear, in alphabetical order, as a regular feature of *Food and Cosmetics Toxicology*.

MATERIALS AND METHODS

The raw materials are selected on the basis of the following criteria: (1) they must be representative of the material in actual use by the industry; (2) they must conform to the specifications and standards, if any, of the Essential Oil Association of the USA (EOA); (3) they must be supplied to the RIFM without indication of the supplier, with name and an identification number only; (4) they must be accompanied by gas-chromatographic, ultraviolet or infra-red curves to "thumb-print" the materials.

The specifications and standards in the monographs will be those of the EOA, where available. The levels of usage to be reported are the result of an industry-wide survey.

When each raw material arrives at the Institute, a retain sample is taken and the rest is sent out to various commercial laboratories for testing. A sample in petrolatum is prepared by the Institute for repeated insult patch testing (Shelanski & Shelanski, *Proc. scient. Sect. Toilet Goods Ass.* 1953, **19,** 46) or maximization testing (Kligman, *J. invest Derm.* 1966, **47,** 393) on human skin using, where feasible, a tenfold exaggeration of the maximum use level to which human skin could be exposed.

Acute oral and acute dermal LD_{50}s are determined as a general measure of toxicity and, wherever pertinent, a test for phototoxicity to human skin is included. The results of these preliminary data are reviewed by the Panel of Experts, who decide whether additional work is indicated. The monographs appearing in this and subsequent issues are the result of this combined effort.

While every attempt has been made to ensure that these monographs will be complete, some of the materials have extensive toxicological documentation in the literature. In such instances, the intention has been to limit the data to those pertinent to the use of the materials as fragrance items (as distinct from possible use as flavourings) and to their use on the skin.

Acknowledgements—Special appreciation is due to all the members of the Board of Directors, without whose financial support and wisdom there would be no Institute, to all the members of the Presidential Scientific Advisory Committee, who validate the levels of usage and select the materials to be tested, to the President of the EOA and the Chairman of that Association's Scientific Committee, who supply the materials, and to the very special Expert Panel, without whose experience and judgemental evaluation the work would be useless.

FOREWORD

The records of man's earliest production and use of fragrances remain shrouded in the mists of antiquity. These were arts that were lost and rediscovered, many times and in many places, growing ever more elaborate and sophisticated while attaining peaks of splendour with each successive flowering of the great civilizations of the past.

Close relationships have traditionally existed between the use in fragrances of essential oils, balsams and spices and the therapeutic and even culinary applications of many of these same ingredients. During the past century, the introduction of many synthetic, often nature-identical, components has maintained the links between flavourings for foods and drugs on the one hand and fragrances for personal and household use on the other. Despite these similarities in regard to the use of certain basic components, the fragrances differ in many important respects. The most obvious of these is the predominance of skin contact in the case of fragrances, with the attendant issues of primary irritation, percutaneous absorption and immediate and delayed hypersensitivity, as well as the possibilities of phototoxic and photoallergic responses. On a long-term basis, the question of skin carcinogenesis has been raised, although no evidence is apparent for such a potential hazard stemming from this source. Beyond the local effects at the sites of skin contact, fragrance components that are absorbed through the skin are, of course, capable of exercising systemic effects. Conceivably, systemic action may result from absorption through the respiratory system.

In theory, therefore, the attainment of that Nirvana-like state of perfection—demonstration of virtually absolute safety—demands an immense effort, embracing not only each individual fragrance ingredient but also each finished product that incorporates a fragrance containing that component. The complexities of fragrances are not the outcome of a conspiracy to 'soak' the consumer: they are an essential basis of a highly skilled art that seeks to create aromatic loveliness appropriate to the particular circumstances of use, while satisfying the exacting technical requirements that have to be met in a wide variety of products. As long as we seek to pander to our aesthetic susceptibilities, and not to outrage them, highly complex fragrances are inescapable and, indeed, play a most important role in a wide range of consumer goods.

Facing up to the facts of real life, one has to establish priorities for safety evaluation in regard to the fragrance components being tested and the tests that are most necessary. In both respects the Research Institute for Fragrance Materials (RIFM) has done sterling pioneer work. Monographs on Fragrance Raw Materials, end-products of the present phase of RIFM activities, have appeared in *Food and Cosmetics Toxicology* during the past 2 years (Opdyke, *Fd Cosmet. Toxicol.* 1973, **11,** 95, 477, 855 & 1011; *idem, ibid* 1974, **12,** 385, 517 & 703). The publication of this Supplement, devoted entirely to such Monographs, represents a considerable leap forward. I am confident that the important and timely information contained in these Monographs will prove valuable to many readers of *Food and Cosmetics Toxicology*, as well as to the wider community of scientists and interested consumers.

L. Golberg

ACKNOWLEDGEMENTS

Special thanks are due to the Scientific Advisory Committee of the Research Institute for Fragrance Materials, Inc., whose contributions to this Special Issue have been invaluable.

A note of special appreciation goes to my Technical Assistant, Miss Charlene Letizia, who patiently organized, revised and edited the monographs, and to her assistant, Miss Lynne Opdyke, who did most of the typing.

D. L. J. Opdyke

FOREWORD

"The rose looks fair, but fairer we it deem
For that sweet odour which doth in it live."
W. Shakespeare (Sonnet LIV)

The systematic assessment of toilet goods and cosmetics for safe use is the concern of the manufacturer, the distributor, the consumer, regulatory agencies and the scientific community, which provides the means by which proper assessments can be made.

Since 1973, *Food and Cosmetics Toxicology* has been publishing on a regular basis monographs containing essential information on fragrance raw materials. These monographs provide a wealth of information about the sources and chemical and physical characteristics of fragrance components, their possible health effects and significant toxicological data. They also include essential information about meaningful evaluation procedures as well as the most up-to-date scientific references.

The work represented in these monographs was initiated in 1967, when a group of responsible fragrance manufacturers decided to give collective support to a programme that would assemble and analyse existing scientific data relating to the properties and use of fragrance ingredients, to determine the gaps in essential knowledge about chemical, physical and biological properties, to develop an assessment programme, which would identify the most rigorous and meaningful methods of assessment for safe use, and to determine and identify the biological hazards, if any, of these components so that they might be removed from consumer products. These data would serve as guidelines for the incorporation of materials at safe levels into cosmetics and other products using fragrance materials and for restricting the use of hazardous components. To carry out these objectives the Research Institute for Fragrance Materials was founded and the monographs that have appeared for the last 3 years represent the work of that Institute.

This systematic toxicological evaluation programme has been concerned with the oral and percutaneous toxicity and allergic and phototoxic effects of fragrance materials. The knowledge and understanding developed are of great importance to the consumer, to the industry manufacturing fragrances used by the consumer, to the regulatory agencies in this and other countries, to the industrial organizations attempting to monitor products for safe use, to the physicians who require such information in their diagnostic, therapeutic and preventive efforts, and to the scientist concerned with the study of mechanisms of biological effects.

While the test methods represent rigorous exposure conditions in a controlled setting, another facet of human experience needs to be examined. This includes human-experience information derived from carefully designed epidemiological studies in populations using fragrance components. This may be done through a systematic study of patients with eczematous or other forms of irritant or allergic disease to uncover possible relationships between fragrance materials and cutaneous disease.

Other parameters for which some components might be considered are carcinogenicity, mutagenicity and teratogenicity, as well as inhalation toxicity. Indications for such tests depend clearly on the molecular structure of a compound in relation to known biological and toxicological effects of related compounds. For example, if an organic amine or nitrosoamine is used in a formulation, such a material should be examined carefully for carcinogenic and mutagenic potential.

The effort represented in this series of monographs can serve as a model to all industries concerned with the safe use of product components. Such collective efforts appear to be efficient from a scientific as well as an economic standpoint.

R. R. Suskind,
7 November 1975

FOREWORD

This issue of *Food and Cosmetics Toxicology* marks the publication of the third Special Issue of monographs concerned with the safe use of fragrance materials. The collection, assessment and updating of this information was initiated by the Research Institute for Fragrance Materials ten years ago. Indeed, an impressive part of these highly useful monographs stems from the Institute's active support of investigational efforts to detect the hazardous potentials of fragrance raw materials on animal and human skin.

Monographs now numbering 825 have been added to the informational bank dealing with the irritant and sensitizing properties of fragrance raw materials on human skin. Of no less importance in content is the continued flow of animal toxicity data (systemic and cutaneous) resulting from the oral, percutaneous and photobiological studies being conducted.

In collating its work with pertinent contributions of other investigators, the Institute is providing a reference base of scientific information not previously available. Besides the direct dividends that are accruing from defining the irritant and sensitizing properties and photobiological and systemic toxicity of fragrance raw materials, several tantalizing side issues have surfaced. For example, why is it that phenylacetaldehyde, citral and cinnamic aldehyde sensitize human skin readily when tested as pure agents, yet each fails to sensitize when contained within its natural oil or when combined with certain alcohols or terpenes known to coexist with it in nature? This curious happening, noted in maximization tests, became the stimulus for a post-doctoral project aimed at providing possible chemical or physical explanations for the suppression, or 'quenching effect' as it is also being termed. Is it possible that 'quenching' is commonplace in the daily use of fragrances? Does the observation offer a partial explanation of why materials that are so widely used and to which great numbers of people are exposed seem to cause comparatively few cases of cutaneous injury? Obviously, these enquiries are speculative. The fact is that we do not have well-validated statistics relating to the incidence of cutaneous injury caused by fragrance materials. This point will not be clarified without closely monitored studies to detect actual causes, define incidence and then prove control measures within a study group who use fragrance materials and who display cutaneous disease reasonably suspected of being causally related to contact with these substances.

Meanwhile, the continued use of rigorous test methods which provide reasonable assurance that a fragrance material is safe or unsafe appears to be a prudent course of action.

Donald J. Birmingham, M.D.

PREFACE NOTES

NO. 1—SPILLOVER EFFECT

In maximization testing, four unrelated materials are tested on each of 25 human subjects. In the event that one of the four test materials turns out to be a very strong sensitizer, false weak positive results may occur with the other three materials. When these three materials are subsequently retested out of the context of the serious allergen, and in the same or a different group of subjects, they prove to be negative. We refer to this as the "spillover effect" (Björnberg, 1958; Kligman & Epstein, 1975).

NO. 2—FALSE-POSITIVE REACTIONS

In August 1974, one of the investigators doing maximization testing relocated his laboratories, going from a prison population of predominantly male blacks to a university student population of mixed male and female, white, black and oriental individuals. The result was an increased susceptibility on the part of the new test subjects to the irritating effects of sodium lauryl sulphate (SLS). Some false-positive results were obtained, which proved to be negative in repeated tests using lower concentrations of SLS. Although considered insignificant, these results are included in the pertinent monographs in the interest of completeness. This observation has been explained in detail in a recent publication (Kligman & Epstein, 1975).

In the process of maximization testing on four materials in any group of 25 subjects, it was observed that the four materials had to be totally unrelated. One could not test four essential oils in one group since a common component could evoke false responses to all if one was positive in any subject. Eventually it was learned never to test more than one essential oil in a group, or more than one aldehyde, ketone, alcohol or related ester. A typical grouping might be:

(1) Rose absolute, French
(2) Phenylacetaldehyde dimethyl acetal
(3) Methyl cinnamate
(4) Alcohol C-8

NO. 3—ODOUR DESCRIPTIONS

The major purpose in the publication of these monographs on fragrance raw materials is to publish the safety data. However, no monographs on fragrance raw materials would be complete without odour descriptions. For this information we refer the reader to three excellent volumes by Steffen Arctander:

Perfume and Flavor Materials of Natural Origin.
S. Arctander, Elizabeth, N.J., 1960.
Perfume and Flavor Chemicals (Aroma Chemicals), Vols I & II.
S. Arctander, Montclair, N.J., 1969.

References

Björnberg, A. (1968). *Skin reactions to Primary Irritants in Patients with Hand Eczema. An Investigation with Matched Controls.* Oscar Isacsons Tryckerc Ab, Götesborg, Sweden.

Kligman, A. M. & Epstein, W. (1975). Updating the maximization test for identifying contact allergens. *Contact Dermatitis* **1**, 231.

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References

Björnberg, A. (1968). *Skin Reactions to Primary Irritants in Patients with Hand Eczema. An Investigation with Matched Controls.* Oscar Isacsons Tryckerc Ab. Götesborg, Sweden.

Kligman, A. M. & Epstein, W. (1975). Updating the maximization test for identifying contact allergens. *Contact Dermatitis* **1**, 231.

PRELIMINARY REMARKS ON ALLYL ESTERS

Monographs on several allyl esters appear on pp. 613–621, and the following general point is relevant to all of them.

During human skin testing with allyl esters a delayed type of irritation has occasionally been observed 2 or 3 days after exposure to the ester and has been thought by the investigator to be a case of sensitization. In every case these reactions have been traced to the presence of at least 0·1% free allyl alcohol. While these esters are said to be quite stable, care should be exercised to obtain them as free as possible from this irritant alcohol.

An extensive review of the safety evaluation of allyl esters from the point of view of their use in flavourings has been made by Drake (1975).

Reference

Drake, J. J.-P. (1975). Safety evaluation of allyl esters. *Int. Flavours Fd Add.* **6** (6), 352.

SUPPLEMENT TO EARLIER MONOGRAPHS ON FRAGRANCE RAW MATERIALS*

Acetate C-9

Irritation. Acetate C-9 applied full strength to intact or abraded rabbit skin was not irritating (Levenstein, 1972). Tested in a concentration of 2% in petrolatum it produced no irritation in a 48-hr closed-patch test in 25 human subjects (Kligman, 1972).

Kligman, A. M. (1972). Report to RIFM, 27 March.
Levenstein, I. (1972). Report to RIFM, 7 April.

Acetophenone

Irritation. Undiluted acetophenone tested on rabbit skin is capable of causing irritation (Rowe & Wolf, 1963). Acetophenone tested at a concentration of 2% in petrolatum produced no irritation in a 48-hr closed-patch test in 25 human subjects (Kligman, 1971).

Kligman, A. M. (1971). Report to RIFM, 9 June.
Rowe, V. K. & Wolf, M. A. (1963). Ketones. In *Industrial Hygiene and Toxicology*. 2nd ed. Edited by F. A. Patty. Vol. II, p. 1763. Interscience Publishers, New York.

Alcohol C-8

Irritation. Alcohol C-8 applied full strength to intact or abraded rabbit skin produced a mild irritation (Levenstein, 1972). Tested in a concentration of 2% in petrolatum it produced no irritation in a 48-hr closed-patch test in 25 human subjects (Kligman, 1972).

Kligman, A. M. (1972). Report to RIFM, 2 May.
Levenstein, I. (1972). Report to RIFM, 13 January.

Alcohol C-9

Irritation. Alcohol C-9 undiluted produced no irritation in the rabbit (Treon, 1963). Tested in a concentration of 2% in petrolatum it produced no irritation in a 48-hr closed-patch test in 25 human subjects (Kligman, 1972).

Kligman, A. M. (1972). Report to RIFM, 2 May.
Treon, J. F. (1963). Alcohols. In *Industrial Hygiene and Toxicology*. 2nd ed. Edited by F. A. Patty. Vol. II. p. 1464. Interscience Publishers, New York.

Alcohol C-10

Irritation. Alcohol C-10 undiluted produced a severe irritation in the rabbit after 24 hr (Treon, 1963). Tested in a concentration of 3% in petrolatum it produced no irritation in a 48-hr closed-patch test in 25 human subjects (Kligman, 1972).

Kligman, A. M. (1972). Report to RIFM, 27 March.
Treon, J. F. (1963). Alcohols. In *Industrial Hygiene and Toxicology*. 2nd ed. Edited by F. A. Patty. Vol. II. p. 1467. Interscience Publishers, New York.

Alcohol C-11

Irritation. Alcohol C-11 applied full strength to intact or abraded rabbit skin produced a mild irritation (Levenstein, 1972). Tested in a concentration of 1% in petrolatum it produced no irritation in a 48-hr closed-patch test in 25 human subjects (Kligman, 1972).

Kligman, A. M. (1972). Report to RIFM, 14 March.
Levenstein, I. (1972). Report to RIFM, 13 January.

Alcohol C-12

Irritation. Alcohol C-12 undiluted was practically non-irritating to the guinea-pig (Treon, 1963). Tested in a concentration of 4% in petrolatum it produced no irritation in a 48-hr closed-patch test in 25 human subjects (Kligman, 1972).

*Addenda to monographs published in *Food and Cosmetics Toxicology* (1973, **11**, 95 & 477).

Kligman, A. M. (1972). Report to RIFM, 2 May.
Treon, J. F. (1963). Alcohols. In *Industrial Hygiene and Toxicology*. 2nd ed. Edited by F. A. Patty. Vol. II. p. 1468. Interscience Publishers, New York.

Aldehyde C-6

Irritation. Aldehyde C-6 undiluted was slightly irritating to rabbit skin (Fassett, 1963). Tested in a concentration of 1% in petrolatum it produced no irritation in a 48-hr closed-patch test in 25 human subjects (Kligman, 1972).

Fassett, D. W. (1963). Aldehydes and acetals. In *Industrial Hygiene and Toxicology*. 2nd ed. Edited by F. A. Patty, Vol. II. p. 1967. Interscience Publishers, New York.
Kligman, A. M. (1972). Report to RIFM, 27 March.

Aldehyde C-8

Irritation. Aldehyde C-8 undiluted produced a mild irritation in the rabbit (Smyth, Carpenter, Weil, Pozzani & Streigel, 1962).

Smyth, H. F., Jr., Carpenter, C. P., Weil, C. S., Pozzani, U. C. & Streigel, Jean A. (1962). Range-finding toxicity data: List VI. *Am. ind. Hyg. Ass. J.* **23**, 95.

Aldehyde C-9

Irritation. Aldehyde C-9 applied full strength to intact or abraded rabbit skin was severely irritating (Shelanski, 1971). Tested in a concentration of 1% in petrolatum it produced no irritation in a 48-hr closed-patch test in 25 human subjects (Kligman, 1971).

Kligman, A. M. (1971). Report to RIFM, 27 September.
Shelanski, M. V. (1971). Report to RIFM, 14 November.

Aldehyde C-10

Irritation. Aldehyde C-10 undiluted produced a mild irritation in the rabbit (Smyth, Carpenter, Weil, Pozzani & Striegel, 1962).

Smyth, H. F., Jr., Carpenter, C. P., Weil, C. S., Pozzani, U. C. & Striegel, Jean A. (1962). Range-finding toxicity data: List VI. *Am. ind. Hyg. Ass. J.* **23**, 95.

Aldehyde C-11, undecylenic

Irritation. Aldehyde C-11, undecylenic, applied full strength to intact or abraded rabbit skin was mildly irritating (Hart, 1971). Tested in a concentration of 1% in petrolatum it produced no irritation in a 48-hr closed-patch test in 25 human subjects (Kligman, 1971).

Hart, E. T. (1971). Report to RIFM, 18 June.
Kligman, A. M. (1971). Report to RIFM, 3 November.

Aldehyde C-11, undecylic

Irritation. Aldehyde C-11, undecylic, applied full strength to intact or abraded rabbit skin was mildly irritating (Shelanski, 1971). Tested in a concentration of 5% in petrolatum it produced no irritation in a 48-hr closed-patch test in 25 human subjects (Kligman, 1971).

Kligman, A. M. (1971). Report to RIFM, 27 September.
Shelanski, M. V. (1971). Report to RIFM, 14 November.

Aldehyde C-12, Lauric

Irritation. Aldehyde C-12, lauric, applied full strength to intact or abraded rabbit skin was moderately irritating (Calandra, 1971). Tested in a concentration of 1% in petrolatum it produced a mild irritation in a 48-hr closed-patch test in 25 human subjects (Kligman, 1970).

Calandra, J. C. (1971). Report to RIFM, 12 April.
Kligman, A. M. (1970). Report to RIFM, 2 December.

Aldehyde C-12, MNA

Irritation. Aldehyde C-12, MNA, tested in a concentration of 4% in petrolatum produced no irritation in a 48-hr closed-patch test in 25 human subjects (Kligman, 1971).

Kligman, A. M. (1971). Report to RIFM, 17 June.

Aldehyde, C-14, myristic

Irritation. Aldehyde C-14, myristic, applied full strength to intact or abraded rabbit skin was moderately irritating (Lynch, 1971). Tested in a concentration of 1% in petrolatum it produced no irritation in a 48 hr closed-patch test in 25 human subjects (Kligman, 1971).

Kligman, A. M. (1971). Report to RIFM, 17 June.
Lynch, T. A. (1971). Report to RIFM, 16 June.

Allyl caproate

Irritation. Allyl caproate applied full strength to intact or abraded rabbit skin was not irritating (Shelanski, 1971). Tested in a concentration of 4% in petrolatum it produced a mild irritation in a 48-hr closed-patch test in 25 human subjects (Kligman, 1971).

Kligman, A. M. (1971). Report to RIFM, 21 September.
Shelanski, M. V. (1971). Report to RIFM, 26 November.

Allyl cyclohexyl propionate

Irritation. Allyl cyclohexyl propionate tested in a concentration of 4% in petrolatum produced no irritation in a 48-hr closed-patch test in 25 human subjects (Kligman, 1971).

Kligman, A. M. (1971). Report to RIFM, 3 November.

Allyl α-ionone

Irritation. Allyl α-ionone applied full strength to intact or abraded rabbit skin was mildly irritating (Shelanski, 1971). Tested in a concentration of 10% in petrolatum it produced no irritation in a 48-hr closed-patch test in 25 human subjects (Kligman, 1972).

Kligman, A. M. (1972). Report to RIFM, 21 February.
Shelanski, M. V. (1971). Report to RIFM, 14 November.

Amyl benzoate

Irritation. Amyl benzoate applied full strength to intact or abraded rabbit skin was mildly irritating (Weir, 1971). Tested in a concentration of 6% in petrolatum it produced no irritation in a 48-hr closed-patch test in 25 human subjects (Kligman, 1972).

Kligman, A. M. (1972). Report to RIFM, 3 November.
Weir, R. J. (1971). Report to RIFM, 25 August.

Supplement to: 5-ACETYL-1,1,2,3,3,6-HEXAMETHYL INDAN*

Phototoxicity. Undiluted 5-acetyl-1,1,2,3,3,6-hexamethyl indan produced phototoxic effects on the skin of the hairless mouse (Forbes, Urbach & Davies, 1978).

Various concentrations of 5-acetyl-1,1,2,3,3,6-hexamethyl indan in methanol were also tested on the skin of the hairless mouse for phototoxic effects. The no effect level was found to be approximately 1% or equal to approximately 0.04 mg/cm^2 of skin (Forbes, 1978).

5-Acetyl-1,1,2,3,3,6-hexamethyl indan was found to be phototoxic in the guinea pig and rabbit in concentrations as low as 5% in ethanol (Ohta, 1978).

References

Forbes, P. D. (1978). Report to RIFM, 12 May.
Forbes, P. D., Urbach, F. and Davies, R. E. (1978). Report to RIFM, 13th April.
Ohta, S. (1978). Personal communication from Shiseido Laboratories, 26 August.

*See monograph in *Fd Cosmet Toxicol* (1975) Vol. 13, p. 693.

Supplement to: 6-METHYL COUMARIN*

Phototoxicity. 6-Methyl coumarin tested at a concentration of 5% in hydrophilic ointment did not produce any phototoxic effects on human subjects (Kaidbey, 1978).

There were no phototoxic effects reported for undiluted 6-methyl coumarin on the skin of the hairless mouse (Forbes, Urbach & Davies, 1978).

Photoallergenicity. 6-Methyl coumarin produced photoallergenic effects on 17 out of 18 subjects when tested at a concentration of 5% in hydrophilic ointment by the photomaximization test (Kaidbey, 1978).

A proprietary sunscreen induced photosensitivity reactions in a small number of users. Laboratory study revealed that the reactions were of the photoallergic type and were due to the presence of 6-methyl coumarin. By photomaximization testing 6-methyl coumarin was found to be a potent photocontact allergen (Kaidbey & Kligman, 1978).

References

Forbes, P. D., Urbach, F. & Davies, R. E. (1978). Report to RIFM, 13 April.
Kaidbey, K. H. (1978). Report to RIFM, 18th January.
Kaidbey, K. H. & Kligman, A. M. (1978). Photocontact allergy to 6-Methyl coumarin. *In Press.*

*See monograph in *Fd. Cosmet. Toxicol.* **14,** 605.

Supplement to: DIMETHYL ANTHRANILATE*

Phototoxicity. Dimethyl anthranilate tested at a concentration of 5% in hydrophilic ointment produced phototoxic effects on 8 out of 10 human subjects (Kaidbey, 1978).

Undiluted dimethyl anthranilate produced phototoxic effects on the skin of the hairless mouse (Forbes, Urbach & Davies, 1978).

Various concentrations of dimethyl anthranilate in methanol were also tested for phototoxic effects on the hairless mouse. The lowest detectable level of phototoxicity was found to be approximately 50% or equal to approximately 2 mg test agent/cm^2 of the skin (Forbes, Urbach & Davies, 1978).

Photoallergenicity. Dimethyl anthranilate did not produce any photoallergenic effects on human subjects when tested at a concentration of 5% in hydrophilic ointment by the photomaximization procedure (Kaidbey, 1978).

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*See monograph in *Fd Cosmet. Toxicol.* 13, 791.

Supplement to: CINNAMIC ALCOHOL*

Biological Data

Irritation. Cinnamic alcohol was non-irritating at 10% when applied in two different vehicles, petrolatum and hydrophilic ointment, on the scarified and normal skin of five volunteers for 3 days (Kligman, 1976).

Cinnamic alcohol tested at 10% in petrolatum produced no irritation after a 48 hour closed patch test on six different panels of human subjects (Epstein, 1977; Kligman, 1975, 1976, & 1977).

Cinnamic alcohol tested at 10% in hydrophilic ointment produced no irritation after a 48 hour closed patch test on human subjects (Kligman, 1976).

Sensitization. Maximization tests (Kligman, 1966; Kligman & Epstein, 1975) were carried out on several panels averaging 25 human subjects each and using different samples of cinnamic alcohol prepared by various methods with the following results:

Cinnamic alcohol tested at 10% in petrolatum produced 3 sensitization reactions in white females, one of which also reacted to farnesol which was in the same group (Kligman, 1975). Two of these three subjects were rechallenged 3 months later with cinnamic alcohol at 10% and again gave positive sensitization reactions (Kligman, 1976).

Cinnamic alcohol tested at 10% in hydrophilic ointment produced 2 sensitization reactions in white females (Kligman, 1976).

Cinnamic alcohol tested at 10% in petrolatum on a virgin panel (no other material was in the study) produced 5 sensitization reactions in white females (Kligman, 1976). These five subjects were subsequently rechallenged with cinnamic alcohol, cinnamic aldehyde and hydroxycitronellal and reacted only to the cinnamic alcohol (Kligman, 1976).

Cinnamic alcohol tested at 10% in petrolatum on white females produced one sensitization reaction. This subject was subsequently rechallenged with cinnamic aldehyde and farnesol but did not react to them (Epstein, 1976).

Cinnamic alcohol† tested at 10% in petrolatum produced 7 sensitization reactions (Kligman, 1976).

Cinnamic alcohol† tested at 10% in petrolatum produced 9 sensitization reactions (Kligman, 1976).

Cinnamic alcohol† tested at 10% in petrolatum produced 3 sensitization reactions (Kligman, 1977).

Cinnamic alcohol† tested at 10% in petrolatum produced 1 sensitization reaction (Epstein, 1977).

Cinnamic alcohol tested at 10% in petrolatum produced 10 sensitization reactions (Epstein, 1977).

A single patch test using cinnamic alcohol at 2% on patients with cosmetic contact dermatitis, produced 2/102 positive allergic reactions (Ishihara, 1978). In cases with facial post-inflammatory pigmentation, patch tests with 2% cinnamic alcohol produced 2^+ positive reactions in 4/51 subjects (Ishihara, 1978).

A maximization test (Magnusson & Kligman, 1969) carried out on guinea pigs using a concentration of 5% cinnamic alcohol produced no sensitization reactions. However, animals in which sensitization was induced with cinnamic aldehyde reacted to a challenge of cinnamic alcohol (Toyama, 1977).

In the Buehler guinea pig test (Buehler, 1965) using 10% cinnamic alcohol in petrolatum, no animals were sensitized (Majeti & Suskind, 1977). However when guinea pigs were sensitized by applications of cinnamic aldehyde 2/8 reacted to a challenge of 5% cinnamic alcohol (Majeti & Suskind, 1977).

IFRA Data

Cinnamic alcohol in concentrations ranging from 0.01% to 17.8% with a maximum concentration on the skin in the 3 groups of tests ranging from 0.14% to 3.2% was tested as a component of perfume compositions, in Repeated Insult Patch Tests on humans (HRIPT). 1763 tests were carried out on 44 fragrance compositions in panels of 10 to 112 subjects and produced no sensitization reactions (IFRA, 1977a).

In another series of HRIPT with concentrations of cinnamic alcohol on the skin ranging from 10^{-5} to 10^{-2}% no sensitization reactions were observed in 1530 tests (IFRA, 1977b).

Closed patch testing on humans of 64 compositions (containing cinnamic alcohol in concentrations ranging from 0.1% to 20%) at an average skin concentration of 2.4%, maximum 13.5% in 5620 single exposures produced no reactions. The panels contained an average of 30% skin sensitive subjects (IFRA, 1977c).

A modified Buehler test on guinea pigs with cinnamic alcohol at concentrations of 10% topical and 0.1% intradermal produced no sensitization reactions (IFRA, 1977d).

In a series of Open Epicutaneous Tests (OET) on guinea pigs, 178 compositions containing an average amount of 2.4%, ranging up to 20% of cinnamic alcohol, produced no sensitization reactions (IFRA, 1977e).

References

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† Especially purified samples.

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Magnusson, B. & Kligman, A. M. (1969). The identification of contact allergens by animal assay. The guinea pig maximization test. *J. invest. Dermatol.* **52**, 268.
Majeti, V. & Suskind, R. (1977). Personal communication to RIFM.
Toyama, M. (1977). Personal communication to RIFM.

ABIES ALBA OIL FROM CONES

Synonym: Templin oil.

Description and physical properties: A colourless to pale-yellow liquid with a fresh, balsamic odour (*Fenaroli's Handbook of Flavor Ingredients*, 1971). The main constituent of Abies alba oil from cones is *l*-limonene (Gildemeister & Hoffman, 1956; Guenther, 1952).

Occurrence: Found in the seed in well-matured cones of *Abies alba* Mill (Fam. Pinaceae) (Guenther, 1952).

Preparation: By water or steam distillation of the crushed cones of *Abies alba* Mill (*Fenaroli's Handbook of Flavor Ingredients*, 1971).

Uses: In public use before the 1900s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·1	0·02	0·03	0·5
Maximum	0·7	0·1	0·25	2·0

Analytical data: Gas chromatogram, RIFM no. 72–77; infra-red curve, RIFM no. 72–77.

Status

The Council of Europe (1970) included Abies alba in the list of substances, spices and seasonings deemed admissible for use with a possible limitation of the active principle in the final product.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Shelanski, 1972).

Irritation. Undiluted Abies alba oil from cones was not irritating when applied to the backs of hairless mice (Urbach & Forbes, 1972). When applied full strength to intact or abraded rabbit skin for 24 hr under occlusion, it was moderately irritating (Shelanski, 1972). Tested at 20% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 20% in petrolatum and produced no sensitization reactions (Kligman, 1972).

Phototoxicity. No phototoxic effects were reported for Abies alba oil from cones (Urbach & Forbes, 1972).

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ABIES ALBA OIL FROM NEEDLES

Description and physical properties: EOA Spec. no. 126. The main constituents include *l*-α-pinene and *l*-limonene (*Fenaroli's Handbook of Flavor Ingredients*, 1971; Gildemeister & Hoffman, 1956).

Occurrence: Found in the needles and twigs of *Abies alba* Mill (Fam. Pinaceae).

Preparation: By the steam distillation of twigs and needles of *Abies alba* Mill.

Uses: In public use before the 1900s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·1	0·02	0·03	0·5
Maximum	0·7	0·1	0·25	2·0

Analytical data: Gas chromatogram, RIFM no. 72–78; infra-red curve, RIFM no. 72–78.

Status

Abies alba was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1163). The Council of Europe (1970) included Abies alba in the list of substances, spices and seasonings deemed admissible for use with a possible limitation of the active principle in the final product.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Shelanski, 1972).

Irritation. Undiluted Abies alba oil from needles was not irritating when applied to the backs of hairless mice (Urbach & Forbes, 1972). When applied full strength to intact or abraded rabbit skin for 24 hr under occlusion it was not irritating (Shelanski, 1972). Tested at 20% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 20% in petrolatum and produced no sensitization reactions (Kligman, 1972).

Phototoxicity. No phototoxic effects were reported for Abies alba oil from needles (Urbach & Forbes, 1972).

References

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ACETALDEHYDE DIETHYL ACETAL

Synonyms: Acetal; diethyl acetal.
Structure: $CH_3 \cdot CH(OCH_2 \cdot CH_3) \cdot OCH_2 \cdot CH_3$.
Description and physical properties: A colourless liquid.
Occurrence: Present in some liquors (e.g. saki and whisky); also detected and quantitatively assessed in rum (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: From acetaldehyde and alcohol with dehydrating agent or catalyst (Arctander, 1969).
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to approximately 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·0005	0·0025	0·1
Maximum	0·06	0·006	0·02	1·0

Analytical data: Gas chromatogram, RIFM no. 74-1; infra-red curve, RIFM no. 74-1.

Status

Acetaldehyde diethyl acetal was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) listed acetaldehyde diethyl acetal giving an ADI of 1 mg/kg.

Biological data

Acute toxicity. The acute oral LD_{50} for rats has been reported as 4570 mg/kg (Smyth, Carpenter & Weil, 1949) and as 4600 mg/kg (Bär & Griepentrog, 1967). Acetal caused some deaths at 20·0–30·0 mmols/kg (2360–3540 mg/kg) when given orally to rabbits and caused death at 7·15–15·0 mmols/kg (885–1770 mg/kg) when given ip to rats (Knoefel, 1934). The acute dermal LD_{50} value in rabbits was reported as >5 g/kg (Wohl, 1974) and as 10 ml/kg (Smyth *et al.* 1949).

Subacute toxicity. When acetal was fed at a level of 5% in the diet to chicks and rats for 6 days, the diet was palatable and no detrimental effects were observed (Yoshida, Ikumo & Suzuki, 1971; Yoshida, Morimoto, Matsui & Oda, 1970).

Inhalation. The maximum time for inhalation of concentrated vapour by rats without deaths was 5 min; inhalation of 4000 ppm for 4 hr caused death in two out of six rats (Carpenter, Smyth & Pozzani, 1949; Smyth *et al.* 1949).

Irritation. Acetal applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Wohl, 1974). The undiluted liquid caused only slight primary irritation when applied to rabbit skin (Smyth *et al.* 1949) and caused only slight eye injury in rabbits (Smyth *et al.* 1949). Tested at 10% in petrolatum, acetal produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 22 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Epstein, 1974).

Intoxication. No cases of industrial intoxication are known. On the basis of animal experiments, acetal is considered to be narcotic and more toxic than paraldehyde. High concentrations in air cause narcosis (Sax, 1968).

Metabolism. When acetal was fed at a level of 5% in the diet for 6 days, availability of energy was 64% in chicks and 29% in rats (Yoshida *et al.* 1970 & 1971). Acetal is rapidly hydrolysed in the stomach (Knoefel, 1934). The resulting acetaldehyde is readily oxidized to acetic acid and eventually to carbon dioxide and water (Williams, 1959).

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ACETALDEHYDE ETHYL *trans*-3-HEXENYL ACETAL

Synonyms: Leaf acetal; leaf alcohol acetal.

Structure: $CH_3 \cdot CH(O \cdot CH_2 \cdot CH_3) \cdot O \cdot CH_2 \cdot CH_2 \cdot \overset{H}{\overset{|}{C}}{:}\overset{H}{\overset{|}{C}} \cdot CH_2 \cdot CH_3$.

Description and physical properties: A colourless liquid.

Occurrence: Has apparently not been reported to occur in nature.

Preparation: From acetaldehyde diethyl acetal (acetal) with *cis*-3-hexenol (Arctander, 1969).

Uses: In public use since the 1950s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·0005	0·0025	0·03
Maximum	0·06	0·006	0·20	0·50

Analytical data: Gas chromatogram, RIFM no. 74-2; infra-red curve, RIFM no. 74-2.

Status

Acetaldehyde ethyl *trans*-3-hexenyl acetal is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974), or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Levenstein, 1974).

Irritation. Acetaldehyde ethyl *trans*-3-hexenyl acetal applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Levenstein, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 26 volunteers. The material was tested at a concentration of 5% in petrolatum and produced no sensitization reactions (Epstein, 1974).

References

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ACETATE C-7

Synonyms: *n*-Heptyl acetate; heptanyl acetate.
Structure: $CH_3 \cdot [CH_2]_6 \cdot OCOCH_3$.
Description and physical properties: A colourless liquid with a slightly floral odour (Arctander, 1969).
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By direct esterification of *n*-heptanol with acetic acid, under azeotropic conditions, or with acetic anhydride (Arctander, 1969).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·08
Maximum	0·09	0·009	0·03	0·8

Analytical data: Gas chromatogram, RIFM no. 74–3; infra-red curve, RIFM no. 74–3.

Status

Acetate C-7 was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included acetate C-7 in the list of admissible artificial flavouring substances at a level of 5 ppm.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1974).

Irritation. Acetate C-7 applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was slightly irritating (Moreno, 1974). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Epstein, 1974).

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Moreno, O. M. (1974). Report to RIFM, 23 January.

ACETATE C-8

Synonyms: *n*-Octyl acetate; *n*-octanyl acetate.
Structure: $CH_3 \cdot [CH_2]_7 \cdot OCOCH_3$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Found in oils of green tea and *Heracleum giganteum* L. and in several other oils (Gildemeister & Hoffman, 1966).
Preparation: By azeotropic esterification of *n*-octanol with acetic acid (Arctander, 1969).
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to less than 5000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·005	0·005	0·08
Maximum	0·1	0·01	0·02	0·8

Analytical data: Infra-red curve, RIFM no. 74–4.

Status

Acetate C-8 was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) listed acetate C-8, giving an ADI of 1 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on acetate C-8.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 3000 mg/kg (Bär & Griepentrog, 1967). The acute dermal LD_{50} in rabbits was reported as > 5 g/kg (Moreno, 1974).

Irritation. Acetate C-8 applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was slightly irritating (Moreno, 1974). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966) was carried out on 24 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Epstein, 1974).

Metabolism. In tests of the availability of energy from various compounds added to the diet, *n*-octyl acetate (5% of the diet) was utilized satisfactorily by chicks (Yoshida, Morimoto & Oda, 1970) and by rats (Yoshida, Ikumo & Suzuki, 1971).

Pharmacology. n-Octyl acetate inhibited acetylcholine at 14°C in isolated guinea-pig ileum by combining with the acetylcholine receptor on the muscle (Takagi & Takayanagi, 1966).

References

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ACETATE C-9

Synonyms: 1-Nonyl acetate; pelargonyl acetate.
Structure: $CH_3 \cdot [CH_2]_8 \cdot OCOCH_3$
Description and physical properties: Food Chemicals Codex (1966).
Occurrence: Apparently it has not been reported to occur in nature.
Preparation: By acetylation of alcohol C-9.
Uses: In public use since the 1900s. Use in fragrances in the USA amounts to less than 5000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	–
Maximum	0·09	0·015	0·02	0·20

Analytical data: Gas chromatogram, RIFM no. 71–5; infra-red curve, RIFM no. 71–5.

Status

Acetate C-9 was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) listed acetate C-9 (nonyl acetate), giving an ADI of 1 mg/kg. The *Food Chemicals Codex* (1966) has a monograph on acetate C-9.

Biological data

Acute toxicity. The acute oral LD_{50} value (RIFM sample no. 71–5) was reported as $> 5{\cdot}0$ g/kg in the rat (Levenstein, 1972). The acute dermal LD_{50} for sample no. 71–5 was reported to be $> 5{\cdot}0$ g/kg (Levenstein, 1972).

Human testing. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at 2% concentration in petrolatum and no case of sensitization was reported (Kligman, 1972).

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ACETATE C-10

Synonym: Decyl acetate.
Structure: $CH_3 \cdot [CH_2]_9 \cdot OCO \cdot CH_3$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Occurs in several oils, such as citronella and mandarin (Gildemeister & Hoffman, 1966).
Preparation: By direct esterification of *n*-decanol with acetic acid or acetic anhydride.
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·2
Maximum	0·1	0·01	0·05	0·8

Analytical data: Gas chromatogram, RIFM, no. 74-5; infra-red curve, RIFM no. 74-5.

Status

Acetate C-10 was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) listed acetate C-10 giving an ADI of 1 mg/kg.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits were reported as >5 g/kg (Levenstein, 1974).

Subacute toxicity. In tests of the availability of energy from various compounds added to the diet, *n*-decyl acetate (5% of the diet) was utilized satisfactorily, without toxic effects, by chicks (Yoshida, Morimoto & Oda, 1970). Both *n*-decyl acetate and *n*-decyl alcohol (5% of the diet) were utilized by rats (Yoshida, Ikumo & Suzuki, 1971). When fed to day-old White Leghorn male chicks for 3 wk, *n*-decyl acetate and *n*-decyl alcohol (10% of the diet) induced nutritional encephalomalacia, which could be prevented completely by dietary supplementation with DL-α-tocopheryl acetate (Yoshida & Hoshii, 1971). The median lethal dietary level of *n*-decyl alcohol for White Leghorn male chicks was found to be 20·1% for a 3-wk feeding period (Yoshida, 1971).

Irritation. When acetate C-10 was applied undiluted to intact or abraded rabbit skin under occlusion for 24 hr mild erythema was observed and lasted for 24 hr (Levenstein, 1974). When tested at 8% concentration in petrolatum in a 48-hr occluded patch test in volunteers, no irritation was produced (Kligman, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) using 8% acetate C-10 in petrolatum was carried out on 25 volunteers without producing any sensitization reactions (Kligman, 1974).

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Yoshida, M., Morimoto, H. & Oda, R. (1970). Availability of energy in esters of aliphatic acids and alcohols by growing chicks. *Agric. biol. Chem.* **34**, 1668.

ACETATE C-11

Synonyms: Undecenyl acetate; 10-undecen-1-yl acetate; 10-hendecen-1-yl acetate.
Structure: $CH_2{:}CH{\cdot}[CH_2]_9{\cdot}OCO{\cdot}CH_3$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By azeotropic-type esterification of 10-undecen-1-ol with acetic acid (Arctander, 1969).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 1000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·001	0·003	0·08
Maximum	0·06	0·01	0·02	0·8

Analytical data: Gas chromatogram, RIFM no. 74–6; infra-red curve, RIFM no. 74–6.

Status

Acetate C-11 was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included acetate C-11 in the list of artificial flavouring substances that may be added temporarily to foodstuffs without hazard to public health.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Levenstein, 1974).

Irritation. Acetate C-11 applied full strength to intact or abraded rabbit skin for 24 hr under occlusion produced a mild erythema which lasted 24 hr (Levenstein, 1974). Tested at 8% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1974).

References

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ACETATE C-12

Synonyms: *n*-Dodecyl acetate; lauryl acetate.
Structure: $CH_3 \cdot [CH_2]_{11} \cdot OCO \cdot CH_3$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Reported to have been found in several natural products (*Fenaroli's Handbook of Flavor Ingredients*. 1975).
Preparation: By direct esterification of lauryl alcohol with acetic acid (under azeotropic conditions) or with acetic anhydride (Arctander, 1969).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 1000 lb/yr. Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·001	0·003	0·08
Maximum	0·06	0·01	0·02	0·8

Status

Acetate C-12 was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) listed acetate C-12, giving an ADI of 1 mg/kg.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1974). In a study of toxicity to fish, the toxic concentration of lauryl acetate to *Carassius auratus* and *Salmo gairdnerii* during a 6-hr observation period at 15°C was found to be 5·20 mg/litre. The surface tension (50·1) was not related directly to the toxicity (Marchetti, 1964).

Subacute toxicity. In feeding studies, Yoshida, Ikumo & Suzuki (1971) found that the related compound, dodecyl alcohol, could be utilized by rats at a level of 5% in the diet but was toxic at 10%. It was also found that dodecyl alcohol induced nutritional encephalomalacia when fed to day-old chicks for 3 wk, with a median lethal dietary level of 18% (Yoshida & Hoshii, 1971). Repeated application of large doses of undiluted dodecyl acetate promoted skin tumours in three of 15 Swiss mice that had received an initiating dose of 7,12-dimethylbenz[a]anthracene. No tumours developed in 15 Swiss mice similarly treated with a 33% solution in acetone, or in mice not given the preliminary initiating treatment (Sicé, Shubik & Feldman, 1957).

Irritation. Acetate C-12 applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was slightly irritating (Moreno, 1974). Tested at 20% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 20% in petrolatum and produced no sensitization reactions (Kligman, 1974).

Micro-organisms. When tested at concentrations up to 4·33 μmol/ml, acetate C-12 did not inhibit 12 Gram-positive and eight Gram-negative organisms (Kabara, Swieczkowski, Conley & Truant, 1972).

References

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Yoshida, M., Ikumo, H. & Suzuki, O. (1971). Evaluation of available energy of aliphatic chemicals by rats. An application of bioassay of energy to mono-gastric animal. *Agric. biol. Chem.* **35**, 1208.

ACETOPHENONE

Synonym: Methyl phenyl ketone.
Structure: $C_6H_5 \cdot CO \cdot CH_3$
Description and physical properties: EOA Spec. no. 37.
Occurrence: In at least 15 essential oils, including green tea, labdanum, orris and castoreum (Gildemeister & Hoffman, 1960).
Preparation: Obtained as a by-product in the manufacture of phenol by the hydroperoxidation of cumene, it may also be prepared by the Friedel–Crafts method or by oxidation of ethyl benzene with air (Bedoukian, 1967).
Uses: In public use since the beginning of this century. Use in fragrances in the USA amounts to less than 10,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·002	0·005	0·09
Maximum	0·15	0·024	0·03	0·20

Status

Acetophenone was considered GRAS by FEMA (1965) and is permitted by the FDA in foods (21 CFR 121.1164). The Council of Europe (1970) listed acetophenone (1-phenyl ethanone) giving an ADI of 1 mg/kg. Browning (1965) has provided an extensive monograph on acetophenone.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was 3·2 g/kg (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964). The LD_{50} by dermal application was >20 ml/kg in the guinea-pig (Rowe & Wolf, 1963).

Chronic toxicity. In an FDA feeding study, 10,000 ppm fed to rats in the diet for 17 wk produced no effects (Hagan, Hansen, Fitzhugh, Jenner, Jones, Taylor, Long, Nelson & Brouwer, 1967).

Human testing. A maximization test (Kligman, 1966) on acetophenone at 2% concentration produced no reaction (Kligman, 1971).

Inhalation toxicity. Apparently no TLV has been established, but Rowe & Wolf (1963) reported no deaths in rats exposed for 8 hr to an atmosphere saturated with acetophenone. [Flash point, 82°C; vapor pressure (% in saturated air), 0·45%; evaporation rate (ether = 1), 0·06.]

Metabolism. At one time, acetophenone was used as a hypnotic. Its conversion to benzoic acid and methylphenylcarbinol in dogs and rabbits was observed by a number of early workers. Small amounts (up to 2%) are also excreted as mandelic acid. In the rabbit about half the dose is excreted as methylphenylcarbinyl glucuronide and about 20% as hippuric acid. It is probable that the ketone is first asymmetrically reduced to the carbinol, which is the precursor of benzoic and mandelic acids (Williams, 1959).

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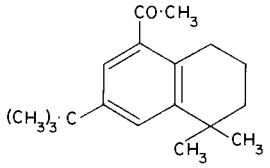
4-ACETYL-6-*tert*-BUTYL-1,1-DIMETHYLINDAN

Synonyms: 4-Acetyl-1,1-dimethyl-6-*tert*-butylindan; celestolide.
Structure:



Description and physical properties: White crystals.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: From *tert*-butylbenzene.
Uses: In public use since the 1960s. Use in fragrances in the USA amounts to less than 5000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·2
Maximum	0·12	0·012	0·04	0·7

Analytical data: Gas chromatogram, RIFM no. 72–96; infra-red curve, RIFM no. 72–96.

Status

4-Acetyl-6-*tert*-butyl-1,1-dimethylindan is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974) or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Denine, 1973).

Subacute toxicity. Exposure of 2-wk-old rats to an odorous environment of 4-acetyl-6-*tert*-butyl-1,1-dimethylindan for 4- and 8-wk periods induced a unique pattern of mitral-cell degeneration in the olfactory bulb (Pinching & Doving, 1974).

Irritation. 4-Acetyl-6-*tert*-butyl-1,1-dimethylindan applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Denine, 1973). Tested at 4% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1973).

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Pinching, A. J. & Doving, K. B. (1974). Selective degeneration in the rat olfactory bulb following exposure to different odours. *Brain Res.* **82**, 195.

ACETYL CARENE

Structure: A mixture of isomers having the general formula $C_{12}H_{19}O$.
Description and physical properties: A colourless to slightly yellow liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By reacting acetic anhydride and Δ^3-carene.
Uses: Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·001	0·005
Maximum	0·1	0·05	0·005	0·1

Analytical data: Gas chromatogram, RIFM no. 74-9; infra-red curve, RIFM no. 74-9.

Status

Acetyl carene is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974), or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 3·1 (2·1–4·1 g/kg) (Moreno, 1974). The acute dermal LD_{50} value in rabbits was reported as >5 g/kg (Moreno, 1974).

Irritation. Acetyl carene applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1974). Tested at a 10% concentration in petrolatum, it produced no irritation after a 48-hr closed-patch test in human subjects (Kligman, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1974).

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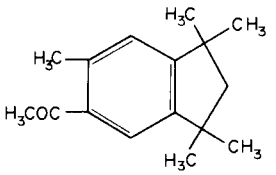
Moreno, O. M. (1974). Report to RIFM, 24 January.

5-ACETYL-1,1,2,3,3,6-HEXAMETHYLINDAN

Structure:



Description and physical properties: An almost white crystalline mass.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By condensation of *p*-cymene with a tertiary alcohol and subsequent acetylation (Bedoukian, 1967).
Uses: In public use since the 1960s. Use in fragrances in the USA amounts to less than 6000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·02	0·2
Maximum	0·15	0·015	0·05	0·4

Analytical data: Gas chromatogram, RIFM no. 74-10.

Status

5-Acetyl-1,1,2,3,3,6-hexamethylindan is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974), or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 1·7 g/kg (Wohl, 1974). The acute dermal LD_{50} was reported as >5 g/kg (Wohl, 1974).

Irritation. When applied full strength to intact or abraded rabbit skin under occlusion for 24 hr this material was not irritating (Wohl, 1974). Neither was it irritating when tested in volunteers by a 48-hr patch-test under occlusion at a concentration of 4% in petrolatum (Kligman, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) carried out on 25 volunteers using 4% acetylhexamethylindan produced no sensitization reactions (Kligman, 1974).

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Wohl, A. J. (1974). Report to RIFM, 15 May.

ALANTROOT OIL

Synonyms: Elecampane oil; oil of Inula.

Description and physical properties: A brown liquid. The greatest part of oil of elecampane consists of a mixture of alantolactone and isoalantolactone (Guenther, 1952).

Occurrence: Found in the roots of *Inula helenium* L. (Fam. Compositae) (Gildemeister & Hoffman, 1961; Guenther, 1952).

Preparation: By steam distillation of the roots of *Inula helenium* (Guenther, 1952).

Uses: In public use before the 1900s.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·002	0·08
Maximum	0·05	0·005	0·025	0·4

Status

Elecampane is approved by the FDA for food use (21 CFR 121.1163 in alcoholic beverages only). The Council of Europe (1974) included elecampane in the list of substances, spices and seasonings deemed admissible for use, with a possible limitation of the active principle in the final product.

Biological data

Irritation. Alantroot oil tested at 4% in petrolatum produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced extremely severe allergic reactions in 23 out of 25 subjects after the second induction application (Kligman, 1975). Subjects previously sensitized to costus root oil gave severe cross-sensitization responses to alantroot oil (Epstein, 1975).

Alantolactone (one of the main constituents of alantroot) elicited positive patch-test responses in sensitized guinea-pigs (Hausen & Schulz, 1975; Schulz, Hausen, Wallhofer & Schmidt-Loffler, 1975). Two individuals initially sensitized to purified alantolactone (derived from Inula, Compositae family) showed positive patch-test reactions to costus root oil (Mitchell, 1974). Alantolactone produced positive patch-test reactions in five patients who were allergic to Frullania (Mitchell, Fritig, Singh & Towers, 1970). Hjorth (1970) sensitized four patients out of 25 with a single patch test with a 1% petrolatum dispersion of alantolactone. That a patch test with alantolactone can cause sensitization was reported also by Foussereau, Muller & Benezra (1975).

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ALCOHOL C-6

Synonyms: *n*-Hexyl alcohol; hexan-1-ol.
Structure: $CH_3 \cdot [CH_2]_4 \cdot CH_2OH$.
Description and physical properties: *Food Chemicals Codex* (1972).
Occurrence: Found among the constituents of several essential oils and aromas, notably apple, strawberry, tea, violet (leaves and flowers), *Java citronella*, Bourbon geranium, lavender, lavandin, spike, *Litsea zeylanica*; also identified in bitter orange (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: By reduction of ethyl caproate with sodium alcoholate or by any other suitable means.
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·05
Maximum	0·1	0·01	0·03	0·1

Analytical data: Gas chromatogram, RIFM no. 74–125; infra-red curve, RIFM no. 74–125.

Status

Alcohol C-6 was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121·1164). The Council of Europe (1974) listed alcohol C-6, giving an ADI of 1 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on alcohol C-6. A maximum permissible concentration of 0·1 mg/litre has been suggested (Zaeva & Fedorova, 1963).

Biological data

Acute toxicity. The acute oral LD_{50} in mice was reported as 4 g/kg (Zaeva & Fedorova, 1963) and in rats as 4·87 g/kg (Bär & Griepentrog, 1967) and 4·59 g/kg (Smyth, Carpenter & Weil, 1951). The acute dermal LD_{50} in rabbits was reported as 3·1 ml/kg (Smyth *et al.* 1951) and as >5 g/kg (Moreno, 1974). The maximum period of survival of rats inhaling the saturated vapours of hexanol was reported as 8 hr (Smyth *et al.* 1951). Gerarde & Ahlstrom (1966) found that aspiration of 0·2 ml alcohol C-6 caused respiratory arrest and instant death. Scala & Burtis (1973) studied the acute toxicity of commercial grade hexanol (containing, by weight, 44% hexan-1-ol, 53% methyl pentan-1-ols and 3% 2-ethylbutan-1-ol) by several routes of administration in various species. The acute oral LD_{50} in rats was 3·67 g/kg and the acute dermal LD_{50} in rabbits was >2·6 g/kg. Dermal application resulted in signs of CNS toxicity. Inhalation exposure of mice, rats and guinea-pigs to atmospheres nearly saturated with the hexanol preparation (1060 ppm) for 6 hr elicited a questionable effect on CNS activity, moderate (but reversible) local irritation mainly involving the mucous membranes and slight lung congestion.

Chronic toxicity. The tumour-promoting activity of *n*-hexanol was studied on mouse skin treated initially with a sub-carcinogenic dose of 7,12-dimethylbenz[*a*]anthracene and then by thrice-weekly applications of 20 µl hexanol in cyclohexane for 60 wk. No skin tumours developed in 36 survivors (Sicé, 1966).

Irritation. Alcohol C-6 applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1974). Tested at 1% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974). Dermal application of commercial grade hexanol to rabbits resulted in a moderate degree of skin irritation, characterized by erythema, oedema and atonia; instillation of 0·1 ml of this preparation into the rabbit eye produced severe eye irritation consisting of persistent iritis, corneal opacity and occasional corneal vascularization (Scala & Burtis, 1973).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 21 volunteers. The material was tested at a concentration of 1% in petrolatum and produced no sensitization reactions (Epstein, 1974).

Metabolism. *n*-Hexanol is metabolized by direct conjugation with glucuronic acid and by oxidation to the carboxylic acid and eventually to CO_2. In the rabbit, direct conjugation is a minor pathway and oxidation the major pathway (Williams, 1959).

Additional published data

Hexyl alcohol at concentrations of 0·5–20% showed a surface anaesthetic action when applied to the outer ear passage of guinea-pigs (Ikebe, 1934).

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ALCOHOL C-7

Synonyms: *n*-Heptyl alcohol; heptan-1-ol.
Structure: $CH_3 \cdot [CH_2]_5 \cdot CH_2OH$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Found in a few essential oils—hyacinth, violet leaves and *Litsea zeylanica* (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: By catalytic reduction of heptaldehyde (Arctander, 1969).
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·05
Maximum	0·1	0·01	0·03	0·1

Analytical data: Gas chromatogram, RIFM no. 74–126; infra-red curve, RIFM no. 74–126.

Status

Alcohol C-7 was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included alcohol C-7 at a level of 3 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health. The *Food Chemicals Codex* (1972) has a monograph on alcohol C-7. Maximum permissible concentrations of 0·013 mg/litre (Egorov & Andrianov, 1961) and 0·1 mg/litre (Zaeva & Fedorova, 1963) have been suggested.

Biological data

Acute toxicity. The acute oral LD_{50} was reported as 4·3 g/kg (Egorov & Andrianov, 1961) and 6 g/kg (Zaeva & Fedorova, 1963) in mice and as 3·25 g/kg in rats (Henson, 1960). The acute dermal LD_{50} in rabbits was reported as >5 g/kg (Moreno, 1974). The acute inhalation LC_{50} in mice was reported as 6·6 mg/litre (Egorov & Andrianov, 1961).

Subacute toxicity. Subacute inhalation exposure in rabbits and rats led to conjunctivitis and a decrease in blood cholinesterase activity (Egorov & Andrianov, 1961). Inhalation of 0·18–0·35 mg/litre, 2 hr/day for 4·5 months in rats caused minor haematological changes and some unspecified histological changes (Zaeva & Fedorova, 1963).

Irritation. Alcohol C-7 applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1974). Tested at 1% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 20 volunteers. The material was tested at a concentration of 1% in petrolatum and produced no sensitization reactions (Epstein, 1974).

Metabolism. In the rabbit, heptan-1-ol is metabolized partly by direct conjugation with glucuronic acid to form an ether glucuronide and mainly by oxidation to the carboxylic acid, which either undergoes further oxidation to CO_2 or forms an ester glucuronide (Williams, 1959).

Additional published data

Brown, Muir & Thorpe (1970) reported the acute oral toxicity of an alcohol mixture (Linevol 7–9) consisting of approximately 45% heptanol, 40% octanol and 15% nonyl alcohol. The oral LD_{50} was reported as 11·1 g/kg in rats and 5·9 g/kg in mice. Consecutive daily dosing with 5 ml/kg/day was not lethal to rats over 7 days but produced in some rats histological changes comprising acanthosis, hyper- and parakeratosis in the cardiac segment of the stomach and cytoplasmic vacuolation in the liver. The alcohol was virtually non-irritant when patch-tested in undiluted form on the skin of rabbits (1 ml, 5 days/wk for 3 wk) and guinea-pigs (0·5 ml, 5 days/wk for 3 wk) but was intensely irritant when instilled into the eye unless washed out immediately. No skin sensitization was seen in guinea-pigs following sc injection or topical application of a 0·1% solution to guinea-pigs.

Heptanol in concentrations of 0·05–20% exerted a surface anaesthetic action following application to the outer ear passage of guinea-pigs (Ikebe, 1934).

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ALCOHOL C-8

Synonyms: 1-Octanol; *n*-octyl alcohol.
Structure: $CH_3 \cdot [CH_2]_6 \cdot CH_2OH$.
Description and physical properties. EOA Spec. no. 166.
Occurrence: Found in several citrus oils and at least ten other natural sources (Gildemeister & Hoffman, 1960).
Preparation: By sodium reduction or high-pressure catalytic hydrogenation of the esters of the naturally occuring caprylic acid, or by oligomerization of ethylene using aluminium alkyl technology.
Uses: In public use since the 1900s. Use in fragrances in the USA amounts to less than 10,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·003	0·005	–
Maximum	0·09	0·014	0·03	0·20

Analytical data: Gas chromatogram, RIFM sample no. 71–7; infra-red curve, RIFM sample no. 71–7.

Status

Alcohol C-8 was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) listed alcohol C-8 (octyl alcohol), giving an ADI of 1 mg/kg. The *Food Chemicals Codex* (1966) has a monograph on alcohol C-8 (octanol).

Biological data

Acute toxicity. The acute oral LD_{50} in the rat was $>3{\cdot}2$ g/kg, while in the guinea-pig, the LD_{50} by dermal application was $>0{\cdot}5$ g/animal and skin irritation was slight (Treon, 1963). The acute oral LD_{50} for alcohol C-8 (RIFM sample no. 71–7) was found to exceed 5·0 g/kg in the rat and the acute dermal LD_{50} in rabbits exceeded 5·0 g/kg (Levenstein, 1972).

Human testing. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at 2% concentration in petrolatum and no evidence of sensitization was reported (Kligman, 1972).

Metabolism. "The primary aliphatic alcohols undergo two general reactions *in vivo*, namely oxidation to carboxylic acids and direct conjugation with glucuronic acid. The first reaction proceeds with the intermediate formation of an aldehyde, and the carboxylic acid from this may be either oxidized completely to carbon dioxide or excreted as such or combined with glucuronic acid as an ester glucuronide. The extent to which an alcohol undergoes the second reaction, i.e. direct conjugation to an ether glucuronide, appears to depend upon the speed of the first reaction, for alcohols which are rapidly oxidized form very little ether glucuronide unless given in high doses" (Williams, 1959).

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ALCOHOL C-9

Synonyms: 1-Nonanol; pelargonic alcohol.
Structure: $CH_3 \cdot [CH_2]_7 \cdot CH_2OH$.
Description and physical properties: Food Chemicals Codex (1966).
Occurrence: Found in a number of citrus oils and about ten other oils (Gildemeister & Hoffman, 1960).
Preparation: Usually by sodium or high-pressure catalytic reduction of esters of pelargonic acid (Bedoukian, 1967).
Uses: In public use since the 1900s. Use in fragrances in the USA amounts to less than 10,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·003	0·005	0·09
Maximum	0·09	0·014	0·03	0·25

Analytical data: Gas chromatogram, RIFM no. 71–8; infra-red curve, RIFM no. 71–8.

Status

Alcohol C-9 has been granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) listed alcohol C-9 (nonyl alcohol), giving an ADI of 1 mg/kg. The *Food Chemicals Codex* (1966) has a monograph on alcohol C-9 and an extensive monograph on nonanol has been compiled by Browning (1965).

Biological data

Acute toxicity. Treon (1963) reported the single-dose oral LD_{50}s in mice and rats as 6·4–12·8 and 3·56 g/kg, respectively, and the 24-hr dermal LD_{50} in the rabbit as 5·66 ml/kg. There was no skin irritation in the rabbit. Gerarde & Ahlstrom (1966) have reported on the aspiration hazard of a series of alcohols, including alcohol C-9.

Human testing. Alcohol C-9 does not appear to produce skin irritation (Peterson & Hall, 1946). A maximization test (Kligman, 1966) was carried out on 25 volunteers using a 2% concentration in petrolatum and no case of sensitization was reported (Kligman, 1972).

Metabolism. See alcohol C-8.

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ALCOHOL C-10

Synonyms: 1-Decanol; *n*-decyl alcohol.

Structure: $CH_3 \cdot [CH_2]_8 \cdot CH_2OH$.

Description and physical properties: EOA Spec. no. 167.

Occurrence: Reported to occur in sweet orange and a few other essential oils (Gildemeister & Hoffman, 1960).

Preparation: By sodium reduction or high-pressure catalytic hydrogenation of the esters of naturally occurring capric acid, or by oligomerization of ethylene using aluminium alkyl technology.

Uses: In public use since the 1900s. Use amounts to approximately 20,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·003	0·005	0·09
Maximum	0·09	0·02	0·03	0·25

Analytical data: Gas chromatogram, RIFM no. 71–9; infra-red curve, RIFM no. 71–9.

Status

Alcohol C-10 was classified GRAS by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included alcohol C-10 (decyl alcohol) in the list of admissible artificial flavouring substances at a level of 5 ppm.

Biological data

Acute toxicity. The acute oral LD_{50} has been reported as 12·8 g/kg in the rat (Bär & Griepentrog, 1967), and as 6·4–12·8 g/kg in the mouse and 9·80 g/kg in the rat (Treon, 1963). The dermal LD_{50} value in the rabbit was 3·56 g/kg and skin irritation in the rabbit after 24 hr was severe with the mixed isomers of decyl alcohol (Treon, 1963).

Human testing. A maximization test (Kligman, 1966) was carried out on 25 volunteers using a 3% concentration in petrolatum. No subject became sensitized to alcohol C-10 (Kligman, 1972).

Metabolism. See alcohol C-8.

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ALCOHOL C-11

Synonyms: 10-Undecen-1-ol; undecylenic alcohol.
Structure: $CH_2 \cdot CH[CH_2]_8 \cdot CH_2OH$.
Description and physical properties: Givaudan Index (1966).
Occurrence: Found in the leaves of *Litsea odorifera* Val. (Gildemeister & Hoffman, 1960).
Preparation: Usually by sodium reduction of the esters of undecylenic acid, which is obtained by the cracking of castor oil (Bedoukian, 1967).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 10,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	–	–	0·005	0·06
Maximum	–	–	0·03	0·10

Analytical data: Gas chromatogram, RIFM no. 71–10; infra-red curve, RIFM no. 71–10.

Status

Alcohol C-11 is permitted by the FDA for use in foods (21 CFR 121.1164).

Biological data

Acute toxicity. Both the oral LD_{50} value in rats and the dermal LD_{50} value in rabbits exceeded 5 g/kg (Levenstein, 1972).

Human testing. A maximization test (Kligman, 1966) was carried out on 25 volunteers, using a 1% concentration in petrolatum and no evidence of sensitization was reported (Kligman, 1972).

Metabolism. See alcohol C-8.

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ALCOHOL C-12

Synonyms: 1-Dodecanol; lauric alcohol.
Structure: $CH_3 \cdot [CH_2]_{10} \cdot CH_2OH$.
Description and physical properties: EOA Spec. no. 184.
Occurrence: In lime oil and several other essential oils (Gildemeister & Hoffman, 1960).
Preparation: By sodium reduction or high-pressure catalytic hydrogenation of esters of naturally occurring lauric acid, or by oligomerization of ethylene using aluminium alkyl technology.
Uses: In public use since the 1900s. Use in fragrances in the USA amounts to approximately 20,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·002	0·005	0·09
Maximum	0·09	0·018	0·02	0·25

Analytical data: Gas chromatogram, RIFM no. 71–11; infra-red curve, RIFM no. 71–11.

Status

Alcohol C-12 (lauryl alcohol) was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) listed alcohol C-12 (lauryl alcohol), giving an ADI of 1 mg/kg. There is a monograph on alcohol C-12 in the *Food Chemicals Codex* (1966).

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported by Treon (1963) to exceed 36·0 ml/kg and the LD_{50} by skin absorption in the guinea-pig to exceed 10 ml/kg. Seven rats and seven rabbits, which survived a dose of either 24 or 36 ml technical lauryl alcohol/kg body weight, demonstrated no significant gross or microscopic change (Treon, 1963). Bär & Griepentrog (1967) reported the oral LD_{50} in rats as 12·8 g/kg.

Human testing. Alcohol C-12 is said to have "low toxicity" (*Merck Index*, 1968). A maximization test (Kligman, 1966) was carried out on 25 volunteers using a 4% concentration in petrolatum, and no case of sensitization was reported (Kligman, 1972).

Metabolism. See alcohol C-8.

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ALCOHOL C-14 MYRISTIC

Synonyms: Myristic alcohol; myristyl alcohol; 1-tetradecanol; tetradecanol.
Structure: $CH_3 \cdot [CH_2]_{12} \cdot CH_2OH$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Found in spermaceti wax and sperm oil (*Givaudan Index*, 1961).
Preparation: By reduction of the fatty acid ester by $LiAlH_4$.
Uses: In public use since the 1940s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·05
Maximum	0·15	0·015	0·05	1·2

Analytical data: Gas chromatogram, RIFM no. 74–11; infra-red curve, RIFM no. 74–11.

Status

Conditions have been prescribed for the safe use of synthetic and natural myristic alcohol in food, in food-contact articles and in the synthesis of food or food-contact components under the Federal Food, Drug, and Cosmetic Act (*Federal Register* 1971. **36**, 20430).

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as >5 g/kg (Levenstein, 1974), and the acute oral LD_{50} of mixed isomers of tetradecanol as 32·5 ml/kg in rats (Smyth, Carpenter, Weil, Pozzani, Striegel & Nycum, 1969). The acute dermal LD_{50} value in rabbits was reported as >5 g/kg by Levenstein (1974) and as 7·13 ml/kg by Smyth *et al.* (1969).

Short-term toxicity. Tetradecanol was toxic to rats at dietary levels of 5 and 10% (Yoshida, Ikumo & Suzuki, 1971). The compound was readily utilized as an energy source by chicks at 5% in the diet (Yoshida, Morimoto, Matsui & Oda, 1970); at 10–16% there were some deaths but no cases of nutritional encephalomalacia (Yoshida & Hoshii, 1971). Toxic symptoms of severe diarrhoea and loss of body weight, accompanied by some prolongation of the lifespan, resulted from ip administration of 2–10 mg/mouse/day to mice implanted ip with Ehrlich ascites tumour (Ando, Kodama, Kato, Tamura & Arima, 1972).

Inhalation toxicity. No deaths resulted from inhalation of concentrated vapour by rats for up to 8 hr (Smyth *et al.* 1969).

Irritation. Alcohol C-14 myristic applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Levenstein, 1974). Also in rabbits, skin irritation and corneal injury were found to be very low (Smyth *et al.* 1969). Alcohol C-14 myristic tested at 12% in petrolatum on two different panels of subjects produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers; the material, tested at a concentration of 12% in petrolatum, produced sensitization reactions in two of the test subjects (Kligman, 1974; see Preface Note no. 1). In another maximization test (Kligman, 1966; Kligman & Epstein, 1975) carried out on a different panel of 25 subjects, a concentration of 12% in petrolatum produced no sensitization reactions (Kligman, 1974).

Metabolism. Tetradecanol supported the growth of Pseudomonas C12B in minimal media (Williams, Mayberry & Payne, 1966). In the oxidation of tetradecanol by *Pseudomonas aeruginosa* cultures, tetradecanol was accumulated as the semicarbazone, supporting the possibility of production of an intermediate aldehyde (Büning-Pfaue & Rehm, 1972).

Tumour promotion. Repeated skin application of purified tetradecanol showed a probable weak activity in promoting skin tumours in female Swiss mice that had received an initiating dose of 7,12-dimethylbenz[*a*]anthracene (Sicé, 1966). In tests of antitumour activity, some prolongation of the lifespan was observed, along with toxic symptoms, when 2–10 mg/mouse/day was administered ip to mice implanted ip with Ehrlich ascites tumour (Ando *et al.* 1972).

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ALDEHYDE C-6

Synonyms: 1-Hexanal; hexaldehyde.

Structure: $CH_3 \cdot [CH_2]_4 \cdot CHO$.

Description and physical properties: A colourless mobile liquid with a powerful fatty-green odour (Arctander, 1969).

Occurrence: Reported to occur in about a dozen essential oils (Gildemeister & Hoffman, 1960).

Preparation: By oxidation of *n*-hexanol.

Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·001	0·0015	0·018
Maximum	0·03	0·005	0·01	0·05

Analytical data: Gas chromatogram, RIFM no. 71–12; infra-red curve, RIFM no. 71–12.

Status

Aldehyde C-6 was classified GRAS by FEMA (1965), and is approved by the FDA for food use (21 CFR 121.1164).

Biological data

Acute toxicity. The oral LD_{50} in rats is given as 5 g/kg in the *Merck Index* (1968) and as 4·9 g/kg by Fassett (1963), who reported the material to be slightly irritating to the skin and eye of the rabbit. Smyth, Carpenter, Weil, Pozzani, Striegel & Nycum (1969) reported an acute oral LD_{50} of 9·51 g/kg for the mixed isomers. The dermal LD_{50} in rabbits is given as >10 ml/kg (Smyth *et al.* 1969).

Human testing. A maximization test (Kligman, 1966) was carried out on 25 volunteers using a 1 % concentration in petrolatum and no case of sensitization was reported (Kligman, 1972).

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ALDEHYDE C-7

Synonyms: *n*-Heptaldehyde; heptanal.
Structure: $CH_3 \cdot [CH_2]_5 \cdot CHO$.
Description and physical properties: EOA Spec. no. 281.
Occurrence: Found in the essential oils of ylang-ylang, clary sage, California lemon, bitter orange, rose and hyacinth (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: By oxidation of the corresponding alcohol or by the cracking of castor oil.
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·0005	0·001	0·04
Maximum	0·06	0·006	0·01	0·4

Status

Aldehyde C-7 was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included aldehyde C-7 at a level of 5 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health. The *Food Chemicals Codex* (1972) has a monograph on aldehyde C-7.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1974). The LD_{50} value for mice was reported for the oral route as 500 mg by Boyland (1940) and as 18 ml/kg body weight by Esposito & Nicolini (1962), and as >500 mg/kg ip in butyl succinate (National Research Council, 1956).

Short-term toxicity. In mice, Esposito & Nicolini (1962) found that high doses did not always cause serious damage to the blood-forming functions of the bone marrow. Even in the presence of massive lesions of the muscles and skin, the only significant haematological change noted was a decrease in leucocytes from 9000 to 6100/mm^3 after 20 days of treatment. In mice with spontaneous or grafted tumours, Boyland (1940) found that daily oral doses of 50 mg/day caused illness and frequently led to death within 1 wk, along with a significant effect on the tumours.

In studies of the blood, lung tissues and bone marrow of rabbits given 0·1 or 0·5 ml/kg/day on 5 days/wk for 4 wk, erythrocyte aldolase activity decreased and disturbances in respiratory tissue occurred (Esposito & Nicolini, 1962). Organic defence indexes (serum bactericidal activity and properdin level) in rabbits were lowered by im injection of 0·1 ml/kg/day for 7 consecutive days, a dose corresponding to the therapeutic antitumour dose (Diomede-Fresa & Fumarola, 1960).

When fed to chicks at 5% in the diet for 6 days, the compound was palatable and caused no deaths, although it was not utilized as an energy source (Yoshida, Morimoto, Matsui & Oda, 1970).

Irritation. Aldehyde C-7 applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was very irritating (Moreno, 1974). No irritation was produced in human subjects tested with a 4% concentration of aldehyde C-7 in petrolatum by a 48-hr patch test under occlusion (Kligman, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers using 4% aldehyde C-7 in petrolatum. No sensitization reactions were produced (Kligman, 1974).

Metabolism. Aldehyde C-7 (heptaldehyde) is readily oxidized in the animal body to the corresponding fatty acid, which then undergoes β-oxidation and is eventually oxidized to carbon dioxide and water (Williams, 1959). Boyland (1940) was unable to detect pimelic acid in the urine of rats fed heptanal, indicating that the compound was probably completely oxidized in the body. The finding of tumour-inhibiting action by malonic acid supported the possibility of ω-oxidation leading to the formation of glutaric and malonic acids, although the intermediate pimelic acid was not isolated. Yoshida *et al.* (1970) found that heptanal was not utilized as an energy source by chicks when fed at 5% in the diet for 6 days, although the diet was palatable and caused no deaths. Direct evidence was obtained by Erwin & Deitrich (1966) for the oxidation in rat, monkey and bovine brain of heptanal and other aldehydes that may arise from biologically active amines in the brain. Aldehyde-oxidizing activity was present in all the areas of bovine brain studied. It was suggested that brain aldehyde dehydrogenase may be important in oxidizing aldehydes from exogenous sources.

Anti-tumour activity. Strong (1938) observed that spontaneous mammary tumours in mice liquefied and regressed in mice receiving heptanal in the diet. Spontaneous tumours of various kinds regressed in dogs receiving sc injections of 0·10–1·00 ml/dose; the site of the injection did not become ulcerated, in contrast to similar treatment in mice (Strong & Whitney, 1938). Boyland (1940) found that,

in mice, 50 mg/day given orally in water with gum produced significant inhibition of growth of both spontaneous and grafted tumours and had a slight effect on induced tumours, although the mice became ill and frequently died within 1 wk. Williams (1959) suggested that heptanal had no specific action on neoplastic cells, but probably inhibits some animal tumours by interfering with their metabolism, since heptanal is known to inhibit glycolysis.

Micro-organisms. Inactivation of vesicular stomatitis virus by heptanal and other aldehydes was found to be a function of the concentration of aldehydic groups (Kremzner & Harter, 1970). Heptanal, like several other aldehydes and ketones without 1,2-dicarbonyl groups, produced only moderate and temporary inhibition of the growth of *Escherichia coli* (Együd, 1967). Heptanal and several other saturated, unbranched aliphatic aldehydes (in 80 μM concentration) stimulated growth of the fungus *Dipodascus aggregatus* in cultures inoculated with cells from the acceleration phase of growth but not from the exponential phase (Nyman, 1969).

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ALDEHYDE C-7 DIMETHYL ACETAL

Synonyms: Heptanal dimethylacetal; heptaldehyde dimethylacetal.
Structure: $CH_3 \cdot [CH_2]_5 \cdot CH(OCH_3)_2$.
Description and physical properties: A colourless liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: From heptaldehyde and methanol in the presence of an acid catalyst, or by reacting heptaldehyde with trimethyl orthoformate.
Uses: Use in fragrances in the USA amounts to approximately 1000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·003	0·05
Maximum	0·06	0·006	0·01	0·5

Analytical data: Gas chromatogram, RIFM no. 75–148.

Status

Aldehyde C-7 dimethyl acetal was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included aldehyde C-7 dimethyl acetal in the list of artificial flavouring substances that may be added temporarily to foodstuffs without hazard to public health.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Levenstein, 1975).

Irritation. Aldehyde C-7 dimethyl acetal applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Levenstein, 1975). Tested at 8% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 22 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Epstein, 1975).

Metabolism. Aliphatic acetals hydrolyse readily in the presence of acid to generate the aldehyde and alcohol (Fassett, 1963).

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ALDEHYDE C-8

Synonyms: 1-Octanal; octyl aldehyde.
Structure: $CH_3 \cdot [CH_2]_6 \cdot CHO$.
Description and physical properties: EOA Spec. no. 106.
Preparation: By catalytic oxidation of octyl alcohol.
Occurrence: In about 20 essential oils, including a number of citrus oils (Gildemeister & Hoffman, 1960).
Uses: In public use since the 1900s. Use in fragrances in the USA amounts to less than 10,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·0025	0·018
Maximum	0·06	0·009	0·01	0·05

Analytical data: Gas chromatogram, RIFM no. 71–13: infra-red curve, RIFM no. 71–13.

Status

Aldehyde C-8 was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) listed aldehyde C-8 (octanal), giving an ADI of 1 mg/kg. The *Food Chemicals Codex* (1966) includes a monograph on aldehyde C-8, and the Joint FAO/WHO Expert Committee on Food Additives (1967) has published a monograph and specifications for octanal.

Biological data

Acute toxicity. The oral LD_{50} in rats was found to be 5·63 ml/kg, the dermal LD_{50} in rabbits was 6·35 ml/kg (4·70–8·59 ml/kg), inhalation of concentrated vapour by rats for 8 hr produced no deaths, and skin and eye irritation was reported as very mild (Smyth, Carpenter Weil, Pozzani & Striegel, 1962). Penetration through intact mouse skin has been reported (Meyer, Meyer & Kerk, 1959).

Human testing. A standard repeated insult patch test using a 0·25% concentration in alcohol did not sensitize any of 40 subjects (Majors, 1972).

Metabolism. Aldehydes C-8, C-10, C-12 and C-14 (myristic), the lower unsubstituted aliphatic aldehydes, are readily oxidized in the animal body to the corresponding fatty acids, which normally undergo oxidation and are eventially oxidized to carbon dioxide and water (Williams, 1959).

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ALDEHYDE C-9

Synonyms: 1-Nonanal; pelargonaldehyde.
Structure: $CH_3 \cdot [CH_2]_7 \cdot CHO$.
Description and physical properties: EOA Spec. no. 91.
Occurrence: Found to occur in at least 20 essential oils, including rose oils, citrus oils and several species of pine oil (Gildemeister & Hoffman, 1960).
Preparation: By catalytic oxidation of alcohol C-9.
Uses: In public use since the 1900s. Use in fragrances in the USA amounts to less than 10,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·002	0·0025	0·018
Maximum	0·06	0·008	0·01	0·05

Analytical data: Gas chromatogram, RIFM no. 71–14; infra-red curve, RIFM no. 71–14.

Status

Aldehyde C-9 was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) listed aldehyde C-9 (nonanal), giving it an ADI of 1 mg/kg. The *Food Chemicals Codex* (1966) includes a monograph on aldehyde C-9 (nonanal) and the Joint FAO/WHO Expert Committee on Food Additives (1967) has also published a monograph on this compound.

Biological data

Acute toxicity. Both the acute oral LD_{50} in albino rats and the acute dermal LD_{50} in albino rabbits exceeded 5·0 g/kg (Shelanski, 1971).

Human testing. A maximization test (Kligman, 1966) was carried out on 25 volunteers using a 1% concentration and no case of sensitization was reported (Kligman, 1971).

Metabolism. See aldehyde C-8.

References

Council of Europe (1970). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List A (1), Series 1, no. 115, p. 54. Strasbourg.

Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. No. 2782. *Fd Technol., Champaign* **19** (2), part 2, 155.

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Kligman, A. M. (1971). Report of RIFM, 27 September.

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ALDEHYDE C-10

Synonyms: Decyl aldehyde; capraldehyde; decanal.
Structure: $CH_3 \cdot [CH_2]_8 \cdot CHO$.
Description and physical properties: EOA Spec. no. 26.
Occurrence: Decyl aldehyde is the most widely occurring of all the fatty aldehydes. Over 50 sources including citrus oils, citronella and lemongrass contain this aldehyde (Gildemeister & Hoffman, 1963).
Preparation: By catalytic oxidation of decyl alcohol.
Uses: In public use since the 1900s. Use in fragrances in the USA amounts to less than 25,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·002	0·025	0·06
Maximum	0·1	0·09	0·01	0·1

Analytical data: Gas chromatogram, RIFM no 70-30; infra-red curve, RIFM no. 70-30.

Status

Aldehyde C-10 was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1972) listed aldehyde C-10 (decanal), giving an ADI of 1 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on aldehyde C-10.

Biological data

Acute toxicity. The acute oral LD_{50} value was reported as > 33·32 g/kg in the rat, and as > 41·75 g/kg in the mouse (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964). Smyth, Carpenter, Weil, Pozzani & Striegel (1962) reported a single-dose oral LD_{50} in rats as 3·73 ml/kg. The acute dermal LD_{50} for rabbits is given as 5·04 ml/kg (Smyth *et al.* 1962).

Human testing. A standard patch test using full strength aldehyde C-10 for 24 hours produced no reactions in any of 28 subjects (Katz, 1946).

Metabolism. See monograph on aldehyde C-8†.

References

Council of Europe (1972). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. Section VI, Series 1, no. 98, p. 42. Strasbourg.

Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. No. 2362. *Fd Technol., Champaign* **19** (2), part 2, 155.

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Gildemeister, E. u. Hoffman, F. (1963). *Die Ätherischen Öle.* Vol. IIIc. p. 28. Akademie Verlag, Berlin.

Jenner, P. M., Hagan, E. C., Taylor, Jean M., Cook, E. L. & Fitzhugh, O. G. (1964). Food flavourings and compounds of related structure. I. Acute oral toxicity. *Fd Cosmet. Toxicol.* **2**, 327.

Katz, A. (1946). *Spice Mill* **69** (July), 46.

Smyth, H. F., Jr., Carpenter, C. P., Weil, C. S., Pozzani, U. C. & Striegel, Jean A. (1962). Range-finding toxicity data: List VI. *Am. ind. Hyg. Ass. J.* **23**, 95.

ALDEHYDE C-11, UNDECYLENIC

Synonyms: Undecenal; undecylenaldehyde; hendecenal; undecene-10-al.
Structure: $CH_2:CH\cdot[CH_2]_8\cdot CHO$.
Description and physical properties: EOA Spec. no. 84.
Occurrence: Apparently has not been reported to occur in nature.
Preparation: By oxidation of the corresponding alcohol or by reduction of the corresponding acid chloride.
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to less than 20,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·002	0·0025	0·04
Maximum	0·06	0·009	0·01	0·125

Analytical data: Gas chromatogram, RIFM no. 70-31; infra-red curve, RIFM no. 70-31.

Status

Aldehyde C-11, undecylenic was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1972) included aldehyde C-11, undecylenic (undec-10-enal) in the list of admissible artificial flavouring substances at a level of 0·2 ppm. The *Food Chemicals Codex* (1972) has a monograph on aldehyde C-11, undecylenic.

Biological data

Acute toxicity. Both the oral LD_{50} value in rats and the dermal LD_{50} value in rabbits exceeded 5 ml/kg (Hart, 1971).

Human testing. A maximization test (Kligman, 1966) carried out on 25 volunteers using a 1% concentration in petrolatum produced no reactions (Kligman, 1971).

References

Council of Europe (1972). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. Section VI, Series 1, no. 122, p. 44. Strasbourg.

Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. No. 3095. *Fd Technol., Champaign* **19** (2), part 2, 155.

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Hart, E. R. (1971). Report to RIFM, 18 June.

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Kligman, A. M. (1971). Report to RIFM, 3 November.

ALDEHYDE C-11, UNDECYLIC

Synonyms: Undecanal; hendecanal.

Structure: $CH_3 \cdot [CH_2]_9 \cdot CHO$.

Description and physical properties: EOA Spec. no. 123.

Occurrence: Has been reported to occur in lemon and mandarin oils (Gildemeister & Hoffman, 1963).

Uses: In public use since the 1940s. Use in fragrances in the USA amounts to less than 20,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·002	0·0025	0·04
Maximum	0·06	0·009	0·1	0·5

Analytical data: Gas chromatogram, RIFM no. 71-15; infra-red curve, RIFM no. 71-15.

Status

Aldehyde C-11, undecylic was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1972) included aldehyde C-11, undecylic (undecanal) in the list of admissible artificial substances at a level of 5 ppm. The *Food Chemicals Codex* (1972) has a monograph on aldehyde C-11, undecylic.

Biological data

Acute toxicity. Both the oral LD_{50} value in rats and the dermal LD_{50} value in rabbits exceeded 5 g/kg (Shelanski, 1971).

Human testing. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 5% in petrolatum and produced no reactions (Kligman, 1971).

References

Council of Europe (1972). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. Section VI, Series 1, no. 121, p. 44. Strasbourg.

Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. No. 3092. *Fd Technol., Champaign* **19** (2), part 2, 155.

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Shelanski, M. V. (1971). Report to RIFM, 14 November.

ALDEHYDE C-12, LAURIC

Synonyms: Lauryl aldehyde; dodecanal; *n*-dodecylic aldehyde; duodecylic aldehyde.
Structure: $CH_3 \cdot [CH_2]_{10} \cdot CHO$.
Description and physical properties: EOA Spec. no. 51.
Occurrence: Reported to occur in pine-needle, lime, sweet-orange and a dozen other essential oils (Gildemeister & Hoffman, 1963).
Preparation: By catalytic oxidation of the corresponding alcohol.
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to less than 20,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·002	0·0025	0·04
Maximum	0·06	0·009	0·1	0·125

Status

Aldehyde C-12, lauric was classified GRAS by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1972) listed aldehyde C-12, lauric (dodecanal), giving an ADI of 1 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on aldehyde C-12, lauric.

Biological data

Acute toxicity. The acute oral LD_{50} was reported as 23·1 g/kg in the rat (Calandra, 1971). The acute dermal LD_{50} was reported to be > 2 g/kg in the rabbit (Calandra, 1971).

Human testing. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 1% in petrolatum and produced no reactions (Kligman, 1970).

Metabolism. See monograph on aldehyde C-8*.

References

Calandra, J. C. (1971). Report to RIFM, 12 April.
Council of Europe (1972). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. Section VI, Series 1, no. 99, p. 42. Strasbourg.
Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. No. 2615. *Fd Technol., Champaign* **19** (2), part 2, 155.
Food Chemicals Codex (1972). 2nd ed. Prepared by the Committee on Specifications, Food Chemicals Codex, of the Committee on Food Protection. p. 441. National Academy of Sciences–National Research Council, Washington, D.C.
Gildemeister, E. u. Hoffman, F. (1963). *Die Ätherischen Öle*. Vol. IIIc. p. 32. Akademie Verlag, Berlin.
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Kligman, A. M. (1970). Report to RIFM, 2 December.

ALDEHYDE C-12, MNA

Synonyms: Methyl n-nonyl acetaldehyde; 2-methyl undecanal.
Structure: $CH_3 \cdot [CH_2]_8 \cdot CH(CH_3) \cdot CHO$.
Description and physical properties: EOA Spec. no. 52.
Occurrence: Apparently has not been reported to occur in nature.
Preparation: By decomposition of the corresponding glycidic acid (Bedoukian, 1967).
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to less than 35,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·002	0·0025	0·04
Maximum	0·06	0·009	0·01	0·4

Analytical data: Gas chromatogram, RIFM no. 71-16; infra-red curve, RIFM no. 71-16.

Status

Aldehyde C-12, MNA was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1972) included aldehyde C-12, MNA (2-methyl undecanal) in the list of temporarily admissible artificial flavouring substances pending further studies. The *Food Chemicals Codex* (1972) has a monograph on aldehyde C-12, MNA.

Biological data

Acute toxicity. The acute oral LD_{50} value (RIFM sample no. 71-16) was reported as > 5 g/kg in the rat (Owen, 1971). The acute dermal LD_{50} for sample no. 71-16 was reported to be > 10 g/kg in the rabbit (Owen, 1971).

Human testing. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no reactions (Kligman, 1971).

Metabolism. See monograph on aldehyde C-8*.

References

Bedoukian, P. Z. (1967). *Perfumery and Flavouring Synthetics.* 2nd ed., p. 21. Elsevier Publishing Co., New York.
Council of Europe (1972). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. Section VII, Series 2, no. 2010, p. 80. Strasbourg.
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Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.
Kligman, A. M. (1971). Report to RIFM, 17 June.
Owen, G. (1971). Report to RIFM, 28 June and 1 July.

Food and Cosmetics Toxicology* 1973, **11, 113.

ALDEHYDE C-14, MYRISTIC

Synonyms: Myristic aldehyde; tetradecanal.
Structure: $CH_3 \cdot [CH_2]_{12} \cdot CHO$.
Description and physical properties: Givaudan Index (1961).
Occurrence: Found in several essential oils.
Preparation: By catalytic oxidation of myristic alcohol.
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to less than 2000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	–	0·001	0·04
Maximum	0·03	–	0·005	0·1

Analytical data: Gas chromatogram, RIFM no. 71-17; infra-red curve, RIFM no. 71-17.

Status

Aldehyde C-14, myristic was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1972) has included aldehyde C-14, myristic (tetradecanal) in the list of admissible artificial flavouring substances at a level of 3 ppm.

Biological data

Acute toxicity. The acute oral LD_{50} value (RIFM sample no. 71-17) was reported as > 5·0 g/kg in the rat (Lynch, 1971). The acute dermal LD_{50} for sample no. 71-17 was reported to be > 10 g/kg (Lynch, 1971).

Human testing: A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 1 % in petrolatum and produced no reactions (Kligman, 1971).

Metabolism: See monograph on aldehyde C-8*.

References

Council of Europe (1972). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. Section VI, Series 1, no. 118, p. 44. Strasbourg.
Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels, No. 2763. *Fd Technol., Champaign* **19** (2), part 2, 155.
Givaudan Index (1961). *Specifications of Synthetics and Isolates for Perfumery.* 2nd ed., p. 40. Givaudan-Delawanna, Inc., New York.
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Kligman, A. M. (1971). Report to RIFM, 17 June.
Lynch, T. A. (1971). Report to RIFM, 16 June.

ALLO-OCIMENOL

Structure: $(CH_3)_2 \cdot C{:}CH \cdot [CH_2]_2 \cdot (CH_3)C(OH) \cdot CH{:}CH_2$.
Description and physical properties: A colourless oily liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: From α-pinene by pyrolysis to allo-ocimene, which is then hydrated (Arctander, 1969).
Uses: In public use since the 1950s.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·02	0·2
Maximum	0·2	0·02	0·06	0·8

Analytical data: Gas chromatogram, RIFM no. 72-200; infra-red curve, RIFM no. 72-200.

Status

Allo-ocimenol is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974) or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 4·18 g/kg (3·77–4·64 g/kg) and the acute dermal LD_{50} as >5 g/kg in the rabbit (Levenstein, 1973).

Irritation. Allo-ocimenol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was mildly irritating (Levenstein, 1973). Tested at 8% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1972).

References

Arctander, S. (1969). *Perfume and Flavor Chemicals (Aroma Chemicals)*. Vol. 1, no. 1030. S. Arctander, Montclair, New Jersey.

Council of Europe (1974). Natural Flavouring Substances, Their Sources, and Added Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. Strasbourg.

Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. *Fd Technol., Champaign* **19**(2), part 2, 155.

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Kligman, A. M. & Epstein, W. (1975). Updating the maximization test for identifying contact allergens. *Contact Dermatitis* **1**, 231.

Levenstein, I. (1973). Report to RIFM, 2 February & 16 February.

ALLYL BUTYRATE

Synonyms: Allyl *n*-butyrate; vinyl carbinyl butyrate.
Structure: $CH_2{:}CH{\cdot}CH_2{\cdot}OCO{\cdot}[CH_2]_2{\cdot}CH_3$.
Description and physical properties. A colourless liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: From allyl alcohol and *n*-butyric acid by direct esterification, or by any other suitable means.
Uses: In public use since the 1950s.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·05	0·04
Maximum	0·1	0·01	0·03	0·4

Status

Allyl butyrate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included allyl butyrate at a level of 1 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health.

Biological data

Acute toxicity. The acute oral LD_{50} value of allyl butyrate in rats was found to be 250 mg/kg, with depression, wet posterior and scrawny appearance for several days and death between 4 hr and 5 days (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964). The toxicity appears to be related to the presence of the allyl group, and in rats receiving allyl butyrate by stomach tube daily for 4 days, 85 mg/kg/day (one third of the LD_{50}) produced some macroscopic liver lesions, although no deaths ensued (Taylor, Jenner & Jones, 1964). The acute dermal LD_{50} value in rabbits was reported to be 0·53 g/kg (0·35–0·84 g/kg) (Moreno, 1977).

Subacute toxicity. In rats receiving allyl butyrate daily by stomach tube, 90 mg/kg/day given for 18 wk produced growth retardation in males and liver damage (bile-duct proliferation, fibrosis and necrosis); 50 mg/kg/day given for 17 wk produced lung changes (peribronchial lymphocytic infiltration) but had no effect on the liver (Hagan, Hansen, Fitzhugh, Jenner, Jones, Taylor, Long, Nelson & Brouwer, 1967).

*Irritation**. Allyl butyrate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1977). Tested at 4% in petrolatum it produced low-grade irritation responses after a 48-hr closed-patch test on human subjects (Epstein, 1976).

*Sensitization**. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 28 volunteers. The material (RIFM no. 76-9) was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Epstein, 1976).

Metabolism. No cumulative effects would be expected for most butyrates in view of their hydrolysis to materials that are either normally in the diet or readily converted to such materials (Fassett, 1963). In the rat, allyl acetate and allyl alcohol are metabolized to 3-hydroxypropylmercapturic acid, which is excreted in the urine (Clapp, Kaye & Young, 1969).

References

Clapp, J. J., Kaye, C. M. & Young, L. (1969). Observations on the metabolism of allyl compounds in the rat. *Biochem. J.* **114**, 6P.

Council of Europe (1974). Natural Flavouring Substances, Their Sources, and Added Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List 1, no. 280, p. 183. Strasbourg.

Epstein, W. L. (1976). Report to RIFM, 20 December.

Fassett, D. W. (1963). Esters. In *Industrial Hygiene and Toxicology.* 2nd Ed. Edited by F. A. Patty. Vol. II, p. 1865. Interscience Publishers, New York.

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Hagan, E. C., Hansen, W. H., Fitzhugh, O. G., Jenner, P. M., Jones, W. I., Taylor, J. M., Long, E. L., Nelson, A. A. and Brouwer, J. B. (1967). Food flavourings and compounds of related structure. II. Subacute and chronic toxicity. *Fd Cosmet. Toxicol.* **5**, 141.

Jenner, P. M., Hagan, E. C., Taylor, J. M., Cook, E. L. & Fitzhugh, O. G. (1964). Food flavourings and compounds of related structure. I. Acute oral toxicity. *Fd Cosmet. Toxicol.* **2**, 327.

*See note on allyl esters, p.7.

Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.

Kligman, A. M. & Epstein, W. (1975). Updating the maximization test for identifying contact allergens. *Contact Dermatitis.* **1**, 231.

Moreno, O. M. (1977). Report to RIFM, 31 January.

Taylor, J. M., Jenner, P. M. & Jones, W. I. (1964). A comparison of the toxicity of some allyl, propenyl, and propyl compounds in the rat. *Toxic appl. Pharmac.* **6**, 378.

ALLYL CAPROATE

Synonyms: Allyl hexanoate; 2-propenyl hexanoate.
Structure: $CH_2{:}CH{\cdot}CH_2{\cdot}OOC[CH_2]_4{\cdot}CH_3$.
Description and physical properties: EOA Spec. no. 122.
Occurrence: Apparently has not been reported to occur in nature.
Preparation: By direct esterification of allyl alcohol with caproic acid.
Uses: In public use since the early 1920s. Use in fragrances in the USA amounts to less than 5000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·0025	0·0003	0·0013	0·05
Maximum	0·015	0·0015	0·005	0·125

Analytical data: Gas chromatogram, RIFM no. 71-20; infra-red curve, RIFM no. 71-20.

Status

Allyl caproate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The *Food Chemicals Codex* (1972) has a monograph on allyl caproate.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was 218 mg/kg and in guinea-pigs 280 mg/kg (Taylor, Jenner & Jones, 1964). The acute dermal LD_{50} for sample no. 71-20 was reported as 0·3 (0·2–0·6) ml/kg in the rabbit (Shelanski, 1971).

Chronic toxicity. In an FDA feeding study, 2500 ppm fed to rats in the diet for 1 yr produced no effects (Hagan, Hansen, Fitzhugh, Jenner, Jones, Taylor, Long, Nelson & Brouwer, 1967). In another feeding study, 0·1–0·5% fed to rats in the diet for 2 yr suppressed growth (Bär & Griepentrog, 1967).

Human testing. A maximization test (Kligman, 1966), carried out on 25 volunteers using a 4% concentration in petrolatum, produced no reactions (Kligman, 1971).

Metabolism. Clapp, Kaye & Young (1969) have reported on the metabolism of allyl compounds in the rat. These compounds react with reduced glutathione in the liver and the resultant product, after hydrolysis and *N*-acetylation gives rise to the mercapturic acid, which is readily excreted in the urine.

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ALLYL CINNAMATE

Synonyms: Allyl β-phenylacrylate; propenyl cinnamate; vinyl carbinyl cinnamate.
Structure: $C_6H_5 \cdot CH:CH \cdot OCO \cdot CH_2 \cdot CH:CH_2$.
Description and physical properties: A colourless or pale straw-coloured liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By direct esterification of allyl alcohol with cinnamic acid under azeotropic conditions, or by any other suitable means.
Uses: In public use since the 1950s.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·04
Maximum	0·1	0·01	0·02	0·4

Analytical data: Gas chromatogram, RIFM no. 74-16; infra-red curve, RIFM no. 74-16.

Status

Allyl cinnamate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) listed allyl cinnamate, giving an ADI of 1·25 mg/kg.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 1·52 g/kg (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964) and the acute dermal LD_{50} value in rabbits as less than 5 g/kg (Levenstein, 1975).

*Irritation**. Allyl cinnamate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Levenstein, 1975), but it was a primary irritant when tested at 4% in petrolatum after a 48-hr closed-patch test on human subjects (Epstein, 1975). Allyl cinnamate produced irritation in concentrations down to 0·25% in the majority of subjects and evoked several borderline irritation reactions at a concentration of 0·1% in a multiple insult irritation test on human subjects (Epstein, 1975).

In tests of acanthogenic activity, application of allyl cinnamate to guinea-pig skin daily for 8–10 days caused very slight histological changes at 5% and severe injury at 40% in acetone, with acanthosis factors of 1·6 and 3·6, respectively, relative to the solvent as 1 (Schaaf, 1961).

*Sensitization**. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 22 volunteers. The material (RIFM no. 74-16) was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Epstein, 1975).

Metabolism. Many esters, including benzyl cinnamate, are rapidly hydrolysed *in vivo*. Cinnamic acid is known to conjugate with glycine in the animal body, or it may be converted to benzoic acid (Williams, 1959). In the rabbit, cinnamic acid is almost entirely excreted as hippuric acid, without formation of cinnamoyl glycine (El Masry, Smith & Williams, 1956). In the dog, Quick (1928) observed a large excretion of glucuronide, probably benzoylglucuronide. Dakin (1909) named β-phenyl-β-oxopropionic acid, cinnamoyl glycine and acetophenone as minor metabolites in the dog.

In the rat, allyl compounds are reported to form mercapturic acids, which are excreted in the urine (Clapp, Kaye & Young, 1969).

Capillary permeability. Allyl cinnamate (20% in a sodium alginate base) rubbed on rabbit skin caused some delay (14 min) in the development of a blue tint from trypan blue solution injected iv 15 min later (Pocidalo & Chaslot, 1958).

Anthelmintic activity. In vitro tests with *Rhabditis macrocerca* indicated moderately strong anthelmintic activity, with a concentration of 1·25 mM (0·235 g/litre) causing 50% mortality within 60 min (Cavier & Chaslot, 1956).

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ALLYL CYCLOHEXYLACETATE

Synonym: Allyl cyclohexaneacetate.
Structure: $C_6H_{11} \cdot CH_2 \cdot OCO \cdot CH_2 \cdot CH{:}CH_2$.
Description and physical properties: A colourless liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By direct esterification of allyl alcohol with cyclohexaneacetic acid under azeotropic conditions, or by any other suitable means.
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to approximately 2000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·04
Maximum	0·1	0·01	0·03	0·4

Analytical data: Gas chromatogram, RIFM no. 74-276; infra-red curve, RIFM no. 74-276.

Status

Allyl cyclohexylacetate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included allyl cyclohexylacetate in the list of artificial flavouring substances that may be added temporarily to foodstuffs without hazard to public health.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 0·90 g/kg (0·56–1·24 g/kg) (Moreno, 1974) and the acute dermal LD_{50} value in rabbits as 1·25 g/kg (0·35–2·15 g/kg) (Moreno, 1974).

*Irritation**. Allyl cyclohexylacetate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1974). Tested at 4% in petrolatum it produced a slight irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

*Sensitization**. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 23 volunteers. The material (RIFM no. 74-276) was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Epstein, 1974).

Metabolism. The hydrolysis of ester linkages in foreign compounds may be catalysed by many different esterases; most of these have a low degree of substrate specificity and they are to be found in all animals and bacteria (Parke, 1968). In the rat, allyl acetate and allyl alcohol are metabolized to 3-hydroxypropylmercapturic acid, which is excreted in the urine (Clapp, Kaye & Young, 1969). In dogs, cyclohexylacetic acid was not aromatized and was probably completely oxidized in the body by β-oxidation (Bernhard, 1937; Williams, 1959).

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*See note on allyl esters, p.7.

ALLYL CYCLOHEXYLPROPIONATE

Synonyms: Allyl 3-cyclopropionate; allyl hexahydrophenylpropionate.
Structure: $CH_2:CH\cdot CH_2\cdot OCOCH_2\cdot CH_2\cdot C_6H_{11}$.
Description and physical properties: EOA Spec. no. 254.
Occurrence: Apparently has not been reported to occur in nature.
Preparation: By esterification of allyl alcohol with cyclohexylpropionic acid.
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to less than 30,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·001	0·0025	0·09
Maximum	0·045	0·009	0·015	0·375

Analytical data: Gas chromatogram, RIFM no. 71-21; infra-red curve, RIFM no. 71-21.

Status

Allyl cyclohexylpropionate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1972) included allyl cyclohexylpropionate in the list of temporarily admissible artificial flavouring substances at a limit of 10 ppm. The *Food Chemicals Codex* (1972) has a monograph on allyl cyclohexylpropionate.

Biological data

Acute toxicity. The acute oral LD_{50} has been reported as 585 mg/kg in the rat (Bär & Griepentrog, 1967).

Chronic toxicity. In feeding studies, 2500 ppm fed to rats in the diet for 52 wk (Bär & Griepentrog, 1967) produced no effects.

Human testing. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no reactions (Kligman, 1971).

Metabolism. Allyl compounds are metabolized to mercapturic acid which is excreted in the urine (Clapp, Kaye & Young, 1969). Cyclohexylpropionic acid is aromatized to benzoic acid and excreted as hippuric acid in the urine. Substituted cyclohexylcarboxylic acids are either excreted unchanged or completely oxidized (Williams, 1959).

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ALLYL HEPTYLATE

Synonyms: Allyl heptanoate; allyl heptoate.
Structure: $CH_2{:}CH{\cdot}CH_2{\cdot}OCO{\cdot}[CH_2]_5{\cdot}CH_3$.
Description and physical properties: A colourless liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By direct esterification of allyl alcohol with heptanoic acid under azeotropic conditions, or by any other suitable means.
Uses: In public use since the 1940s. Use in fragrances in the USA amounts to approximately 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·04
Maximum	0·1	0·01	0·03	0·4

Analytical data: Gas chromatogram, RIFM no. 74-275; infra-red curve, RIFM no. 74-275.

Status

Allyl heptylate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1974) included allyl heptylate at a level of 5 ppm (except in chewing gum) in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health.

Biological data

Acute toxicity. The acute oral LD_{50} values in rats, mice and guinea-pigs were reported as 500, 630 and 444 mg/kg, respectively (Hagan, Jenner, Jones, Fitzhugh, Long, Brouwer & Webb, 1965). The acute dermal LD_{50} value in rabbits was reported as 0·81 g/kg (0·44–1·18 g/kg) (Moreno, 1974). Administration of 165 mg/kg (one third of the LD_{50}) by stomach tube daily for 4 days caused death in one of the six rats. Macroscopic liver lesions were observed in all animals; the livers were yellow in colour and approximately half of the hepatic tissue was necrotic (Taylor, Jenner & Jones, 1964).

Subacute and chronic toxicity. Hagan *et al.* (1965) reported that allyl heptylate fed to weanling rats for 18 wk at a dietary level of 10,000 ppm caused severe growth depression in both males and females; the effect was less marked in males at the lower dietary levels and was dose-related. Food efficiency was impaired at 10,000 ppm, but not at 2500 and 1000 ppm. Gross liver enlargement resulted at all three levels, and there were enlarged kidneys in both males and females, enlarged hearts in males given 10,000 ppm, and enlarged testes at 10,000 and 2500 ppm. Microscopic changes consisting of hydropic degeneration of the liver cells in the periportal areas were moderate at 10,000 ppm and less marked at lower levels, showing a dose-related effect. The extent of new bile-duct formation correlated with the degree of hydropic degeneration. Hepatic cell enlargement was noted in some groups.

The same authors reported that all dogs receiving daily oral doses of 75 mg allyl heptylate/kg died within 3–7 months, while those receiving 25 or 5 mg/kg/day were alive after 18 months and showed no gross effects. Administration at 75 mg/kg/day depressed growth and produced a mottled appearance with rough surfaces in the liver and haemorrhagic mucosae in the stomach. Changes observed less constantly were small grey or red cysts of clear aspect in the urinary bladders, and marked congestion in the lungs, digestive tract, kidneys, spleen and lymph nodes. Some organs exhibited terminal haemorrhages. On microscopic examination, all livers showed a slight to moderate fibrosis of the portal areas; this tended to surround hepatic cell lobules of irregular size and shape and was associated with slight to moderate proliferation of the bile-duct epithelium. Slight increases in fat occurred in all but one animal. In the stomach, diffuse haemorrhage and some necrosis of the mucosae were accompanied in some cases by focal submucosal haemorrhages.

In a 2-yr feeding study (Taylor, Hagan & Habermann, 1965), rats received allyl heptylate in combination with seven other fragrance materials and six pesticides at five test levels ranging from the amount occurring in the human daily diet to an amount slightly less than that producing effects in individual toxicity studies. With the exception of growth depression at the highest test level, the findings in the test groups and pesticide control group were similar in all respects to those in the untreated control group.

*Irritation**. Allyl heptylate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1974). Tested at 4% in petrolatum it produced a mild irritation (Epstein, 1974) but at 2% in petrolatum it produced no irritation (Kligman, 1975) after similar 48-hr closed-patch tests on human subjects.

*Sensitization**. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 24 volunteers. The material (RIFM no. 74-275) was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Epstein, 1974). The same maximization test was repeated on 25 new volunteers, the material (RIFM no. 74-275) producing no sensitization reactions (Kligman, 1975) when retested at a concentration of 2% in petrolatum.

Metabolism. The hydrolysis of ester linkages in foreign compounds may be catalysed by many different esterases; most of these have a low degree of substrate specificity and they are to be found in all animals and bacteria (Parke, 1968). In the rat, allyl acetate and allyl alcohol are metabolized to 3-hydroxypropylmercapturic acid, which is excreted in the urine (Clapp, Kaye & Young, 1969). Heptanoic acid, like other odd-carbon fatty acids, is converted to glycogen with little or no formation of ketone bodies. The mechanism probably involves β-oxidation with formation of two acetic acid molecules plus one propionic acid molecule (Deuel, 1957).

Micro-organisms. The vapour of allyl heptylate inhibited the *in vitro* growth of the four fungi, *Candida albicans*, *Phoma betae*, *Geotrichum candidum* and *Oospora lactis* (Maruzzella, Chiaramonte & Garofalo, 1961), but did not inhibit *in vitro* growth of three wood-destroying fungi (*Lenzites trabea*, *Polyporus versicolor* and *Lentinus lepideus*) in tests using the filter-paper disc method (Maruzzella, Scrandis, Scrandis & Grabon, 1960). In a 1:500 dilution it did not inhibit *in vitro* growth of *Bacillus subtilis*, *Escherichia coli* or two strains of *Staphylococcus aureus* (Maruzzella & Bramnick, 1961).

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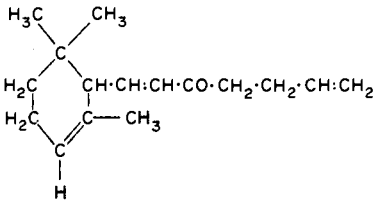
*See note on allyl esters, p. 7.

ALLYL-α-IONONE

Synonyms: Allyl ionone.
Structure:



Description and physical properties: Food Chemicals Codex (1972).
Occurrence: Apparently has not been reported to occur in nature (*Givaudan Index*, 1961).
Preparation: By condensation with allyl acetone from citral, followed by cyclization (Arctander, 1969).
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to less than 2000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·0005	0·0025	0·09
Maximum	0·03	0·0045	0·02	1·0

Analytical data: Gas chromatogram, RIFM no. 71-22; infra-red curve, RIFM no. 71-22.

Status

Allyl-α-ionone was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1972) included allyl-α-ionone in the list of temporarily admissible artificial flavouring substances pending further studies. *The Food Chemicals Codex* (1972) has a monograph on allyl-α-ionone.

Biological data

Acute toxicity. The acute dermal LD_{50} was reported to be > 5 g/kg in the rabbit (Shelanski, 1971).

Human testing. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no reactions (Kligman, 1972).

Metabolism. α-Ionones are metabolized by ring hydroxylation at the carbon atom alpha to the ring double bond to give 5-hydroxy-α-ionone (Williams, 1959). Allyl compounds are reported to form mercapturic acids (Clapp, Kaye & Young, 1969).

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ALLYL PHENOXYACETATE

Synonym: Acetate P.A.
Structure: $CH_2{:}CH \cdot CH_2 \cdot OCO \cdot CH_2 \cdot O \cdot C_6H_5$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By direct esterification of allyl alcohol with phenoxyacetic acid under azeotropic conditions (Arctander, 1969).
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·001	0·003	0·05
Maximum	0·1	0·01	0·03	0·1

Analytical data: Gas chromatogram, RIFM no. 74–19; infra-red curve, RIFM no. 74–19.

Status

Allyl phenoxyacetate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included allyl phenoxyacetate at a level of 2 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 0·475 ml/kg (0·389–0·579 ml/kg) (Levenstein, 1974). The acute dermal LD_{50} in rabbits was reported as 0·82 ml/kg (Levenstein, 1974).

Irritation. Allyl phenoxyacetate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Levenstein, 1974). The material has been reported to be a mild primary irritant when tested under occlusion at 1% in a 48-hr closed-patch test in petrolatum in man (Epstein, 1974), but tested at 1% in petrolatum, it produced no irritation after another 48-hr closed-patch test on human subjects (Kligman, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 26 volunteers. The material (RIFM no. 74–1–19) was tested at a concentration of 1% in petrolatum and produced no sensitization reactions (Epstein, 1974). In a maximization test (Kligman, 1966; Kligman & Epstein, 1975) carried out on 25 volunteers, the material (N-1-R(0)) was tested at a concentration of 1% in petrolatum and produced no sensitization reactions (Kligman, 1974).

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Epstein, W. L. (1974). Report to RIFM, 16 April.

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Kligman, A. M. & Epstein, W. (1975). Updating the maximization tests for identifying contact allergens. *Contact Dermatitis* **1**, 231.

Levenstein, I. (1974). Report to RIFM, 22 March.

ALLYL PHENYLACETATE

Synonym: 2-Propenyl phenylacetate.
Structure: $C_6H_5 \cdot CH_2 \cdot OCO \cdot CH_2 \cdot CH{:}CH_2$.
Description and physical properties: A colourless slightly viscous liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By direct esterification of allyl alcohol with phenylacetic acid under azeotropic conditions, or by any other suitable means.
Uses: In public use since the 1940s. Use in fragrances in the USA amounts to less than 1000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·002	0·005	0·1
Maximum	0·15	0·015	0·03	0·25*

Status

Allyl phenylacetate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included allyl phenylacetate in the list of artificial flavouring substances that may be added temporarily to foodstuffs without hazard to public health.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 0·65 g/kg (0·51–0·79 g/kg) and the acute dermal LD_{50} value in rabbits as >0·31 g/kg (Moreno, 1976).

Irritation†. Allyl phenylacetate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating even when applied at 0·31 g/kg (Moreno, 1976). When it was first tested at 12% in petrolatum, no irritation reactions were reported after a 48-hr closed-patch test on human subjects (Kligman, 1975), but retested at 12% in petrolatum, it produced irritation after a 48-hr closed-patch test (Kligman, 1975). Tested in a 48-hr closed-patch test at 6% in petrolatum, it was a significant irritant in a majority of human subjects, even when it was reduced to 1/4 strength (Epstein, 1976).

Sensitization†. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material (RIFM no. 75-IFRA-20) was tested at a concentration of 12% in petrolatum and produced sensitization reactions in 12 of the 25 subjects (Kligman, 1975). In a second maximization test, in which the material (RIFM no. 75-IFRA-20) was retested at a concentration of 12% in petrolatum, sensitization reactions were produced in all 25 of the volunteers and the test had to be stopped because of the severity of the reactions on the third induction day (Kligman, 1975).

Because so many reactions to allyl phenylacetate occurred although there had been no similar reactions with the other allyl compounds, it was considered possible that the allyl phenylacetate had an unusually high content of free allyl alcohol. Consequently, the allyl alcohol, which was present at a level of 0·3%, was removed by preparative gas chromatography and a sample that was pure allyl phenylacetate (no. C-37330-R) was obtained. This material was tested by the maximization test (Kligman, 1966; Kligman & Epstein, 1975) in 33 volunteers at a concentration of 3% in petrolatum. It still elicited irritant responses but it induced no sensitization reactions (Epstein, 1976).

Metabolism. In the rat, allyl acetate and allyl alcohol are metabolized to 3-hydroxypropylmercapturic acid, which is excreted in the urine (Clapp, Kaye & Young, 1969).

References

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*Because of the irritant properties of this material it should probably not be used above 0·25% unless the final product is tested for irritation.

†See note on allyl esters, p. 611.

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Moreno, O. M. (1976). Report to RIFM, 5 January.

AMBERGRIS TINCTURE

Synonyms: Ambra; amber; gray amber.

Description and physical properties: *Merck Index* (1968). Ambergris is composed of only a few characteristic chemical components, chiefly ambrein (a tricyclic terpene alcohol; 25–45%) and epicoprosterol (5β-cholestan-3α-ol; 30–40%), as well as other steroids and their products, ketones (6–8%), free and esterified acids (10–13%), and porphyrins. The odour of ambergris is probably due to oxidation products of ambrein (Lederer, 1949); its quality depends on the amounts of ambrein and epicoprosterol and their ratio (Korzh & Strigina, 1972). After separation of ambrein, volatile products have been isolated including dihydro-γ-ionone (Ruzicka, Seidel & Pfeiffer, 1948), an oxide, $C_{13}H_{22}O$, a hydroxyaldehyde, $C_{17}H_{30}O_2$, and a ketone, $C_{13}H_{20}O$ (Ruzicka & Seidel, 1950), and γ-cyclohomogeraniol, which is the chief component of the volatile non-ketonic fraction (Seidel & Stoll, 1957).

Occurrence: In a gastric or intestinal secretion of the cachalot or sperm whale, *Physeter catodon* L. (Physeteridae).

Preparation: By extraction with ethanol (*Fenaroli's Handbook of Flavor Ingredients*, 1975).

Uses: In public use before the 1860s.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	—	0·01	0·3
Maximum	0·15	—	0·05	2·0

Status

As a product of an endangered species, it is prohibited from being brought into the USA.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1976).

Irritation. Undiluted ambergris tincture applied to the backs of hairless mice and swine was not irritating (Urbach & Forbes, 1976), but applied to intact or abraded rabbit skin for 24 hr under occlusion it was slightly irritating (Moreno, 1976). Tested at 30% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 21 volunteers. The material was tested at a concentration of 30% in petrolatum and produced no sensitization reactions (Epstein, 1975). Ambergris tincture applied at full strength for 48 hr in the standard occluded aluminium patch test used by the North American Contact Dermatitis Research Group (NACDRG) did not produce any irritation or sensitization in a 62-yr-old subject with a perfume dermatitis (Larsen, 1975).

Phototoxicity. No phototoxic effects were reported for undiluted ambergris tincture on hairless mice and swine (Urbach & Forbes, 1976).

Additional published data

Several odorous substances including grey amber were found to be attractive to rats (Reiff, 1956).

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Ruzicka, L., Seidel, C. F. u. Pfeiffer, M. (1948). Über die flüchtigen Bestandteile des grauen Ambra. I. Isolierung von Dihydro-γ-jonon. *Helv. chim. Acta* **31,** 827.

Seidel, C. F. u. Stoll, M. (1957). Uber die flüchtigen Bestandteile des grauen Ambra. III. Isolierung und Identifizierung von γ-Cyclohomogeraniol im grauen Ambra. Synthese von 1,1-Dimethyl-2-(β-hydroxyäthyl)-3-methylencyclohexan (γ-Cyclohomogeraniol) und 1,1-Dimethyl-2-(γ-hydroxypropyl)-3-methylencyclohexan. *Helv. chim. Acta* **40,** 1990.

Urbach, F. & Forbes, P. D. (1976). Report to RIFM, 9 February.

AMBRETTE SEED OIL

Description and physical properties: EOA Spec. no. 147. The principal constituents of ambrette seed oil are farnesol and ambrettolide (Guenther, 1952).
Occurrence: Found in the seed of *Abelmoschus moschatus* Moench, syn. *Hibiscus abelmoschus* L. (Fam. Malvaceae).
Preparation: By steam distillation of the seed of *A. moschatus* and refinement of the crude distillate.
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·001	0·0001	0·0005	0·02
Maximum	0·015	0·0015	0·005	0·12

Status

Ambrette seed oil was given GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1974) included ambrette seed in the list of substances, spices and seasonings deemed admissible for use, with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on ambrette seed oil.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} in rabbits were reported to be >5 gm/kg (Moreno, 1974).

Irritation. Ambrette seed oil applied undiluted to the backs of hairless mice (Urbach & Forbes, 1974) or to intact or abraded rabbit skin for 24 hr under occlusion (Moreno, 1974) was not irritating. Tested at 1% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers, using 1% ambrette seed oil in petrolatum, without producing sensitization reactions (Kligman, 1974).

Phototoxicity. No phototoxic effects were reported for undiluted ambrette seed oil on hairless mice and swine (Urbach & Forbes, 1974).

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Moreno, O. M. (1974). Report to RIFM, 20 May.

Urbach, F. & Forbes, P. D. (1974). Report to RIFM, 12 April.

AMBRETTOLIDE

Synonyms: ω-6-Hexadecenlactone; 16-hydroxy-7-hexadecenoic acid lactone; cyclohexadecen-7-olide.
Structure: $O{:}C\cdot[CH_2]_5\cdot CH{:}CH\cdot[CH_2]_7\cdot CH_2$ (O)

Description and physical properties: *Givaudan Index* (1961).
Occurrence: Found in oil of ambrette seed (*Givaudan Index*, 1961).
Preparation: From bromohexadecenoic acid (Bedoukian, 1967).
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·001	0·0001	0·001	0·03
Maximum	0·02	0·002	0·01	0·1

Analytical data: Gas chromatogram, RIFM no. 74–23; infra-red curve, RIFM no. 74–23.

Status

Ambrettolide was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included ambrettolide at a level of 0·2 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Wohl, 1974).

Irritation. Ambrettolide applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Wohl, 1974). Tested at a 1% concentration in petrolatum, it produced no irritation after a 48-hr closed-patch test in human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 26 volunteers. The material was tested at a concentration of 1% in petrolatum and produced no sensitization reactions (Epstein, 1974).

References

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Wohl, A. J. (1974). Report to RIFM, 2 April.

AMYL BENZOATE

Synonyms: Isoamyl benzoate; 3-methyl-1-butyl benzoate.
Structure: $(CH_3)_2 \cdot CH \cdot CH_2 \cdot CH_2 \cdot OCOC_6H_5$.
Description and physical properties: Givaudan Index (1961).
Occurrence: Reported to occur in cherry oil (Stinson, Dooley, Filipic & Hills, 1969).
Preparation: By esterification of isoamyl alcohol with benzoic acid.
Uses: In public use since the 1900s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·18
Maximum	0·09	0·009	0·03	0·6

Analytical data: Gas chromatogram, RIFM no. 71-24; infra-red curve, RIFM no. 71-24.

Status

Amyl benzoate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1972) has listed amyl benzoate (isoamyl benzoate) giving an ADI of 5 mg/kg.

Biological data

Acute toxicity. The acute oral LD_{50} value (RIFM sample no. 71-24) was reported as 6·33 g/kg in the rat (Weir, 1971). The acute dermal LD_{50} for sample no. 71-24 was reported to be > 5 g/kg in the rabbit (Weir, 1971).

Human testing. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 6% in petrolatum and produced no reactions (Kligman, 1972).

Metabolism. Benzoic acid is metabolized in the mammalian body after conjugation with glycine to form hippuric acid and benzoylglucuronic acid, which are excreted in the urine (Williams, 1959).

References

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Weir, R. J. (1971). Report to RIFM, 25 August.
Williams, R. T. (1959). *Detoxication Mechanisms. The Metabolism and Detoxication of Drugs, Toxic Substances and Other Organic Compounds.* 2nd ed., p. 349. Chapman & Hall Ltd., London.

AMYL CINNAMATE

Synonyms: Isoamyl cinnamate; isoamyl 3-phenyl propenoate; isopentyl cinnamate.
Structure: $CH_3 \cdot CH(CH_3) \cdot [CH_2]_2 \cdot OCO \cdot CH{:}CH \cdot C_6H_5$.
Description and physical properties: EOA Spec. no. 264.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By the esterification of cinnamic acid with commercial isoamyl alcohols which vary in isomer distribution according to source.
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·02	0·2
Maximum	0·2	0·02	0·1	0·8

Status

Amyl cinnamate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) listed amyl cinnamate, giving an ADI of 1·25 mg/kg.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1974).

Irritation. Amyl cinnamate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was very slightly irritating (Moreno, 1974). When tested on human skin at 8% in petrolatum under an occlusive patch test for 48 hr, it was not irritating (Kligman, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers using 8% amyl cinnamate in petrolatum. No sensitization reactions were produced (Kligman, 1974).

Anthelmintic activity. In vitro tests with the nematode worm *Rhabditis macrocerca* indicated moderately strong anthelmintic activity for *n*-amyl cinnamate, a concentration of 0·001 M (0·218 g/litre) causing 50% mortality within 60 min (Cavier & Chaslot, 1956).

Micro-organisms. n-Pentyl cinnamate showed some *in vivo* activity against the fungus *Venturia inaequalis* (apple scab) when sprayed on apple leaves (Kirkham & Hunter, 1965). Growth of four bacteria was not inhibited by "amyl cinnamate" (not further identified) at 1:500 dilution (Maruzzella & Bramnick, 1961).

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Council of Europe (1974). Natural Flavouring Substances, Their Sources, and Added Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List 1, no. 328. p. 193. Strasbourg.

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Moreno, O. M. (1974). Report to RIFM, 23 January.

AMYL CINNAMIC ACETATE

Synonyms: α-Pentyl cinnamyl acetate; amyl cinnamyl acetate; α-*n*-amyl-β-phenylacryl acetate.
Structure: $C_6H_5 \cdot CH:C([CH_2]_4 \cdot CH_3) \cdot CH_2 \cdot OCO \cdot CH_3$.
Description and physical properties: A colourless oily liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: From amyl cinnamic alcohol and acetic acid under azeotropic conditions (Arctander, 1969).
Uses: Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·05	0·005	0·03	0·4
Maximum	0·3	0·03	0·1	0·8

Analytical data: Gas chromatogram, RIFM no. 74–26; infra-red curve, RIFM no. 74–26.

Status

Amyl cinnamic acetate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included amyl cinnamic acetate at a level of 3 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1974).

Irritation. Amyl cinnamic acetate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was slightly irritating (Morena, 1974). Tested at 8% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1975).

Metabolism. Cinnamic alcohol is mainly metabolized to benzoic acid, presumably via cinnamic acid. Substitution apparently prevents oxidation to benzoic acid, since 2-ethylcinnamic alcohol is partly excreted as α-ethylcinnamic acid (30–33% in rabbits) (Williams, 1959).

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α-AMYLCINNAMIC ALCOHOL

Synonyms: 2-*n*-Amyl-3-phenyl-2-propen-1-ol; α-amylcinnamyl alcohol.
Structure: $C_6H_5 \cdot CH:C(CH_2 \cdot [CH_2]_3 \cdot CH_3) \cdot CH_2OH$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Has apparently not been reported to occur in nature.
Preparation: From amylcinnamic aldehyde by reduction.
Uses: In public use since the 1940s. Use in fragrances in the USA amounts to approximately 10,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·05	0·005	0·03	0·4
Maximum	0·3	0·03	0·1	0·8

Status

Amylcinnamic alcohol was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included amylcinnamic alcohol in the list of admissible artificial flavouring substances at a level of 3 ppm.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 4·0 g/kg (3·08–5·20 g/kg) (Denine, 1973). The acute dermal LD_{50} in rabbits was reported as >5 g/kg (Denine, 1973).

Irritation. α-Amylcinnamic alcohol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Denine, 1973). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1973).

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AMYL CINNAMIC ALDEHYDE

Synonyms: α-Amyl cinnamic aldehyde; α-*n*-amyl-β-phenylacrolein.
Structure: $C_6H_5 \cdot CH:C(CH_2 \cdot [CH_2]_3 \cdot CH_3) \cdot CHO$.
Description and physical properties: EOA Spec. no. 45.
Occurrence: Apparently has not been reported to occur in nature.
Preparation: By the condensation of benzaldehyde with heptaldehyde, usually in an alkaline medium (Bedoukian, 1967).
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to about 800,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·04	0·004	0·015	0·36
Maximum	0·40	0·03	0·05	1·2

Analytical data: Gas chromatogram, RIFM no. 70–22; infra-red curve, RIFM no. 70–22.

Status

Amyl cinnamic aldehyde was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included amyl cinnamic aldehyde (α-amyl cinnamaldehyde), in the list of admissible artificial flavouring substances at a level of 1 ppm. The *Food Chemicals Codex* (1972) has a monograph on amyl cinnamic aldehyde.

Biological data

Acute toxicity. The acute oral LD_{50} value was reported as 3·73 g/kg in the rat (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964) and the acute dermal LD_{50} in rabbits as >2 g/kg (Moreno, 1973).

Human testing. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at 6% concentration in petrolatum and produced no reactions (Greif, (1967).

Metabolism. So far as is known, all aromatic aldehydes are metabolized in the animal body by oxidation to the corresponding acids. In some instances, the aldehydes are excreted as glucuronides. Cinnamic aldehyde is oxidized to cinnamic acid which is then degraded to benzoic acid, but ethyl cinnamic aldehyde is oxidized to the corresponding acid and is not further metabolized (Williams, 1959).

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AMYL CINNAMIC ALDEHYDE DIETHYL ACETAL

Synonyms: 1,1-Diethoxy-2-amyl-3-phenyl-2-propene; 1,1-diethoxyl-2-*n*-amyl-3-phenylacrolein.

Structure: $C_6H_5 \cdot CH:C(CH_2 \cdot [CH_2]_3 \cdot CH_3) \cdot CH(OC_2H_5)_2$.

Description and physical properties: Almost colourless oily liquid with a leafy floral odour (Arctander, 1969).

Occurrence: Apparently has not been reported to occur in nature.

Preparation: From amyl cinnamic aldehyde and ethyl alcohol by condensation (Arctander, 1969).

Uses: In public use since the 1950s. Use in fragrances in the USA amounts to less than 3000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	—	—	0·015	0·036
Maximum	—	—	0·05	1·2

Analytical data: Gas chromatogram, RIFM no. 71–26; infra-red curve, RIFM no. 71–26.

Biological data

Acute toxicity. Both the acute oral LD_{50} in rats and the acute dermal LD_{50} in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. Amyl cinnamic aldehyde diethyl acetal tested at 10% in petrolatum produced no irritation after a 48-hr closed patch test in 25 human subjects (Kligman, 1971).

Human testing. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no reactions (Kligman, 1971).

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α-AMYLCINNAMIC ALDEHYDE DIMETHYL ACETAL

Synonyms: α-*n*-Amylcinnamal dimethylacetal; 1,1-dimethoxy-2-amyl-3-phenyl-2-propene.
Structure: $C_6H_5 \cdot CH:C([CH_2]_4 \cdot CH_3) \cdot CH(OCH_3)_2$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Has apparently not been reported to occur in nature.
Preparation: From amylcinnamic aldehyde and methyl alcohol.
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to less than 3000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·04	0·004	0·02	0·3
Maximum	0·3	0·03	0·1	0·8

Analytical data: Gas chromatogram, RIFM no. 74–27; infra-red curve, RIFM no. 74–27.

Status

α-Amylcinnamic aldehyde dimethyl acetal was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included α-amylcinnamic aldehyde dimethyl acetal at a level of 2 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1974).

Irritation. α-Amylcinnamic aldehyde dimethyl acetal applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was slightly irritating (Moreno, 1974). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Epstein, 1974).

Metabolism. Acetals hydrolyse readily in the presence of acids to generate the corresponding aldehydes and alcohols (Fassett, 1963). *trans*-α,β-Unsaturated aldehydes and possibly acetals, such as *trans*-cinnamaldehyde and its dimethyl acetal, are substrates for glutathione *S*-alkenetransferases (Boyland, 1970).

Micro-organisms. In contrast to most other acetals tested, amylcinnamic aldehyde dimethyl acetal was found by a zone-inhibition technique to be ineffective as an antibacterial agent against six gram-negative bacteria and against gram-positive *Staphylococcus aureus* (Felton & Kapp, 1970).

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4-*tert*-AMYLCYCLOHEXANONE

Structure: $O:C_6H_9 \cdot C(CH_3)_2 \cdot CH_2 \cdot CH_3$.

Description and physical properties: A colourless liquid with a powerful earthy odour (Arctander, 1969).

Occurrence: Has apparently not been reported to occur in nature.

Preparation: From 4-*tert*-amylcyclohexanol by chromic acid oxidation (Arctander, 1969).

Uses: In public use since the 1960s. Use in fragrances in the USA amounts to less than 10,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·005	0·01	0·2
Maximum	0·2	0·02	0·05	0·8

Analytical data: Gas chromatogram, RIFM no. 72–81; infra-red curve, RIFM no. 72–81.

Status

4-*tert*-Amylcyclohexanone is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1970), nor in the Food Chemicals Codex (1972).

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 4·7 g/kg (4·02–5·50 g/kg) (Denine, 1973). The acute dermal LD_{50} in rabbits was reported as 4·7 g/kg (4·20–5·26 g/kg) (Denine, 1973).

Irritation. 4-*tert*-Amylcyclohexanone applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was irritating (Denine, 1973). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximum test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1973).

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Kligman, A. M. (1973). Report to RIFM, 12 February.

AMYLCYCLOHEXYL ACETATE (MIXED ISOMERS)

Synonym: 2-*tert*-Amylcyclohexyl acetate.
Structure: $CH_3 \cdot CH_2 \cdot (CH_3)C(CH_3) \cdot C_6H_{10} \cdot OCO \cdot CH_3$.
Description and physical properties: A colourless liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: From 2-*tert*-amylcyclohexanol (Arctander, 1969).
Uses: Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0.03	0.003	0.015	0.15
Maximum	0.25	0.025	0.05	1.2

Analytical data: Gas chromatogram, RIFM no. 74–28; infra-red curve, RIFM no. 74–28.

Status

Amylcyclohexyl acetate is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974) or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1974).

Irritation. Amylcyclohexyl acetate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1974). Tested at 12% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 12% in petrolatum and produced no sensitization reactions (Kligman, 1975).

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Moreno, O. M. (1974). Report to RIFM, 10 December.

AMYL SALICYLATE

Synonyms: Isoamyl *o*-hydroxybenzoate; isoamyl salicylate.
Structure: $C_6H_4 \cdot COOC_5H_{11}$.
Description and physical properties: EOA Spec. no. 27.
Occurrence: Apparently has not been reported to occur in nature.
Preparation: By esterification of salicylic acid with the isomeric amyl alcohols obtained from fusel oil and other sources.
Uses: In public use since the 1900s. Use in fragrances in the USA amounts to about 600,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·015	0·4
Maximum	0·30	0·03	0·05	1·2

Analytical data: Gas chromatogram, RIFM no. 70–13; infra-red curve, RIFM no. 70–13.

Status

Amyl salicylate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included amyl salicylate (isoamyl salicylate) in the list of admissible artificial flavouring substances at a level of 3 ppm. The *Food Chemicals Codex* (1972) has a monograph on amyl salicylate.

Biological data

Acute toxicity. The LD_{50} value iv in dogs was reported as 0·5–0·8 g/kg (Fassett, 1963).

Human testing. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no reactions (Kligman, 1970). Aspirin-containing drugs will cause exacerbation in some patients with chronic urticaria. The action is probably due to the salicylate radical. It is suggested that aspirin acts in chronic urticaria by enhancing the effect of histamine in the skin (Moore-Robinson & Warin, 1967).

Metabolism. Most of the esters of salicylic acid are decomposed to salicylic acid in the body and excreted as such. Besides the unchanged acid, salicuric acid, genticic acid and salicyl glucuronide have been known to be excreted. The lower esters of salicylic acid decompose more readily than the higher esters and as a consequence, little of the amyl ester is split. The whole subject of salicylic esters is covered in an extensive literature by Gross & Greenberg (1948).

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AMYLVINYLCARBINOL

Synonyms: 1-Octen-3-ol; matsutake alcohol.
Structure: $CH_3 \cdot [CH_2]_4 \cdot CH(OH) \cdot CH{:}CH_2$.
Description and physical properties: A colourless liquid.
Occurrence: Originally reported to be found in the mushroom *Armillaria matsutake*, a parasite growing on the radical hairs of *Pinus densiflora* in the forests of Japan. It has been isolated also from the essential oils of *Mentha pulegium* L., lavender and *M. timjia* (*Fenaroli's Handbook of Flavor Ingredients*, 1975).
Preparation: By a vinyl Grignard reaction on hexaldehyde or from amyl magnesium bromide and acrolein (Arctander, 1969).
Uses: Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·1
Maximum	0·15	0·015	0·05	1·0

Analytical data: Gas chromatogram, RIFM no. 74–30; infra-red curve, RIFM no. 74–30.

Status

Amylvinylcarbinol was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included amylvinylcarbinol at a level of 5 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 0·34 g/kg and the acute dermal LD_{50} in rabbits as 3·3 g/kg (Wohl, 1974).

Irritation. Amylvinylcarbinol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Wohl, 1974). Tested at 10% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 22 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Epstein, 1974).

Metabolism. In the animal body secondary alcohols can undergo either conjugation with glucuronic acid or oxidation to a ketone, which may be excreted in the urine or expired air or further oxidized or reduced back to the alcohol. Studies of secondary alcohols containing more than seven carbon atoms have been limited to octan-2-ol. The conjugation of this alcohol in rabbits is low and much of the alcohol may be excreted unchanged (Williams, 1959). A dilute solution of synthetic (*dl*)-1-octen-3-ol fed directly into the rumen of a cow produced after 2–4 hr a maximum concentration in the milk of 20 μg octenol/litre. This concentration did not give the milk an off-flavour, and was not reported to have any other effects (Honkanen & Moisio, 1963; Honkanen, Karvonen & Virtanen, 1964).

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AMYRIS OIL ACETYLATED

Description and physical properties: A yellowish liquid with a lighter and greener odour than that of amyris oil (Arctander, 1960).
Occurrence: Apparently has not been reported to occur in nature.
Preparation: By acetylation of amyris oil (Arctander, 1960).
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to less than 5000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·04	0·004	0·015	0·54
Maximum	0·24	0·024	0·06	1·5

Analytical data: Gas chromatogram, RIFM no. 72–9; infra-red curve, RIFM no. 72–9.

Status

Amyris oil acetylated is not listed by the Council of Europe (1970), by the FDA or by the Food Chemicals Codex (1972), but the parent substance is.

Amyris oil is approved by the FDA for food use (21 CFR 121.1163). The Council of Europe (1970) included amyris oil (*Amyris balsamifera*) in the list of temporarily admitted flavouring substances. The *Food Chemicals Codex* (1972) has a monograph on amyris oil.

Biological data

Acute toxicity. Both the oral LD_{50} value in rats and the dermal LD_{50} value in rabbits exceeded 5 g/kg (Keating, 1972).

Irritation. Amyris oil acetylated tested at 10% in petrolatum produced no irritation after a 48-hr closed patch test in 25 human subjects (Kligman, 1972).

Human testing. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a 10% concentration in petrolatum and produced no reactions (Kligman, 1972).

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ANETHOLE

Synonyms: *p*-Propenylphenyl methyl ether; *p*-propenylanisole.
Structure: $CH_3 \cdot CH{:}CH \cdot C_6H_4 \cdot OCH_3$. (Most commercial anethole consists of mixed isomers.)
Description and physical properties: Food Chemicals Codex (1972).
Occurrence: Found in oils of aniseed, star-anise, fennel and leaves of *Clausena anisata* Hook., *Backhousia anisata* and *Magnolia salicifolia* Maxim. (Givaudan, 1961).
Preparation: By isomerization of estragole using alcoholic potassium hydroxide as agent (Arctander, 1969).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to about 16,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·008	0·001	0·0025	0·054
Maximum	0·06	0·006	0·01	0·25

Status

Anethole was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) listed *trans*-anethole (propenyl anisole), giving an ADI of 1·5 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on anethole and the Joint FAO/WHO Expert Committee on Food Additives (1967) has published a monograph and specifications for *trans*-anethole giving an ADI of 0–1·25 mg/kg for man.

Biological data

Acute toxicity. The acute oral LD_{50} has been reported as 2090 mg/kg in the rat, 3050 mg/kg in the mouse and 2160 mg/kg in the guinea-pig (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964). The acute dermal LD_{50} was reported as >5 g/kg in the rabbit (Hart, 1971). No percutaneous absorption of anethole occurred through the skin of a mouse within 2 hr (Meyer & Meyer, 1959).

Chronic toxicity. In a feeding study, 10,000 ppm fed to rats in the diet for 15 wk produced slight hydropic changes in the liver of the male animals (Hagan, Hansen, Fitzhugh, Jenner, Jones, Taylor, Long, Nelson & Brouwer, 1967). In other feeding studies in rats, neither 2500 ppm fed in the diet for 1 yr (Bär & Griepentrog, 1967) nor 10,000 ppm in the diet for 15 wk produced any effects (Bär & Griepentrog, 1967). The level causing no effect in the rat was 2500 ppm in the diet or 125 mg/kg body weight/day (Joint FAO/WHO Expert Committee on Food Additives, 1967). In a feeding study, in which dietary levels of 1000, 3000, 10,000 and 30,000 ppm were fed to rats for 90 days, death occurred with the highest level, and survival was affected at the 10,000 ppm level. Hepatocellular oedema, degeneration and regeneration were found, in proportion to the level fed, at 3000 ppm and above. No effect was seen at 1000 ppm (Joint FAO/WHO Expert Committee on Food Additives (1967).

Irritation. Anethole tested at 2% in petrolatum produced no irritation after a 48-hr closed patch test in 25 human subjects (Kligman, 1971).

Human testing. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a 2% concentration in petrolatum and produced no reactions (Kligman, 1971).

Metabolism. Anethole is metabolized by oxidation of the propenyl group and is excreted as anisic acid (Williams, 1959). The metabolism of *trans*-anethole used in the preparation

of anis-flavoured alcoholic beverages was studied in the rabbit and rat after iv and oral administration. It was excreted rapidly from the animal regardless of the method of administration. After iv injection it was found concentrated in the liver, lungs and brain; after oral administration, absorption was slight and most of it remained in the stomach. Ethyl alcohol has no effect on the metabolism (Le Bourhis, 1968).

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ANGELICA ROOT OIL

Description and physical properties: EOA Spec. no. 96. The chief constituents of angelica root oil are *d*-α-phellandrene and cyclopentadecalactone (Gildemeister & Hoffman, 1961).
Occurrence: Found in the roots of the plant *Archangelica officinalis* Hoffm. (*Angelica archangelica* L.) (Fam. Umbelliferae).
Preparation: By steam distillation of the dried slender rootlets of the plant.
Uses: In public use before the 1900s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·001	0·0001	0·0005	0·02
Maximum	0·015	0·0015	0·005	0·12

Analytical data: Infra-red curve, RIFM no. 74–127.

Status

Angelica root oil was given GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1974) included angelica root in the list of substances, spices and seasonings deemed admissible for use, with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on angelica root oil.

Biological data

Acute toxicity. The acute oral LD_{50} value in mice was reported as 2·2 g/kg (Wohl, 1974). The acute oral LD_{50} value of angelica oil in rats was found to be 11·16 g/kg (von Skramlik, 1959). Death was preceded by decreased activity, and was associated with severe liver and kidney damage, but animals surviving for 3 days recovered completely, with reversal of any liver and kidney damage. The acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Wohl, 1974).

Subacute toxicity. When angelica oil was administered orally to rats daily for 8 wk at doses of 0·5, 1·0, 2·0 or 3·0 g/kg, it was concluded that the tolerated dose was 1·5 g/kg, corresponding to 109·0 g/70-kg man (von Skramlik, 1959). Daily doses of 2·0 or 3·0 g/kg caused decreased activity and weight loss, and deaths were associated with severe liver and kidney damage. It was pointed out that 1·5 g/kg/day was not truly tolerated for 8 wk, as rats receiving the 0·5 or 1·0 g/kg daily doses weighed less than the control animals.

Irritation. Angelica root oil applied undiluted to the backs of hairless mice (Urbach & Forbes, 1974) or to intact or abraded rabbit skin for 24 hr under occlusion (Wohl, 1974) was not irritating. Tested at 1% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974). A sample of angelica root oil was reported to possess strong skin-irritant properties (Birggal, 1969).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 24 volunteers. The material was tested at a concentration of 1% in petrolatum and produced no sensitization reactions (Epstein, 1974).

Phototoxicity. Phototoxic effects were reported for undiluted angelica root oil tested on hairless mice and swine (Urbach & Forbes, 1974).

Various concentrations of angelica root oil in methanol were also tested for phototoxicity in mice, applications of 20 μl/5 cm^2 of skin being exposed to simulated sunlight for 1 hr (Urbach & Forbes, 1975). Positive reactions were obtained with concentrations of 3·125, 6·25, 12·5, 25, 50 and 100%, while 1·56% evoked a doubtful reaction and 0·78% showed no phototoxic effect.

Micro-organisms. Vapour of angelica root oil showed antibacterial activity against *Myobacterium avium* but not against *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis*, *Streptococcus fecalis* or *Salmonella typhosa* (Maruzzella & Sicurella, 1960). Angelica root oil exhibited *in vitro* antifungal activity against 14 out of 15 fungi tested (Maruzzella & Liguori, 1958).

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ANGELICA SEED OIL

Description and physical properties: EOA Spec. no. 97. One of the main constituents of angelica seed oil is β-phellandrene (Gildemeister & Hoffman, 1961; Guenther, 1950).
Occurrence: Found in the seed of *Archangelica officinalis* Hoffm. (*Angelica archangelica* L., Fam. Umbelliferae).
Preparation: By steam distillation of fresh seeds of the plant.
Uses: In public use before the 1900s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·001	0·0001	0·001	0·02
Maximum	0·006	0·0006	0·005	0·1

Analytical data: Gas chromatogram, RIFM no. 73–42; infra-red curve, RIFM no. 73–42.

Status

Angelica seed oil was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) included angelica seed oil (*Archangelica officinalis* Hoffm.) in the list of substances, spices and seasonings deemed admissible for use with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on angelica seed oil.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. Undiluted angelica seed oil applied to the backs of hairless mice was not irritating (Urbach & Forbes, 1973). Applied full strength to intact or abraded rabbit skin for 24 hr under occlusion, it was mildly irritating (Moreno, 1973). Tested at 1% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 21 volunteers. The material was tested at a concentration of 1% in petrolatum and produced no sensitization reactions (Epstein, 1973).

Phototoxicity. No phototoxic effects were reported for Angelica seed oil (Urbach & Forbes, 1973).

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ANISE OIL

Description and physical properties: Food Chemicals Codex (1972). The characteristic odour of anise oil is due to its high content (80–90%) of anethole. Small quantities of methyl chavicol, *p*-methoxyacetophenone and other materials have also been reported to occur in this oil (Gildemeister & Hoffman, 1961).

Occurrence: Found in the dried ripe fruit of *Pimpinella anisum* L. (Umbelliferae) (*Merck Index*, 1968).

Preparation: By steam distillation of the dried fruits of the herb *Pimpinella anisum* L. (Umbelliferae) (Arctander, 1960).

Uses: In public use since the 1860s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·008	0·001	0·0025	0·054
Maximum	0·06	0·006	0·01	0·25

Analytical data: Gas chromatogram, RIFM no. 71–30; infra-red curve, RIFM no. 71–30.

Status

Anise oil was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) included anise oil (Pimpinella anisum) in the list of substances, spices and seasonings whose use it deemed admissible with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on anise oil.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 2·25 (1·82–2·74) g/kg (Weir, 1971). The acute dermal LD_{50} was reported as >5 g/kg in the rabbit (Weir, 1971). No percutaneous absorption of anise oil occurred through the skin of a mouse within 2 hr (Meyer & Meyer, 1959).

Irritation. Anise oil tested at a concentration of 2% in petrolatum produced no irritation after a 48-hr closed patch test in 25 human subjects (Kligman, 1971).

Human testing. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a 2% concentration in petrolatum and produced no reactions (Kligman, 1971). One authority states that aniseed oil is not a primary irritant to normal skin (Harry, 1948).

Sensitization. Several cases of sensitivity have been reported (Loveman, 1938; Schwartz, 1934; Tulipan, 1938). The irritating substance is anethole and the dermatitis consists of erythema, scaling and vesiculation (Schwartz, Tulipan & Peck, 1947).

Metabolism. See monograph on anethole.

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STAR ANISE OIL

Description and physical properties: A pale yellow to amber yellow liquid. The principal constituent of star anise oil is anethole (Guenther, 1952).
Occurrence: Found in the seeds of the plant *Illicium verum* Hook. f. (Fam. Magnoliaceae) (Guenther, 1952).
Preparation: By steam distillation of well ripened, brown coloured seeds of the plant *I. verum* Hook. f. (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Uses: In public use before the 1900s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·003	0·08
Maximum	0·1	0·01	0·03	0·4

Status

Star anise oil was given GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1974) included star anise in the list of flavouring substances temporarily admitted for use, possibly with a limitation on the active principle in the final product.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as $2{\cdot}57 \pm 0{\cdot}453$ g/kg (McGee, 1974). The acute dermal LD_{50} value in rabbits was reported as >5 g/kg (McGee, 1974).

Irritation. Star anise oil applied undiluted to the backs of hairless mice (Urbach & Forbes, 1974) or to intact or abraded rabbit skin for 24 hr under occlusion (McGee, 1974) was not irritating. Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1974).

Phototoxicity. No phototoxic effects were reported for undiluted star anise oil on hairless mice and swine (Urbach & Forbes, 1974).

Additional published data

Both *cis*- and *trans*-anethole, differing in their toxicity (Colombo & Manitto, 1971; Naves, 1958), and *p*-propenylphenyl 3,3-dimethylallyl ether ($CH_3 \cdot CH{:}CH \cdot C_6H_4 \cdot O \cdot CH_2(CH_3)_2$) (Okely & Grundon, 1971) have been identified in star anise oil from *I. verum*.

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ANISIC ALDEHYDE

Synonyms: *p*-Methoxybenzaldehyde; anisaldehyde; aubepine.
Structure: $CH_3O \cdot C_6H_4 \cdot CHO$.
Description and physical properties: EOA Spec. no. 42.
Occurrence: Reported to be found in various essential oils and extracts: Vanilla, *Acacia farnesiana* Willd., *Magnolia salicifolia* Maxim., *Erica arborea*, *Pirus communis*, *Boswelha senata*, anise, fennel, star anise and others (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: By methylation and oxidation of *p*-cresol and also by oxidation of anethole (Bedoukian, 1967).
Uses: In public use before the 1900s. Use in fragrances in the USA amounts to approximately 50,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·005	0·02	0·4
Maximum	0·3	0·03	0·1	1·0

Analytical data: Gas chromatogram, RIFM no. 73–1; infra-red curve, RIFM no. 73–1.

Status

Anisic aldehyde was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) listed anisic aldehyde giving an ADI of 1 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on anisic aldehyde.

Biological data

Acute toxicity. The acute oral LD_{50} value was reported as 1510 mg/kg in rats and 1260 mg/kg in the guinea-pig (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964). The acute dermal LD_{50} value in rabbits was reported as >5 g/kg (Moreno, 1973).

Chronic toxicity. In a feeding study, 10,000 ppm fed to rats in the diet for 15 wk produced no effects (Hagan, Hansen, Fitzhugh, Jenner, Jones, Taylor, Long, Nelson & Brouwer, 1967). In another feeding study, 1000 ppm fed to rats in the diet for 28 wk produced no effects (Hagan *et al.* 1967).

Irritation. Anisic aldehyde applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1973). Tested at 10% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1973).

Metabolism. Anisic aldehyde undergoes a very slight degree of demethylation with oxidation of its aldehyde group to an acid group, the major metabolite excreted being anisic acid (Williams, 1959).

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ANISYL ALCOHOL

Synonyms: Anisic alcohol; *p*-methoxybenzyl alcohol.
Structure: $CH_3O \cdot C_6H_4 \cdot CH_2OH$.
Description and physical properties: EOA Spec. no. 217.
Occurrence: Reported to be found in vanilla pods (Tahitian production) and anise seed oil (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: From anisic aldehyde by reduction.
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to approximately 5000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·005	0·02	0·3
Maximum	0·3	0·03	0·1	0·5

Analytical data: Gas chromatogram, RIFM no. 73–6; infra-red curve, RIFM no. 73–6.

Status

Anisyl alcohol was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) listed anisyl alcohol, giving an ADI of 1 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on anisyl alcohol.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 1200 mg/kg (Woodward & Hagan, 1948). The acute dermal LD_{50} value in rabbits was reported as 3·0 g/kg (1·94–4·06 g/kg) (Moreno, 1973).

Irritation. Anisyl alcohol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1973). Tested at 5% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1971).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 5% in petrolatum and produced no sensitization reactions (Kligman, 1971).

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ANISYL *n*-BUTYRATE

Synonym: *p*-Methoxybenzyl butyrate.
Structure: $CH_3O \cdot C_6H_4 \cdot CH_2 \cdot OCO \cdot [CH_2]_2 \cdot CH_3$.
Description and physical properties: A colourless liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: From anisyl alcohol and *n*-butyric acid by direct esterification under azeotropic conditions (Arctander, 1969).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 1000 lb/yr. Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·1
Maximum	0·09	0·09	0·03	0·5

Status

Anisyl *n*-butyrate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included anisyl *n*-butyrate at a level of 10 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 3·4 g/kg (3·02–3·78 g/kg) and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1976).

Irritation. Anisyl *n*-butyrate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was slightly irritating (Moreno, 1976). Tested at 8% in petrolatum it produced no irritation after a 48-hr closed-patch test on two different panels of human subjects (Kligman, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced sensitization reactions in four of the 25 (Kligman, 1975; see preface note no. 2). Using the same maximization test on another 25 volunteers, the material was retested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1975).

Metabolism. Esters of benzyl alcohol, such as the acetate, are rapidly hydrolysed *in vivo* to benzyl alcohol, which is then oxidized. The expected general reaction of primary aromatic alcohols in the animal body is oxidation to the corresponding aromatic acid, which is usually excreted as a glycine conjugate and to a lesser extent as an ester glucuronide. In rabbits, benzyl alcohol is almost entirely converted to benzoic acid, which is excreted mainly as hippuric acid (Bray, Thorpe & White, 1951). In substituted anisoles with a carboxyl group or a potential carboxyl group attached to the aromatic ring, the ether link is relatively stable (Williams, 1959).

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ANISYL FORMATE

Synonyms: *p*-Methoxybenzyl formate.
Structure: $CH_3O \cdot C_6H_4 \cdot CH_2 \cdot OCO \cdot H$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Reported to be found in *Vanilla fragrans* and Ribes species (*Fenaroli's Handbook of Flavor Ingredients*, 1975).
Preparation: From anisalcohol and formic acid (Arctander, 1969).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to approximately 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·1
Maximum	0·1	0·01	0·03	0·5

Status

Anisyl formate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) listed anisyl formate, giving an ADI of 1 mg/kg.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 1·55 ml/kg and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Levenstein, 1975).

Irritation. Anisyl formate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Levenstein, 1975). Tested at 4% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 22 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Epstein, 1975).

Metabolism. Esters of benzyl alcohol, such as the acetate, are rapidly hydrolysed *in vivo* to benzyl alcohol, which is then oxidized. The expected general reaction of primary aromatic alcohols in the animal body is oxidation to the corresponding aromatic acid, which is usually excreted as a glycine conjugate and to a lesser extent as an ester glucuronide. In rabbits, benzyl alcohol is almost entirely converted to benzoic acid, which is excreted mainly as hippuric acid (Bray, Thorpe & White, 1951). In substituted anisoles with a carboxyl group or a potential carboxyl group attached to the aromatic ring, the ether link is relatively stable (Williams, 1959).

Micro-organisms. Anisyl formate diluted 1:500 had no inhibitory effect *in vitro* on growing cultures of four bacteria (Maruzzella & Bramnick, 1961).

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ANISYLIDENE ACETONE

Synonyms: Methyl-*p*-methoxycinnamylketone; 4-(*p*-methoxyphenyl)-3-buten-2-one.
Structure: $CH_3 \cdot O \cdot C_6H_4 \cdot CH{:}CH \cdot CO \cdot CH_3$.
Description and physical properties: White or yellowish leafy crystals.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: From anisaldehyde and acetone by condensation using a suitable catalyst.
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to less than 1000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·01	0·06
Maximum	0·1	0·01	0·1	0·2

Status

Anisylidene acetone is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974), nor in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Wohl, 1974).

Irritation. Anisylidene acetone applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Wohl, 1974). Tested at a concentration of 2% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966, modified) was carried out on 22 volunteers. The material was tested at a concentration of 2% in petrolatum and produced two sensitization reactions out on the 22 tested (Epstein, 1974).

Antitumour activity. In vitro studies indicated weak antitumour activity for anisylidene acetone (Doré, 1973).

Metabolism. When the side chain of a mixed ketone contains a double bond, both the keto group and the double bond are potentially reducible *in vivo*. In a related material, methyl styryl ketone ($C_6H_5 \cdot CH{:}CH \cdot CO \cdot CH_3$), the keto group appears to be more readily reduced than the double bond, with reduction via $C_6H_5 \cdot CH{:}CH \cdot CH(OH) \cdot CH_3$ to the completely reduced carbinol compound $C_6H_5 \cdot [CH_2]_2 \cdot CH(OH) \cdot CH_3$, which is found as the main product (Fischer & Bielig, 1940). The ether link is relatively stable in substituted anisoles, such as anethole (p-$CH_3 \cdot OC_6H_4 \cdot CH{:}CH \cdot CH_3$), containing a potential carboxyl group attached to the aromatic ring (Williams, 1959).

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Wohl, A. J. (1974). Report to RIFM, 2 April.

ANISYL PROPIONATE

Synonym: *p*-Methoxybenzyl propionate.
Structure: $CH_3O \cdot C_6H_4 \cdot CH_2 \cdot OCO \cdot CH_2 \cdot CH_3$.
Description and physical properties: A colourless, slightly yellow liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By direct esterification of anisyl alcohol with propionic acid or propionic anhydride (Arctander, 1969).
Uses: In public use since the 1940s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·08
Maximum	0·1	0·01	0·05	0·4

Analytical data: Gas chromatogram, RIFM no. 74–37, infra-red curve, RIFM no. 74–37.

Status

Anisyl propionate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included anisyl propionate at a level of 20 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 3·33 g/kg (Wohl, 1974). The acute dermal LD_{50} value in rabbits was reported as >5 g/kg (Wohl, 1974).

Irritation. Anisyl propionate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Wohl, 1974). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 22 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Epstein, 1974).

Micro-organisms. Anisyl propionate in 1:500 dilution had no inhibitory effect *in vitro* on growing cultures of four bacteria (*Bacillus subtilis*, *Escherichia coli*, *Staphylococcus aureus* (penicillin sensitive) and *S. aureus* (penicillin resistant) (Maruzzella & Bramnick, 1961).

The vapour of anisyl propionate had no inhibitory effect *in vitro* on growing cultures of four fungi (*Candida albicans*, *Phoma betae*, *Geotrichum candidum* and *Oospora lactis*) (Maruzzella, Chiaramonte & Garofalo, 1961).

Metabolism. In substituted anisoles with a carboxyl group or a potential carboxyl group attached to the aromatic ring, the ether link is relatively stable (Williams, 1959). In the fungicidin-producing soil organism *Actinomyces aureus*, anisyl alcohol is metabolized to anisic acid, followed by demethylation and hydroxylation to give protocatechuic acid, which is degraded to succinic acid (Tsai, Chu, Yank & Tsao, 1965).

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ARMOISE OIL

Description and physical properties: A pale yellow or almost colourless liquid. Cineole and dehydromatricaria ester are constituents of armoise oil (Guenther, 1952).
Occurrence: Found in the perennial shrub *Artemisia vulgaris* L. (Fam. Compositae) (Guenther, 1952).
Preparation: By steam distillation of the leaves and flowering tops of *A. vulgaris* L. (*Fenaroli's Handbook of Flavor Ingredients*, 1971). A paper describing the sesquiterpene lactones of Artemesia has been written by Geissman (1970).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to approximately 5000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·1
Maximum	0·15	0·015	0·05	1·2

Status

Armoise (*A. vulgaris*) is approved by the FDA for food use (21 CFR 121.1163), provided the finished food is thujone free, and the Council of Europe (1974) included armoise (*A. vulgaris*) in the list of substances, spices and seasonings deemed admissible for use, with a possible limitation of the active principle in the final product.

Biological data

Acute toxicity. The acute oral LD_{50} value in mice was reported as 0·37 (0·26–0·48 g/kg) (Moreno, 1974). The acute dermal LD_{50} value in guinea-pigs was reported as >5 g/kg (Moreno, 1974).

Irritation. Undiluted armoise oil applied to the backs of hairless mice was not irritating (Urbach & Forbes, 1974). Applied full strength to intact or abraded rabbit or guinea-pig skin for 24 hr under occlusion, it was slightly irritating (Moreno, 1974). Tested at 12% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 24 volunteers. The material was tested at a concentration of 12% in petrolatum and produced no sensitization reactions (Epstein, 1974). Allergic contact dermatitis was caused by a species of Artemesia (*A. ludoviciana*) and was found to be due to some sesquiterpene lactones, notably ludovicins (Mitchell, Geissman, Dupuis & Towers, 1971).

Phototoxicity. No phototoxic effects were reported for undiluted armoise oil on hairless mice and swine (Urbach & Forbes, 1974).

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ARTEMISIA OIL (WORMWOOD)

Description and physical properties: EOA Spec. no. 114. The chief constituent of artemisia (wormwood) is thujone (Guenther, 1952).

Occurrence: Found in the plant *Artemisia absinthium* L. (Fam. Compositae) (Guenther, 1952).

Preparation: By steam distillation of *A. absinthium* L. (*Fenaroli's Handbook of Flavor Ingredients*, 1971).

Uses: In public use since the 1920s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·01	0·08
Maximum	0·1	0·01	0·03	0·25

Analytical data: Gas chromatogram, RIFM no. 74–39; infra-red curve, RIFM no. 74–39.

Status

Artemisia (wormwood) was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1163) provided the finished food is thujone free. The Council of Europe (1974) included artemisia (wormwood) in the list of substances, spices and seasonings deemed admissible for use, with a possible limitation of the active principle in the final product.

Wormwood oil is used extensively in flavour work in spite of the fact that the herb itself was responsible for the 1915 French ban on the production of "absinth" containing it. It was claimed that the thujone in the plant acts as a narcotic in greater doses, and that it was habit-forming. Thujone is the main constituent of wormwood oil, and this ketone is responsible for the similarity in odour to the oils of tansy and cedarleaf, and partly also to that of Dalmatian sage oil (Arctander, 1960).

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 0·96 (0·54–1·38 g/kg) (Moreno, 1974). The acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1974).

Irritation. Undiluted artemisia (wormwood) oil applied to the backs of hairless mice was not irritating (Urbach & Forbes, 1974). Applied full strength to intact or abraded rabbit skin for 24 hr under occlusion, it was slightly irritating (Moreno, 1974). Tested at 2% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 2% in petrolatum and produced no sensitization reactions (Kligman, 1974).

Phototoxicity. No phototoxic effects were reported for undiluted artemisia (wormwood) oil on hairless mice and swine (Urbach & Forbes, 1974).

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BASIL OIL, SWEET

Description and physical properties: Food Chemicals Codex (1972). European sweet basil oil may contain about 55% methyl chavicol and 35% of alcohols calculated as linalool, along with other components (Gildemeister & Hoffman, 1961).
Occurrence: Found in the leaves of *Ocimum basilicum* L. (Labiatae) (*Merck Index*, 1968).
Preparation: By steam distillation of the flowering tops of the plant *Ocimum basilicum* L. (Labiatae) (Arctander, 1960).
Uses: In public use since the 1900s. Use in fragrances in the USA amounts to less than 2000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	—	—	0·0025	0·09
Maximum	—	—	0·01	0·4

Analytical data: Gas chromatogram, RIFM no. 71–33; infra-red curve, RIFM no. 71–33.

Status

Basil oil, sweet, was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) included basil oil, sweet (*Ocimum basilicum*), in the list of substances, spices and seasonings whose use it deemed admissible with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on basil oil.

Biological data

Acute toxicity. The acute oral LD_{50} value in the rat was reported to be 1·4 (0·56–3·5) ml/kg (Levenstein, 1972). The acute dermal LD_{50} was reported as >5 ml/kg (Levenstein, 1972).

Irritation. Basil oil applied undiluted to the backs of hairless mice produced mildly irritating effects (Urbach & Forbes, 1972). Basil oil tested at a concentration of 4% in petrolatum produced no irritation after a 48-hr closed patch test in 25 human subjects (Kligman, 1972).

Human testing. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a 4% concentration in petrolatum and produced no reactions (Kligman, 1972).

Phototoxicity. No phototoxic effects were reported for basil oil (Urbach & Forbes, 1972).

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BAY OIL

Description and physical properties: EOA Spec. no. 251. The oil consists mainly of eugenol and chavicol (55–65%). The major portion of the balance consists of terpenes (α-pinene, myrcene and dipentene). Small quantities of citral, nerol, cineol and other terpenoids have also been identified in bay oil (Gildemeister & Hoffman, 1961).
Occurrence: Found in the leaves of the bay tree, *Pimenta racemosa* (Miller) J. W. Moore (Myrtaceae).
Preparation: By steam distillation of the leaves of the bay tree, *Pimenta racemosa* (Miller) J. W. Moore (Myrtaceae).
Uses: In public use since the 1860s. Use in fragrances in the USA amounts to less than 10,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·0025	0·09
Maximum	0·09	0·009	0·01	1·5

Analytical data: Gas chromatogram, RIFM no. 71–34; infra-red curve, RIFM no. 71–34.

Status

Bay oil was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) included bay oil (*Pimenta acris*) in the list of substances, spices and seasonings whose use it deemed admissible with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on bay oil.

Biological data

Acute toxicity. The acute oral LD_{50} value in the rat was reported as 1800 (1406–2304) mg/kg (Owen, 1971a). The acute dermal LD_{50} was reported as >5 ml/kg in the rabbit (Owen, 1971b).

Irritation. Bay oil tested at a concentration of 10% in petrolatum produced no irritation after a 48-hr closed patch test in 25 human subjects (Kligman, 1971).

Human testing. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a 10% concentration in petrolatum and produced no reactions (Kligman, 1971).

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BEESWAX ABSOLUTE

Synonym: *Cire d'abeille.*

Description and physical properties: A yellow waxy solid. Beeswax from *Apis mellifera* is an ester wax composed of up to 13% hydrocarbons, the remainder being mainly esters: as much as 23% of the beeswax is myricyl palmitate (McLoud, 1970).

Occurrence: Wax from the honeycomb of the bee, *Apis mellifera* L.

Preparation: By alcoholic extraction of the raw wax (*Fenaroli's Handbook of Flavor Ingredients*, 1975).

Uses: In public use before the 1960s.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	—	0·005	0·1
Maximum	0·15	—	0·03	0·4

Analytical data: Infra-red curve, RIFM no. 74–133.

Status

Beeswax was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1163). The *Food Chemicals Codex* (1972) has a monograph on beeswax.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (McGee, 1974).

Irritation. Undiluted beeswax absolute was not irritating when applied to the backs of hairless mice and swine (Urbach & Forbes, 1974) or to intact or abraded rabbit skin for 24 hr under occlusion (McGee, 1974). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1975). Beeswax was a component of a non-irritative medium used in closed-patch primary irritation tests of natural and synthetic perfumes (Fujii, Furukawa & Suzuki, 1972).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 22 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Epstein, 1975). One case of occupational dermatitis from beeswax used in moulding art objects has been reported; 30 control subjects exhibited no sensitivity (Camarasa, 1975).

Phototoxicity. No phototoxic effects were reported for undiluted beeswax absolute on hairless mice and swine (Urbach & Forbes, 1974).

Metabolism by insects. Under proper experimental conditions beeswax can be used as the sole carbon source for the growth of *Galleria mellonella*, the greater wax moth (Dadd, 1964). Beeswax (10%) added to the basal diet of the greater wax moth larvae stimulated growth by 13–76%. However addition of beeswax that had been hydrolysed did not promote growth (Young, 1961). *G. mellonella* larvae raised on a diet containing beeswax showed greater morphogenetic response to juvenile hormone than larvae deprived of beeswax (Reddy & Krishnakumaran, 1973). Studies indicated that wax moth larvae may metabolize only a small portion of the beeswax and excrete the remaining 50–71%, the actual proportion depending on the composition of the honeycomb (Bonner, 1961). Detailed analysis of the excreta of wax moth larvae showed that the wax eaten and that excreted differed greatly, since the insects preferentially utilized some of the lower-molecular-weight esters originally present in the honeycomb (Young, 1964). Desaturation of fatty acids occurred in the intestine of the wax moth after consumption of honeycomb; high activity of alkaline phosphatase was also observed (Niemierko, 1963).

Metabolism by micro-organisms. A medium containing purified beeswax as the only carbon source supported the growth of *Nocardia asteroides* (Miyamoto, 1959). Seven of eight extracts of micro-organisms studied were able to digest beeswax (myricyl palmitate). Only one culture of intact cells showed esterase activity, suggesting that de-esterification was an initial step in utilization (Millman & Yotis, 1958).

Mutagenicity. Beeswax was evaluated for genetic activity in a series of *in vitro* microbial assays with and without metabolic activation. In tests using the indicator strains of *Salmonella typhimurium* and *Saccharomyces cerevisiae* in plate tests and nonactivating and activating suspension tests, it did not produce any genetic activity (National Technical Information Service, 1975).

Additional published data

In a comparison of several natural wax-impregnated rubbers used to coat electronic devices implanted within the body, beeswax-impregnated silicone rubber showed the best tissue compatibility in rabbits (Enger & Rhinelander, 1970).

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BENZALDEHYDE

Synonym: Benzoic aldehyde.
Structure: $C_6H_5 \cdot CHO$.
Description and physical properties: *Merck Index* (1968).
Occurrence: Present as cyanuric glucoside (amygdalin) in bitter almond, peach, apricot kernel and other Prunus species. Amygdalin is also present in various parts of the following plants: *Sambucus nigra, Chrysophyllum arten, Anacyclus officinarum, A. pedunculatus, Davallia brasiliensis, Lacuma deliciosa, L. multiflora* and others. Free benzaldehyde has been reported in several essential oils, notably hyacinth, citronella, orris, cinnamon, sassafras, labdanum and patchouli (*Fenaroli's Handbook of Flavor Ingredients*, 1975).
Preparation: By chlorination of toluene to benzal chloride, which is hydrolysed to benzaldehyde (Bedoukian, 1967).
Uses: In public use before the 1900s. Use in fragrances in the USA amounts to approximately 75.000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·08
Maximum	0·75	0·075	0·25	0·4

Analytical data: Gas chromatogram, RIFM no. 73-2; infra-red curve, RIFM no. 73-2.

Status

Benzaldehyde was given GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1974) listed benzaldehyde giving an ADI of 4 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on benzaldehyde and the Joint FAO/WHO Expert Committee on Food Additives (1967) has published a monograph and specifications, giving an unconditional ADI of 0–5 mg/kg.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats has been reported as 1·3 g/kg (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964; Taylor, Jenner & Jones, 1964) and as 2·85 g/kg (Sporn, Dinu & Stanciu, 1967), while that in guinea-pigs was reported as 1·0 g/kg (Jenner *et al.* 1964). In rabbits, the acute dermal LD_{50} exceeded 1·25 g/kg (Moreno, 1973) and the sc LD_{50} was reported as 5 g/kg (Fassett, 1963). The acute ip LD_{50} in mice was reported as 3·27 g/kg (Sporn *et al.* 1967) and as 1·02 g/kg, with no deaths at 0·848 g/kg and 100% deaths at 1·113 g/kg (Caujolle, Meynier, Auriac, Frajdenrach & Troplent, 1956). In rats, the sc lethal dose of benzaldehyde was about 5 ml/kg, but this dose injected ip was not always lethal (Macht, 1922).

In short-term experiments on the inhibition of peptic activity, an effective dose (0·2–0·4 g) of benzaldehyde was not toxic to man (Kleeberg, 1959). Benzaldehyde is described as being narcotic to man at high concentrations (*Merck Index*, 1968), and from a study of two cases, it was concluded that 50–60 ml benzaldehyde taken by mouth would be followed by death in the absence of prompt treatment (Dadley, 1928).

Subacute toxicity. In feeding studies in rats, no effects were induced by 10,000 ppm given in the diet for 16 wk or 1000 ppm fed for 27–28 wk (Hagan, Hansen, Fitzhugh, Jenner, Jones, Taylor, Long, Nelson & Brouwer, 1967). Rats given 10 mg benzaldehyde orally every second day for 12 wk were found to have normal nitrogen and lipid levels and enzyme activities in the liver and a normal ascorbic acid content in the adrenals (Sporn *et al.* 1967). Benzaldehyde (1%) fed to rats for 14 days decreased body- and liver-weight gains (Hruban, Swift & Slesers, 1966), while oral administration of 435 mg/kg (approximately one third of the LD_{50}) to rats daily for 4 days caused the death of one out of six rats; livers appeared normal, with no macroscopic lesions (Taylor *et al.* 1964).

Irritation. Benzaldehyde applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1973). Tested at 4% in petrolatum it produced no irritation after a 48-hr closed-patch test on two different panels of human subjects (Kligman, 1973). Thomas (1958) reported, however, that benzaldehyde, like other aldehydes and aldehyde-containing essential oils, was strongly irritating to the skin.

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum (Kligman, 1973) and produced three false sensitization reactions (spillover effect from costus oil—see preface note no. 2). The same material retested by the maximization test at a concentration of 4% in petrolatum

produced no sensitization reactions in a further 25 volunteers (Kligman, 1973). In patch tests using 5% benzaldehyde in vaseline, positive reactions were observed in ten of 100 patients. Positive reactions occurred in patients with sensitivity to benzoic acid or vanillin (Hjorth, 1961).

Metabolism. Benzaldehyde was among 300 volatile constituents detected in the urine of ten adults (Zlatkis & Liebich, 1971). It is commonly converted to hippuric acid *in vivo*. In the rabbit and dog, hippuric acid appears to be the only metabolite (Bray, Thorpe & White, 1951; Friedmann & Turk, 1913) there being practically no formation of benzoyl glucuronide. The conversion of benzaldehyde to benzoic acid in the rabbit follows first-order reaction kinetics (Williams, 1959).

After ip administration to rats, 29·3% (21–37%) was excreted in the urine as hippuric acid (Teuchy, Quatacker, Wolf & Van Sumere, 1971). Honecker (1975) found that benzaldehyde, a cleavage product of amphetaminil, was rapidly converted to hippuric acid in the blood, brain and adipose tissue of rats and then excreted in the urine, while Smith & Packer (1972) showed that it was oxidized by rat-liver mitochondria.

During fermentation, several yeasts converted benzaldehyde (present in concentrations of 0·2–0·8%) to phenylacetylcarbinol (up to 70% conversion) and benzyl alcohol (Becvarova & Hanc, 1963; Becvarova, Hanc & Macek, 1963). Under anaerobic conditions, benzaldehyde formed by metabolism of benzoic acid was reduced to benzyl alcohol by *Aspergillus niger* (Raman & Shanmugasundaram, 1962). Benzaldehyde was oxidized by Pseudomonas species (Madhyastha & Bhattacharyya, 1968; Omori & Yamada, 1970) and could be utilized by Klebsiella (Grant, 1967), soil bacteria (Claus & Walker, 1964), glutamate-producing bacteria (Yamamoto, Nishida, Inui & Ozaki, 1972) and some but not all species of Arthrobacter (Mullakhanbhai & Bhat, 1966). It was oxidized by the aldehyde dehydrogenase of human liver (Johns, 1967), by bovine liver (Robbins, 1966), and by the livers of other species (Deitrich, Hellerman & Wein, 1962), by the perillaldehyde dehydrogenase of a soil pseudomonad (Ballal, Bhattacharyya & Rangachari, 1967) and by tissue enzymes of the silkworm larva, *Bombyx mori* (Hayashi, 1961). It was reduced by the aldehyde reductase of bakers' yeast (Uehara & Takeda, 1964).

Pharmacology. Benzaldehyde significantly inhibited peptic activity in artificial gastric juice *in vitro* (20–45% inhibition) and *in vivo* to the extent of 87% in normal healthy persons and ulcer patients (Kleeberg, 1959). As a freshly prepared 1:500 solution, it exerted a marked antispasmodic effect, relaxing the tonus and inhibiting contractions of various isolated smooth muscles of dog, cat, rat, rabbit, mouse, guinea-pig, pig and frog and of a few human tissues. Injected into rabbits and other animals it produced a marked relaxation of the intestines and urinary bladder and marked vasodilation of the splanchnic vessel. Injection of 4 ml of a 5% solution iv into a cat caused a fall in blood pressure and slowing of respiration. In dogs, 1 ml injected iv or sc or 2 ml/kg given orally produced only a slight slowing of respiration. Injection of larger doses iv produced only a drop in blood pressure, slight slowing of respiration and inhibition of intestinal contractions, with vasodilation of the splanchnic vessel. In rabbits, iv injection of 20 ml of a 0·2% solution did not produce dangerous results. Large injected doses of benzaldehyde exert their most important toxic effects on the medulla, with slowing or paralysis of respiration. In the intact animal, the heart is very little affected; but benzaldehyde acts as a muscular depressant on isolated frog heart (Macht, 1922).

Treatment of isolated rat striated muscle for 1–5 min with 30 mM-benzaldehyde increased the rate of propagation of contractures and the rate of structural breakdown of injured striated muscle fibres. After more prolonged application (for 30 min), the rapid propagation of contracture continued but the structural breakdown was inhibited (Bilsing, 1972).

Benzaldehyde possessed definite local anaesthetic properties in the sciatic nerves of cats, dogs and frogs, in the eyes of rabbits and dogs (accompanied by irritation) and in the skin of frogs, but was considered unsuitable for practical use because of its rapid oxidation to benzoic acid (Macht, 1922).

In a study of the toxic effects of cherry laurel water on mice and on isolated rat intestine, benzaldehyde was found to aid in the detoxication of HCN by the formation of $C_6H_5 \cdot CH(OH) \cdot CN$ (Lanza & Conte, 1964).

Benzaldehyde did not act as a cross-linking (tanning) agent for corium and aorta, since in a 0·15 M solution it did not increase the observed *in vitro* hydrothermal shrinkage temperatures of goat skin and human, bovine and canine aortae (Milch, 1965).

The intestinal absorption-rate coefficients of benzaldehyde and related compounds were determined by perfusion of aqueous solutions through the small intestines of anaesthetized rats (Nogami, Hanano & Yamada, 1968).

No changes in gastric motor patterns, including gastric motility, were observed in rats after inhalation of "toxic levels" (not specified) of benzaldehyde from a liquid sample placed in a test chamber using recirculated air, or from a saturated paper applied to the trachea (Roth & Tansy, 1972).

Benzaldehyde in a concentration of 0·1 mmol/litre caused a 16% depression of the frequency of electric-organ discharge in the mormyrid electric fish *Gnathonemus moori* (Walsh & Schopp, 1966).

Anthropods. Benzaldehyde has been identified in the defensive secretions of harvester ants (Blum, Padovani, Curley & Hawk, 1969) and millipedes (Blum, MacConnell, Brand, Duffield & Fales, 1973; Blum & Woodring, 1962; Duffey, Underhill & Towers, 1974; Eisner, Eisner & Hurst, 1963; Weatherston & Gardiner, 1973) and as a major male pheromone of several noctuid Lepidoptera

(Aplin & Birch, 1968; Clearwater, 1972 & 1975; Grant, Brady & Brand, 1972). It is present in the alarm pheromone of Trigona stingless bees (Luby, Regnier, Clarke, Weaver & Weaver, 1973; Weaver, Weaver & Clarke, 1975), releases alarm behaviour in honey bees, *Apis mellifera* (Boch & Shearer, 1971), and is effective as a repellant for honey bees during the harvesting of honey (Food and Drug Administration, 1964; Papadopoulo, 1966; Propravko, 1968).

Nematodes. In *in vitro* tests, benzaldehyde (1:1000 in a 0·9% saline solution) was lethal to male pork ascarids within 4 hr (Ishii, 1958).

Micro-organisms. Benzaldehyde has shown antimicrobial activity against several bacteria and fungi (Chirkina & Patudin, 1971). It inhibited the growth of nine species of bacteria (Kellner & Kober, 1955 & 1956). in dilutions of 1:500–1:1000 inhibited the *in vitro* growth of four Gram-positive and Gram-negative bacteria (Maruzzella & Bramnick, 1961) and in dilutions of 1:100 in cottonseed oil was germicidal to *Bacillus coli* (Macht, 1922). It showed very little fungistatic activity when tested against six species of fungi (Izgü, 1959), inhibited *in vitro* growth of *Saprolegnia parasitica* at 2000 ppm but not at 200 ppm, and failed to control growth of the fungus on trout eggs at 22 ppm (Cline & Post, 1972).

A concentration of 0·001 M stimulated germination of basidiospores of *Coprinus radiatus*, particularly when combined with heat treatment (Mills & Eilers, 1973).

Cells. Benzaldehyde (0·01 M) was somewhat toxic to Ehrlich ascites carcinoma cells; the much greater toxicity of amygdalin glucosidase was found to be due to the synergistic action of benzaldehyde and cyanide formed by enzymic hydrolysis (Burk, McNaughton & von Ardenne, 1971).

Plants. In a study of Allium roots, benzaldehyde was found to have a stathmokinetic effect on mitosis (Barthelmess & Elkabarity, 1962). At 52 ppm it caused a 64·7% decrease in the chlorophyll content of *Euglena gracilis*, with higher concentrations causing death (Tabachnik, 1973). It was found to be an effective inhibitor of seed germination (Helfrich, 1962) and in a concentration of 10^{-3} M inhibited growth and stimulated respiration of the alga, *Chlorella vulgaris* (Dedonder & Van Sumere, 1971).

Enzyme inhibition. Benzaldehyde has been shown to inhibit the activity of ox-brain or ox-kidney pyruvic dehydrogenase (Blass & Lewis, 1973), rabbit-muscle aldolase (Spolter, Adelman & Weinhouse, 1965), pig-heart muscle carboligase (Okuyama, 1959), glutamic dehydrogenase (Yoshida, 1959), yeast decarboxylase (Becvarova & Hanc, 1963), *Aspergillus soya* esterase (Hanaoka, 1962) and apricot phenolase (Soler-Martinez, Sabater-Garcia & Lozano, 1965). Because of its activity as an enzyme inhibitor, benzaldehyde has been used in studies of enzyme kinetics relating to horse-liver alcohol dehydrogenase (Tatemoto, 1975), rat-liver mitochondrial monoamine oxidase (Houslay & Tipton, 1973), beef-liver monoamine oxidase (Oi, Yasunobu & Westley, 1971), beef-plasma amine oxidase (Oi, Inamasu & Yasunobu, 1970) and pig-plasma benzylamine oxidase (Taylor, Taylor, Rasmussen & Knowles, 1972), and in thermodynamic studies of chymotrypsin (Berezin, Levashov & Martinek, 1970).

Olfaction. Benzaldehyde has been used in studies of olfactory mechanisms in humans and rats (Laing, 1975), frogs (Mozell, 1969; Ottoson & von Sydow, 1964) and aphids (Pettersson, 1970).

Additional published data

Benzaldehyde, like other aldehydes, increased the rate of lipolysis in rat adipose tissue *in vitro*, probably by interfering with carbohydrate metabolism, producing a marked decrease in the glucose uptake of tissue and in pyruvate output and a stimulation of lactate output and of the lactate/pyruvate ratio (Giudicelli, Nordmann & Nordmann, 1973).

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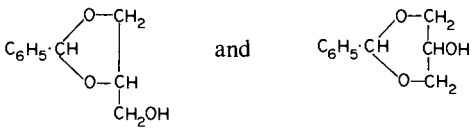
BENZAL GLYCERYL ACETAL

Synonyms: 2-Phenyl-*m*-dioxan-5-ol; benzylidene glycerol.
Structure:



Description and physical properties: A colourless viscous liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: From benzaldehyde and glycerol by acid-catalysed condensation and using azeotropic distillation to remove reaction water.
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to less than 1000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·005	0·1
Maximum	1·0	0·1	0·3	0·4

Analytical data: Gas chromatogram, RIFM no. 74–44; infra-red curve, RIFM no. 74–44.

Status

Benzal glyceryl acetal was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) listed benzal glyceryl acetal, giving an ADI of 5 mg/kg.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 3·15 ml/kg (2·42–4·09 ml/kg) and the acute dermal LD_{50} value in rabbits as 5 ml/kg (Levenstein, 1974).

Irritation. Benzal glyceryl acetal applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Levenstein, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 26 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Epstein, 1974).

Antibacterial activity. Benzal glyceryl acetal was found by a zone-inhibition technique to be an effective antibacterial agent, particularly against Gram-negative organisms. When formulated at 1% in a nonionic body lotion, the bactericidal effectiveness was greatly increased by addition of propylparaben, suggesting the possibility of a synergistic relationship between the acetal and other antibacterial agents (Felton & Kapp, 1970).

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Levenstein, I. (1974). Report to RIFM, 18 March.

BENZOIN (RESINOID)

Description and physical properties: An amber coloured resinoid with a characteristic balsamic odour. Both Siam and Sumatra benzoins contain vanillin and esters of benzoic and cinnamic acids (Naves & Mazuyer, 1947).

Occurrence: Benzoin Siam is obtained from *Styrax tonkinensis* P. *S. mycrothyrsus* P. Benzoin Sumatra is derived from *Styrax benzoin* D. *S. benzoides* C. (Naves & Mazuyer, 1947).

Preparation: The resinoid is obtained by extracting the natural benzoin with benzene and then distilling off the solvent (Naves & Mazuyer, 1947).

Uses: In public use since the 1900s. Use in fragrances in the USA amounts to about 100,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·0075	0·27
Maximum	0·21	0·002	0·03	0·8

Analytical data: Infra-red curve, RIFM no. 70–8.

Status

Benzoin was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1163). The Council of Europe (1970) included benzoin in the list of substances, spices and seasonings whose use it deemed admissible with a possible limitation of the active principle in the final product. The *United States Pharmacopeia* (1965) has a monograph on benzoin.

Biological data

Acute toxicity. The acute oral LD_{50} was reported as 10 g/kg in the rat (Margolin, 1970a). The acute dermal LD_{50} in the rabbit was reported as 8·87 (3·98–19·75) g/kg (Margolin, 1970b).

Human testing. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no reactions (Kligman, 1970).

Sensitization. Numerous cases of compound tincture of benzoin sensitivity have been reported in the literature, with eczema as the major dermatological manifestation (Spott & Shelley, 1970). There have been cross-sensitization reactions to benzoin when subjects were sensitized to Balsam Peru (Hjorth, 1961). Benzoin in the concentrations and forms employed in toilet preparations and dermatological preparations is not a primary irritant and there is no evidence that it is a sensitizer (Harry, 1948). Dermatitis has been reported from the use of a Compound Tincture of Benzoin, but this contains other substances such as Tolu, Balsam Peru and styrax, to which some persons are known to be sensitized (James, 1930).

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BENZOPHENONE

Synonyms: Diphenyl ketone; benzoylbenzene.
Structure: $C_6H_5 \cdot CO \cdot C_6H_5$.
Description and physical properties: EOA Spec. no. 83.
Occurrence: Apparently has not been reported to occur in nature.
Preparation: By standard Friedel–Craft type reactions (Bedoukian, 1967).
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to about 100,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·004	0·09
Maximum	0·15	0·015	0·015	0·3

Status

Benzophenone was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included benzophenone in the list of admissible artificial flavouring substances at a level of 2 ppm. The *Food Chemicals Codex* (1972) has a monograph on benzophenone.

Biological data

Acute toxicity. The acute oral LD_{50} was reported as > 10,000 mg/kg in the rat (Margolin, 1970a). The acute dermal LD_{50} was reported to be 3535 (2007–6226) mg/kg in the rabbit (Margolin, 1970b).

Human testing. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a 6% concentration in petrolatum and produced no reactions (Kligman, 1970).

Sensitization. Because of their extensive use as sunscreens (Knox, Guin & Cockerell, 1958) substituted benzophenones have been reported as capable of producing allergic reactions, but even here the incidence as reported by the authors "is extremely low" (Ramsay, Cohen & Baer, 1972).

Metabolism. Benzophenone's main metabolic pathway in the rabbit is by reduction to benzhydrol, which is excreted conjugated with glucuronic acid (Williams, 1959).

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BENZYL ACETATE

Structure: $C_6H_5 \cdot CH_2 \cdot OCOCH_3$.
Description and physical properties: EOA Spec. no. 33.
Occurrence: Found in a dozen essential oils including jasmin, hyacinth and gardenia (Gildemeister & Hoffman, 1960).
Preparation: By the interaction of benzyl chloride and sodium acetate or by acetylation of benzyl alcohol.
Uses: In public use since the 1900s. Use in fragrances in the USA amounts to less than 1,000,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·05	0·005	0·015	0·54
Maximum	0·36	0·036	0·15	3·0

Analytical data: Gas chromatogram, RIFM no. 70–63; infra-red curve, RIFM no. 70–63.

Status

Benzyl acetate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) listed benzyl acetate, giving an ADI of 5 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on benzyl acetate, and the Joint FAO/WHO Expert Committee on Food Additives (1967) has published a monograph and specification for benzyl acetate, giving an unconditional ADI of 0·5 mg/kg body weight in man.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 2·49 g/kg by Jenner, Hagan, Taylor, Cook & Fitzhugh (1964) and as 3·69 g/kg by Boyd & Kuizenga (1945). The LD_{50} by dermal application was reported as > 5 g/kg in the rabbit (Moreno, 1972). Benzyl acetate caused hyperaemia of the lungs and moderate pulmonary oedema in mice that died from exposure to the vapour of the ester (von Oettingen, 1960).

Human testing. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no reactions (Greif, 1967).

Inhalation effects. The vapour of benzyl acetate is irritating to the eyes and to respiratory passages, exciting cough (Lehmann & Flury, 1943). Benzyl acetate is absorbed through the lungs and from the gastro-intestinal tract and its vapours have an irritating effect on the mucous membranes (von Oettingen, 1960). The threshold limit value for benzyl acetate has been set at 15 ppm, at which level it has an irritant and narcotic effect (*Handbook of Organic Industrial Solvents*, 1961). Both cyclohexyl and benzyl acetates appear to produce narcosis and lethal effects in animals at levels considerably below those of the other esters. They are of low volatility, however, and except for local irritation no effects have been reported in man (Fassett, 1963).

Metabolism. The esters of benzyl alcohol, such as the acetate, benzoate, cinnamate and hydrocinnamate, are rapidly hydrolysed *in vivo* to benzyl alcohol which is then oxidized to benzoic acid and excreted as hippuric acid (Williams, 1959).

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BENZYL ALCOHOL

Synonym: Phenyl carbinol.
Structure: $C_6H_5 \cdot CH_2OH$.
Description and physical properties: Food Chemicals Codex (1972).
Occurrence: Found in jasmine, hyacinth, ylang-ylang oils and at least two dozen other essential oils (Gildemeister & Hoffman, 1962).
Preparation: By the action of alkalis on benzyl chloride (Bedoukian, 1967).
Uses: In public use since the 1900s. Use in fragrances in the USA amounts to about 250,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·05	0·01	0·05	0·40
Maximum	0·15	0·025	0·15	1·0

Status

Benzyl alcohol was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) listed benzyl alcohol, giving an ADI of 5 mg/kg. The *Food Chemicals Codex* (1972) and the National Formulary (1970) have monographs on benzyl alcohol and another extensive monograph has been provided by Browning (1965).

Biological data

Acute toxicity. The single-dose oral LD_{50}s in rats and rabbits were reported as 2·08 and 1·94 g/kg, respectively (Graham & Kuizenga, 1945). The acute oral LD_{50} was reported as 1230 mg/kg in rats (Bär & Griepentrog, 1967) and as 1580 mg/kg in the mouse (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964). The acute dermal LD_{50} in guinea-pigs was reported to be $< 5{\cdot}0$ ml/kg (Jones, 1967). The approximate LD_{50} ip was reported as 400–800 mg/kg in rats and guinea-pigs (Treon, 1963).

Irritation. The undiluted material applied to the depilated skin of guinea-pigs for a period of 24 hr caused moderately strong primary irritation (Treon, 1963).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at 10% concentration in petrolatum and produced no sensitization reactions (Kligman, 1970).

Metabolism. Esters of benzyl alcohol (acetate, benzoate, cinnamate and hydrocinnamate) are rapidly hydrolysed *in vivo* to benzyl alcohol, which is then oxidized (Williams, 1959). The animal (and human) organism readily oxidizes benzyl alcohol to benzoic acid, which after conjugation with glycine is rapidly eliminated as hippuric acid in the urine (Treon, 1963).

Additional published data

Slow iv injection of 1 ml 0·9% benzyl alcohol/kg into unanaesthetized and anaesthetized dogs and anaesthetized monkeys failed to alter the blood, heart rate, respiration or ECG pattern, and produced no changes in the haematological picture. Intracarotid and intrarenal injection of the same dose into anaesthetized dogs did not affect either these parameters or the EEG tracing. The lethal iv dose of benzyl alcohol in anaesthetized dogs was 830–1060 mg/kg and the LD_{50} in rats was 314 mg/kg, while in mice 480 mg/kg was uniformly fatal when injected rapidly. In rats, 94% benzyl alcohol was 23 times more toxic iv than 95% ethanol, and again in mice, in which the LD_{50} of benzyl alcohol was below 480 mg/kg, the

LD_{50} for 95% ethanol was 1460 mg/kg (Kimura, Darby, Krause & Brondyk, 1971).

Two methylprednisolone sodium succinate formulations with different preservatives (benzyl alcohol and parabens) and a placebo were administered iv in single doses of 2·0 g to 24 subjects. Both formulations were well tolerated and no important drug-related side effects were encountered. No clinically significant changes in the vital signs, electrocardiograms, electroencephalograms or laboratory parameters were noted. All expected corticosteroid-induced changes were reversible. The higher antibacterial activity of benzyl alcohol shown in the challenge tests plus comparable tolerance to parabens favour the use of benzyl alcohol as a preservative (Novak, Stubbs, Sanborn & Eustice, 1972).

Cross-sensitizations to benzyl alcohol have been reported in subjects sensitized to Peru balsam (Hjorth, 1961).

Benzyl alcohol vapours can penetrate the intact skin, and vapour concentrations of approximately 100 ppm can cause systemic effects and deaths in laboratory animals. A tentative vapour exposure level of 1 ppm may prove acceptable for workroom atmospheres. Due to its lachrymatory effects, exposures much above 1 ppm would probably not be tolerated for any prolonged period (Jones, 1967).

Hypersensitivity to phenyl carbinol preservative in Vitamin B_{12} (for injection) has been reported (Lagerholm, 1958).

Benzyl alcohol exerts a narcotic action but is of low toxicity. High exposure can cause a decrease in blood pressure, a depressant effect on the system and death through respiratory paralysis (*Handbook of Organic Industrial Solvents*, 1961).

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BENZYL BENZOATE

Synonym: Benzoic acid benzyl ester.
Structure: $C_6H_5 \cdot CH_2 \cdot CO_2 \cdot C_6H_5$.
Description and physical properties: Food Chemicals Codex (1972).
Occurrence: Found in Peru and Tolu balsams, in ylang-ylang and in about twenty other essential oils (Gildemeister & Hoffman, 1966).
Preparation: By the interaction of sodium benzoate and benzyl chloride (Bedoukian, 1967).
Uses: In public use since the 1900s. Use in fragrances in the USA amounts to about 500,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·005	0·10	0·40
Maximum	0·10	0·010	0·25	3·00

Status

Benzyl benzoate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) listed benzyl benzoate, giving an ADI of 5 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on benzyl benzoate.

Biological data

Acute toxicity. The single-dose oral LD_{50}s in rats and rabbits were reported as 2·8 and 1·68 g/kg, respectively, while in the cat the LD_{50} was reported as 2·24 g/kg and in the dog as >22·44 g/kg (Graham & Kuizenga, 1945). The acute dermal LD_{50} in the rabbit was reported as 4 ml/kg (Fassett, 1963).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at 30% concentration in petrolatum and produced no sensitization reactions (Kligman, 1970).

Metabolism. Benzyl benzoate, a relatively non-toxic liquid widely used for the treatment of scabies, is converted into benzoic acid *in vivo* (Williams, 1959).

Additional published data

Cross-sensitization reactions to benzyl benzoate have been reported in subjects sensitized to Peru balsam (Hjorth, 1961).

Benzyl benzoate is a primary skin irritant (Schwartz, Tulipan & Birmingham, 1957), but used as a 20% emulsion in the treatment of scabies in 1000 persons it produced no dermatitis (Graham, 1943). Four cases of dermatitis have been attributed to benzyl benzoate by Dougherty (1945). Benzyl benzoate is an effective treatment against scabies and does not often cause dermatitis (Mellanby, 1963).

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BENZYL BUTYRATE

Synonyms: Benzyl *n*-butyrate; benzyl *n*-butanoate.
Structure: $C_6H_5 \cdot CH_2O \cdot CO \cdot [CH_2]_2 \cdot CH_3$.
Description and physical properties: EOA Spec. no. 168.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By the esterification of benzyl alcohol with butyric acid in the presence of a catalyst.
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to approximately 5000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·01	0·1
Maximum	0·1	0·01	0·03	0·4

Analytical data: Gas chromatogram, RIFM no. 72–84; infra-red curve, RIFM no. 72–84.

Status

Benzyl butyrate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) listed benzyl butyrate, giving an ADI of 5 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on benzyl butyrate.

Biological data

Acute toxicity. The acute oral LD_{50} in rats has been reported as 1·85 g/kg (1·06–2·56 g/kg) (Moreno, 1973) and as 2·33 g/kg (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964). The acute dermal LD_{50} in rabbits was reported as > 5 g/kg (Moreno, 1973).

Irritation. Benzyl butyrate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Moreno, 1973). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1973).

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BENZYL CINNAMATE

Synonyms: Benzyl-β-phenylacrylate; cinnamein.
Structure: $C_6H_5 \cdot CH_2 \cdot CO_2 \cdot CH:CH \cdot C_6H_5$.
Description and physical properties: EOA Spec. no. 124.
Occurrence: Found in balsams of Peru, tolu, styrax, copaiba and others.
Preparation: By the esterification of benzyl alcohol and cinnamic acid, or by the interaction of benzyl chloride and sodium cinnamate.
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 20,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·005	0·05	0·2
Maximum	0·10	0·02	0·2	0·8

Analytical data: Gas chromatogram, RIFM no. 71–35; infra-red curve, RIFM no. 71–35.

Status

Benzyl cinnamate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) listed benzyl cinnamate, giving an ADI of 1·25 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on benzyl cinnamate.

Biological data

Acute toxicity. The acute oral LD_{50} was found to be 3·28 g/kg (2·62–4·10 g/kg) in rats (Levenstein, 1972a) and 3·76 g/kg int he guinea-pig (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964). The acute dermal LD_{50} was reported to be > 3·0 g/kg in the rabbit (Levenstein, 1972).

Chronic toxicity: In a feeding study, 10,000 ppm fed to rats in the diet for 19 weeks produced no macroscopic effects (Hagan, Hansen, Fitzhugh, Jenner, Jones, Taylor, Long, Nelson & Brouwer, 1967).

Irritation. Benzyl cinnamate applied full strength to intact or abraded rabbit skin was mildly irritating (Levenstein, 1972b). Tested in a concentration of 8% in petrolatum, it produced no irritation in a 48-hr closed-patch test in 25 human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1972).

Metabolism. See monograph on Benzyl alcohol (p. 1011).

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Council of Europe (1970). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List A(1), Series 1, no. 332, p. 67. Strasbourg.

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BENZYL FORMATE

Synonym: Formic acid benzyl ester.
Structure: $C_6H_5 \cdot CH_2 \cdot CO_2 \cdot H$.
Description and physical properties: Givaudan Index (1961).
Occurrence: Apparently has not been reported to occur in nature.
Preparation: From formic acid and benzyl alcohol (*Merck Index*, 1968).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 2000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·010	0·002	0·005	0·05
Maximum	0·020	0·008	0·020	0·95

Analytical data: Gas chromatogram, RIFM no. 71–36; infra-red curve, RIFM no. 71–36.

Status

Benzyl formate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) listed benzyl formate, giving an ADI of 5 mg/kg.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was found to be 1·7 ml/kg (1·4–2·1 ml/kg) (Shelanski & Moldovan, 1971). The acute dermal LD_{50} in rabbits was found to be 2·0 ml/kg (1·3–3·0 ml/kg) (Shelanski & Moldovan, 1971).

Irritation. Benzyl formate tested at a 10% concentration in petrolatum produced no irritation in a 48-hr closed-patch test in 25 human subjects (Kligman, 1971).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a 10% concentration in petrolatum and produced no sensitization reactions (Kligman, 1971). Benzyl formate at full strength produced no reactions in a single patch test on 20 humans (Peterson & Hall, 1946).

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Council of Europe (1970). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List A (1), Series 1, no. 325, p. 68. Strasbourg.

Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. No. 2145. *Fd Technol., Champaign* **19** (2), part 2, 155.

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BENZYLIDENE ACETONE

Synonyms: 4-Phenyl-3-buten-2-one; benzalacetone.

Structure: $C_6H_5 \cdot CH : CH \cdot CO \cdot CH_3$.

Description and physical properties: Givaudan Index (1961).

Occurrence: Apparently has not been reported to occur in nature.

Preparation: By condensing acetone and benzaldehyde by means of aqueous alkali (*Merck Index*, 1968).

Uses: In public use since the 1920s.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·001	0·005	0·005
Maximum	0·01	0·005	0·01	0·05

Analytical data: Gas chromatogram, RIFM no. 71–41; infra-red curve, RIFM no. 71–41.

Status

Benzylidene acetone was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164).

Biological data

Acute toxicity. The acute oral LD_{50} was reported as >5 g/kg in the rat (Levenstein, 1972a). The acute dermal LD_{50} was reported as >3 g/kg in the rabbit (Levenstein, 1972b).

Irritation. Benzylidene acetone applied full strength to intact or abraded rabbit skin was mildly irritating (Levenstein, 1972b). Tested at a 2% concentration in petrolatum it produced no irritation in a 48-hr closed-patch test in 25 human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a 2% concentration in petrolatum and produced sensitization reactions in 12 out of 25 subjects (Kligman, 1972).

Additional published data

Benzylidene acetone is listed as a strongly irritant perfume material (Thomssen, 1947), and has been cited many times in the literature as a skin irritant.

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BENZYL ISOBUTYRATE

Synonym: Benzyl 2-methyl propionate.
Structure: $C_6H_5 \cdot CH_2 \cdot CO_2 \cdot CH(CH_3) \cdot CH_3$.
Description and physical properties: EOA Spec. no. 267.
Occurrence: Apparently has not been reported to occur in nature.
Preparation: By esterification of benzyl alcohol with isobutyric acid.
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfumes*
Usual	0·02	0·004	0·021	0·041
Maximum	0·06	0·010	0·075	0·41

Analytical data: Gas chromatogram, RIFM no. 71–37; infra-red curve, RIFM no. 71–37.

Status

Benzyl isobutyrate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included benzyl isobutyrate in the list of admissible artificial flavouring substances at a level of 10 ppm.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was found to be 2850 mg/kg (2111–3847 mg/kg) (Owen, 1971a). The acute dermal LD_{50} was reported to be > 5 ml/kg in the rabbit (Owen, 1971b).

Irritation. Benzyl isobutyrate tested at a concentration of 4% in petrolatum produced no irritation in a 48-hr closed-patch test in 25 human subjects (Kligman, 1971).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1971).

References

Council of Europe (1970). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List A(1), Series 1, no. 302, p. 65. Strasbourg.
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BENZYL ISOEUGENOL

Synonyms: Isoeugenol benzyl ether; benzyl 2-methoxy-4-propenylphenyl ether.
Structure: $C_6H_5 \cdot CH_2O \cdot C_6H_3(OCH_3) \cdot CH{:}CH \cdot CH_3$.
Description and physical properties: EOA Spec. no. 237.
Occurrence: Apparently has not been reported to occur in nature.
Preparation: By benzylation of isoeugenol.
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·02
Maximum	0·10	0·015	0·05	0·5

Analytical data: Gas chromatogram, RIFM no. 71–38; infra-red curve, RIFM no. 71–38.

Status

Benzyl isoeugenol is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) listed benzyl isoeugenol, giving an ADI of 5 mg/kg.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 4·9 g/kg (4·71–5·1 g/kg) (Levenstein, 1972a). The acute dermal LD_{50} was reported as >3 g/kg in the rabbit (Levenstein, 1972b).

Irritation: Benzyl isoeugenol applied full strength to intact or abraded rabbit skin was mildly irritating (Levenstein, 1972b). Tested at a concentration of 5% in petrolatum it produced no irritation in a 48-hr closed-patch test in 25 human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a 5% concentration in petrolatum and produced no sensitization reactions (Kligman, 1972).

References

Council of Europe (1970). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List A(1), Series 1, no. 554, p. 77. Strasbourg.
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Levenstein, I. (1972b). Report to RIFM, 7 April.

BENZYL ISOVALERATE

Synonym: Benzyl 3-methyl butyrate (and other isomers).
Structure: $C_6H_5 \cdot CH_2 \cdot OCO \cdot CH_2 \cdot CH(CH_3)_2$.
Description and physical properties: EOA Spec. no. 266.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By the esterification of benzyl alcohol with isovaleric acid.
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·08
Maximum	0·1	0·01	0·03	0·4

Analytical data: Gas chromatogram, RIFM no. 74–77; infra-red curve; RIFM no. 74–77.

Status

Benzyl isovalerate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) listed benzyl isovalerate, giving an ADI of 5 mg/kg.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1974).

Irritation. Benzyl isovalerate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was slightly irritating (Moreno, 1974). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Epstein, 1974).

References

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Moreno, O. M. (1974). Report to RIFM, 23 January.

BENZYL PHENYLACETATE

Synonym: Benzyl α-toluate.
Structure: $C_6H_5 \cdot CH_2 \cdot CO_2 \cdot CH_2 \cdot C_6H_5$.
Description and physical properties: Food Chemicals Codex (1972).
Occurrence: Apparently has not been reported to occur in nature.
Preparation: By direct esterification of benzyl alcohol with phenylacetic acid under azeotropic conditions (Arctander, 1969).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 2000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·010	0·07
Maximum	0·08	0·010	0·080	0·2

Analytical data: Gas chromatogram, RIFM no. 71–39; infra-red curve, RIFM no. 71–39.

Status

Benzyl phenylacetate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included benzyl phenylacetate in the list of admissible artificial flavouring substances at a level of 5 ppm. The *Food Chemicals Codex* (1972) has a monograph on benzyl phenylacetate.

Biological data

Acute toxicity. The acute oral LD_{50} was reported as >5000 mg/kg in the rat (Owen, 1971a). The acute dermal LD_{50} was reported as >10 ml/kg in the rabbit (Owen, 1971b).

Irritation. Benzyl phenylacetate was tested at a concentration of 2% in petrolatum and produced no irritation in a 48-hr closed-patch test in 25 human subjects (Kligman, 1971).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a 2% concentration in petrolatum and produced no sensitization reaction (Kligman, 1971). Benzyl phenylacetate has not been reported to cause irritation or sensitivity (Caryl & Ericks, 1939).

References

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Owen, G. (1971a). Report to RIFM, 28 June.
Owen, G. (1971b). Report to RIFM, 1 July.

BENZYL PROPIONATE

Synonym: Benzyl propanoate.
Structure: $C_6H_5 \cdot CH_2 \cdot OCO \cdot CH_2 \cdot CH_3$.
Description and physical properties: EOA Spec. no. 209.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By esterification of benzyl alcohol with propionic acid.
Uses: In public use before the 1920s. Use in fragrances in the USA amounts to approximately 8000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·04	0·004	0·02	0·2
Maximum	0·2	0·02	0·1	0·4

Analytical data: Gas chromatogram, RIFM nos 70–43, 71–40, 73–07; infra-red curve, RIFM nos 70–43, 71–40, 73–07.

Status

Benzyl propionate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) listed benzyl propionate, giving an ADI of 5 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on benzyl propionate.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 3·3 (3·03–3·57 g/kg) (Moreno, 1973). The acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. Benzyl propionate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was irritating (Moreno, 1973). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1973).

References

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Moreno, O. M. (1973). Report to RIFM, 19 July.

BENZYL SALICYLATE

Synonym: Benzyl *o*-hydroxybenzoate.
Structure: $HO \cdot C_6H_4 \cdot CO_2 \cdot CH_2 \cdot C_6H_5$.
Description and physical properties: EOA Spec. no. 93.
Occurrence: Found in about a dozen essential oils (Gildemeister & Hoffman, 1966).
Preparation: By the interaction of sodium salicylate with benzyl chloride (Bedoukian, 1967)
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to about 300,000 lb/yr.

	Soap	*Detergent*	*Creams, lotions*	*Perfpme*
Usual	0·05	0·005	0·05	0·20
Maximum	0·1	0·01	0·10	3·00

Analytical data: Gas chromatogram, RIFM no. 2883 (HKC); infra-red curve, RIFM no. 2883 (HKC).

Status

Benzyl salicylate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included benzyl salicylate in the list of admissible artificial flavouring substances at a level of 2 ppm. The *Food Chemicals Codex* (1972) has a monograph on benzyl salicylate.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 2227 mg/kg (1925–2580 mg/kg) (Fogleman, 1970a). The acute dermal LD_{50} in rabbits was reported as 14,150 mg/kg (13,860–14,560 mg/kg) (Fogleman, 1970b).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 30% in petrolatum and produced no sensitization reactions (Kligman 1970).

Additional published data

Benzyl salicylate has been suggested as a causative agent in patients with dermatitis produced by Peru balsam (Hjorth, 1961). Hypersensitivity or excessive use may cause skin to blister, leading to an increase in pigmentation (Sulzberger & Wolf, 1942). Benzyl salicylate was reported to cause severe pruritus in six of 15 patients who applied it in a trioxsalen lotion. Reactivity to benzyl salicylate was enhanced by the phototoxic effects of methoxsalen. Only one of 14 control patients reacted to the benzyl salicylate (Kahn, 1971).

Benzyl salicylate was studied *in vitro* and *in vivo* in a group of normal subjects and in patients suffering from polymorphic light eruption, solar urticaria, porphyria or xeroderma pigmentosum. It was found that a preparation with an apparently adequate protection factor in normal subjects not infrequently failed to give comparable protection in patients with abnormal skin responses either on phototesting or during clinical use. A combined chemical and physical light-protective preparation was formulated and shown to be more effective (MacLeod & Frain-bell, 1971).

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BERGAMOT OIL EXPRESSED

Description and physical properties: EOA Spec. no. 256.
Occurrence: Found in the fruit of *Citrus bergamia* Risso et Poiteau (Fam. Rutaceae).
Preparation: By cold expression from the peel of the fresh fruit of *Citrus bergamia* Risso et Poiteau (Fam. Rutaceae).
Uses: In public use since the early 1860s. Use in fragrances in the USA amounts to approximately 300,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·05	—	0·05	0·2
Maximum	0·12	—	0·25	3·00

Status

Bergamot oil was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) included bergamot oil (*Citrus bergamia*) in the list of substances, spices and seasonings whose use is deemed admissible, with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on bergamot oil.

Biological data

Acute toxicity. The acute oral LD_{50} (on the rectified oil) was reported as > 10 g/kg in the rat (Fogleman, 1970a). The acute dermal LD_{50} (on the rectified oil) was reported as > 20 g/kg in the rabbit (Fogleman, 1970b).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 30% in petrolatum and produced no sensitization reactions (Kligman, 1970).

Phototoxicity. Severe phototoxic effects have been reported for bergamot oil expressed, using simulated sunlight on hairless mice, pigs and man (Urbach & Forbes, 1972). Severe phototoxic reactions to bergamot oil, expressed, were induced in man using natural sunlight (Wild, 1971). No phototoxic reaction has been encountered in the absence of a characteristic absorption in the ultraviolet spectrum between 312 and 320 nm. The peak may be present without phototoxic properties but so far the reverse has not been found.

Additional published data

There is an abundant literature on bergamot oil; too extensive to report in its entirety. The following references are considered important examples.

There are several articles in the dermatological literature relating bergamot oil and berloque dermatitis. The photodermatitis has been attributed to the content of 5-methoxypsoralen in the expressed oil. This may be as high as 0·39%.

Various components isolated from bergamot oil have been tested for phototoxic effects on human skin. Results suggest that berloque dermatitis is due to a single active component of bergamot, namely bergapten or 5-methoxypsoralen, and that this must be reduced to 0·001% or lower to obviate the effect. The term "bergapten dermatitis" has been suggested as a more accurate name (Marzulli & Maibach, 1970).

The use of furocoumarins in the curing of skin depigmentation problems has been reported to date back to ancient times (Fitzpatrick & Pathak, 1959). Bergamot oil is used as an effective, permanent treatment against vitiligo (Kenney, 1971). A method for the reproduction of berloque dermatitis has been developed (Harber, Harris & Leider, 1964).

Synthetic furocoumarins, which have their molecules altered with certain groups that cause a change in their absorption and fluorescent spectra, have decreased biological responses (Pathak, Fellman & Kaufman, 1960). A linear fusion of furan and coumarin

rings, as in the psoralen molecule, appears to be essential for the phototoxic response; a non-linear structure like isopsoralen has no phototoxic action (Pathak & Fitzpatrick, 1959). Studies on the various phototoxic activities of different psoralens and the mechanisms of their action have been reported (Caporale, Musajo, Rodighiero & Baccichetti, 1967).

A method for identifying, quantitating and characterizing the coumarins and furocoumarins present in the steam non-volatile portion of bergamot oil has been presented (Cieri, 1968).

One study compared the photoreactivity with DNA of psoralen and its 8-methyl, 8-methoxy, 5-methyl, 5-methoxy, 8-hydroxy and 4',5-dihydro derivatives and isopsoralen. Small quantities of tritium-labelled psoralens were irradiated at 365 nm with aqueous calf-thymus DNA at 22°C. After precipitation and re-solution of the DNA, its radioactivity was measured with a liquid scintillation counter to determine the amount of psoralen derivative linked to the DNA. The irradiation time needed to link 20% of the added psoralen to DNA was taken as the measure of photoreactivity. *In vivo* determinations of the activity of these compounds in producing phototoxicity in the skin of guinea-pigs showed a trend parallel to the photoreactivities determined *in vitro*, both types of activity increasing in the order iso-, 5-methoxy-, unsubstituted, 5-methyl- and 8-methyl psoralen. The 8-hydroxy and 4,5-dihydro derivatives were inactive both *in vivo* and *in vitro* (Rodighiero, Musajo, Dall'Acqua, Marciani, Caporale & Ciavatta, 1969). Other related papers have been contributed by Kuske (1938), Pathak, Daniels & Fitzpatrick (1962), Klaber (1942), Musajo & Rodighiero (1962) and Auerbach & Pearlstein (1971). The hairless mouse is an ideal animal for demonstrating phototoxicity (Gloxhuber, 1970).

Dermatological accidents attributed to tanning agents based on bergamot oil have been reported (Meyer, 1970).

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BERGAMOT OIL RECTIFIED

See monograph on Bergamot Oil Expressed (p.143).

Preparation: By rectification of bergamot oil expressed, under vacuum, to remove completely the furocoumarins and other related non-volatile residues.

Biological data

Acute toxicity. The acute oral LD_{50} was reported as greater than 10 g/kg in the rat (Fogleman, 1970a). The acute dermal LD_{50} was reported to be >20 g/kg in the rabbit (Fogleman, 1970b).

Irritation. Bergamot oil rectified applied full strength to intact or abraded rabbit skin produced a mild irritation (Fogleman, 1970b).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at 30% concentration in petrolatum and produced no sensitization reaction (Kligman, 1970).

Phototoxicity. No phototoxic effects have been reported for bergamot oil rectified (Urbach, 1972). No phototoxic reactions to bergamot oil rectified were induced using natural sunlight (Wild, 1971).

No phototoxic reaction has been encountered in the absence of a characteristic absorption in the ultraviolet spectrum between 312 and 320 nm. The peak may be present without phototoxic properties but so far the reverse has not been found.

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BIRCH TAR OIL

Description and physical properties: EOA Spec. no. 105.
Occurrence: Found in the tar of the bark and wood of *Betula pendula* Roth (fam. Betulaceae).
Preparation: By steam-distillation of the tar obtained by dry distillation of the bark and the wood of *Betula pendula* Roth (fam. Betulaceae).
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·001	0·002	0·02
Maximum	0·01	0·005	0·01	0·2

Status

Birch tar oil is approved by the FDA for food use (21 CFR 121.1164). The *Food Chemicals Codex* (1972) has a monograph on birch tar oil.

Biological data

Acute toxicity. The acute oral LD_{50} was reported as >5 g/kg in the rat (Moreno, 1972a). The acute dermal LD_{50} was reported as >2 g/kg in the rabbit (Moreno, 1972b).

Irritation. Undiluted birch tar oil applied to the backs of hairless mice produced no irritating effects (Urbach & Forbes, 1972). Birch tar oil applied full strength to intact or abraded rabbit skin produced irritation (Moreno, 1972b). Birch tar oil tested at a concentration of 2% in petrolatum produced no irritation in a 48-hr closed-patch test in 25 human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 2% in petrolatum and produced no sensitization reactions (Kligman, 1972).

Phototoxicity. No phototoxic effects have been reported for birch tar oil (Urbach, 1972)

Additional published data

An occasional individual may be hypersensitive to birch tar oil (Schwartz, 1934).

References

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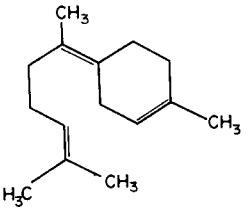
BISABOLENE

Synonym: Limene.
Structure: A mixture of isomers with the γ form (shown here) predominating:



Description and physical properties: A colourless, slightly viscous oil.
Occurrence: Reported to have been found in several essential oils, including Bisabol myrrh, lemon, lime, bergamot, camphor, Siberian pine needle oil, Chinese star anise, cardamom, sandalwood and many others (Guenther, 1949).
Preparation: From nerolidol by dehydration (Arctander, 1969).
Uses: In public use since the 1960s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·005	0·2
Maximum	0·15	0·015	0·04	1·0

Analytical data: Gas chromatogram, RIFM no. 74–167; infra-red curve, RIFM no. 74–167.

Status

Bisabolene is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974), or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1974).

Irritation. Bisabolene applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was slightly irritating (Moreno, 1974). Tested at 10% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 21 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Epstein, 1974).

Metabolism. The metabolism of monocyclic terpenes involves reduction or hydration of double bonds (Parke, 1968).

Medicinal use. Preparations containing terpenes or essential oils, including γ-bisabolene, plus surfactants and solubilization stabilizers, have been patented as solubilizing agents for cholesterol-containing biliary calculi (Igimi & Ide, 1973 & 1974).

Insects. γ-Bisabolene possessed no juvenile hormone activity when injected into pupae of the wax moth *Galleria mellonella* (Schneiderman, Krishnakumaran, Kulkarni & Friedman, 1965).

Micro-organisms. Bisabolene did not show antimicrobial activity against *Staphylococcus aureus* (Stepanov & Komarova, 1972).

Plants. The elongated growth of lettuce or cress roots was suppressed by bisabolene isolated from wormwood (Schwaer, 1962).

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BOIS DE ROSE ACETYLATED

Description and physical properties: A colourless or pale-yellow liquid with a spicy-lavender odour (Arctander, 1960).

Occurrence: The rosewood oil prior to acetylation is obtained by steam-distillation of the wood of *Aniba rosaeodora.*

Preparation: By acetylation of Bois de Rose oil (Arctander, 1960).

Uses: In public use since the 1940s. Use in fragrances in the USA amounts to less than 30,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·1	0·01	0·1	0·4
Maximum	0·3	0·03	0·3	1·2

Analytical data: Gas chromatogram, RIFM no. 72–10; infra-red curve, RIFM no. 72–10.

Status

Bois de rose acetylated is not listed by the Council of Europe (1970), FEMA, the FDA or the *Food Chemicals Codex* (1972), but the parent substance is. Bois de rose oil was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) included bois de rose oil (*Aniba rosaeodora*), in the list of temporarily admitted flavouring substances. The *Food Chemicals Codex* (1972) has a monograph on bois de rose.

Biological data

Acute toxicity. The acute oral LD_{50} was reported as >5 g/kg in the rat (Keating, 1972). The acute dermal LD_{50} was reported as >5 g/kg in the rabbit (Keating, 1972).

Irritation. Bois de rose acetylated applied undiluted to the backs of hairless mice produced no irritating effects (Urbach, 1973). At a concentration of 12% in petrolatum, it produced no irritation in a 48-hr closed-patch test in 25 human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 12% in petrolatum and produced no sensitization reactions (Kligman, 1972).

Phototoxicity. No phototoxic effects have been reported for bois de rose acetylated (Urbach, 1973).

References

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laevo-BORNYL ACETATE

Synonym: l-1,7,7,-Trimethyl-2-*endo*-acetyloxy-bicyclo-(2,2,1)-heptane.
Structure: $CH_3 \cdot CO \cdot OC_{10}H_{17}$.
Description and physical properties: EOA Spec. no. 170.
Occurrence: Found in many oils distilled from the leaves of plants of the family Pinaceae as well as in other volatile oils such as Coriander seed and Valerian root oil.
Preparation: By isolation from various pine needle oils by fractional distillation or by acetylation of *l*-borneol.
Uses: In public use since the 1940s. Use in fragrances in the USA amounts to less than 3000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·05	0·020	0·05	0·05
Maximum	0·60	0·100	0·30	0·2

Analytical data: Gas chromatogram, RIFM no. 71–43; infra-red curve, RIFM no. 71–43.

Status

l-Bornyl acetate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included *l*-bornyl acetate in the list of admissible artificial flavouring substances at a level of 2 ppm. The *Food Chemicals Codex* (1972) has a monograph on *l*-bornyl acetate.

Biological data

Acute toxicity. An acute oral LD_{50} was reported as >5000 mg/kg in the rat (Owen, 1971a). The acute dermal LD_{50} was reported as >10 ml/kg in the rabbit (Owen, 1971b).

Irritation. l-Bornyl acetate tested at a concentration of 2% in petrolatum produced no irritation in a 48-hr closed-patch test in 25 human subjects (Kligman, 1971).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 2% in petrolatum and produced no sensitization reactions (Kligman, 1971).

Additional published data

Various tobacco leaf and tobacco smoke components and related synthetic compounds were tested for co-carcinogenic activity on mouse skin by simultaneous and repeated application with benzo[*a*]pyrene. The three corresponding bornyl esters showed no co-carcinogenic activity (Van Duuren, Blazej, Goldschmidt, Katz, Melchionne & Sivak, 1971).

References

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BORNYL ISOVALERATE

Synonym: Bornyl 3-methyl butyrate (and other isomers).
Structure: $C_{10}H_{17} \cdot OCO \cdot CH_2 \cdot CH(CH_3)_2$.
Description and physical properties: Colourless liquid with an odour and taste of valerian and camphor (*Merck Index*, 1968).
Occurrence: Bornyl isovalerate has been reported in valerian root oil (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: By esterification (simple heating) of borneol with isovaleric acid (Arctander, 1969).
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·01	0·1
Maximum	0·1	0·01	0·05	0·4

Analytical data: Gas chromatogram, RIFM no. 72–85; infra-red curve, RIFM no. 72–85.

Status

Bornyl isovalerate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included bornyl isovalerate in the list of admissible artificial flavouring substances at a level of 15 ppm.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Denine, 1973).

Irritation. Bornyl isovalerate tested at 4% in petrolatum produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1972).

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BROMSTYROL

Synonym: α-Bromo-β-phenylethylene.
Structure: $C_6H_5 \cdot CH:CHBr$.
Description and physical properties: EOA Spec. no. 150.
Occurrence: Apparently has not been reported to occur in nature.
Preparation: By the action of aqueous alkali on cinnamic acid dibromide.
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·001	0·002	0·001
Maximum	0·02	0·01	0·01	0·04

Analytical data: Gas chromatogram, RIFM no. 71–44; infra-red curve, RIFM no. 71–44.

Status

The Council of Europe (1970) included bromstyrol in the list of temporarily admissible artificial flavouring substances.

Biological data

Acute toxicity. An acute oral LD_{50} in rats was reported as 1·25 ml/kg (0·82–189 ml/kg) (Levenstein, 1972a). The acute dermal LD_{50} was reported as >6 ml/kg in the rabbit (Levenstein, 1972b).

Irritation. Bromstyrol tested at a concentration of 4% in petrolatum produced no irritation in a 48-hr closed-patch test in 25 human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1972).

Additional published data

Bromstyrol is one of the strongly irritant perfume materials (Thomssen, 1947). Bromstyrol should be excluded from preparations for infants (Richardson, 1937).

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n-BUTYL ANTHRANILATE

Synonym: *n*-Butyl *o*-aminobenzoate.
Structure: $CH_3 \cdot [CH_2]_3 \cdot OCO \cdot C_6H_4 \cdot NH_2$.
Description and physical properties: A colourless or very pale straw-coloured liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By the interaction of isatoic anhydride with butyl alcohol in the presence of alkali (Bedoukian, 1967).
Uses: In public use since the 1940s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·005	0·1
Maximum	0·15	0·015	0·03	0·4

Analytical data: Gas chromatogram, RIFM no. 74–51; infra-red curve, RIFM no. 74–51.

Status

Butyl anthranilate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included butyl anthranilate, at a level of 10 ppm, in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Wohl, 1974).

Irritation. *n*-Butyl anthranilate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Wohl, 1974). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 24 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Epstein, 1974).

Metabolism. Esters of benzoic acid are presumably either hydrolysed and then metabolized according to the normal pattern for the alcohol and acid produced, or possibly in some cases the ring may be hydroxylated and the product excreted as a glucuronide or sulphate ester (Fassett, 1963). *n*-Butanol and isobutanol are rapidly oxidized *in vivo*, presumably to the aldehyde and acid (Williams, 1959); only small amounts (2–4%) were excreted by rabbits as the glucuronic acid conjugates (Kamil, Smith & Williams, 1953).

Micro-organisms. *n*-Butyl anthranilate at 250 ppm completely inhibited the growth of *Erwinia amylovora* and *Xanthomonas malvacearum* colonies and partially inhibited the growth of *Staphylococcus aureus* and *Aspergillus niger*, but did not inhibit the growth of *Escherichia coli*; at 60 and 15 ppm, the ester demonstrated minimum effectiveness and was of no commercial interest (Heindel, Lemke, Lemke & Fish, 1968).

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4-*tert*-BUTYLCYCLOHEXANOL

Structure: $HO \cdot C_6H_{10} \cdot C(CH_3)_3$.

Description and physical properties: White needles or crystalline powder with a musty, woody odour.

Occurrence: Has apparently not been reported to occur in nature.

Preparation: From 4-*tert*-butylphenol by hydrogenation (Arctander, 1969).

Uses: In public use since the 1960s. Use in fragrances in the USA amounts to approximately 10,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·03	0·12
Maximum	0·2	0·02	0·05	0·4

Analytical data: Gas chromatogram, RIFM no. 72–86; infra-red curve, RIFM no. 72–86.

Status

4-*tert*-Butylcyclohexanol is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1970), nor in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 4·2 g/kg (3·62–4·87 g/kg) (Denine, 1973). The acute dermal LD_{50} in rabbits was reported as > 5 g/kg (Denine, 1973).

Irritation. 4-*tert*-Butylcyclohexanol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Denine, 1973). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1973).

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Kligman, A. M. (1973). Report to RIFM, 9 May.

p-tert-BUTYLCYCLOHEXANONE

Structure: $O{:}C_6H_9 \cdot C(CH_3)_3$.
Description and physical properties: Colourless or white crystals.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By hydrogenation of *p-tert*-butylphenol. Care must be taken that no free *p-tert*-butylphenol remains, because it is a sensitizer and depigmenting agent (Opdyke, 1974).
Uses: Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·003	0·1
Maximum	0·2	0·02	0·03	0·6

Analytical data: Gas chromatogram, RIFM no. 74–169; infra-red curve, RIFM no. 74–169.

Status

p-tert-Butylcyclohexanone is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974), or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits were reported to be 5 g/kg (Wohl, 1974).

Irritation. *p-tert*-Butylcyclohexanone applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Wohl, 1974). Tested at 6% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 22 volunteers. The material was tested at a concentration of 6% in petrolatum and produced no sensitization reactions (Epstein, 1974).

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BUTYL ISOBUTYRATE

Synonym: *n*-Butyl 2-methylpropanoate.
Structure: $CH_3 \cdot [CH_2]_3 \cdot OCO \cdot CH(CH_3)_2$.
Description and physical properties: EOA Spec. no. 258.
Occurrence: Reported to be found in Roman camomile essential oil (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: By the esterification of isobutyric acid and *n*-butyl alcohol.
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to approximately 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·01	0·1
Maximum	0·1	0·01	0·03	0·4

Status

Butyl isobutyrate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included butyl isobutyrate at a level of 40 ppm (except for chewing gum) in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Levenstein, 1974).

Irritation. Butyl isobutyrate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Levenstein, 1974). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1974a). Retested at 4% in petrolatum, it again produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1974b).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced a sensitization reaction in one of the 25 (Kligman, 1974a; see Preface Note no. 2). When retested by the same maximization test in 50 volunteers at a concentration of 4% in petrolatum, it produced no sensitization reactions (Kligman, 1974b).

Metabolism. Isobutyrates are hydrolysed to materials that are or are readily converted to normal dietary constituents (Fassett, 1963). When 1 g butyl isobutyrate was fed into the rumen of a cow, 0·016% was transferred to the milk, reaching a maximum level of 300 μg/litre after 2–4 hr (Honkanen, Karvonen & Virtanen, 1964).

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p-tert-BUTYLPHENOL

Synonym: 1-Hydroxy-4-*tert*-butylbenzene.

Structure: $HO \cdot C_6H_4 \cdot C(CH_3)_3$.

Description and physical properties: White needle-like crystals with a phenolic odour (Arctander, 1969).

Occurrence: Has apparently not been reported to occur in nature.

Preparation: By heating phenol with isobutanol in the presence of zinc chloride (*Merck Index*, 1968).

Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 2000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·003	0·08
Maximum	0·1	0·01	0·03	0·1

Analytical data: Gas chromatogram, RIFM no. 72–87; infra-red curve, RIFM no. 72–87.

Status

p-tert-Butylphenol is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1970), nor in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 1·4 g/kg (0·56–3·50 g/kg) (Denine, 1973). The acute dermal LD_{50} in rabbits was reported as > 5 g/kg (Denine, 1973).

Irritation. p-tert-Butylphenol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was irritating (Denine, 1973). Tested at 1% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization and depigmentation of human skin. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 1% in petrolatum and produced no sensitization reactions (Kligman, 1973). There is an abundant literature dealing with the well-established sensitization and depigmentation properties of *p-tert*-butylphenol and/or closely related material (Beetz, 1971; Bleehen, Pathak, Hori & Fitzpatrick, 1968; Calnan, 1973; Calnan & Harman, 1959; Gaul, 1960; Gellin, Possick & Perone, 1970; Hasegawa, Levit & Bluefarb, 1958; Kahn, 1970; McGuire & Hendee, 1971; Malten, 1958, 1964, 1967 & 1973; Malten, Seutter, Hara & Nakajima, 1971; Matz & Blank, 1959; Odom & Stein, 1973).

Metabolism. p-tert-Butylphenol is believed to be excreted by dogs in the form of a conjugate with sulphuric acid; presumably it behaves as a typical phenol (Williams, 1959).

Enzyme induction. The relative abilities of substituted phenols to induce drug-metabolizing enzymes were measured either 24 hr after a single dose or after 6–10 daily doses. The phenols carried various combinations of substituents, one of which was the *tert*-butyl group. When the effect was measured 24 hr after a single dose, a close relationship was found between the induction of drug-metabolizing enzymes and the lipid–water partition coefficient of the test compound. When the effect was measured after six daily doses, this relationship was less distinct; further dosing could lead either to an accentuation or a diminution of the effect. Many of the substituted phenols also induce uridine diphosphate glucose dehydrogenase, an effect apparently unrelated either to the lipid–water partition coefficient or to the induction of drug-metabolizing enzymes (Gilbert, Martin, Gangolli, Abraham & Golberg, 1969).

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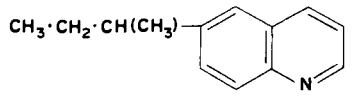
sec-BUTYLQUINOLINE*

Synonym: 6- and 8-*sec*-butylquinoline (80/20) (often erroneously called isobutylquinoline in the trade).
Structure:



Description and physical properties: A colourless liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: From acrolein and secondary butylaniline followed by dehydration and oxidation (Bedoukian, 1967).
Uses: Use in fragrances in the USA amounts to approximately 4000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	—	—	—	—
Maximum	—	—	—	0·2

Analytical data: Gas chromatogram, RIFM no. 72-169; infra-red curve, RIFM no. 72-169.

Status

sec-Butylquinoline is not included in the listings of the FDA, FEMA or the Council of Europe (1974), or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 1·02 g/kg (0·78–1·26 g/kg) and the acute dermal LD_{50} in rabbits was reported as > 5 g/kg (Moreno, 1973).

Irritation. *sec*-Butylquinoline applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Moreno, 1973). Tested at 2% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 2% in petrolatum and produced no sensitization reactions (Kligman, 1973).

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*ERRATUM: Please replace monograph entitled Isobutyl quinoline (*Food and Cosmetics Toxicology* 1976, **14**, 311) with this corrected monograph.

CADE OIL RECTIFIED (JUNIPER TAR)

Description and physical properties: A dark red-brown, clear, viscous liquid. The main constituents of cade oil are *d*-cadinene and *l*-cadinol (Guenther, 1952).
Preparation: By destructive distillation of the chopped wood of *Juniperus oxycedrus* L. (Fam. Pinaceae) (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Uses: In public use before the 1920s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·003	0·04
Maximum	0·05	0·005	0·02	0·2

Status

The Council of Europe (1974) included cade in the list of flavouring substances temporarily admitted for use, possibly with a limitation on the active principle in the final product. Oil of cade or juniper tar has been used as a dermatological medicament, as a keratolytic and antipruritic agent (*Merck Index*, 1968; *National Formulary*, 1970).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Wohl, 1974). The acute oral LD_{50} of juniper tar to rats was found to be 8014 mg/kg (Bär & Griepentrog, 1967; Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964). Toxic signs included depression and gastro-intestinal irritation (Jenner *et al.* 1964).

Irritation. Cade oil applied undiluted to the backs of hairless mice was not irritating (Urbach & Forbes, 1974). Applied full strength to intact or abraded rabbit skin for 24 hr under occlusion, it was not irritating (Wohl, 1974). Tested at 2% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 2% in petrolatum and produced no sensitization reactions (Kligman, 1974). Cade oil is reported to have slight local activity as an allergen (Sax, 1968).

Phototoxicity. No phototoxic effects were reported for undiluted cade oil on hairless mice and swine (Urbach & Forbes, 1974).

Micro-organisms. Juniper tar oil alone or combined with olive oil (1:1) showed some *in vitro* antibacterial activity against *Micrococcus citreus*, *Bacillus brevis* and *M. pyogenes*, but not against *Salmonella typhosa* and *Proteus morgani* (Maruzzella & Henry, 1958).

Vapour of cade oil (rectified, USP) showed antibacterial activity against *Mycobacterium avium*, but not against *Escherichia coli*, *Staphylococcus aureus*, *B. subtilis*, *Streptococcus fecalis* or *S. typhosa* (Maruzzella & Sicurella, 1960). Juniper tar oil exhibited *in vitro* antifungal activity against 13 out of 15 fungi tested (Maruzzella & Liguori, 1958). Cade oil (rectified, USP) showed slight inhibitory activity against three wood-destroying fungi (Maruzzella, Scrandis, Scrandis & Grabon, 1960).

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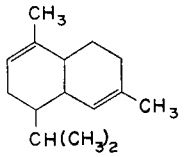
CADINENE

Synonym: 3,4,7,8,9,10-Hexahydro-4-isopropyl-1,6-dimethylnaphthalene.
Structure: α-Cadinene has the following structure but several isomers occur in nature with the double bond in various positions; unconjugated:



Description and physical properties: A colourless slightly viscous oil generally carrying the odour of the oil from which it is derived (Gildemeister & Hoffman, 1960).
Occurrence: Cadinene in its isomeric forms occurs in over 150 essential oils (Gildemeister & Hoffman, 1960).
Preparation: By isolation from various essential oils (Gildemeister & Hoffman, 1960).
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to less than 4000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0.001	0·01	0·04
Maximum	0·05	0·005	0·05	0·5

Analytical data: Gas chromatogram, RIFM no. 72–11; infra-red curve, RIFM no. 72–11

Status

Cadinene is approved by the FDA for food use (21 CFR 121.1164).

Biological data

Acute toxicity. The acute oral LD_{50} was reported to be >5 g/kg in the rat (Keating, 1972). The acute dermal LD_{50} was reported to be >5 g/kg in the rabbit (Keating, 1972).

Irritation. Cadinene tested at a concentration of 10% in petrolatum produced no irritation in a 48-hr closed-patch test in 25 human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 10% petrolatum and produced no sensitization reactions (Kligman, 1972).

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CAJEPUT OIL

Synonym: Cajuput oil.

Description and physical properties: EOA Spec. no. 22. The main constituent of cajeput oil is cineole (Guenther, 1950).

Occurrence: Found in the leaves, branches and twigs of *Melaleuca leucadendron* L. (Fam. Myrtaceae) and other Melaleuca species (Guenther, 1950).

Preparation: By steam distillation of the leaves and twigs of the Melaleuca varieties.

Uses: In public use since the 1850s. Use in fragrances in the USA amounts to less than 1000 lb/yr. Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·04
Maximum	0·1	0·01	0·03	0·4

Analytical data: Gas chromatogram, RIFM no. 74–53; infra-red curve, RIFM no. 74–53.

Status

Cajeput oil was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1163). The Council of Europe (1974) included cajeput oil in the list of substances, spices and seasonings deemed admissible for use with a possible limitation of the active principle in the final product.

Biological data

Acute toxicity. The oral LD_{50} value in rats was reported as 3·87 g/kg (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964) and the acute dermal LD_{50} value in rabbits as more than 5 g/kg (Wohl, 1974).

Irritation. Undiluted cajeput oil was not irritating when applied to the backs of hairless mice and swine (Urbach & Forbes, 1974) or to intact or abraded rabbit skin for 24 hr under occlusion (Wohl, 1974). Tested at 4% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 22 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Epstein, 1974).

Phototoxicity. No phototoxic effects were reported for undiluted cajeput oil on hairless mice and swine (Urbach & Forbes, 1974).

Micro-organisms. Cajeput oil showed antibacterial activity against *Micrococcus citreus*, *Bacillus brevis* and *M. pyogenes* but not against *Salmonella typhosa* and *Proteus morgani* either when tested alone or in 1:1 mixtures with eucalyptus oil or olive oil (Maruzzella & Henry, 1958). The vapour of cajeput oil showed antibacterial activity against *Mycobacterium avium* but not against *Escherichia coli*, *Staphylococcus aureus*, *B. subtilis*, *Streptococcus fecalis*, and *S. typhosa* (Maruzzella & Sicurella, 1960). Cajeput oil exhibited moderately strong *in vitro* antifungal activity against all of 15 fungi tested (Maruzzella & Liguori, 1958).

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CALAMUS OIL

Description and physical properties: EOA Spec. no. 101. Typical components of calamus oil are *d*-α-pinene, camphene, cineole, camphor, calamene, calamenol, asaronaldehyde, eugenol, methyl-eugenol, asarone, calamol, calameone and azulene (Guenther, 1952).
Occurrence: Found in the root of the plant *Acorus calamus* L. (Fam. Araceae).
Preparation: By steam distillation of either the fresh root or the unpeeled dried root of the plant.
Uses: In public use before 1860. Use in fragrances in the USA amounts to less than 2000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·04
Maximum	0·1	0·01	0·02	0·4

Status

The Council of Europe (1974) included calamus in the list of flavouring substances temporarily admitted for use, possibly with a limitation on the active principle in the final product. However, because a 2-yr feeding study carried out in rats by the US Food and Drug Administration indicated that the Jammu variety of calamus oil (Indian) displayed carcinogenic potential, any food or drug within the jurisdiction of the US Federal Food, Drug, and Cosmetic Act containing any form of calamus will be regarded as in violation of the Act (Food and Drug Administration, 1968).

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 777 mg/kg by Jenner, Hagan, Taylor, Cook & Fitzhugh (1964) and as 888 mg/100 g rat (corresponding to 622 g/70-kg man) by von Skramlik (1959), the signs of toxicity in the latter study being convulsions and severe liver and kidney damage, although animals that survived for 3 days recovered completely with no permanent liver or kidney changes. The acute dermal LD_{50} in guinea-pigs was reported as >5 g/kg (Moreno, 1974). The acute LD_{50} of the steam-volatile fraction of the roots and rhizomes of Indian *A. calamus* oil injected ip into rats was found to be 221 mg/kg, and the treatment caused convulsions (Dandiya & Cullumbine, 1959). An oleoresin from rhizomes of Indian *A. calamus* injected ip into mice was toxic in doses of 0·4 and 0·8 g/kg (Dandiya, Baxter & Cullumbine, 1958).

Subacute toxicity. Dietary levels of 2500, 5000 and 10,000 ppm fed to rats for 18 wk depressed growth and caused macroscopic and microscopic liver changes, the effects being less severe at the lower levels; heart changes with minimal to slight myocardial degeneration, characterized by varying degrees of necrosis of muscle fibres, early fibrosis and infiltration with mononuclear cells, were also observed at all levels (Hagan, Hansen, Fitzhugh, Jenner, Jones, Taylor, Long, Nelson & Brouwer, 1967).

Irritation. Undiluted calamus oil was not irritating when applied to the backs of hairless mice and swine (Urbach & Forbes, 1974) or to intact or abraded rabbit and guinea-pig skin for 24 hr under occlusion (Moreno, 1974). Tested at 4% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 23 volunteers. The material (RIFM no. 74-54) was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Epstein, 1974). Bath preparations containing calamus oil have been reported to cause skin erythema (Finkenrath, 1941), and Tulipan (1938) reported dermatitis in hypersensitive individuals. Fifty patients who had reacted to Peruvian balsam, wood tars, colophony and turpentine did not react to calamus oil, and no sensitization reactions were produced by calamus oil in 200 consecutive patients with dermatitis (Rudzki, Grzywa & Bruo, 1976).

Phototoxicity. No phototoxic effects were reported for undiluted calamus oil on hairless mice and swine (Urbach & Forbes, 1974).

Carcinogenicity. In a 2-yr feeding study of the Jammu variety of calamus oil in rats, all the dietary levels tested (500, 1000, 2500 and 5000 ppm) caused growth depression, gross and microscopic (degenerative and regenerative) changes in the liver and damage to the heart. Malignant tumours developed in the duodenum at all dietary levels after wk 59 (Taylor, Jones, Hagan, Gross, Davis & Cook, 1967).

Percutaneous absorption. Calamus oil was not absorbed within 2 hr of application to the intact shaved abdominal skin of the mouse (Meyer & Meyer, 1959). The oil did not aid deep penetration of Rhodamine B into guinea-pig skin (Meyer, 1965).

Micro-organisms. Calamus oil exhibited only slight fungistatic or fungicidal activity against nine of 15 fungi in tests by Maruzzella & Liguori (1958), and slightly inhibited the growth of three wood-destroying fungi (Maruzzella, Scrandis, Scrandis & Grabon, 1960). The oil showed no activity against six bacteria tested by Maruzzella & Sicurella (1960), but Kar & Jain (1971) reported that the essential oil of *A. calamus* showed *in vitro* bactericidal activity against 13 of 15 bacteria tested. In a study of the antifolic-acid activity of anti-epileptic drugs, oil of *A. calamus* repressed the growth of *Lactobacillus casei* and *Streptococcus faecalis*; the repression was complete at 3200 μg/6 ml but could be reversed at lower concentration (Patil, Chitre & Sheth, 1966).

Pharmacology. European Oleum Calami (from *A. calamus*) demonstrated strong spasmolytic properties when tested on smooth muscle of isolated rat and rabbit intestine, cat trachea, rabbit aorta and rat uterus, and reduced guinea-pig mortality caused by histamine inhalation from 83 to 16% (Maj, Malec & Lastowski, 1966).

The essential oil of Indian *A. calamus* showed anticonvulsant, antiveratrinic and anti-arrhythmic activity (Madan, Arora & Kapila, 1960). Like quinidine, it combated experimental auricular fibrillation in dogs, prolonged the conduction time and refractory period in the electrocardiogram in cats, antagonized the action of dilute solutions of veratridine on frogs (*Rana tigrina*) and had an anticonvulsant action against experimental shock, but was not effective in modifying convulsions produced by metrazole.

At concentrations of 50–100 μg/ml the essential oil of *A. calamus* (European) produced spasmolytic effects, considered to be chiefly myotropic, on isolated smooth muscles from rabbits, guinea-pigs and cats (Shipochliev, 1968a). A 5% emulsion of this oil given iv to cats in a dose of 5–10 mg/kg in physiological saline increased respiratory volume and depressed blood pressure, while guinea-pigs given the oil ip in a dose of 35 mg/kg after preliminary sensitization with egg albumin went into anaphylactic shock (Shipochliev, 1968a). General depression without ataraxia was observed in mice given ip injections of 50 mg/kg as the 5% emulsion, with or without preliminary ip treatment with 150 mg iproniazid phosphate/kg 24 hr earlier. The effect on the central nervous system did not resemble that of reserpine (Shipochliev, 1968b).

An oleoresin from rhizomes of Indian *A. calamus* injected ip into mice at 0·2 g/kg showed only slight sedative activity but considerable potentiation of the sedative activity of sodium pentobarbitone (Dandiya *et al.* 1958).

The steam-volatile fraction of the roots and rhizomes of Indian *A. calamus* reduces the body temperature of mice and prolongs sleeping time when used with pentobarbitone, hexobarbitone and ethanol. It exacerbates the tonic seizures provoked by convulsive doses of metrazole in rats and potentiates the action of reserpine in reducing amphetamine toxicity in mice excited by aggregation. In anaesthetized cats, iv injection of the oil causes a fall in blood pressure which is not prevented by vagal, adrenergic, or ganglionic blockade and does not appear to be due to any nervous mechanism. The oil causes dilation of the blood vessels of the splanchnic area in cats, constricts the blood vessels of the hind legs of frogs, and prevents the action of acetylcholine, histamine, and barium chloride on isolated guinea-pig ileum (Dandiya & Cullumbine, 1959).

Indian acorus oil (50 mg/kg) potentiated pentobarbitone hypnosis in mice; the potentiating action was antagonized by LSD and dibenzyline hydrochloride either separately or combined (Malhotra, Das & Dhalla, 1962). The same dose delayed the rate of disappearance of sodium pentobarbitone from the blood in dogs.

The content of 5-hydroxytryptamine and noradrenaline in the rat brain was depleted by ip injection of Indian acorus oil (100 mg/kg), and it has been suggested that the mechanism of action of the oil may be similar to that of reserpine (Malhotra, Prasad, Dhalla & Das, 1961).

In subacute and acute experiments in mice, rats, cats and rabbits, the essential oil from *A. calamus* (European) exerted a significant sedative and analgesic effect, reduced spontaneous mobility, potentiated the effect of morphine, caused ptosis and reduced body temperature and blood pressure (Maj, Malec & Lastowski, 1964). Enhancement of the effect of barbiturates did not result from changes in barbiturate metabolism. The oil did not exert cataleptic effects nor reduce the toxicity of amphetamine, and its effect was not influenced by iproniazid, as was characteristic of the oil of Asiatic origin. The oil studied was 12–16% as toxic as the Asiatic oil.

Aqueous and alcoholic extracts of the rhizomes of *A. calamus* (European) were administered ip to mice, rats, rabbits, and cats by Maj, Lastowski & Lukowski (1965). The aqueous extract had a sedative effect in mice in doses up to 4 g/kg. The minimum lethal dose of the alcoholic extract in mice was 4 g/kg and the LD_{100} was 8 g/kg. The extracts had no cataleptic or analgesic action in mice in doses up to 1·0 g/kg, did not potentiate the cataleptic action of chlorpromazine and did not show anticonvulsant action in mice and rats. Their effect was not influenced by iproniazid, but they did exhibit hypothermic and hypotensive activity. Only the alcoholic extract potentiated the action of narcotics and diminished the toxicity of amphetamine in mice housed in groups. Both extracts administered in doses of 10–400 mg/kg lowered blood pressure in rabbits and cats by 10–70% (Maj *et al.* 1965).

Indian acorus oil (10–100 mg/kg) administered ip was found to have a sedative–tranquilizing action when administered ip to rats, mice, cats, dogs and monkeys, but vomiting was observed in the latter three species (Dhalla & Bhattacharya, 1968). Acorus oil (10–150 mg) given ip to mice depressed

both spontaneous and forced motor activities, with a greater effect on the former. In cats, flexor, patellar and lingomandibular reflexes were inhibited to a varying degree by iv injection of 10–100 mg acorus oil/kg, while the drug did not block the neuromuscular junction or the facilitation of patellar response due to the stimulation of reticular formation. At 0·5 mg/ml, acorus oil inhibited monoamine oxidase activity and stimulated *D*- and *L*-amino acid oxidases *in vitro*. It was suggested that acorus oil might effect its neuropharmacological actions at the spinal cord or subcortical levels of the central nervous system (Dhalla & Bhattacharya, 1968).

Anti-adrenergic activity of Indian acorus oil in the central nervous system was demonstrated by its action in antagonizing the agitational symptoms induced by dexamphetamine in mice, cats, rats, dogs and monkeys, and by the dexamphetamine blockage of its potentiating action on hexobarbitone sleeping time (Bhattacharya, 1968). The oil inhibited the conditioned avoidance response in rats, the effects being more prominent at dose levels inhibiting also the unconditioned response, suggesting some type of ataxic motor impairment (Bhattacharya, 1968).

Medicinal use. Calamus has been used in therapeutic baths for the treatment of weakness and paralysis, including diseases of the bones and muscles such as rickets and poliomyelitis (Birggal, 1969). As the root, oil or extract, it has also been used in drug preparations as a carminative and as a topical counter-irritant (Food and Drug Administration, 1968). Rhizomes of *A. calamus* have been widely used to treat various mental and nervous disorders in India in the Ayurvedic system of medicine (Malhotra *et al.* 1962).

Pest control. Acorus oil has insecticidal and leech-repellent properties which may be synergized by synthetic pine oil (Perti & Agarwal, 1969; Raquibuddowla, Siddiqueullah, Dewan & Haq, 1967; Saxena, Khalsa & Pillai, 1969).

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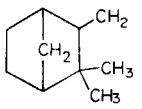
CAMPHENE

Synonyms: 3,3-Dimethyl-2-methylenenorcamphene; 2,2-dimethyl-3-methylenenorbornane.
Structure:



Description and physical properties: A colourless, granular-crystalline, tenacious mass.
Occurrence: Has been reported to occur in over 150 essential oils (Gildemeister & Hoffman, 1960).
Preparation: From α-pinene via the hydrochloride and subsequent treatment with alkali.
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to about 6000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·08
Maximum	0·1	0·01	0·05	0·4

Analytical data: Gas chromatogram, RIFM no. 74–130; infra-red curve, RIFM no. 74–130.

Status

Camphene was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included camphene at a level of 0·5 ppm in the list of artificial flavouring substances that may be added temporarily to foodstuffs without hazard to public health.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as >5 g/kg (Moreno, 1974). The acute dermal LD_{50} value in rabbits was reported as >2·5 g/kg (Moreno, 1974).

Irritation. Camphene applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was slightly irritating (Moreno, 1974). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Epstein, 1974). In a study of the sensitizing properties of 17 terpenes and related compounds present in essential oils, camphene was found not to be a sensitizer for human skin (Woeber & Krombach, 1969).

Metabolism. Unlike most terpenes, camphene forms a glycol in the rabbit. The compound excreted is camphene glycol monoglucuronide, which was isolated as a laevorotatory potassium salt. On hydrolysis with acid, the compound breaks up to glucuronic acid and camphene glycol, which itself undergoes further change to camphenilaldehyde (Fromm, Hildebrandt & Clemens, 1902–3; Williams, 1959).

When 0·6 μg camphene/kg body weight (0·05 ml camphene in 2·5 ml 1,2-propanediol) was injected iv into a human subject or a young pig, 3·6% was eliminated unchanged in the expired air within 3 hr, the major portion appearing within 5 min and 90% within 30 min (Römmelt, Zuber, Dirnagl & Drexel, 1974). Camphene absorbed through the skin was also partially excreted in the expired air, appearing within 20 min of the start of a 30-min full bath containing 150 ml pine bath oil (pine needle-Pinus pumilio oil, Kneipp-Heilmittelwerk, Würzburg) in 450 litres water and still being detectable 1 day after the bath, although inhalation of volatiles from the bath was prevented. A maximum level was reached after 75 min, 60% was exhaled within the first 2 hr and a total of 0·67 μl was exhaled during the first 5 hr. Suggested major routes of elimination of camphene include its solution unchanged in the bile with excretion through the intestinal tract, and glucuronide formation with excretion via the kidney (Römmelt *et al.* 1974).

Camphene is converted by *Aspergillus niger* into 2-nonene-2,3-dicarboxylic acid anhydride, with formation of diacetone alcohol as an artefact (Bhattacharyya, Prema, Dhavalikar & Ramachandran, 1963).

Percutaneous absorption. The permeability of human skin to terpenes was studied by Römmelt *et al.* (1974), who demonstrated percutaneous absorption from baths (Kneipp) containing pine oil additives by measuring camphene and other terpene components in the expired air of young pigs and one human subject. As reported above, a human subject immersed in a bath containing pine

needle oil exhaled terpenes, including 0·67 μl camphene, within 5 hr. Since 3·6% of an iv injected dose of camphene was detected in the expired air, a constant of 81 μl/cm²/hr was calculated for the percutaneous absorption of camphene from the bath. The total quantity of Kneipp pine oil extract absorbed through the skin of an adult person from a 20-min full bath containing 1 ml oil/10 litres bath water was estimated to be 0·04 mg, which must be considered to be within a range capable of producing therapeutic effects.

Inhalation. Inhalation of camphene by urethanized rabbits in doses of 3–27 mg/kg (added to the water vapourizer) produced a significant increase in the volume output of respiratory tract fluid, accompanied by a decrease in specific gravity and an increase in total solids. The expectorant action began to disappear following inhalation of a dose of 81 mg/kg, which is well below the level detectable by odour (243 mg/kg) and far below the probably fatal dose (Boyd & Sheppard, 1970).

Pharmacology. Oral administration of camphene (260 mmols/kg) to rats increased bile flow by 50% 4 hr after administration (Mörsdorf, 1966). Development of atheromatosis of the aorta in rabbits fed 1 g cholesterol/day for 3 months was considerably inhibited by simultaneous administration of a mixture of terpenes including camphene, injected sc in a dose of 1 ml every other day for 6 wk and then given orally in doses of 2 ml/day (Benkö, Macher, Szarvas & Tiboldi, 1961). The effect of 1 g cholesterol/day for 8 wk in the diet of rabbits in increasing the number and volume of mast cells in the aortic adventitia and increasing the total lipid content of the aortic wall was slightly enhanced by the simultaneous addition of 1·1 g camphene/day (Lesznyak, Benko, Szabo & Muller, 1972). This camphene treatment also decreased the lipid accumulation in the liver, but had no effect on the cholesterol-induced atheromatosis of the aorta (Benko, Szabo, Muller & Lesznyak, 1972).

Insects. Lethal concentrations (LC_{50}) of camphene were found to be 0·9221 and 0·5434 mg/cm³ for the adult spruce bark beetles *Ips typographus* and *I. amitinus*, respectively (Vasechko & Kuznetsov, 1969), and 0·6129 mg/cm³ for larvae of the flour beetle *Tribolium destructor* (Vasechko, Kuznetsov, Smelyanets & Guznenok, 1970). The LD_{50} of camphene for *Tanymecus palliatus* (grey sugar-beet weevil) was 0·760 mg/g; the toxic effects of camphene differed for mites and mite eggs (Rudnev, Smelyanets & Voitenko, 1970). Because of their toxicity and repellency, terpenoids such as camphene in the tissues of pine were found to be important natural protectors against insects, mites and fungi. Camphene was toxic to the spider mite, *Tetranychus telarius* (Rudnew & Smeljanez, 1969).

Several articles discuss the insect-attracting and repelling properties of camphene. Camphene and other host terpenes of the Douglas fir and other conifers are attractants for bark beetles, Dendroctonus (Pitman & Vite, 1971; Rudinsky, 1966; Rudinsky, Furniss, Kline & Schmitz, 1972) and Ips (Rudinsky, Novák & Švihra, 1971) and their predators, acting alone or enhancing the attraction of frontalin and other insect pheromones. Camphene acts as a repellent for silkworm larvae, *Bombyx mori* (Ishikawa & Hirao, 1965), for pea aphids, *Macrosiphum pisi* (Thomas & Chamberlain, 1959) and for Douglas fir beetles, *Dendroctonus pseudotsugae*, at close range (Rudinsky, 1966).

Micro-organisms. When tested as a saturated vapour (16·7 mg/litre) or as a substrate component (2·5%), camphene caused some inhibition of the growth of five fungi, including four species of Ceratocystis and *Fomes annosus* (Cobb, Krstic, Zavarin & Barber, 1968). A saturated atmosphere of *dl*-camphene caused 62–85% inhibition of linear growth of the wood-inhabiting fungi *Trichoderma viride*, *Peniophora gigantea*, *Lenzites saepiaria* and *Schizophyllum commune*, and 43% inhibition of *Ceratocystis minor* (De Groot, 1972). Camphene did not show antimicrobial activity against *Staphylococcus aureus* (Stepanov & Komarova, 1972). It promoted slightly the activity of microbes of sheep and deer rumen; thus its presence in forage would not discourage voluntary intake (Oh, Sakai, Jones & Longhurst, 1967).

Cells. Camphene dissolved in dimethylformamide and water at 1, 10, and 100 μg/ml showed no cytotoxic effects on HeLa cells in monolayer culture (Nachev, Zolotovitch, Siljanowska & Stojcev, 1968).

Plant growth. Camphene and other plant terpenes inhibit the growth of other plants by suppressing mitosis after they have been absorbed into the root from the soil (Muller, 1966).

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CAMPHOR OIL BROWN

Description and physical properties: Pale yellow-to-brown liquid. The chief constituent of camphor oil brown is safrole (Guenther, 1950).

Occurrence: Found in the trees of *Cinnamomum camphora* (L.) Nees & Ebermeier (Fam. Lauraceae) (*Fenaroli's Handbook of Flavor Ingredients*, 1975).

Preparation: By vacuum rectification of filtered true camphor oil (*Fenaroli's Handbook of Flavor Ingredients*, 1975).

Uses: In public use before the 1920s. Use in fragrances in the USA amounts to approximately 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·005	0·04
Maximum	0·2	0·02	0·05	0·4

Analytical data: Gas chromatogram, RIFM no. 75–8; infra-red curve, RIFM no. 75–8.

Status

Camphor oil brown is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974) or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 2·53 ml/kg and the acute dermal LD_{50} value in rabbits exceeded 4 ml/kg (Levenstein, 1975).

Irritation. Undiluted camphor oil brown was not irritating when applied to the backs of hairless mice and swine (Urbach & Forbes, 1975) or to intact or abraded rabbit skin for 24 hr under occlusion (Levenstein, 1975). Tested at 4% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 27 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Epstein, 1975).

Phototoxicity. No phototoxic effects were reported for undiluted camphor oil brown on hairless mice and swine (Urbach & Forbes, 1975).

Insects. In 3-yr tests, impregnation with brown camphor oil or with a kerosene solution of the oil did not protect wood from attack by the Formosan termite, *Reticulitermes speratus* (Tu, 1957).

Micro-organisms. Camphor oil brown (ranshoku-yu) did not inhibit the growth of four bacteria studied (Mashimo, Serisawa & Kuroda, 1953).

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CAMPHOR OIL WHITE

Description and physical properties: A white viscous liquid with cineole as the principal component along with monoterpenes (Guenther, 1950).

Occurrence: Found in the trees and bark of *Cinnamomum camphora* Sieb (fam. Lauraceae).

Preparation: By fractional distillation of crude camphor oil after the camphor has been crystallized out (Arctander, 1960).

Uses: In public use since the 1920s. Use in fragrances in the USA amounts to less than 15,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·05	0·005	0·01	0·04
Maximum	0·1	0·02	0·1	0·4

Status

Camphor oil white was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1163). The Council of Europe (1970) included camphor oil (*Cinnamonum camphora*) in the list of temporarily admissible flavouring substances (provided no safrole is present in the final product).

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported to be 5·10 ml/kg (2·73–7·47 ml/kg) (Hart, 1971). The acute dermal LD_{50} was reported to be >5 ml/kg in the rabbit (Hart, 1971).

Irritation. Camphor oil white applied full strength to intact or abraded rabbit skin was mildly irritating (Hart, 1971). Camphor oil tested at a concentration of 20% in petrolatum produced no irritation in a 48-hr closed-patch test in 25 human subjects (Kligman, 1971).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 20% in petrolatum and produced no sensitization reactions (Kligman, 1971).

Metabolism. Cineole, the principal ingredient of white camphor oil, undergoes oxidation *in vivo* with the formation of hydroxycineole, which is excreted as hydroxycineoleglucuronic acid (Williams, 1959).

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CAMPHOR OIL YELLOW

Synonym: Oil camphor sassafrassy.
Description and physical properties: EOA Spec. no. 99. The main constituents of camphor oil yellow include safrole, α-terpineol and camphor (Guenther, 1950).
Occurrence: Found in the trees of Cinnamomum camphora (L.) Nees & Ebermeier (Fam. Lauraceae) (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: By vacuum rectification of filtered true camphor oil (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Uses: In public use since the 1900s. Use in fragrances in the USA amounts to approximately 20,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·05	0·005	0·01	0·04
Maximum	0·2	0·02	0·1	0·4

Status

Camphor (safrole free) is approved by the FDA for food use (21 CFR 121.1163). The Council of Europe (1974) included camphor in the list of currently used flavouring substances for which the toxicological and technological data are deemed insufficient; their use is temporarily admitted, possibly with a limitation on the active principle in the final product.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 3·73 ± 0·422 g/kg (McGee, 1974). The acute dermal LD_{50} value in rabbits exceeded 5 g/kg (McGee, 1974).

Irritation. Camphor oil yellow applied undiluted to the backs of hairless mice was not irritating (Urbach & Forbes, 1974). Applied full strength to intact or abraded rabbit skin for 24 hr under occlusion, it was slightly irritating (McGee, 1974). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 23 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Epstein, 1974).

Phototoxicity. No phototoxic effects were reported for undiluted camphor oil yellow (Urbach & Forbes, 1974).

Micro-organisms. Camphor oil sassafrassy was found to possess some antifungal activity against all of a group of 12 phytopathogenic fungi (Maruzzella & Balter, 1959) and against three wood-destroying fungi (Maruzzella, Scrandis, Scrandis & Grabon, 1960).

Insects. In 3-yr tests, impregnation with yellow camphor oil or with a kerosene solution of the oil did not protect wood from attack by the Formosan termite, *Reticulitermes speratus* (Tu, 1957).

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BALSAM, CANADIAN

Description and physical properties: EOA Spec. no. 214. One of the chief constituents of this oil is 1-β-phellandrene (Guenther, 1952).
Occurrence: A liquid oleoresin found in the bark of the tree *Abies balsamea* (L.) Mill. (Fam. Pinaceae).
Preparation: The balsam is collected by breaking the blisters on the bark of the balsam tree. It is purified and clarified by filtration.
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 5000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·005	0·05
Maximum	0·15	0·02	0·03	0·2

Analytical data: Infra-red curve, RIFM no. 72-146.

Status

Fir balsam, Canadian was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1163). The Council of Europe (1974) included fir balsam, Canadian in the list of flavouring substances temporarily admitted for use, possibly with a limitation on the active principle in the final product.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Shelanski, 1973).

Irritation. Fir balsam, Canadian applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Shelanski, 1973). Tested at 2% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966, modified) was carried out on 25 volunteers. The material was tested at a concentration of 2% in petrolatum and produced no sensitization reactions (Kligman, 1973).

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CANANGA OIL

Description and physical properties: EOA Spec. no. 75.
Occurrence: Found in the flowers of the tree *Cananga odorata* Hook. f. et Thomsen, syn *Canangium odoratum* Baill. forma macophylla (fam. Anonaceae).
Preparation: By the steam-distillation of the flowers of the cannaga tree.
Uses: In public use since the 1900s. Use in fragrances in the USA amounts to less than 2000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·05	0·005	0·05	0·2
Maximum	0·2	0·02	0·2	0·8

Status

Cananga oil was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) included cananga oil (*Cananga odorata*) in the list of temporarily admitted flavoring substances. The *Food Chemicals Codex* (1972) has a monograph on cananga oil.

Biological data

Acute toxicity. The acute oral LD_{50} was reported to be >5 g/kg in the rat (Hart, 1971). The acute dermal LD_{50} was reported to be >5 g/kg in the rabbit (Hart, 1971).

Irritation. Cananga oil applied full strength to intact or abraded rabbit skin was irritating (Hart, 1971). Cananga oil tested at a concentration of 10% in petrolatum produced no irritation in a 48-hr closed-patch test in 25 human subjects (Kligman, 1971).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1971).

References

Council of Europe (1970). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List N(1), Series 2, no. 103, p. 16. Strasbourg.
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Kligman, A. M. (1971). Report to RIFM, 14 June.

CARAWAY OIL

Description and physical properties: Food Chemicals Codex (1972).
The main constituent of caraway oil is *l*-carvone.
Occurrence: Found in the fruits of *Carum carvi* L. (fam. Umbelliferae)
Preparation: By steam-distillation of the dried ripe fruit of *Carum carvi* L.
Uses: In public use since the 1920s.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	—	0·01	0·02
Maximum	0·05	—	0·05	0·4

Analytical data: Gas chromatogram, RIFM no. 72–88; infra-red curve, RIFM no. 72–88.

Status

Caraway oil was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) included caraway oil (*Carum carvi*) in the list of substances, spices and seasonings whose use is deemed admissible, with a possible limitation of the active principle in the final product. Both the *Food Chemicals Codex* (1972) and the National Formulary (1970) have monographs on caraway oil.

Biological data

Acute toxicity. The acute oral LD_{50} in the rats was reported to be 3·5 ml/kg (2·7–4·7 ml/kg) (Shelanski & Moldovan, 1972). The acute dermal LD_{50} in the rabbit was reported to be 1·78 ml/kg (1·46–2·18 ml/kg) (Shelanski & Moldovan, 1972).

Irritation. Undiluted caraway oil applied to the backs of hairless mice produced no irritating effects (Urbach, 1972). Caraway oil applied full strength to intact or abraded rabbit skin was irritating (Shelanski & Moldovan, 1972). Tested at a concentration of 4% in petrolatum, it produced no irritation in a 48-hr closed-patch test in 25 human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1972).

Phototoxicity. Low-level phototoxic effects have been reported for caraway oil, but these are not considered significant (Urbach & Forbes, 1972).

References

Council of Europe (1970). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List N(1), Series 1(b), no. 112, p. 16. Strasbourg.

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CARDAMOM OIL

Description and physical properties: EOA Spec. no. 289. The main constituents of cardamom oil are limonene and terpinyl acetate (*Fenaroli's Handbook of Flavor Ingredients*, 1971; Gildemeister & Hoffman, 1956; Guenther, 1952).
Occurrence: Found in the seed of *Elettaria cardamomum* (L.) Maton (Fam. Zingiberaceae).
Preparation: By steam distillation of the seed of *Elettaria cardamomum* (L.) Maton.
Uses: In public use before the 1900s. Use in fragrances in the USA amounts to less than 2000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·005	0·002	0·04
Maximum	0·05	0·005	0·01	0·4

Analytical data: Gas chromatogram, RIFM no. 72–89; infra-red curve, RIFM no. 72–89.

Status

Cardamom oil was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) included cardamom oil in the list of substances, spices and seasonings commonly added to foodstuffs in small quantities with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on cardamom oil.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as ≥ 5 g/kg (Moreno, 1973). The acute dermal LD_{50} in rabbits was reported as > 5 g/kg (Moreno, 1973).

Irritation. Undiluted cardamom oil applied to the backs of hairless mice produced no irritating effects (Urbach & Forbes, 1973). Applied full strength to intact or abraded rabbit skin for 24 hr under occlusion, it produced no irritation (Moreno, 1973). Tested as 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1973).

Phototoxicity. No phototoxic effects were reported for cardamom oil (Urbach & Forbes, 1973).

Additional published data

The cold-pressed essential oils derived from three varieties of cardamom seeds and oil of cardamom (NF) were investigated by a gas-chromatographic procedure and the following previously unreported constituents were tentatively identified: camphene, α-phellandrene, camphor, citronellal, citral, citronellol, ascaridole, geranyl acetate, bisabolene and farnesol (Bernhard, Wijesekera & Chichester, 1971).

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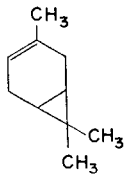
Urbach, F. & Forbes, P. D. (1973). Report to RIFM, 8 February.

Δ^3-CARENE

Synonyms: Isodiprene; 3,7,7-trimethylbicyclo-[*0,1,4*]-3-heptene.
Structure:



Description and physical properties: A colourless mobile liquid with a sweet odour (Arctander, 1969).
Occurrence: Δ^3-Carene has been identified in many volatile oils such as Swedish and Finnish turpentine oils, galanga root oil and in German pine needle oils such as those from *Pinus pumilio & Pinus sylvestris* (Guenther, 1949).
Preparation: By isolation from turpentine fractions (Arctander, 1969).
Uses: In public use since the 1940s.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·001	0·005
Maximum	0·1	0·05	0·005	0·01

Analytical data: Gas chromatogram, RIFM no. 72–12; infra-red curve, RIFM no. 72–12.

Specifications of sample no. 72–12: Specific gravity (25°/25°C), 0·8590; optical rotation (αD), +11·56; refractive index (n_D^{20}), 1·4733; soln in 90% alcohol, 5·5 vols, and in 95% alcohol, 2·0 vols; Δ^3-carene content (by GLC) 95·1%. This sample was collected and stored under nitrogen, washed several times and kept refrigerated under nitrogen.

Status

There is an extensive review of the chemistry of carene by Cocker (1971).

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported to be 4·8 g/kg (4·0–5·6 g/kg) (Moreno, 1972a). The acute dermal LD_{50} was reported to be > 5 g/kg in the rabbit (Moreno, 1972b).

Irritation. Δ^3-Carene applied full strength to intact or abraded rabbit skin produced irritation (Moreno, 1972b). Tested at a concentration of 10% in petrolatum, it produced no irritation in a 48-hr closed-patch test in 25 human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1972).

Additional published data

The oxidation products of Δ^3-carene, which is an important constituent of oil of turpentine and is also present as an impurity in α-pinene, are responsible for the eczematogenic effect of oil of turpentine and of the terpenes distilled from it (Pirilä & Siltanen, 1956). Autoxidation of Δ^3-carene to the hydroperoxide forms the actual eczematogen in turpentine oil (Pirilä & Siltanen, 1957). The eczematogenic effect of oil of turpentine is mainly due to the oxidation products (hydroperoxide) of Δ^3-carene (Pirilä, Siltanen & Pirilä, 1964).

Δ^3-Carene was shown to be a sensitizer in a study of the sensitizing potential of some essential oils and their constituents (Woeber & Krombach, 1969). Δ^3-Carene exerts an allergic effect upon the skin (Mikhailov & Berova, 1970). Applied undiluted to the skin

of guinea-pigs, it produced skin reactions within 24 and 48 hr, consisting of widespread erythematous papular reactions with infiltration and desquamation (Hellerstrom, Lodin, Rajka, Swedin & Widmark, 1963). Of nine distillation fractions of turpentine oil, mainly Δ^3-carene and limonene were responsible for dermatitis (Lejhancová & Wolf, 1955).

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CARROT SEED OIL

Description and physical properties: EOA Spec. no. 136. Formic acid, acetic acid, butyric acid, palmitic acid, *l*-α-pinene, *l*-limonene, daucol, asarone, carotol and bisabolene are among the constituents of carrot seed oil (Guenther, 1950). Using gas–liquid chromatographic separation of components and characterization by infra-red absorption and mass spectrometry, Seifert, Buttery & Ling (1968) identified 23 components, including camphene, α-terpinene, terpinen-4-ol, α-terpineol, bornyl acetate, γ-decanolactone, β-selinene, α-gurjunene and coumarin, which had not previously been reported as constituents of carrot seed oil.

Occurrence: Found in the seeds of *Daucus carota* L. (Fam. Umbelliferae).

Preparation: By steam distillation of the crushed seeds of *D. carota*.

Uses: In public use since before the 1900s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·04
Maximum	0·1	0·01	0·03	0·4

Status

Carrot seed oil was given GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1974) included carrot seed oil in the list of currently used flavouring substances temporarily admitted for use, possibly with a limitation on the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on carrot seed oil.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in mice and the acute dermal LD_{50} value in guinea-pigs exceeded 5 g/kg (Moreno, 1974).

Irritation. Undiluted carrot seed oil applied to the backs of hairless mice and swine was not irritating (Urbach & Forbes, 1974). Applied full strength to intact or abraded rabbit or guinea-pig skin for 24 hr under occlusion, it was very slightly irritating (Moreno, 1974). Tested at 4% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Epstein, 1974). Carrot seed oil applied full strength for 48 hr in the standard occluded aluminium patch test used by the North American Contact Dermatitis Research Group (NACDRG) did not produce any irritation or sensitization in a 62-yr-old subject with a perfume dermatitis (Larsen, 1975). The standard aluminium patch test was designed by the International Contact Dermatitis Research Group to standardize testing for contact dermatitis worldwide and is described extensively by Malten, Nater & van Ketel (1976).

Phototoxicity. No phototoxic effects were reported for undiluted carrot seed oil on hairless mice and swine (Urbach & Forbes, 1974).

Pharmacology. Extracts of *D. carota* fruit with 50% ethanol or other solvents were shown to have a dilating effect on the coronary vessels of the isolated heart of the cat (Jastrezebska, Kaczmarek, Kedziora, Raszejowa & Wrocinski, 1964), but were among several dilating drugs that were unable to counteract oxygen-induced coronary vessel contraction and blood-pressure increase in cats (Wrocinski, 1968). The dried extract may be useful in the treatment of coronary vessels (Jastrezebska *et al.* 1964).

Carrot seed oil given iv lowered arterial blood pressure in the anaesthetized dog, with depression of respiration at higher doses. The oil depressed cardiac action in frog and dog hearts. It did not show any analgesic effect in rats, but markedly depressed central nervous system action in both rats and fish. The oil offered moderate protection to frogs from the convulsant effect of strychnine and Metrazol, and produced a relaxant effect on isolated rat and rabbit intestine and isolated rat uterus. The oil decreased acetylcholine-induced contractions in these preparations and in isolated skeletal muscles of the frog (Bhargava, Ali & Chauhan, 1967).

References

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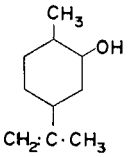
l-CARVEOL

Synonyms: *l*-Methyl-4-isopropenyl-6-cyclohexen-2-ol; *l*-*p*-mentha-6,8-dien-2-ol.
Structure:



Description and physical properties: A colourless liquid with a spearmint-like odour (Arctander, 1969).
Occurrence: Found in small quantities in spearmint oil (Arctander, 1969).
Preparation: *l*-Carveol is produced from *l*-carvone by selective reduction (Arctander, 1969).
Uses: In public use since the 1940's. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·001	0·001	0·001	0·005
Maximum	0·005	0·005	0·005	0·4

Analytical data: Gas chromatogram, RIFM no. 72–13; infra-red curve RIFM no. 72–13.

Status

Carveol was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included carveol in its list of temporarily admissible artificial flavouring substances.

Biological data

Acute toxicity. The acute oral LD_{50} in the rat was reported to be 3·0 g/kg (2·34–3·83 g/kg) (Keating, 1972). The acute dermal LD_{50} was reported to be >5 g/kg in the rabbit (Keating, 1972).

Irritation. *l*-Carveol applied full strength to intact or abraded rabbit skin produced irritation (Keating, 1972). Tested at a concentration of 4% in petrolatum, it produced no irritation in a 48-hr closed-patch test on 25 human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1972).

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Keating, J. W. (1972). Report to RIFM, 7 June.
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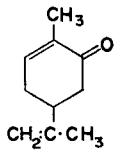
Kligman, A. M. (1972). Report to RIFM, 19 July.

l-CARVONE

Synonyms: *l*-6,8(9)-*p*-Menthadien-2-one; *l*-1-methyl-4-isopropenyl-6-cyclohexen-2-one.
Structure:



Description and physical properties: EOA Spec no. 131.
Occurrence: Found in a score of essential oils and is the main constituent of spearmint oil.
Preparation: By isolation from oil of spearmint or synthesized commercially from *d*-limonene.
Uses: In public use since the 1900s. Use in fragrances in the USA amounts to less than 2000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	Trace	0·005	0·02
Maximum	0·05	Amounts	0·01	0·1

Analytical data: Gas chromatogram, RIFM no. 70–20; infra-red curve, RIFM no. 70–20.

Status

l-Carvone was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) listed carvone, giving an ADI of 1·25 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on *l*-carvone, and the Joint FAO/WHO Expert Committee on Food Additives (1967) has published a monograph and specifications for *l*-carvone, giving an ADI of 1·25 mg/kg.

Biological data

Acute toxicity. The acute oral LD_{50} was reported to be 1640 mg/kg in rats and 766 mg/kg in the guinea-pig (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964).

Chronic toxicity. In the feeding study in rats, 10,000 ppm fed in the diet for 16 wk caused growth retardation and testicular atrophy (Hagan, Hansen, Fitzhugh, Jenner, Jones Taylor, Long, Nelson & Brouwer, 1967), while 1000 ppm fed for 28 wk and 2500 ppm fed for 1 yr produced no effects.

Irritation. *l*-Carvone tested at a concentration of 1 % in petrolatum produced no irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1971).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 1 % in petrolatum and produced no sensitization reactions (Kligman, 1971).

Metabolism. Carvone was metabolized by the rabbit to 1,5-dimethyl-1,5-hexadien-1,6-dicarboxylic acid and a carbinol in which one ethylene linkage was saturated and the keto group was reduced (Fischer & Bielig, 1940).

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Jenner, P. M., Hagan, E. C., Taylor, Jean M., Cook, E. L. & Fitzhugh, O. G. (1964). Food flavourings and compounds of related structure. I. Acute oral toxicity. *Fd Cosmet. Toxicol.* **2**, 327.

Joint FAO/WHO Expert Committee on Food Additives (1967). Toxicological Evaluation of Some Flavouring Substances and Non-nutritive Sweetening Agents. *F.A.O. Nutr. Mtg. Rep. Ser. no.* 44A, Geneva, p. 14. WHO/Food Add./68.33.

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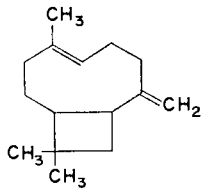
CARYOPHYLLENE

Synonym: β-Caryophyllene
Structure:



Description and physical properties: Givaudan Index (1961).
Occurrence: Found in oils of clove, cinnamon leaves and copaiba balsam and in minor quantities in various other essential oils, especially lavender (*Givaudan Index*, 1961).
Preparation: By isolation from clove leaf oil, clove stem oil, cinnamon leaf oil or pine oil fractions (Arctander, 1969).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 20,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·01	0·04
Maximum	0·1	0·01	0·1	0·4

Status

Caryophyllene was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included caryophyllene in the list of temporarily admissible artificial flavouring substances. The *Food Chemicals Codex* (1972) has a monograph on caryophyllene.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Hart, 1971).

Irritation. Caryophyllene applied full strength to intact or abraded rabbit skin was irritating (Hart, 1971). Tested at a concentration of 4% in petrolatum, it produced no irritation in a 48-hr closed-patch test in 25 human subjects (Kligman, 1971).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1971).

References

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Flavouring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. No. 2252. *Fd Technol., Champaign* **19** (2), part 2, 155.

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Hart, E. R. (1971). Report to RIFM, 30 July.

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Kligman, A. M. (1971). Report to RIFM, 14 June.

CARYOPHYLLENE ACETATE

Synonym: Caryophyllene alcohol acetate.

Structure: $C_{15}H_{25} \cdot OCO \cdot CH_3$; for structure of caryophyllene, $C_{14}H_{22}:CH_2$, see monograph thereon (Opdyke, *Fd Cosmet. Toxicol.* 1973, **11**, 1059).

Description and physical properties: A colourless slightly viscous liquid with a mild fruity-woody odour (Arctander, 1969).

Occurrence: Has apparently not been reported to occur in nature.

Preparation: By direct acetylation of caryophyllene.

Uses: In public use since the 1940s. Use in fragrances in the USA amounts to approximately 4000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·1
Maximum	0·1	0·01	0·03	0·4

Analytical data: Gas chromatogram, RIFM no. 72–90; infra-red curve, RIFM no. 72–90.

Status

Caryophyllene acetate is approved by the FDA for food use (21 CFR 121.1164).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Russell, 1973).

Irritation. Caryophyllene acetate applied full strength to intact or abraded rabbit skin under occlusion for 24 hr was not irritating (Russell, 1973). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1973).

References

Arctander, S. (1969). *Perfume and Flavor Chemicals (Aroma Chemicals)*. Vol. 1, no. 585. S. Arctander, Montclair, New Jersey.

Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. Invest. Derm.* **47**, 393.

Kligman, A. M. (1973). Report to RIFM, 10 July.

Russell, T. J. (1973). Report to RIFM, 6 March.

CARYOPHYLLENE ALCOHOL

Structure: $C_{15}H_{25}\cdot OH$; for structure of caryophyllene, $C_{14}H_{22}{:}CH_2$, see monograph thereon (Opdyke, *Fd Cosmet. Toxicol.* 1973, **11**, 1059).

Description and physical properties: A solid crystalline mass with a basically woody odour (Arctander, 1969).

Occurrence: Occurs in the high-boiling fraction of the oils of *Mentha arvensis* and *Mentha piperita* (*Fenaroli's Handbook of Flavor Ingredients*, 1971).

Preparation: By saponification of caryophyllene acetate.

Uses: In public use since the 1940s. Use in fragrances in the USA amounts to approximately 5000 lb/yr.

Concentration in final products (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·1
Maximum	0·1	0·01	0·03	0·4

Analytical data: Gas chromatogram, RIFM no. 72–91; infra-red curve, RIFM no. 72–91.

Status

Caryophyllene alcohol is approved by the FDA for food use (21 CFR 121.1164).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Russell, 1973).

Irritation. Caryophyllene alcohol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Russell, 1973). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1973).

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CASCARILLA OIL

Synonym: Sweet-wood bark oil.

Description and physical properties: EOA Spec. no. 175. The main constituents of cascarilla oil include *l*-limonene, *p*-cymene, dipentene, eugenol and cascarillic acid (*Fenaroli's Handbook of Flavor Ingredients*, 1975).

Occurrence: Found in the dried bark of *Croton eluteria* Bennett (Fam. Euphorbiaceae).

Preparation: By steam distillation of the dried bark.

Uses: In public use since the 1920s. Use in fragrances in the USA amounts to less than 1000 lb/yr. Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·04
Maximum	0·1	0·01	0·05	0·4

Analytical data: Gas chromatogram, RIFM no. 74–57; infra-red curve, RIFM no. 74–57.

Status

Cascarilla oil was given GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1974) included cascarilla in the list of substances, spices and seasonings deemed admissible for use, with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on cascarilla oil.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in mice and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Wohl, 1974).

Irritation. Undiluted cascarilla oil was not irritating when applied to the backs of hairless mice and swine (Urbach & Forbes, 1974) or to intact or abraded rabbit skin for 24 hr under occlusion (Wohl, 1974). Tested at 4% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 22 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Epstein, 1974).

Phototoxicity. No phototoxic effects were reported for undiluted cascarilla oil on hairless mice and swine (Urbach & Forbes, 1974).

Micro-organisms. Vapour of cascarilla oil showed antibacterial activity against *Mycobacterium avium* but not against four other bacteria studied by Maruzzela & Sicurella (1960). Cascarilla oil exhibited only slight *in vitro* antifungal activity against four out of 15 fungi tested by Maruzzella & Liguori (1958).

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CASSIA OIL

Description and physical properties: *Food Chemicals Codex* (1972). The main constituent of cassia oil is cinnamic aldehyde (Guenther, 1950).
Occurrence: Found in the leaves and twigs of *Cinnamonum cassia* Blume (Fam: Lauraceae) (Guenther, 1950).
Preparation: By distillation of the leaves and twigs of *C. cassia* Blume (Guenther, 1950).
Uses: In public use since the 1800s. Use in fragrances in the USA amounts to about 9000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·05
Maximum	0·1	0·01	0·03	0·4

Analytical data: Gas chromatogram, RIFM no. 72–92; infra-red curve, RIFM no. 72–92.

Status

Cassia oil was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) included cassia oil in its list of substances, spices and seasonings whose use is deemed admissible with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on cassia oil.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 2·8 ml/kg (2·5–3·2 ml/kg) and the acute dermal LD_{50} value in rabbits as 0·32 ml/kg (0·21–0·48 ml/kg) (Shelanski, 1972).

Irritation. Undiluted cassia oil applied to the backs of hairless mice was mildly irritating (Urbach & Forbes, 1972), and applied to intact or abraded rabbit skin for 24 hr under occlusion was severely irritating (Shelanski, 1972). Tested at 4% in petrolatum, cassia oil produced no irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1972). A patch test of the full-strength oil on 24 human subjects for 24 hr produced two reactions (Katz, 1946).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced two sensitization reactions (Kligman, 1972).

Phototoxicity. Low-level phototoxic effects were reported for cassia oil, but were not considered significant (Urbach & Forbes, 1972).

Additional published data

Cassia oil is listed as a sensitizer by Schwartz & Peck (1946) and Schwartz, Tulipan & Peck (1947). A girl employed in dipping toothpicks in oil of cassia had a skin reaction affecting the hands, face and abdomen (Prosser-White, 1923; White, 1897). Irritation may occur in hypersensitive individuals (Tulipan, 1938).

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CASTOREUM

Description and physical properties: EOA Spec no. 194. The material on which the testing was carried out was castoreum tincture.

Occurrence: Found as the secretion obtained from the oil glands of the beaver *Castor fiber* L. (Castoridae).

Preparation: By alcoholic extraction of the macerated castoreum pods of the beaver, a by-product of the fur industry (Arctander, 1960).

Uses: In public use since the 1920s. Use in fragrances in the USA amounts to less than 20,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	—	0·01	0·04
Maximum	0·05	—	0·1	0·4

Status

Castoreum was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) included castoreum in the list of flavouring substances whose use is temporarily admitted, with a possible limitation on the active principle in the final product.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported to be >5 g/kg (Keating, 1972). The acute dermal LD_{50} in the rabbit was reported to be >5 g/kg (Keating, 1972).

Irritation. Undiluted castoreum tincture applied to the backs of hairless mice produced no irritation (Urbach & Forbes 1973). Castoreum tincture applied full strength to intact or abraded rabbit skin was not irritating (Keating, 1972). Castoreum tested at a concentration of 4% in petrolatum produced no irritation in a 48-hr closed-patch test in 25 human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1972).

Phototoxicity. No phototoxic effects were reported for castoreum tincture (Urbach 1973).

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CEDAR LEAF OIL

Synonym: Oil thuja.

Description and physical properties: EOA Spec. no. 86. The chief constituent of cedar leaf oil is *d*-α-thujone (Gildemeister & Hoffman, 1956; Guenther, 1952).

Occurrence: Found in the leaves and branch ends of *Thuja occidentalis* L. (Fam. Cupressaceae).

Preparation: By steam distillation of the fresh branch ends and leaves.

Uses: In public use before the 1900s. Use in fragrances in the USA amounts to approximately 10,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·2
Maximum	0·1	0·01	0·03	0·4

Analytical data: Gas chromatogram, RIFM no. 72–93; infra-red curve, RIFM no. 72–93.

Status

Cedar leaf oil was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1163). The Council of Europe (1970) included cedar leaf oil (*Thuja occidentalis* L.) in the list of flavouring substances temporarily admitted for use, possibly with a limitation on the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on cedar leaf oil.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 0·83 g/kg (0·69–0·97 g/kg) (Moreno, 1973). The acute dermal LD_{50} in rabbits was reported as 4·1 g/kg (2·8–6·8 g/kg) (Moreno, 1973).

Irritation. Undiluted cedar leaf oil applied to the backs of hairless mice produced no irritating effects (Urbach & Forbes, 1973). Applied full strength to intact or abraded rabbit skin for 24 hr under occlusion, it was moderately irritating (Moreno, 1973). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1973).

Phototoxicity. No phototoxic effects were reported for cedar leaf oil (Urbach & Forbes, 1973).

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CEDARWOOD OIL ATLAS

Synonyms: Cedrus atlantica oil; cedarwood oil Moroccan.
Description and physical properties: EOA Spec. no. 229. The chief constituents of cedarwood oil atlas are α- and γ-atlantone (Guenther, 1952).

The essential oil of *Cedrus atlantica* contains α-ionone, α-caryophyllene alcohol, epi-β-cubenol, epoxy-β-himachalene and its epimer, deodarone, and a new ketone (Adams, Bhatnagar & Cookson, 1975; Adams, Bhatnagar, Cookson & Tuddenham, 1974). The chemical composition of tannins and polyphenols extracted from the wood and bark of *C. atlantica* was reported by Hergert (1960).
Occurrence: Found in the wood of *C. atlantica* Manelli (Fam. Pinaceae).
Preparation: By steam distillation of the wood of *C. atlantica* Manelli.
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to approximately 25,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·05	0·005	0·02	0·2
Maximum	0·2	0·02	0·05	0·8

Analytical data: Gas chromatogram, RIFM no. 74–171; infra-red curve, RIFM no. 74–171.

Status

Cedarwood oil atlas is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974) or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1974).

Irritation. Undiluted cedarwood oil atlas applied to the backs of hairless mice and swine was not irritating (Urbach & Forbes, 1974) but applied to intact or abraded rabbit skin for 24 hr under occlusion it was slightly irritating (Moreno, 1974). Tested at 8% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1974).

Phototoxicity. No phototoxic effects were reported for undiluted cedarwood oil atlas on hairless mice and swine (Urbach & Forbes, 1974).

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CEDARWOOD OIL TEXAS

Description and physical properties: EOA Spec. no. 36A. The main constituents of cedarwood oil Texas include cedrene, cedrol and pseudocedrol (Guenther, 1952).

Occurrence: Found in the trunk and branches of *Juniperus mexicana* Schiede (Fam. Cupressaceae) (Guenther, 1952).

Preparation: By distillation of the wood of *J. mexicana* Schiede (Guenther, 1952).

Uses: In public use before the 1900s. Use in fragrances in the USA amounts to approximately 25,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·05	0·005	0·02	0·2
Maximum	0·3	0·03	0·05	0·8

Analytical data: Gas chromatogram. RIFM no. 75-12; infra-red curve, RIFM no. 75-12.

Status

Cedarwood oil Texas is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974) or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Levenstein, 1975).

Irritation. Undiluted cedarwood oil Texas was not irritating when applied to the backs of hairless mice and swine (Urbach & Forbes, 1975) or to intact or abraded rabbit skin for 24 hr under occlusion (Levenstein, 1975). Tested at 8% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1975). Cedarwood oil (unspecified) caused no primary skin irritation in closed patch tests on 59 normal subjects at concentrations of 20 or 2% or on 148 subjects with dermatoses at 0.2% (Fujii, Furukawa & Suzuki, 1972). It has been reported to possess slight activity as an acute or chronic local irritant or allergen (Sax, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1975).

Phototoxicity. No phototoxic effects were reported for undiluted cedarwood oil Texas on hairless mice and swine (Urbach & Forbes, 1975).

Pharmacology. Cedarwood oil (unspecified) had no sedative effect on tadpoles within 6 hr (LeNouene, 1966).

Micro-organisms. Cedarwood oil exhibited no antibacterial activity against five bacteria studied. Combination of cedarwood oil with other essential oils resulted in a decrease in antibacterial activity (Maruzzella & Henry, 1958). The vapour of cedarwood oil inhibited the growth of two of five bacteria studied (Maruzzella & Sicureila, 1960), and an oil–water mixture of cedarwood oil suppressed the growth of *Staphylococcus aureus* in approximately 2–3 hr (Schürmann & Spitzner, 1960). Cedarwood oil exhibited slight antifungal activity against 1 of 15 fungi studied (Maruzzella & Liguori, 1958).

Cedarwood oil (10 mg as a 2% solution in olive oil injected im once weekly) exhibited a weak therapeutic effect on experimental tuberculosis of the guinea-pig when combined with subeffective doses of dihydrostreptomycin. Cedarwood oil (100 μg/ml) had no antibacterial action *in vitro* on tubercle bacilli (Kato & Gözsy, 1958).

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CEDARWOOD OIL VIRGINIA

Synonyms: Red cedarwood oil; oil cedar.

Description and physical properties: EOA Spec. no. 36-B. The main constituents of cedarwood oil Virginia are cedrene, thujopsene and cedrol.

Occurrence: Found in the wood of *Juniperus virginiana* L. (Fam. Cupressaceae).

Preparation: By steam distillation of sawdust or finely chopped wood of *Juniperus virginiana* L.

Uses: In public use before the 1900s. Use in fragrances in the USA exceeds 100,000 lb/yr. Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·05	0·005	0·02	0·2
Maximum	0·3	0·03	0·05	0·8

Analytical data: Gas chromatogram, RIFM no. Z-42713; infra-red curve, RIFM no. Z-42713.

Status

The Council of Europe (1970) included cedarwood oil Virginia (*Juniperus virginiana*) in the list of flavouring substances temporarily admitted for use, possibly with a limitation on the active principle in the final product.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. Undiluted cedarwood oil Virginia applied to the backs of hairless mice was not irritating (Urbach & Forbes, 1973). Applied full strength to intact or abraded rabbit skin for 24 hr under occlusion, it was moderately irritating (Moreno, 1973). Cedarwood oil was reported by Roe & Field (1965) to be neither systemically toxic nor locally irritant on mouse skin. Cedarwood oil Virginia, tested at 8% in petrolatum, produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1973). Patch tests were used to investigate "cedar-poisoning" in 43 persons exposed to wood products or vegetation. The results that were obtained suggested that the term "cedar-poisoning" was a misnomer. Twenty-one showed positive results: eight to usnic acid or chemicals derived from lichens, six to oleoresins of plants, one to various moss species, one to tree oleoresins and five to other contactants (Tan & Mitchell, 1968).

Phototoxicity. No phototoxic effects were reported for cedarwood oil (Urbach & Forbes, 1973). The use of toilet preparations containing cedarwood oils followed by exposure to various rays is sometimes the cause of dermatitis (Bray, 1937; Greenbaum, 1934; Tulipan, 1938). Pigmentation may follow the topical application of cedarwood oil (del Vivo, 1930; Sandler, 1939).

Additional published data

Mice exposed to cedarwood bedding exhibited reduced hypnotic effects with hexobarbitone. These effects were due to the induction of microsomal enzymes responsible for hexobarbitone degradation (Ferguson, 1966; Vesell, 1967; Wade, Holl, Hilliard, Molton & Greene, 1968).

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Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47,** 393.

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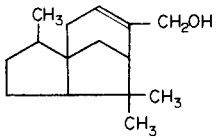
Vesell, E. S. (1967). Induction of drug-metabolizing enzymes in liver microsomes of mice and rats by softwood bedding. *Science, N.Y.* **157,** 1057.

Wade, A. E., Holl, J. E., Hilliard, C. C., Molton, E. & Greene, F. E. (1968). Alteration of drug metabolism in rats and mice by an environment of cedarwood. *Pharmacology* **1,** 317.

CEDRENOL

Structure:



Description and physical properties: A viscous slightly yellow to yellow liquid.
Occurrence: Found in the wood of several conifers. particularly cypresses and cedars—*Cedrus atlantica*, *Cupressus sempervirens*, *Juniperus virginiana* and others (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: By isolation from cedarwood oil Virginia or by oxidation of cedrene via cedrenyl acetate (Arctander, 1969).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to about 8000 lb/yr. Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·02	0·2
Maximum	0·2	0·02	0·1	0·8

Analytical data: Gas chromatogram, RIFM no. 74–172; infra-red curve, RIFM no. 74–172.

Status

Cedrenol is approved by the FDA for food use (21 CFR 121.1164).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Wohl, 1974).

Irritation. Cedrenol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Wohl, 1974). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1974).

References

Arctander, S. (1969). *Perfume and Flavor Chemicals (Aroma Chemicals)*. Vol. 1, no. 595. S. Arctander, Montclair, New Jersey.

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Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.

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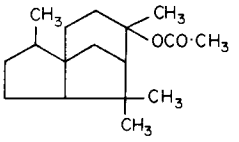
Wohl, A. J. (1974). Report to RIFM, 19 August.

CEDRENYL ACETATE

Structure:



Description and physical properties: A colourless viscous liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By oxidation of cedrene with selenium dioxide in acetic anhydride or by any other suitable means.
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to approximately 45,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·02	0·2
Maximum	0·2	0·02	0·1	0·8

Analytical data: Gas chromatogram, RIFM no. 74–173; infra-red curve, RIFM no. 74–173.

Status

Cedrenyl acetate is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974), or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Wohl, 1974).

Irritation. Cedrenyl acetate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was irritating (Wohl, 1974). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 24 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Epstein, 1974).

References

Council of Europe (1974). Natural Flavouring Substances, Their Sources, and Added Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. Strasbourg.

Epstein, W. L. (1974). Report to RIFM, 27 August.

Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. *Fd Technol., Champaign* **19** (2), part 2, 155.

Food Chemicals Codex (1972). 2nd ed. Prepared by the Committee on Specifications, Food Chemicals Codex, of the Committee on Food Protection. National Academy of Sciences–National Research Council Publ. 1406, Washington, D.C.

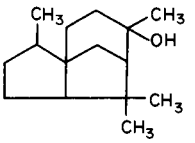
Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.

Kligman, A. M. & Epstein, W. (1975). Updating the maximization test for identifying contact allergens. *Contact Dermatitis* **1**, 231.

Wohl, A. J. (1974). Report to RIFM, 19 August.

CEDROL

Synonyms: Cedarwood oil alcohols.
Structure:



Description and physical properties: EOA Spec. no. 171.
Occurrence: Found in the wood of several conifers, particularly cypresses and cedars, including *Cedrus atlantica, Cupressus sempervirens, Juniperus virginiana* (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: From cedarwood by fractional distillation followed by recrystallization from suitable solvents of appropriate solid fractions.
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to about 50,000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·015	0·2
Maximum	0·2	0·02	0·05	1·0

Analytical data: Gas chromatogram, RIFM nos 70–25, 73–10; infra-red curve, RIFM no. 73–10.

Status

Cedrol is approved by the FDA for food use (21 CFR 121.1164).

Biological data

Acute toxicity. The acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. Cedrol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was slightly irritating (Moreno, 1973). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973a).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced sensitization reactions in two of the 25 test subjects (Kligman, 1973a; see Preface Note no. 1). Retested by the same maximization test on 25 volunteers, a concentration of 8% in petrolatum produced no sensitization reactions (Kligman, 1973b).

Enzyme induction. Evidence of microsomal-enzyme induction was obtained in mice and rats exposed to cedarwood bedding or to bedding sprayed with ether extracts of cedarwood, cedrol or cedrene. The animals exhibited reductions in hexobarbitone and pentobarbitone sleeping times and elevated activities of various hepatic microsomal enzymes (Ferguson, 1966; Vesell, 1967; Wade, Holl, Hilliard, Molton & Greene, 1968).

References

Fenaroli's Handbook of Flavor Ingredients (1971). Edited by T. E. Furia and N. Bellanca. p. 328. Chemical Rubber Co., Cleveland, Ohio.

Ferguson, H. C. (1966). Effect of red cedar chip bedding on hexobarbital and pentobarbital sleep time. *J. pharm. Sci.* **55**, 1142.

Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.

Kligman, A. M. (1973a). Report to RIFM, 11 October.

Kligman, A. M. (1973b). Report to RIFM, 10 December.

Kligman, A. M. & Epstein, W. (1975). Updating the maximization test for identifying contact allergens. *Contact Dermatitis* **1**, 231.

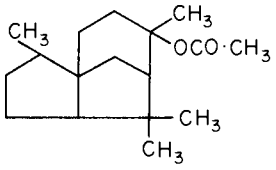
Moreno, O. M. (1973). Report to RIFM, 16 July.

Vesell, E. S. (1967). Induction of drug-metabolizing enzymes in liver microsomes of mice and rats by softwood bedding. *Science, N.Y.* **157**, 1057.

Wade, A. E., Holl, J. E., Hilliard, C. C., Molton, E. & Greene, F. E. (1968). Alteration of drug metabolism in rats and mice by an environment of cedarwood. *Pharmacology* **1**, 317.

CEDRYL ACETATE

Structure:



Description and physical properties: EOA Spec. no. 127.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By the acetylation of cedrol and related fractions of oil of cedarwood.
Uses: In public use since the 1930s. Use in fragrances in the USA exceeds 100,000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·05	0·005	0·02	0·3
Maximum	0·3	0·03	0·1	0·8

Analytical data: Gas chromatogram, RIFM nos. 70–24 & 73–11; infra-red curve, RIFM nos. 70–24 & 73–11.

Status

The Council of Europe (1970) included cedryl acetate in the list of admissible artificial flavouring substances at a level of 1 ppm.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 44·75 g/kg (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964). The acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. Cedryl acetate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1973). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 26 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Epstein, 1973).

References

Council of Europe (1970). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List A(1), Series 1, no. 529, p. 77. Strasbourg.
Epstein, W. L. (1973). Report to RIFM, 17 July.
Jenner, P. M., Hagan, E. C., Taylor, Jean M., Cook, E. L. & Fitzhugh, O. G. (1964). Food flavourings and compounds of related structure. I. Acute oral toxicity. *Fd Cosmet. Toxicol.* **2**, 327.
Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.
Moreno, O. M. (1973). Report to RIFM, 9 April.

CELERY SEED OIL

Description and physical properties: EOA Spec. no. 85. The chief constituent of celery seed oil is *d*-limonene (Gildemeister & Hoffman, 1956; Guenther, 1950).
Occurrence: Found in the seed of *Apium graveolens* L.
Preparation: By steam distillation of the crushed seeds of *Apium graveolens* L.
Uses: In public use before the 1900s. Use in fragrances in the USA amounts to less than 2000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·003	0·0003	0·001	0·04
Maximum	0·03	0·003	0·01	0·4

Analytical data: Gas chromatogram, RIFM no. 72–85; infra-red curve, RIFM no. 72–85.

Status

Celery seed oil was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) included celery seed oil in the list of substances, spices and seasonings deemed admissible for use with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on celery seed oil.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. Undiluted celery seed oil applied to the backs of hairless mice produced no irritating effects (Urbach & Forbes, 1972). Applied full strength to intact or abraded rabbit skin under occlusion for 24 hr, it was not irritating (Moreno, 1973). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1973).

Phototoxicity. No phototoxic effects were reported for celery seed oil (Urbach & Forbes, 1972).

Additional published data

Field and laboratory studies among celery harvesters in the Michigan celery-growing regions have shown that pink-rot celery does contain a photoreactive material which can produce vesicular and bullous lesions on human skin after the sites of application are irradiated by natural sunlight or a carbon–arc lamp emitting wavelengths between 320 and 370 nm (Birmingham, Key, Tubich & Perone, 1961). A form of dermatitis confined to the upper limbs and associated with itching affected approximately 4% of workers preparing celery for canning (Henry, Cantab & Cantab, 1933). Of 391 celery workers, 119 suffered from dermatitis including 25 cases of total disability for an average of 25 days (Henry, 1938). In another study, 77 cases of dermatitis were observed in celery workers; the dermatitis was of the contact type and appeared to be due to the oil of the celery plant (Wiswell *et al.* 1948).

References

Birmingham, O. J., Key, M. M., Tubich, G. E. & Perone, V. B. (1961). Phototoxic bullae among celery harvesters. *Archs Derm.* **83**, 73.

Council of Europe (1970). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List A(1), Series 1, no. 52, p. 14. Strasbourg.

Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. No. 2268. *Fd Technol., Champaign* **19**(2), part 2, 155.

Food Chemicals Codex (1972). 2nd ed. Prepared by the Committee on Specifications, Food Chemicals Codex, of the Committee on Food Protection, p. 184. National Academy of Sciences–National Research Council Publ. 1406, Washington, D.C.

Gildemeister, E. u. Hoffman, F. (1956). *Die Ätherischen Öle*. Vol. IV, p. 377. Akademie Verlag, Berlin.

Guenther, E. (1950). *The Essential Oils*. Vol. IV, p. 599. D. Van Nostrand, Inc., Princeton, New Jersey.

Henry, S. A. (1938). Further observations of dermatitis due to celery in vegetable canning. *Br. J. Derm.* **50,** 342.

Henry, S. A., Cantab, M. D. & Cantab, D. P. H. (1933). Celery itch: Dermatitis due to celery vegetable canning. *Br. J. Derm.* **45,** 301.

Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47,** 393.

Kligman, A. M. (1973). Report to RIFM, 10 July.

Moreno, O. M. (1973). Report to RIFM, 1 February.

Urbach, F. & Forbes, P. D. (1972). Report to RIFM, 19 December.

Wiswell, J. *et al.* (1948). Contact dermatitis of celery farmers. *J. Allergy* **19,** 396.

CHAMOMILE OIL GERMAN

Synonyms: Blue chamomile oil; Hungarian chamomile oil.
Description and physical properties: EOA Spec. no. 156. A constituent of chamomile oil German is chamazulene (Gildemeister & Hoffman, 1961; Guenther, 1952).
Occurrence: Found in the plant *Matricaria chamomilla* L. (Fam. Compositae).
Preparation: By steam distillation of the flowers and stalks of *Matricaria chamomilla* L.
Uses: In public use before the 1900s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·0005	0·002	0·04
Maximum	0·06	0·006	0·02	0·4

Analytical data: Gas chromatogram, RIFM no. 72–98; infra-red curve, RIFM no. 72–98.

Status

Chamomile oil German was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) included chamomile oil (*Matricaria chamomilla*) in the list of substances, spices and seasonings deemed admissible for use with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on chamomile oil German.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. Undiluted chamomile oil applied to the backs of hairless mice produced no irritating effects (Urbach & Forbes, 1973). Applied full strength to intact or abraded rabbit skin for 24 hr under occlusion, it was moderately irritating (Moreno, 1973). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1973).

Phototoxicity. No phototoxic effects were reported for chamomile oil German (Urbach & Forbes, 1973).

References

Council of Europe (1970). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List N(1), Series 1(b), no. 273, p. 22. Strasbourg.
Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. No. 2273. *Fd Technol., Champaign* **19**(2), part 2, 155.
Food Chemicals Codex (1972). 2nd ed. Prepared by the Committee on Specifications, Food Chemicals Codex, of the Committee on Food Protection. p. 187. National Academy of Sciences–National Research Council Publ. 1406, Washington, D.C.
Gildemeister, E. u. Hoffman, F. (1961). *Die Ätherischen Öle.* Vol. VII, p. 649. Akademie Verlag, Berlin.
Guenther, E. (1952). *The Essential Oils.* Vol. V, p. 438. D. Van Nostrand, Inc., Princeton, New Jersey.
Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.
Kligman, A. M. (1973). Report to RIFM, 31 October.
Moreno, O. M. (1973). Report to RIFM, 18 July.
Urbach, F. & Forbes, P. D. (1973). Report to RIFM, 18 July.

CHAMOMILE OIL ROMAN

Synonyms: Camomile oil; English chamomile oil.
Description and physical properties: EOA Spec. no. 177. The chief constituents of chamomile oil Roman are *n*-butyl angelate and isoamyl angelate (Gildemeister & Hoffman, 1961; Guenther, 1952).
Occurrence: Found in the flowers of the plant *Anthemis nobilis* L. (Fam. Compositae).
Preparation: By steam distillation of the dried flowers of *Anthemis nobilis* L.
Uses: In public use before the 1900s. Use in fragrances in the USA amounts to less than 3000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·0005	0·002	0·04
Maximum	0·06	0·006	0·02	0·4

Status

Chamomile oil Roman was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) included chamomile oil in the list of substances, spices and seasonings deemed admissible for use with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on chamomile oil Roman.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. Undiluted chamomile oil Roman applied to the backs of hairless mice produced no irritating effects (Urbach & Forbes, 1973). Applied full strength to intact or abraded rabbit skin for 24 hr under occlusion, it was moderately irritating (Moreno, 1973). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1973).

Phototoxicity. No phototoxic effects were reported for chamomile oil Roman (Urbach & Forbes, 1973).

References

Council of Europe (1970). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List N(1), Series 1(b), no. 48, p. 14. Strasbourg.
Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. No. 2275. *Fd Technol., Champaign* **19**(2), part 2, 155.
Food Chemicals Codex (1972). 2nd ed. Prepared by the Committee on Specifications, Food Chemicals Codex, of the Committee on Food Protection. p. 186. National Academy of Sciences–National Research Council Publ. 1406, Washington, D.C.
Gildemeister, E. u. Hoffman, F. (1961). *Die Ätherischen Öle*. Vol. VII, p. 634. Akademie Verlag, Berlin.
Guenther, E. (1952). *The Essential Oils*. Vol. V, p. 433. D. Van Nostrand, Inc., Princeton, New Jersey.
Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.
Kligman, A. M. (1973). Report to RIFM, 11 October.
Moreno, O. M. (1973). Report to RIFM, 14 June.
Urbach, F. & Forbes, P. D. (1973). Report to RIFM, 18 July.

CHENOPODIUM OIL

Synonym: American wormseed oil.

Description and physical properties: *Merck Index* (1968). The main constituent of chenopodium oil is ascaridole (1,4-peroxido-*p*-menth-2-ene), which has been found in amounts as high as 90% depending on the geographical source and species (Gupta & Behari, 1972; Nakolaev, 1956). American chenopodium oil from *Chenopodium ambrosioides* L. var. *anthelminticum* has been reported to contain 60–70% ascaridole, plus *p*-cymene, α-terpinene, *l*-limonene, methadiene and camphor (*Merck Index*, 1968; Van Prooijen, 1970). Oil of *C. ambrosioides* from Indian sources contains only 20% ascaridole, plus *p*-cymene, higher saturated hydrocarbons (predominantly C_{29}), heptacosan-14-one, triacontyl alcohol and α-spinasterol (Gupta & Behari, 1972). Aritasone has been isolated from *C. ambrosioides* (Nakajima, 1962).

Occurrence: Found in the flowers and fruit of the plant *C. ambrosioides* and *C. ambrosioides* L. var. *anthelminticum* (L.) A. Gray (Fam. Chenopodiaceae) (Guenther, 1952).

Preparation: By steam distillation from the overground parts of the flowering and fruiting plant, *C. ambrosioides* (Guenther, 1952).

Uses: In public use since before the 1900s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·04
Maximum	0·1	0·01	0·03	0·4

Status

The Council of Europe (1974) included chenopodium oil (*C. ambrosioides*) in the list of natural flavouring substances not admitted at present but open to reconsideration.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 0·255 g/kg while the acute dermal LD_{50} in rabbits was reported as 0·415 g/kg (McGee, 1974). At full strength, chenopodium oil applied to the backs of hairless mice was toxic (Urbach & Forbes, 1974). The acute oral LD_{50} in mice was found to be 0·38 ml/kg (Kasahara, 1956).

The lethal dose of chenopodium oil for the hen was reported as 0·6 ml/kg; toxic signs were seen in hens at 0·3 ml/kg and in dogs as 0·28–0·4 ml/kg (Szakáll, 1940).

When 23 rats were given a single ip injection of 0·12 ml/kg, the toxic effects seen included disturbances of balance and generalized tetanic contractions; all animals died within 18 hr. In a further group of ten rats given four ip injections each of 0·07 ml/kg on alternate days, disturbances of balance and orientation were milder than in the previous group and were accompanied by torpor, anorexia and weight loss but no fatalities occurred. Autopsy revealed cerebral hyperaemia and oedema with degeneration of the nerve cells together with loss of RNA. A primary action on the CNS was suggested (Cheli & Soragni, 1953).

Acute poisoning of rats with chenopodium oil produced an increase in liver lipids, but no change in liver RNA content (Rezza & Soragni, 1951).

Human toxicity and fatal poisoning. Toxic effects include skin and mucous-membrane irritation, headache, vertigo, nausea, vomiting, constipation, tinnitus, temporary deafness, diplopia and blindness, transient stimulation followed by depression of the CNS leading to delirium and coma, occasional convulsions, circulatory collapse due to vasomotor paralysis and sometimes pulmonary oedema. Chenopodium oil is also toxic to the kidneys and liver and haematuria, albuminuria and jaundice have been observed. Doses of 0·2–1·2 ml have been used but the usual adult dose is 1 ml (Gleason, Gosselin, Hodge & Smith, 1969; Goodman & Gilman, 1960; *Martindale, The Extra Pharmacopoeia*, 1972).

Several reports of fatal poisoning followed the therapeutic use of chenopodium oil in man (Campagne, 1939; Ibru-Määr, 1932; Kröber, 1936; Mele, 1952; Wolf, 1935). For example, a 14-month-old baby given one teaspoonful of chenopodium oil exhibited vomiting, convulsions, weakness, sleepiness and cardiac and respiratory disturbances followed by death 12 hr later (Mele, 1952). Autopsy showed hyperaemia of the CNS, pulmonary oedema with bronchopneumonic foci, changes in the myocardium and the kidneys, fatty liver degeneration and gastritis.

In another case of fatal poisoning, a 2-yr-old child suffering from sickle-cell anaemia was given 16 minims of oil of chenopodium in divided doses over 3 wk; she became comatose and died after a further 2 days. Albuminuria, degenerative changes in the liver and kidneys and cerebral oedema were evident (Wolf, 1935).

Irritation. Undiluted chenopodium oil applied to the backs of hairless mice and swine was irritating (Urbach & Forbes, 1974). Applied full strength to intact or abraded rabbit skin for 24 hr under occlusion, it was slightly irritating (McGee, 1974). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1975).

Phototoxicity. No phototoxic effects were reported for undiluted chenopodium oil on hairless mice and swine (Urbach & Forbes, 1974).

Metabolism. The oil is readily absorbed from the gastro-intestinal tract. It is partially eliminated in the lungs, but excretion via the urine or faeces does not appear to have been reported (Goodman & Gilman, 1960). Traces of ascaridole were found in the stomach and intestinal tract of a 14-month-old baby who died from poisoning with chenopodium oil (Mele, 1952).

Anthelmintic activity. Although it was one of the most effective drugs for the treatment of worms and parasites in horses, dogs and man, its use has been discontinued because of its toxic properties (*Drill's Pharmacology in Medicine*, 1958; *Merck Index*, 1968; *US Dispensatory*, 1967).

Pharmacology. In tests of antispasmodic activity, a saturated aqueous solution of chenopodium oil showed musculotropic spasmolytic activity against $BaCl_2$-induced spasms in rat duodenum, had a clear antihistaminic action in guinea-pig ileum and inhibited nicotine-induced spasms in rabbit jejunum (Debelmas & Rochat, 1967). Frogs, toads and guinea-pigs responded to chenopodium oil by a decrease in the rate and amplitude of the heart beat, ascribed to vagus excitation and myocardium intoxication (Donatelli, 1935).

Nematodes. When used for the mass treatment of hookworm carriers, chenopodium oil produced some temporary side effects including a feeling of intoxication, headache, dizziness, enervation and nausea (Komiya, Ishizaki, Sato, Yokokawa, Komiyama & Ohtake, 1954). Chenopodium oil killed eggs of *Ascarius lumbricoides* in 20–40 days (Piringer & Motta-Montes, 1956). It was only 14% effective against *Ascaridia galli* in chicks (Zarnowski & Darski, 1957). Against oxyurids in rats the oil was very efficient but also toxic (Coppi, Ciani-Bonardi & Genova, 1968). Chenopodium oil was not effective against *Trichuris muris* in the albino mouse (Keeling, 1961). It was effective in the mass treatment of hookworm carriers (Komiya *et al.* 1954). Chenopodium oil was effective against larvae and adults of the soil nematode *Rhabditis axei*, with total mortality in 10–20 min (Frick, 1963). Chenopodium oil containing 60–70% ascaridole produced, at concentrations of 0·001–1·0%, an excitatory action, with subsequent fatal paralysis, on pig ascaris; a fraction of American wormseed oil had a similar effect (Kasahara, 1956). The effects of chenopodium oil on enzymes of pig roundworm were studied by Honda (1958): phosphatase activity was decreased with progressive paralysis, and succinic dehydrogenase and phosphorylase activities were also decreased. Chenopodium oil had an effect on the motility of ascarids similar to that of oxygen but the reaction mechanism was different. The catalase activity was inhibited but not completely destroyed, so that H_2O_2 did not accumulate in the organism (Krotov & Kats, 1958).

Micro-organisms. The vapour of chenopodium oil inhibited the growth of *Mycobacterium avium* but not of four other bacteria tested by Maruzzella & Sicurella (1960). Chenopodium oil alone or in combination with other volatile or fixed oils showed some *in vitro* antibacterial activity in tests against five bacteria (Maruzzella & Henry, 1958). It also showed strong *in vitro* antifungal activity, inhibiting the growth of 17 of 18 fungi tested (Maruzzella & Liguori, 1958), and was found to possess antifungal activity against all 12 phytopathogenic fungi tested by Maruzzella & Balter (1959) and to cause marked inhibition of the growth of three wood-destroying fungi tested by Maruzzella, Scrandis, Scrandis & Grabon (1960). Plant oils, including chenopodium oil, showed distinct but not always complete bacteriostatic activity against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Candida albicans* (Koscik, 1955).

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CINNAMIC ALCOHOL

Synonym: Cinnamyl alcohol.
Structure: $C_6H_5 \cdot CH:CH \cdot CH_2OH$.
Description and physical properties: EOA Spec. no. 28.
Occurrence: Found as an ester or in the free state in several natural products (cinnamon leaves, hyacinth, *Aristolochia clematis*, and *Xanthorrhoea hastilis*) and also in the essence of daffodil flowers (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: By reduction of cinnamic aldehyde.
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to approximately 150,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·05	0·005	0·03	0·3
Maximum	0·3	0·03	0·15	1·2

Analytical data: Gas chromatogram, RIFM no. 73–12; infra-red curve, RIFM no. 73–12.

Status

Cinnamic alcohol was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) listed cinnamic alcohol giving an ADI of 1·25 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on cinnamic alcohol.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 2·0 g/kg (1·73–2·27 g/kg) (Moreno, 1973). The acute dermal LD_{50} value in rabbits was reported as >5 g/kg (Moreno, 1973).

Irritation. Cinnamic alcohol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1973). A patch test using full-strength cinnamic alcohol for 24 hr produced no reactions in twenty human subjects (Katz, 1946).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Greif, 1967). Positive reactions to 5% cinnamic alcohol in vaseline were reported in 26 out of 144 patients who were already sensitized to Peru balsam (Hjorth, 1961).

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CINNAMIC ALDEHYDE DIMETHYL ACETAL

Synonym: 3-Phenyl-2-propenal dimethyl acetal.
Structure: $C_6H_5 \cdot CH:CH \cdot CH(OCH_3)_2$.
Description and physical properties: EOA Spec. no. 278.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By the interaction of cinnamic aldehyde and methanol in the presence of a catalyst or by treating cinnamic aldehyde with trimethyl orthoformate.
Uses: In public use since the 1950s.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·002	0·003	0·08
Maximum	0·2	0·03	0·03	0·25

Analytical data: Gas chromatogram, RIFM no. 72–16; infra-red curve, RIFM nos 72–16, 74–155.

Status

Cinnamic aldehyde dimethyl acetal is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974), or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 3·7 g/kg (3·3–4·1 g/kg) (Moreno, 1972a). The acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1972b).

Irritation. Cinnamic aldehyde dimethyl acetal applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1972b). Tested at 10% in petrolatum in a 48-hr closed-patch test on human subjects, sample RIFM no. 72–10–16 produced irritation (Kligman, 1972), sample RIFM no. 72–10–261 produced no irritation (Kligman, 1973) and sample RIFM no. 74–10–155R6G produced irritation (Epstein, 1974). The latter sample still produced irritant reactions at 5%.

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material (RIFM no. 72–10–16) was tested at a concentration of 10% in petrolatum and produced sensitization reactions in six of the 25 subjects (Kligman, 1972). This material contained 0·8% free cinnamic aldehyde. When the material RIFM no. 72–10–261 was subjected to the same maximization test in a concentration of 10% in petrolatum, it produced no sensitization reactions in the 25 volunteers tested (Kligman, 1973). This material contained no free cinnamic aldehyde. RIFM no. 74–10–155R6G, which contained trace amounts of free cinnamic aldehyde, produced ten reactions in 26 test subjects when tested at a concentration of 10% in petrolatum by this maximization test. [Unlike the other two samples, the sample that produced no reactions was made by reacting cinnamic aldehyde and trimethyl orthoformate, a method that leaves no residual free aldehyde and produces a product that does not readily hydrolyse to give any. It appears that the sensitization reactions were attributable to the presence of cinnamic aldehyde.]

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CINNAMON BARK OIL, "CEYLON"

Description and physical properties: EOA Spec. no. 87. The chief constituent of cinnamon bark oil is cinnamic aldehyde (Gildemeister & Hoffman, 1959; Guenther, 1950).
Occurrence: Found in the bark of the shrub *Cinnamomum zeylanicum* Nees (Fam: Lauraceae).
Preparation: By steam distillation of the dried inner bark of the shrub *C. zeylanicum* Nees (Guenther, 1950).
Uses: In public use since the 1860s. Use in fragrances in the USA amounts to less than 4000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	—	—	0·003	0·09
Maximum	—	—	0·01	0·8

Analytical data: Gas chromatogram, RIFM no. 72–99; infra-red curve, RIFM no. 72–99.

Status

Cinnamon bark oil, Ceylon, was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) included cinnamon bark oil, Ceylon, in its list of substances, spices and seasonings whose use is deemed admissible with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on cinnamon bark oil, Ceylon.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 3·4 ml/kg (2·9–4·0 ml/kg) and the acute dermal LD_{50} value in rabbits as 0·69 ml/kg (0·58–0·82 ml/kg) (Shelanski, 1972).

Irritation. Undiluted cinnamon bark oil, Ceylon, applied to the backs of hairless mice was mildly irritating (Urbach & Forbes, 1972), and applied to intact or abraded rabbit skin for 24 hr under occlusion was severely irritating (Shelanski, 1972). Tested at 8% in petrolatum, the oil produced no irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1972; RIFM no. 72–8–99). Retested at 8% in petrolatum, it again produced no irritation (Kligman, 1973; RIFM no. 72–8–248R).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material (RIFM no. 72–8–99) was tested at a concentration of 8% in petrolatum and produced 18 sensitization reactions (Kligman, 1972). A further maximization test (Kligman, 1966) carried out on 25 volunteers using the material (RIFM no. 72–8–248R) at a concentration of 8% in petrolatum produced 20 out of 25 sensitization reactions (Kligman, 1973).

Phototoxicity. Low-level phototoxic effects were reported for cinnamon bark oil, Ceylon, but were not considered significant (Urbach & Forbes, 1972).

Metabolism. Cinnamic aldehyde, the chief constituent of cinnamon bark oil, is oxidized to cinnamic acid, which is then degraded to benzoic acid (Williams, 1959).

Additional published data

Three cases of acute contact sensitivity to a dentifrice have been reported. Subsequent testing attributed these reactions to cinnamon oil (Millard, 1973).

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CINNAMON LEAF OIL, CEYLON

Description and physical properties: EOA Spec. no. 56. The main constituent of cinnamon leaf oil is eugenol (Guenther, 1950).
Occurrence: Found in the plant *Cinnamomum zeylanicum* Nees (Fam. Lauraceae).
Preparation: By steam distillation of the leaves and twigs of *C. zeylanicum* Nees.
Uses: In public use since the 1900s. Use in fragrances in the USA amounts to less than 4000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·1
Maximum	0·2	0·03	0·03	0·8

Analytical data: Gas chromatogram, RIFM no. 72–100; infra-red curve, RIFM no. 72–100.

Status

Cinnamon leaf oil was given GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1974) included cinnamon leaf oil (*C. zeylanicum*) in the list of substances, spices and seasonings deemed admissible for use, with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on cinnamon leaf oil.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 2·65 g/kg (2·16–3·14 g/kg) (Moreno, 1973). The acute dermal LD_{50} in rabbits was reported as >5 g/kg (Moreno, 1973).

Irritation. Cinnamon leaf oil applied undiluted to the backs of hairless mice was moderately irritating (Urbach & Forbes, 1973). Applied full strength to intact or abraded rabbit skin for 24 hr under occlusion, it was strongly irritating (Moreno, 1973). Tested at 10% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1973). Sensitization of human skin has been caused by eugenol, eugenol derived from clove oil eliciting stronger reactions than that derived from cinnamon leaf oil (Woeber & Krombach, 1969).

Phototoxicity. No phototoxic effects were reported for cinnamon leaf oil (Urbach & Forbes, 1973).

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CINNAMYL ACETATE

Synonym: 3-Phenyl-2-propen-1-yl acetate.
Structure: $C_6H_5 \cdot CH:CH \cdot CH_2 \cdot CO_2 \cdot CH_3$.
Description and physical properties: Food Chemicals Codex (1972).
Occurrence: Found in cassia oil and several other essential oils (*Givaudan Index*, 1961).
Preparation: By direct esterification of cinnamic alcohol with acetic acid (or anhydride) under azeotropic conditions (Arctander, 1969).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 5000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·01	0·04
Maximum	0·1	0·01	0·1	0·5

Analytical data: Infra-red curve, RIFM no. 72–232.

Status

Cinnamyl acetate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) listed cinnamyl acetate, giving an ADI of 1·25 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on cinnamyl acetate.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported to be 3·3 g/kg (2·9–3·7 g/kg) (Moreno, 1972). The acute dermal LD_{50} was reported to be > 5 g/kg in the rabbit (Moreno, 1972).

Irritation. Cinnamyl acetate applied full strength to intact or abraded rabbit skin produced no irritation (Moreno, 1972). Tested at a concentration of 5% in petrolatum, it produced no irritation in a 48-hr closed-patch test in 25 human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 5% in petrolatum and produced no sensitization reactions (Kligman, 1972).

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CINNAMYL ANTHRANILATE

Synonyms: 3-Phenyl-2-propen-1-yl anthranilate; cinnamyl *o*-aminobenzoate.
Structure: $C_6H_5 \cdot CH{:}CH \cdot CH_2 \cdot OCO \cdot C_6H_4 \cdot NH_2$.
Description and physical properties: The *Givaudan Index* (1961).
Occurence: Has apparently not been reported to occur in nature.
Preparation: From isatoic anhydride plus cinnamic alcohol (Arctander, 1969).
Uses: In public use since the 1940s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·08
Maximum	0·1	0·01	0·02	0·4

Status

Cinnamyl anthranilate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included cinnamyl anthranilate at a level of 25 ppm (except for chewing gum) in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health. The *Food Chemicals Codex* (1972) has a monograph on cinnamyl anthranilate.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1974).

Subacute toxicity. The maximum tolerated dose (MTD) of cinnamyl anthranilate for mice was found to be 0·5 g/kg, determined as the maximum single dose tolerated by all of five mice after receiving six ip injections over a 2-wk period (Stoner, Shimkin, Kniazeff, Weisburger, Weisburger & Gori, 1973).

Irritation. Cinnamyl anthranilate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was slightly irritating (Moreno, 1974). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 24 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Epstein, 1974).

Carcinogenicity. Primary lung-tumour induction was significantly increased ($P < 0{\cdot}05$) compared with untreated controls when male and female A/He mice received ip injections of the MTD or 0·2 MTD 3 times/wk for 8 wk (total dose 12·00 or 2·40 g/kg, respectively), with 13–15 mice in each group of 15 surviving for 24 wk (Stoner *et al.* 1973).

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CINNAMYL BENZOATE

Structure: $C_6H_5 \cdot CH{:}CH \cdot CH_2 \cdot OCO \cdot C_6H_5$.
Description and physical properties: A white crystalline powder.
Occurrence: Reported to be found in Siam benzoin (*Fenaroli's Handbook of Flavor Ingredients*. 1975).
Preparation: From cinnamyl chloride and sodium benzoate or by reaction of cinnamyl alcohol with benzoic acid.
Uses: In public use since the 1940s. Use in fragrances in the USA amounts to less than 1000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·04
Maximum	0·1	0·01	0·05	0·5

Status

Cinnamyl benzoate is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included cinnamyl benzoate in the list of artificial flavouring substances not fully evaluated.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 4·0 g/kg (3·56–4·44 g/kg) and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1975).

Irritation. Cinnamyl benzoate applied undiluted to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1975). Tested at 5% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 5% in petrolatum and produced no sensitization reactions (Kligman, 1975).

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CINNAMYL CINNAMATE

Synonyms: Phenylallyl cinnamate; styracin.

Structure: $C_6H_5 \cdot CH{:}CH \cdot CH_2 \cdot OCO \cdot CH{:}CH \cdot C_6H_5$.

Description and physical properties: White or colourless crystals.

Occurrence: One of the most important constituents of styrax (*Liquidambar orientale, L. styraciflуum* L.), it is also found in White Peru and Honduras balsams (*Fenaroli's Handbook of Flavor Ingredients*, 1971).

Preparation: From cinnamic aldehyde plus aluminium ethylate in ether or by any other suitable means. It must not contain any free cinnamic aldehyde.

Uses: In public use before the 1920s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·08
Maximum	0·1	0·01	0·02	0·4

Status

Cinnamyl cinnamate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) listed cinnamyl cinnamate, giving an ADI of 1·25 mg/kg.

Biological data

Acute toxicity. The acute oral LD_{50} value for cinnamyl cinnamate in rats was reported as 4·2 g/kg, and the acute dermal LD_{50} value was greater than 5 g/kg (Wohl, 1974).

Irritation. Cinnamyl cinnamate applied full strength to the intact or abraded skin of rabbits produced no irritation (Wohl, 1974). Tested at 4% in petrolatum, it produced no irritation in a 48-hr closed-patch test on human subjects (Kligman, 1974). No acanthogenic effect was observed when cinnamyl cinnamate as a 40% solution in acetone was applied to guinea-pig skin daily for 8–10 days (Schaaf, 1961).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers using 4% cinnamyl cinnamate in petrolatum. No sensitization reactions were produced (Kligman, 1974).

Insects. Cinnamyl cinnamate was found to be a termite attractant (Watanabe & Casida, 1963).

Metabolism. Esters such as benzyl cinnamate are rapidly hydrolysed *in vivo*. Cinnamic alcohol is mainly metabolized to benzoic acid, presumably via cinnamic acid. In rabbits, cinnamic alcohol is oxidized (75%) to benzoic acid (Fischer & Bielig, 1940). Cinnamic acid is known to conjugate with glycine in the animal body, and it may also be converted to benzoic acid. In the rabbit, cinnamic acid is almost entirely excreted as hippuric acid without formation of cinnamoyl glycine (El Masry, Smith & Williams, 1956). In the dog, Quick (1928) observed a large excretion of glucuronide, probably benzoylglucuronide. Dakin (1909) found cinnamoyl glycine and acetophenone as minor metabolites in the dog (Williams, 1959).

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CINNAMYL FORMATE

Synonym: 3-Phenyl-2-propen-1-yl formate.
Structure: $C_6H_5 \cdot CH{:}CH \cdot CH_2 \cdot OCOH$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Has apparently not been reported to occur in nature.
Preparation: From cinnamic alcohol and mixed formic-acetic anhydride at low temperatures.
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to about 1000 lb/yr. Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·04
Maximum	0·1	0·01	0·03	0·4

Analytical data: Gas chromatogram, RIFM no. 72–101; infra-red curve, RIFM no. 72–101.

Status

Cinnamyl formate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) listed cinnamyl formate giving an ADI of 1·25 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on cinnamyl formate.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 2·9 g/kg (2·38–3·54 g/kg) and the acute dermal LD_{50} in rabbits as >5 g/kg (Denine, 1973).

Irritation. Cinnamyl formate applied undiluted to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Denine, 1973). Tested at 4% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1973).

Metabolism. Cinnamyl formate is hydrolysed by porcine pancreatic lipase 2·6 times more rapidly than is cinnamyl oleate under identical conditions (Brockerhoff, 1970).

Micro-organisms. Cinnamyl formate inhibited the growth of each of three species of wood-destroying fungi tested *in vitro* by the filter-paper-disc method (Maruzzella, Scrandis, Scrandis & Grabon, 1960) and the vapour inhibited the growth of each of four fungal species tested (Maruzzella, Chiaramonte & Garofolo, 1961), but in dilutions between 1:500 and 1:10,000 the ester did not show bactericidal activity against any of four species of bacteria (Maruzzella & Bramnick, 1961).

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CINNAMYL ISOVALERATE

Synonyms: Cinnamyl 3-methyl butyrate and other isomers.
Structure: $C_6H_5 \cdot CH:CH \cdot CH_2 \cdot OCO \cdot CH_2 \cdot CH(CH_3)_2$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By direct esterification of cinnamic alcohol with isovaleric acid under azeotropic conditions (Arctander, 1969).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·01	0·05
Maximum	0·05	0·005	0·03	0·2

Analytical data: Gas chromatogram, RIFM no. 72–102; infra-red curve, RIFM no. 72–102.

Status

Cinnamyl isovalerate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) listed cinnamyl isovalerate, giving an ADI of 1·25 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on cinnamyl isovalerate.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as ≥ 5 g/kg (Moreno, 1973). The acute dermal LD_{50} in rabbits was reported as > 5 g/kg (Moreno, 1973).

Irritation. Cinnamyl isovalerate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Moreno, 1973). Tested at 2% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 2% in petrolatum and produced no sensitization reactions (Kligman, 1973).

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CINNAMYL NITRILE

Synonym: Cinnamonitrile.
Structure: $C_6H_5 \cdot CH{:}CH \cdot CN$.
Description and physical properties: A colourless oily liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: From styryl bromide and potassium cyanide (Arctander, 1969).
Uses: Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·04
Maximum	0·1	0·01	0·03	0·4

Analytical data: Gas chromatogram. RIFM no. 74–174; infra-red curve, RIFM no. 74–174.

Status

Cinnamyl nitrile is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974) or in the Food Chemicals Codex (1972).

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 4·15 g/kg (3·67–4·63 g/kg) and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1974). In rabbits, iv injection of cinnamyl nitrile (20·3 mg/kg) caused death in 10 min. In guinea-pigs and rabbits, cinnamyl nitrile was found to produce the same effects as hydrogen cyanide, with almost equal toxicity, and rabbits given doses higher than the lethal dose were found to die almost as rapidly as those given hydrogen cyanide (Hunt, 1923).

Irritation. Cinnamyl nitrile applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1974). Tested at 4% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1975).

Metabolism. The toxicity of organic cyanides appears to depend almost entirely on whether they can be metabolized in the body to the free cyanide ion, and on the rate and extent of this conversion and the rate of detoxication of cyanide to thiocyanate. In general, alkyl and arylalkyl cyanides are metabolized with the formation of hydrogen cyanide, while the nitrile group of aryl cyanides is relatively stable. The high toxicity of iv-administered cinnamyl nitrile and the rapidity of death suggest that in rabbits this compound is metabolically converted to hydrogen cyanide (Hunt, 1923; Williams, 1959).

The reaction of cinnamyl nitrile with glutathione was found to be catalysed by glutathione *S*-alkenetransferases present in rat liver and to lesser degrees in rat kidney and in the livers of eight other vertebrate species. Although cinnamyl nitrile is not known to be metabolized to the mercapturic acid, the results suggest that the glutathione conjugate and related catabolites (cysteine derivatives and mercapturic acids) could be secreted in the bile, and eliminated from the body in the faeces after probable deconjugation by the gut flora, without being detected *in vivo* (Chasseaud, 1973).

Inhalation. Exposure of mice for 3 min to an aerosol of cinnamyl nitrile in polyethylene glycol-200 produced a maximum decrease of 40% in the respiratory rate. A concentration of 0·357 μmol/litre was required to produce a decrease of 50% of this maximum response. The decrease in respiratory rate was used as an index of sensory irritation of the upper respiratory tract. The sensory irritation reaction was apparently initiated by association of the compound with SH groups of a receptor molecule on the free endings of the afferent trigeminal nerve located at the surface of the nasal mucosa (Alarie, 1973).

Skin. Cinnamyl nitrile applied to the skin of mice on three consecutive days at concentrations of 5, 1 or 0·1% in acetone did not suppress non-specific esterase activity in the sebaceous glands of the skin. The method has been used as a predictive screening test for carcinogenesis, since the degree of suppression has been found to correlate with the known potency of carcinogenic compounds (Barry, Chasseaud, Hunter & Robinson, 1972).

Micro-organisms. Cinnamyl nitrile showed little or no activity against nine bacteria and fungi (Ishida, Senfu, Matsuda, Kawamura & Yamanaka, 1960).

Cytotoxicity. Cinnamyl nitrile showed no cytotoxic activity against cultured tumour cells at concentrations of 50, 100 or 200 μmol/litre (Doré, Sekera, Redeuilh & Viel, 1973; Viel & Doré, 1972).

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CINNAMYL PROPIONATE

Synonym: 3-Phenyl-2-propenyl propionate.
Structure: $C_6H_5 \cdot CH{:}CH \cdot CH_2 \cdot OCO \cdot CH_2 \cdot CH_3$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By direct esterification of cinnamic alcohol with propionic acid under azeotropic conditions, or with propionic anhydride (Arctander, 1969).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·1
Maximum	0·1	0·01	0·03	0·4

Status

Cinnamyl propionate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) listed cinnamyl propionate giving an ADI of 1·25 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on cinnamyl propionate.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 3·4 g/kg (3·2–3·6 g/kg) (Moreno, 1973). The acute dermal LD_{50} value in rabbits was reported as >5 g/kg (Moreno, 1973).

Irritation. Cinnamyl propionate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was mildly irritating (Moreno, 1973). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1973).

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CINNAMYL TIGLATE

Synonym: Cinnamyl *trans*-α-methylcrotonate.
Structure: $C_6H_5 \cdot CH{:}CH \cdot CH_2 \cdot OCO \cdot C(CH_3){:}CH \cdot CH_3$.
Description and physical properties: A colourless oily liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By direct esterification of cinnamic alcohol with tiglic acid under azeotropic conditions (Arctander, 1969).
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to less than 1000 lb/yr. Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·04
Maximum	0·1	0·01	0·03	0·4

Analytical data: Gas chromatogram, RIFM no. 75–15; infra-red curve, RIFM no. 75–15.

Status

Cinnamyl tiglate was not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974) or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Levenstein, 1975).

Irritation. Cinnamyl tiglate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Levenstein, 1975). Tested at 4% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 24 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Epstein, 1975).

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CITRAL DIMETHYL ACETAL

Synonyms: *cis-* and *trans*-3,7-Dimethyl-1,1-dimethoxy-2,6-octadienes; *cis-* and *trans*-2,6-dimethyl-8,8-dimethoxy-2,6-octadiene.

Structure: $CH_3 \cdot C(CH_3):CH \cdot [CH_2]_2 \cdot C(CH_3):CH \cdot CH(OCH_3)_2$.

Description and physical properties: EOA Spec. no. 273.

Occurrence: Apparently has not been reported to occur in nature.

Preparation: From citral and methyl alcohol in the presence of a catalyst, or by reacting citral with trimethyl orthoformate.

Uses: In public use since the 1920s. Use in fragrances in the USA amounts to less than 50,000 lb/yr.

Concentration in final product (%).

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·005	0·03	0·05
Maximum	0·15	0·02	0·15	0·4

Status

Citral dimethyl acetal was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) listed citral dimethyl acetal, giving an ADI of 5 mg/kg.

Biological data

Acute toxicity. Both the oral LD_{50} value in rats and the dermal LD_{50} value in rabbits exceeded 5 g/kg (Hart, 1971).

Irritation. Citral dimethyl acetal applied full strength to intact or abraded rabbit skin was irritating (Hart, 1971). Tested at a concentration of 4% in petrolatum, it produced no irritation in a 48-hr closed-patch test in 25 human subjects (Kligman, 1971).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1971).

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CITRONELLA OIL

Description and physical properties: EOA Spec. nos 12 and 14. The main constituents of citronella oil are geraniol and citronellal (Guenther, 1950).
Occurrence: Found in the grasses of *Cymbopogon Nardus* (Rendle), *Andropogon Nardus* (L) and *Andropogon Nardus* Ceylon, de Jong (Fam. Gramineae).
Preparation: By direct steam-distillation of the dried grass.
Uses: In public use since the 1900s. Use in fragrances in the USA amounts to about 400,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·01	0·03	0·2
Maximum	0·60	0·03	0·30	0·80

Analytical data: Gas chromatogram, RIFM no. 2008, 71–92, 71–93; infra-red curve, RIFM no. 2008, 71–92, 71–93.

Status

Citronella was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) included citronella (*Cymbopogon Nardus*) in the list of substances, spices and seasonings whose use is deemed admissible, with a possible limitation on the active principle in the final product.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as > 5 g/kg (Shelanski & Moldovan, 1971). The acute dermal LD_{50} in rabbits was reported as 4·7 ml/kg (3·4–6·7 ml/kg) (Shelanski & Moldovan, 1971).

Irritation. Citronella oil applied at full strength to intact or abraded rabbit skin caused irritation (Shelanski & Moldovan, 1971). Three different samples of citronella oil, RIFM nos 2008 (citronella Formosa), 71–92 (citronella Ceylon) and 71–93 (citronella Java), tested at a concentration of 8% in petrolatum produced no irritation in a 48-hr closed-patch test in 25 human subjects (Kligman, 1971).

Sensitization. Maximization tests (Kligman, 1966) carried out on 25 volunteers at a concentration of 8% in petrolatum using three different samples of citronella oil, RIFM nos 2008 (citronella Formosa), 71–92 (citronella Ceylon) and 71–93 (citronella Java) produced no sensitization reactions (Kligman, 1971).

Additional published data

Three cases of an eczematous, contact-type of hypersensitivity to oil of citronella have been reported (Keil, 1947). Folliculitis of the acneform type has been induced by citronella oil (Lane, 1922). A case of papulovesicular eczema of the hands, fingers and forearms, verified by a patch test with oil of citronella, has also been reported (Flandin, Rabeau & Ukrainczyk, 1937). Oil of citronella in perfumes is listed as a primary irritant and sensitizer by Schwartz & Peck (1946) and Schwartz, Tulipan & Peck (1947).

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Shelanski, M. V. & Moldovan, M. (1971). Report to RIFM, 14 November and 26 November.

CITRONELLAL

Synonym: 3,7-Dimethyl-6-octen-1-al.
Structure: $(CH_3)_2C{:}CH\cdot[CH_2]_2\cdot CH(CH_3)\cdot CH_2\cdot CHO$.
Description and physical properties: EOA Spec. no. 227.
Occurrence: The *d*-form of citronellal has been reported in the oil of citronella (Ceylon, Jammus, Kaschmis), in the oil from leaves of *Barosma pulchella*, in the oil from roots of *Phebalium nudum* and in the oils of *Eucalyptus citriodora*, *Leptospermum citratum* and *Baeckea citriodora*. The *l*-form is present in the oils of *Backhousia citriodora* var. A, *E. citriodora*, *Litsea cubeba* (fruits) and lemongrass. Citronellal is generally present also in the oils of lemon, mandarin, *Lavandula delphinensis*, *Ocimum canum* f. *citrata* and many others (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: By fractional distillation of natural oils such as citronella or by chemical synthesis (Bedoukian, 1967).
Uses: In public use since the 1900s. Use in fragrances in the USA amounts to approximately 4000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·08
Maximum	0·1	0·01	0·03	0·3

Analytical data: Gas chromatogram, RIFM nos 70–19, 73–14; infra-red curve, RIFM nos 70–19, 73–14.

Status

Citronellal was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) listed citronellal, giving an ADI of 0·25 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on citronellal.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as >5 g/kg (Moreno, 1973). The acute dermal LD_{50} value in rabbits was reported as $>2{\cdot}5$ g/kg (Moreno, 1973).

Irritation. Citronellal applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1973). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1973).

Three cases of eczematous contact-type hypersensitivity to oils of citronella are recorded. In two instances detailed patch-test studies were made with the ingredients of oil of citronella and some related substances. The essential allergen in oil of citronella was reported to be citronellal (Keil, 1947).

Metabolism. Feeding 50 g citronellal to rabbits was followed by the isolation of 13 g of a crystalline glucuronide, which proved to be *p*-menthane-3,8-diol-D-glucuronide. The citronellal appeared to have been cyclized and the glucuronide obtained was identical with that obtained on feeding *p*-menthane-3,8-diol (menthoglycol) (Kühn & Löw, 1938). However, evidence was produced to show that the cyclization was not, strictly speaking, a biological reaction, but a chemical one which took place in the stomach under the influence of the gastric hydrochloric acid. The conjugation of the menthoglycol with glucuronic acid was, of course, a purely biological reaction. It was found that on shaking 20 g citronellal with 200 ml 0·5% HCl for 48 hr at 37°C, 12 g menthoglycol was formed (Kühn & Löw, 1938).

Additional published data

Citronellal has been used experimentally in the treatment of human carcinoma (Osato, 1965; Osato, Oda & Sato, 1954).

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Moreno, O. M. (1973). Report to RIFM, 19 July.

Osato, S. (1965). Chemotherapy of human carcinoma with citronellal and citral and their actions on carcinoma tissue in its histological aspects up to healing. *Tohoku J. exp. Med.* **86,** 102.

Osato, S., Oda, K. et Sato, F. (1954). Action directe du citral et du citronellal sur la cellule cancéreuse. *C.r. Séanc. Soc. Biol.* **148,** 768.

CITRONELLOL

Synonym: 3,7-Dimethyl-6-octen-1-ol.
Structure: $(CH_3)_2C{:}CH \cdot [CH_2]_2 \cdot CH(CH_3) \cdot CH_2 \cdot CH_2OH$.
Description and physical properties: EOA Spec. no. 17.
Occurrence: *l*-Citronellol has been found in nature in the plants of the Rosaceae family. The *d*- and *dl*-forms have been identified in Verbenaceae, Labiatae, Rutaceae, Geraniaceae and others. Citronellol has been reported in about 70 essential oils and in the oil of *Rosa bourbonia*. Bulgarian rose oil has been reported to contain more than 50% *l*-citronellol, while East African geranium contains more than 80% of the *d*-isomer (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: By reduction of citronellal or geraniol or by fractional distillation of such essential oils as geranium and citronella (Bedoukian, 1967).
Uses: In public use since the 1900s. Use in fragrances in the USA amounts to approximately 150,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·04	0·004	0·025	0·5
Maximum	0·3	0·03	0·1	1·5

Analytical data: Gas chromatogram, RIFM nos 70–38, 73–15; infra-red curve, RIFM nos 70–38, 73–15.

Status

Citronellol was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) listed citronellol, giving an ADI of 0·25 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on citronellol and the Joint FAO/WHO Expert Committee on Food Additives (1967) has published a monograph and specifications for citronellol, giving a conditional ADI of 0–0·25 mg/kg.

Biologic[illegible]ata

Acute toxicity. The acute oral LD_{50} value in rats was reported as 3·45 g/kg (3·21–3·69 g/kg) (Moreno, 1973). The acute dermal LD_{50} value in rabbits was reported as 2·65 g/kg (1·78–3·52 g/kg) (Moreno, 1973). The im LD_{50} value in mice was reported as 4 g/kg (Northover & Verghese, 1962).

Irritation. Citronellol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1973). A 24-hr patch test using full strength citronellol produced no irritation reactions in 20 subjects (Katz, 1946).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 6% in petrolatum and produced no sensitization reactions (Greif, 1967).

A patch test using a 1% concentration of citronellol in acetone gave a positive reaction in subjects allergic to citronella oil (Keil, 1947).

Antimicrobial activity. Citronellol was studied for its activity against certain gram-negative and gram-positive organisms, using the agar-cup plate method. The most susceptible organisms were found to be *Staphylococcus aureus*, *S. albus*, *Vibrio cholerae*, *Escherichia coli* and *Corynebacterium diptheria* (Narasimha & Nigam, 1970).

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Council of Europe (1974). Natural Flavouring Substances, Their Sources, and Added Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List 1, no. 59, p. 136. Strasbourg.

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CITRONELLYL ACETATE

Synonyms: 2,6-dimethyl-(1 or 2)-octene-8-yl acetate; 3,7-dimethyl-6-octen-1-yl acetate.
Structure: $CH_3 \cdot C(CH_3):CH \cdot [CH_2]_2 \cdot CH(CH_3) \cdot [CH_2]_2 \cdot CO_2 \cdot CH_3$.
Description and physical properties: EOA Spec. no. 125.
Occurrence: Found in oils of citronella Ceylon, geranium and about twenty other oils (Gildemeister & Hoffman, 1966).
Preparation: By esterification of citronellol with acetic acid or acetic anhydride.
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to less than 20,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·03	0·12
Maximum	0·10	0·01	0·10	0·40

Analytical data: Gas chromatogram, RIFM no. 70–40; infra-red curve, RIFM no. 70–40.

Status

Citronellyl acetate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) listed citronellyl acetate, giving an ADI of 0·25 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on citronellyl acetate.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported to be 6·8 g/kg (Calandra, 1971). The acute dermal LD_{50} in rabbits was reported to be >2 g/kg (Calandra, 1971).

Irritation. Citronellyl acetate applied full strength to intact or abraded rabbit skin was irritating (Calandra, 1971). Tested at a concentration of 4% in petrolatum, it produced a mild irritation in a 48-hr closed-patch test in 25 human subjects (Kligman, 1971).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1971).

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Kligman, A. M. (1971). Report to RIFM, 25 March.

CITRONELLYL *n*-BUTYRATE

Synonyms: 3,7-Dimethyl-6-octen-1-yl *n*-butyrate; 2,6-dimethyl-2-octen-8-yl *n*-butyrate.
Structure: $CH_3 \cdot C(CH_3):CH \cdot [CH_2]_2 \cdot CH(CH_3) \cdot [CH_2]_2 \cdot CO_2 \cdot [CH_2]_2 \cdot CH_3$.
Description and physical properties: Food Chemicals Codex (1972).
Occurrence: Found in oil of citronella Ceylon and the leaf oil of *Phebalium dentatum* (Gildemeister & Hoffman, 1966).
Preparation: By direct esterification of citronellol with butyric acid under azeotropic conditions or by treatment with butyric anhydride (Gildemeister & Hoffman, 1966).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·01	0·04
Maximum	0·05	0·005	0·05	0·4

Analytical data: Infra-red curve, RIFM no. 72–104.

Status

Citronellyl butyrate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) listed citronellyl butyrate, giving an ADI of 0·25 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on citronellyl butyrate.

Biological data

Acute toxicity. Both the oral LD_{50} value in rats and the dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1972).

Irritation. Citronellyl butyrate applied full strength to intact or abraded rabbit skin was not irritating (Moreno, 1972). Tested at a concentration of 5% in petrolatum, it produced no irritation in a 48-hr closed-patch test in 25 human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 5% in petrolatum and produced no sensitization reactions (Kligman, 1972).

References

Council of Europe (1970). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List A(1), Series 1, no. 276, p. 64. Strasbourg.
Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. No. 2312. *Fd Technol., Champaign* **19**(2), part 2, 155.
Food Chemicals Codex (1972). 2nd ed. Prepared by the Committee on Specifications, Food Chemicals Codex, of the Committee on Food Protection. p. 209. National Academy of Sciences-National Research Council Publ. 1406, Washington, D.C.
Gildemeister, E. & Hoffman, F. (1966). *Die Ätherischen Öle.* Vol. IIId. p. 270. Akademie Verlag, Berlin.
Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.
Kligman, A. M. (1972). Report to RIFM, 13 October.
Moreno, O. M. (1972). Report to RIFM, 1 November.

CITRONELLYL CROTONATE

Synonyms: Citronellyl 2-butenoate; citronellyl α-crotonate.
Structure: $CH_3 \cdot C(CH_3):CH \cdot [CH_2]_2 \cdot CH(CH_3) \cdot [CH_2]_2 \cdot OCO \cdot CH:CH \cdot CH_3$.
Description and physical properties: A colourless or pale straw-coloured liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By direct esterification of citronellol with 2-butenoic acid under azeotropic conditions (Arctander, 1969).
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to less than 1000 lb/yr. Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·015	0·2
Maximum	0·2	0·02	0·06	0·8

Analytical data: Gas chromatogram, RIFM no. 75–16; infra-red curve, RIFM no. 75–16.

Status

Citronellyl crotonate is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974) or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1975).

Irritation. Citronellyl crotonate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1975). Tested at 8% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1975).

References

Arctander, S. (1969). *Perfume and Flavor Chemicals (Aroma Chemicals)*. Vol. 1, no. 679. S. Arctander, Montclair, New Jersey.

Council of Europe (1974). Natural Flavouring Substances, Their Sources, and Added Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. Strasbourg.

Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. *Fd Technol., Champaign* **19**(2), part 2, 155.

Food Chemicals Codex (1972). 2nd Ed. Prepared by the Committee on Specifications, Food Chemicals Codex, of the Committee on Food Protection. National Academy of Sciences–National Research Council Publ. 1406, Washington, D.C.

Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.

Kligman, A. M. (1975). Report to RIFM 19 May.

Kligman, A. M. & Epstein, W. (1975). Updating the maximization test for identifying contact allergens. *Contact Dermatitis* **1**, 231.

Moreno, O. M. (1975). Report to RIFM, 22 May.

CITRONELLYL FORMATE

Synonyms: 2,6-Dimethyl-(1-or-2)-octen-8-yl formate; 3,7-dimethyl-6-octen-yl formate.
Structure: $CH_3 \cdot C(CH_3):CH \cdot [CH_2]_2 \cdot CH(CH_3) \cdot [CH_2]_2 \cdot CO_2 \cdot H$.
Description and physical properties: EOA Spec. no. 206.
Occurrence: Found in nature in geranium oil.
Preparation: By esterification of citronellol with formic acid.
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to less than 40,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·04
Maximum	0·05	0·05	0·03	0·4

Analytical data: Gas chromatogram, RIFM no. 70–41; infra-red curve, RIFM no. 70–41.

Status

Citronellyl formate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) listed citronellyl formate giving an ADI of 0·25 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on citronellyl formate.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported to be 8·4 g/kg (Calandra, 1971). The acute dermal LD_{50} in rabbits was reported to be >2 g/kg (Calandra, 1971).

Irritation. Citronellyl formate applied full strength to intact or abraded rabbit skin was irritating (Calandra, 1971). Tested at a concentration of 4% in petrolatum, it produced a mild irritation in a 48-hr closed-patch test in 25 human subjects (Kligman, 1971).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1971).

References

Calandra, J. C. (1971). Report to RIFM, 12 April.
Council of Europe (1970). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List A(1), Series 1, no. 346, p. 68. Strasbourg.
Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. No. 2314. *Fd Technol., Champaign* **19**(2), part 2, 155.
Food Chemicals Codex (1972). 2nd ed. Prepared by the Committee on Specifications, Food Chemicals Codex, of the Committee on Food Protection. p. 210. National Academy of Sciences–National Research Council Publ. 1406, Washington, D.C.
Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.
Kligman, A. M. (1971). Report to RIFM, 25 March.

CITRONELLYL OXYACETALDEHYDE

Synonym: 6,10-Dimethyl-3-oxa-9-undecenal.

Structure: $CH_3 \cdot C(CH_3):CH \cdot [CH_2]_2 \cdot CH(CH_3) \cdot [CH_2]_2 \cdot O \cdot CH_2 \cdot CHO$.

Description and physical properties: A colourless viscous liquid with a powerful sweet lily-muguet-like odour (Arctander, 1969).

Occurrence: Has apparently not been reported to occur in nature.

Preparation: From citronellol, by reaction with sodium methylate or sodium isopropylate. The acetal is then prepared by reaction with chlorodimethylacetal. The resulting acetal is finally hydrolysed with diluted oxalic acid to yield the aldehyde (Arctander, 1969; Bedoukian, 1967).

Uses: In public use since the 1940s. Use in fragrances in the USA amounts to less than 4000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·001	0·003	0·08
Maximum	0·1	0·01	0·02	0·8

Analytical data: Gas chromatogram, RIFM no. 72–106; infra-red curve, RIFM no. 72–106.

Status

Citronellyl oxyacetaldehyde was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included citronellyl oxyacetaldehyde (citronell oxyacetaldehyde) in the list of temporarily admissible artificial flavouring substances.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. Citronellyl oxyacetaldehyde applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Moreno, 1973). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1973).

References

Arctander, S. (1969). *Perfume and Flavor Chemicals (Aroma Chemicals)*. Vol. 1, no. 688. S. Arctander, Montclair, New Jersey.

Bedoukian, P. Z. (1967). *Perfumery and Flavoring Synthetics*. 2nd ed., p. 378. Elsevier Publishing Co., New York.

Council of Europe (1970). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List A(1), Series 2, no. 14, p. 94. Strasbourg.

Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. No. 2310. *Fd Technol., Champaign* **19**(2), part 2, 155.

Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.

Kligman, A. M. (1973). Report to RIFM, 10 July.

Moreno, O. M. (1973). Report to RIFM, 1 February.

CITRONELLYL PROPIONATE

Synonym: 3,7-Dimethyl-6-octen-1-yl propionate.
Structure: $CH_3 \cdot C(CH_3):CH \cdot [CH_2]_2 \cdot CH(CH_3) \cdot [CH_2]_2 \cdot OCO \cdot CH_2 \cdot CH_3$.
Description and physical properties: EOA Spec. no. 283.
Occurrence: Has apparently not been found in nature.
Preparation: By the esterification of citronellol with propionic acid or anhydride.
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to approximately 2000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·2
Maximum	0·2	0·02	0·1	0·4

Analytical data: Gas chromatogram, RIFM no. 72–107; infra-red curve, RIFM no. 72–107.

Status

Citronellyl propionate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) listed citronellyl propionate, giving an ADI of 0·25 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on citronellyl propionate.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. Citronellyl propionate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Moreno, 1973). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1973).

References

Council of Europe (1974). Natural Flavouring Substances, Their Sources, and Added Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List 1, no. 410, p. 209. Strasbourg.

Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. No. 2316. *Fd Technol., Champaign* **19** (2), part 2, 155.

Food Chemicals Codex (1972). 2nd ed. Prepared by the Committee on Specifications, Food Chemicals Codex, of the Committee on Food Protection. p. 212. National Academy of Sciences–National Research Council Publ. 1406, Washington, D.C.

Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.

Kligman, A. M. (1973). Report to RIFM, 23 July.

Kligman, A. M. & Epstein, W. (1975). Updating the maximization test for identifying contact allergens. *Contact Dermatitis* **1**, 231.

Moreno, O. M. (1973). Report to RIFM, 1 February.

CIVET ABSOLUTE

Description and physical properties: EOA Spec. no. 195. The important constituents of civet are civetone, skatol and civetol (Guenther, 1949).

Occurrence: Natural civet is a glandular secretion from both sexes of the *Viverra civetta*, a mammal of the Viverridae family.

Preparation: By extraction of natural civet (Naves, 1974).

Uses: In public use before the 1860s. Use in fragrances in the USA amounts to less than 3500 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·15
Maximum	0·1	0·01	0·03	0·4

Analytical data: Infra-red curve, RIFM no. 72–108.

Status

Civet was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) included civet in the list of substances, spices and seasonings deemed admissible for use with a possible limitation of the active principle in the final product.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Denine, 1973).

Irritation. Civet absolute applied undiluted to the backs of hairless mice was mildly irritating (Urbach & Forbes, 1973). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1972).

Phototoxicity. No phototoxic effects were reported for civet absolute (Urbach & Forbes, 1973).

References

Council of Europe (1970). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List N(1), Series 1(b), no. 6, p. 30. Strasbourg.

Denine, E. P. (1973). Report to RIFM, 26 February.

Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. No. 2319. *Fd Technol., Champaign* **19**(2), part 2, 155.

Guenther, E. (1949). *The Essential Oils*. Vol. II, p. 490. D. Van Nostrand, Inc., Princeton, New Jersey.

Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.

Kligman, A. M. (1972). Report to RIFM, 1 November.

Naves, Y. R. (1974). *Technologie et Chemie des Parfums Naturels*. p. 289. Masson & Cie., Paris.

Urbach, F. & Forbes, P. D. (1973). Report to RIFM, 8 February.

CIVETONE

Synonym: 9-Cycloheptadecen-1-one.
Structure: $CH_2 \cdot [CH_2]_6 \cdot CH{:}CH \cdot [CH_2]_7 \cdot CO$

Description and physical properties: *Merck Index* (1968).
Occurrence: Reported to be found in the *cis* form of civet (*Fenaroli's Handbook of Flavor Ingredients*. 1975).
Preparation: Produced by cyclization of methyl-18-iodo-3-oxo-11-octadecenoate followed by decarboxylation (Bedoukian, 1967).
Uses: In public use since the 1940s. Use in fragrances in the USA amounts to less than 1000 lb/yr. Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·0005	0·003	0·04
Maximum	0·06	0·006	0·02	0·4

Analytical data: Gas chromatogram. RIFM no. 74-60; infra-red curve. RIFM no. 74-60.

Status

Civetone was given GRAS status by FEMA (1974) and was included by the Council of Europe (1974) in the list of artificial flavouring substances not fully evaluated.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as >5 g/kg and the acute dermal LD_{50} value in rabbits exceeded 2 g/kg (Moreno, 1974).

Irritation. Civetone applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1974). Tested at 4% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1974).

References

Bedoukian, P. Z. (1967). *Perfumery and Flavoring Synthetics*. p. 256. Elsevier Publishing Co., New York.
Council of Europe (1974). Natural Flavouring Substances. Their Sources, and Added Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List 3. no. 4066. p. 362. Strasbourg.
Fenaroli's Handbook of Flavor Ingredients (1975). Edited by T. E. Furia and N. Bellanca. 2nd Ed. Vol. II. p. 110. CRC Press, Cleveland, Ohio.
Flavoring Extract Manufacturers' Association (1974). Survey of flavoring ingredient usage levels. No. 3425. *Fd Technol., Champaign* **28**(9), 76.
Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.
Kligman, A. M. (1974). Report to RIFM, 19 November.
Kligman, A. M. & Epstein, W. (1975). Updating the maximization test for identifying contact allergens. *Contact Dermatitis* **1**, 231.
Merck Index (1968). *An Encyclopedia of Chemicals and Drugs*. 8th Ed., p. 268. Merck & Co., Inc., Rahway, New Jersey.
Moreno, O. M. (1974). Report to RIFM, 10 December.

CLARY SAGE OIL

Description and physical properties: EOA Spec. no. 77. The main constituents of clary sage oil are linalyl acetate and linalool (Gildemeister & Hoffman, 1961; Guenther, 1949).

Occurrence: Found in the leaves and flowering tops of *Salvia sclarea* L. (Fam. Labiatae) (Gildemeister & Hoffman, 1961; Naves, 1974).

Preparation: By steam distillation of the flowering tops and leaves of *Salvia sclarea* L. (Naves, 1974).

Uses: In public use before the 1900s. Use in fragrances in the USA amounts to about 10,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·003	0·12
Maximum	0·1	0·01	0·03	0·8

Analytical data: Gas chromatogram, RIFM no. 72–48; infra-red curve, RIFM no. 72–48.

Status

Clary sage oil was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) included clary sage oil in the list of substances, spices and seasonings deemed admissible for use, with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on clary sage oil.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 5·6 g/kg (5·0–6·2 g/kg) (Moreno, 1972a). The acute dermal LD_{50} value in rabbits was reported as >2 g/kg (Moreno, 1972b).

Irritation. Clary sage oil applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1972b). A patch test using full strength clary sage oil for 24 hr produced no irritation reactions in 30 subjects (Katz, 1946). Tested at 8% in petrolatum, the oil produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972). Several cases of dermatitis due to sage have been reported and positive patch tests were obtained from the mucous membranes but not from the skin (Urbach & Wiethe, 1931).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1972).

References

Council of Europe (1970). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List N(1), Series 1(b), no. 415, p. 27. Strasbourg.

Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. No. 2321. *Fd Technol., Champaign* **19**(2), part 2, 155.

Food Chemicals Codex (1972). 2nd ed. Prepared by the Committee on Specifications, Food Chemicals Codex, of the Committee on Food Protection. p. 213. National Academy of Sciences–National Research Council Publ. 1406, Washington, D.C.

Gildemeister, E. u. Hoffman, F. (1961). *Die Ätherischen Öle*. Vol. VII, p. 122. Akademie Verlag, Berlin.

Guenther, E. (1949). *The Essential Oils*. Vol. III, p. 724. D. Van Nostrand, Inc., Princeton, New Jersey.

Katz, A. (1946). *Spice Mill* **69** (July), 46.

Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.

Kligman, A. M. (1972). Report to RIFM, 19 July.

Moreno, O. M. (1972a). Report to RIFM, 5 May.

Moreno, O. M. (1972b). Report to RIFM, 31 May.

Naves, Y. R. (1974). *Technologie et Chemie des Parfums Naturels*. p. 212. Masson & Cie., Paris.
Urbach, E. u. Wiethe, C. (1931). Ätherische Öle als Ursache von allergischen Haut- und Schleimhauterkrankungen. *Münch. med. Wschr.* **78,** 2030.

CLOVE BUD OIL

Description and physical properties: *Food Chemicals Codex* (1972). The main constituent of clove bud oil is eugenol (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Occurrence: Found in the buds of *Eugenia caryophyllata* Thunb. (Fam. Myrtaceae) (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: By water distillation of the buds of *E. caryophyllata* Thunb. (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Uses: In public use before the 1800s. Use in fragrances in the USA amounts to approximately 100,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·005	0·2
Maximum	0·15	0·015	0·03	0·7

Analytical data: Gas chromatogram, RIFM no. 70–9; infra-red curve, RIFM no. 70–9.

Status

Clove oil was given GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1974) included clove oil in the list of substances, spices and seasonings deemed admissible for use, with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) and the *United States Pharmacopeia* (1965) have monographs on clove oil.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 2·65 g/kg (2·18–3·12 g/kg) (Moreno, 1973). The acute dermal LD_{50} value in rabbits was reported as approximately 5 g/kg (Moreno, 1973). The acute oral LD_{50} of clove oil for rats was found to be 372 mg/100-g rat (von Skramlik, 1959). Clove oil was toxic to mice when applied to the skin in two doses 7 days apart (Roe & Field, 1965).

Chronic toxicity. Daily oral doses of 35 or 70 mg clove oil given for 8 wk were well tolerated by rats (von Skramlik, 1959), but with higher doses there was inactivity leading to weight loss. Death accompanied by severe liver and kidney changes occurred after 2–3 wk on 105 mg/day and rapidly followed one dose of 140 mg (von Skramlik, 1959).

Irritation. Clove bud oil applied undiluted to the backs of hairless mice was not irritating (Urbach & Forbes, 1973). Applied full strength to intact or abraded rabbit skin for 24 hr under occlusion, it was moderately irritating (Moreno, 1973). In closed-patch tests on human skin, clove oil caused primary irritation (erythema) in two of 25 normal subjects when applied at 20% in vaseline or ointment and evoked no reaction when applied at 2% concentration on 30 normal subjects or at 0·2% on 35 subjects with dermatoses (Fujii, Furukawa & Suzuki, 1972). Clove bud oil tested at 5% in petrolatum produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 5% in petrolatum and produced no sensitization reactions (Kligman, 1973). Sensitization of human skin caused by clove oil was attributed to the presence of eugenol (Woeber & Kromback, 1969).

Phototoxicity. No phototoxic effects were reported for clove bud oil applied undiluted to hairless mice and swine (Urbach & Forbes, 1973).

Human dental pulp. Treatment of human dental cavities with zinc oxide–clove oil paste damaged the dental pulp and did not promote the development of irritation dentine (Zahlavova & Kourik, 1966).

Pharmacology. In a pharmacological study using rat, guinea-pig and rabbit organs, clove oil was found to have antihistaminic and musculotropic spasmolytic activity (Debelmas & Rochat, 1967). Clove oil showed musculotropic (papaverine-like) antispasmodic activity against isolated small intestine from the mouse (Imaseki & Kitabatake, 1962).

Micro-organisms. Clove oil has been reported to be effective against several pathogenic bacteria (Birggal, 1969). It was one of the most active bactericides among 17 essential oils tested against Gartner's bacillus, swing erysipelas bacteria and a sporeless culture of *Bacillus anthracis* (Abdullin, 1962). The relative bactericidal action of clove oil was reported to be 8·5 times that of phenol (concentrations not given) (Führer, 1972). Clove oil showed some *in vitro* antibacterial activity against three of five bacteria studied. The activity was only slightly affected by mixing with other essential oils (Maruzzella & Henry, 1958). Vapour of USP clove oil showed antibacterial activity against

two of five bacteria tested by Maruzzella & Sicurella (1960), while rectified clove leaf oil was active against only one of the five bacteria. Clove oil was found to inhibit six gram-positive and gram-negative bacteria (Ramadan, El-Zanfaly, Alian & El-Wakeil, 1972; Ramadan, El-Zanfaly, El-Wakeil & Alian, 1972), the effect being dose-dependent. In liquid seasonings containing emulsified essential oils, antibacterial activity was present only in formulations containing clove oil (1·1–5·5%) (Pirie & Clayson, 1964).

Clove oil exhibited *in vitro* antifungal activity against all of 15 fungi studied by Maruzzella & Liguori (1958), and showed fungistatic activity but no fungicidal activity against *Trichophyton mentagrophytes* and *Candida albicans* (Korbely & Florian, 1971).

Medicinal uses. Oil of clove is used as a local anaesthetic in toothache, as a counter-irritant and as a carminative (*Merck Index*, 1968) and is recommended as a hygienic agent and antiseptic (Uzdennikov, 1970). It is included in a patented topical analgesic composition (Shahawi, 1970), in patented formulations for food preservation, air disinfection and cosmetic and medical use (Maple Leaf Trust, 1964) and in a patented anti-inflammatory composition for external use in the treatment of degeneration of the bone, inflammation of the joints, bursitis and treatment of the sinuses (Vittone, 1972). Extracts of clove buds and other medicinal plants and spices have beneficial antibacterial, soothing and sedative properties when incorporated into cosmetic lotions and shampoos (Getmanskii, Kudryashov, Ereschchenko & Prokopchuk, 1969).

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CLOVE STEM OIL

Description and physical properties: EOA Spec. no. 178. The chief constituent of clove stem oil is eugenol (Guenther, 1950).
Occurrence: Found in the stems of the tree *Eugenia caryophyllata* Thunb. (Fam. Myrtaceae) (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: By steam distillation of the dried stems of *E. caryophyllata* Thunb. after removal of the buds.
Uses: In public use before the 1900s. Use in fragrances in the USA amounts to approximately 40,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·01	0·2
Maximum	0·25	0·025	0·05	1·0

Status

Clove stem oil was given GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1974) included clove oil in the list of substances, spices and seasonings deemed admissible for use, with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) and the *United States Pharmacopeia* (1965) have monographs on clove oil.

Biological data

Acute toxicity. The acute oral LD_{50} value for rats was reported as 2·02 g/kg with confidence limits of 1·71–2·33 g/kg (Moreno, 1974). The acute oral LD_{50} of clove oil was found to be 372 mg/100-g rat (von Skramlik, 1959). Clove oil was toxic to mice when applied to the skin in two doses 7 days apart (Roe & Field, 1965). The acute dermal LD_{50} value in rabbits was reported as >5 g/kg (Moreno, 1974).

Chronic toxicity. Daily oral doses of 35 or 70 mg clove oil given for 8 wk were well tolerated by rats (von Skramlik, 1959), but with higher doses there was inactivity leading to weight loss. Death, accompanied by severe liver and kidney changes, occurred after 2–3 wk on 105 mg/day and rapidly followed one dose of 140 mg (von Skramlik, 1959).

Irritation. Clove stem oil applied undiluted to the backs of hairless mice was severely irritating (Urbach & Forbes, 1974). Applied full strength to the abraded and intact skin of the rabbit for 24 hr under occlusion, it produced moderate erythema and oedema (Moreno, 1974). Tested at 10% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1974). In closed-patch tests on human skin, clove oil caused primary irritation (erythema) in two of 25 normal subjects when applied at 20% in vaseline or ointment, and evoked no reaction when applied at 2% concentration on 30 normal subjects or at 0·2% on 35 subjects with dermatoses (Fujii, Furukawa & Suzuki, 1972).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers using 10% clove stem oil in petrolatum. No sensitization reactions were produced (Kligman, 1974). Sensitization of human skin reported to be caused by clove oil was attributed to the presence of eugenol (Woeber & Kromback, 1969).

Phototoxicity. No phototoxic effects were reported for undiluted clove stem oil in hairless mice and swine (Urbach & Forbes, 1974).

Human dental pulp. Treatment of human dental cavities with zinc oxide–clove oil paste damaged the dental pulp and did not promote the development of irritation dentine (Zahlavova & Kourik, 1966).

Pharmacology. In a pharmacological study using rat, guinea-pig and rabbit organs, clove oil was found to have antihistaminic and musculotropic spasmolytic activity (Debelmas & Rochat, 1967). Clove oil showed musculotropic (papaverine-like) antispasmodic activity against the isolated small intestine of the mouse (Imaseki and Kitabatake, 1962).

Micro-organisms. Clove oil has been reported to be effective against several pathogenic bacteria (Birggal, 1969) and was one of the most active bactericides among 17 essential oils tested against Garner's bacillus, swing erysipelas bacteria and a sporeless culture of *Bacillus anthracis* (Abdullin, 1962). The relative bactericidal action of clove oil was reported to be 8·5 times that of phenol (concentrations not given) (Führer, 1972). Clove oil showed some *in vitro* antibacterial activity against three of five bacteria studied. The activity was only slightly affected by mixing with other essential

oils (Maruzzella & Henry, 1958). The vapour of USP clove oil showed antibacterial activity against two of five bacteria tested by Maruzzella & Sicurella (1960), while rectified clove leaf oil was active against only one of the five bacteria. Clove oil was found to inhibit six gram-positive and gram-negative bacteria (Ramadan, El-Zanfaly, Alian & El-Wakeil, 1972; Ramadan, El-Zanfaly, El-Wakeil & Alian, 1972), the effect being dose-dependent. In liquid seasonings containing emulsified essential oils, antibacterial activity was present only in formulations containing clove oil (1·1–5·5%) (Pirie & Clayson, 1964). Clove oil exhibited *in vitro* antifungal activity against all of 15 fungi studied by Maruzzella & Liguori (1958), and several types (USP clove, Madagascar redistilled clove leaf, rectified clove leaf and Zanzibar redistilled clove stem) markedly inhibited the growth of three wood-destroying fungi studied by Maruzzella, Scrandis, Scrandis & Grabon (1960). Clove oil showed fungistatic activity but no fungicidal activity against *Trichophyton mentagrophytes* and *Candida albicans* (Korbely & Florian, 1971).

Medicinal uses. Oil of clove is used as a local anaesthetic in toothache, as a counter-irritant and as a carminative (*Merck Index*, 1968) and is recommended as a hygienic agent and antiseptic (Uzdennikov, 1970). It is included in a patented topical analgesic composition (Shahawi, 1970), in patented formulations for food preservation, air disinfection and cosmetic and medical use (Maple Leaf Trust, 1964) and in a patented anti-inflammatory composition for external use in the treatment of degeneration of the bone, inflammation of the joints, bursitis and treatment of the sinuses (Vittone, 1972).

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COGNAC OIL, GREEN

Description and physical properties: EOA Spec. no. 157. The main constituents of cognac oil, green are ethyl heptanoate and other fatty acid esters.
Occurrence: Found in the yeast and other sediment in wine lees.
Preparation: By steam distillation of the yeast and other sediment in wine lees.
Uses: In public use since the 1900s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·04
Maximum	0·1	0·01	0·02	0·2

Analytical data: Gas chromatogram, RIFM no. 74–62; infra-red curve, RIFM no. 74–62.

Status

Cognac oil was given GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The *Food Chemicals Codex* (1972) has a monograph on cognac oil, green.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in mice and the acute dermal LD_{50} value in guinea pigs exceeded 5 g/kg (Moreno, 1974).

Irritation. Undiluted cognac oil, green, applied to the backs of hairless mice was not irritating (Urbach & Forbes, 1974). Applied full strength to intact or abraded rabbit and guinea-pig skin for 24 hr under occlusion, it was slightly irritating (Moreno, 1974). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1974).

Phototoxicity. No phototoxic effects were reported for cognac oil, green (Urbach & Forbes, 1974).

Micro-organisms. Vapour of cognac green oil showed antibacterial activity against *Mycobacterium avium* but not against *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis*, *Streptococcus fecalis* or *Salmonella typhosa* (Maruzzella & Sicurella, 1960). The oil did not inhibit the growth of three wood-destroying fungi (Maruzzella, Scrandis, Scrandis & Grabon, 1960).

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BALSAM COPAIBA*

Description and physical properties: EOA Spec. no. 213. Copaiba balsam contains substantial quantities of a volatile oil, the balance being resinous substances and small quantities of acids (Guenther, 1952).

Occurrence: In the oleoresin obtained from the trunk of several species of Copaifera L. (Fam. Leguminosae).

Preparation: By tapping of the Copaifera tree.

Uses: In public use before the 1800s. Use in fragrances in the USA amounts to approximately 40,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·01	0·2
Maximum	0·2	0·02	0·05	0·8

Analytical data: Infra-red curve, RIFM no. 74–41.

Status

Balsam copaiba is approved by the FDA for food use (21 CFR 121.1163).

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 5 g/kg and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Wohl, 1974).

Irritation. Undiluted balsam copaiba was not irritating when applied to the backs of hairless mice and swine (Urbach & Forbes, 1974) or under occlusion to intact or abraded rabbit skin for 24 hr (Wohl, 1974). Tested at 8% in petrolatum on two different panels of human subjects, it produced no irritation after a 48-hr closed-patch test (Kligman, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced a sensitization reaction in one of the 25 (Kligman, 1974; see preface note no. 1). Using the same maximization test, the same sample was retested at a concentration of 8% in petrolatum and produced no sensitization reactions in a further 50 volunteers (Kligman, 1974).

Phototoxicity. No phototoxic effects were reported for undiluted balsam copaiba on hairless mice and swine (Urbach & Forbes, 1974).

Antibacterial activity. Copaiba balsam oil showed some antibacterial activity when tested against three micro-organisms, Gartner's bacillus, swine erysipelas bacteria and a sporeless culture of *Bacillus anthracis* (Abdullin, 1962). The vapour of copaiba oil showed antibacterial activity against *Mycobacterium avium* but not against *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis*, *Streptococcus fecalis* and *Salmonella typhosa* (Maruzzella & Sicurella, 1960). Copaiba oil did not inhibit the growth of three wood-destroying fungi (Maruzzella, Scrandis, Scrandis & Grabon, 1960).

Skin absorption. In studies on the intact shaved abdominal skin of the mouse, Meyer & Meyer (1959) showed that percutaneous absorption of copaiba balsam oil was fairly slow (92 min). In an evaluation of skin-penetrating agents, copaiba balsam oil did not aid deep penetration of Rhodamine B into the corium or subcutis of guinea-pig skin (Meyer, 1965).

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COPAIBA OIL

Description and physical properties: EOA Spec. no. 10. The principal constituent of copaiba oil is caryophyllene (Guenther, 1952). It also contains other sesquiterpenes (Gildemeister & Hoffman, 1959).

Occurrence: Found in the exudation from the trunk of the Copaifera L. (fam. Leguminosae).

Preparation: By the steam-distillation of copaiba balsam.

Uses: In public use since the 1920s. Use in fragrances in the USA amounts to less than 33,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·05	0·005	0·05	0·20
Maximum	0·20	0·02	0·20	0·80

Status

Copaiba oil is approved by the FDA for food use (21 CFR 121.1163). The *Food Chemicals Codex* (1972) has a monograph on copaiba oil.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Hart, 1971).

Irritation. Copaiba oil applied full strength to intact or abraded rabbit skin was irritating (Hart, 1971). Tested at a concentration of 8% in petrolatum, it produced no irritation in a 48-hr closed-patch test in 25 human subjects (Kligman, 1971).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1971).

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CORIANDER OIL

Description and physical properties: Food Chemicals Codex (1972). The main constituent of coriander oil is *d*-linaloöl (Guenther, 1950).
Occurrence: Found in the fruit of *Coriandrum sativum* L. (Fam. Umbelliferae).
Preparation: By steam-distillation of the dried ripe fruit.
Uses: In public use since the 1900s. Use in fragrances in the USA amounts to less than 10,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	—	0·02	0·04
Maximum	0·05	—	0·06	0·6

Status

Coriander oil was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) included coriander oil (*Coriandrum sativum*) in the list of substances, spices and seasonings whose use is deemed admissible, with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) and the United States Pharmacopeia (1965) have monographs on coriander oil.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported to be 4·13 g/kg (2·48–6·14 g/kg) (Hart, 1971). The acute dermal LD_{50} in rabbits was reported to be >5 g/kg (Hart, 1971).

Irritation. Coriander oil applied full strength to intact or abraded rabbit skin was irritating (Hart, 1971). Tested at a concentration of 6% in petrolatum, it produced no irritation in a 48-hr closed-patch test in 25 human subjects (Kligman, 1971).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 6% in petrolatum and produced no sensitization reactions (Kligman, 1971).

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CORNMINT OIL

Synonyms: Oil Mentha arvensis; Japanese mint oil.
Description and physical properties: A pale yellow oil. The main constituent of cornmint oil is *l*-menthol (Guenther, 1949).
Occurrence: Found in the plant *Mentha arvensis* var. *piperascens* Holmes (Fam. Labiatae) (Gildemeister & Hoffman, 1961; Guenther, 1949).
Preparation: By steam distillation of the dried plant of *M. arvensis* var. *piperascens* Holmes (Guenther, 1949).
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·2
Maximum	0·2	0·02	0·05	0·8

Status

Cornmint oil is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974), or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 1·24 g/kg and the acute dermal LD_{50} value in rabbits as >5 g/kg (Wohl, 1974).

Irritation. Cornmint oil applied full strength to the backs of hairless mice and swine (Urbach & Forbes, 1974) or to intact or abraded rabbit skin for 24 hr under occlusion (Wohl, 1974) was not irritating. Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 22 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Epstein, 1974).

Phototoxicity. No phototoxic effects were reported for undiluted cornmint oil on hairless mice and swine (Urbach & Forbes, 1974).

Skin penetration. In an evaluation of skin-penetrating agents, "Oleum Menthae" increased deep penetration of Rhodamine B into the corium and subcutis of guinea-pig skin, while "peppermint oil" and "Oleum Menthae piperitae" caused only a slight increase in penetration (Meyer, 1965).

Micro-organisms. M. arvensis oils from the Punjab, Jammu and Kashmir, and from Formosa inhibited the *in vitro* growth of eight out of ten bacteria and fungi tested. The Formosan oil had the highest antibacterial activity, and also the highest antifungal activity except against *Candida albicans* (Sanyal & Varma, 1969).

Additional published data

The essential oil of *M. arvensis* produced moderate cytotoxic effects, which could not be attributed to its content of menthol (85%) and related menthyl compounds (Siljanowska, Stojcev, Zolotovitch & Nachev, 1969).

Japanese peppermint oil from *M. arvensis* showed antispasmodic action on excised mouse intestine, but did not accelerate transfer of the intestinal content after oral administration (Haginiwa, Harada & Morishita, 1963).

The essential oils of various types of mint stimulate digestion and exert an antispasmodic action on smooth muscles (Tucakov, 1960).

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COSTUS ROOT, ESSENTIAL OIL, ABSOLUTE AND CONCRETE

Description and physical properties: EOA Spec. no. 179.

Occurrence: Found in the roots of the herbaceous plant *Saussurea lappa* Clarke (*Aplotaxis lappa* Dec; *Aplotaxis auriculata* DC; *Aucklandia costus* Falc.) (Fam. Compositae) (Gildemeister & Hoffman, 1961; Guenther, 1952).

Preparation: By steam distillation of the dried and triturated root (for the oil), but a solvent-extraction procedure using alcohol, benzene, petroleum ether, ether etc. has often been employed, with subsequent vacuum distillation of the solvent to leave a concrete or absolute depending on the process used.

Uses: In public use before the 1900s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	—	—	0·003	0·05
Maximum	—	—	0·02	0·4

Analytical data: Gas chromatogram, RIFM no. 72–109; infra-red curve, RIFM no. 72–109.

Status

Costus oil was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1163). It was included by the Council of Europe (1970) in the list of fruits and vegetables or parts thereof consumed as food: parts for which no restriction is proposed. Costus oil is the subject of a *Food Chemicals Codex* (1972) monograph.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 3·4 g/kg (2·66–4·35 g/kg) (Denine, 1973). The acute dermal LD_{50} value in rabbits was reported as >5 g/kg (Denine, 1973).

Short-term toxicity. In a 90-day feeding study, 1·88 mg/kg fed to rats in the diet produced no effects (Bär & Griepentrog, 1967).

Irritation. Undiluted costus oil applied to the backs of hairless mice was mildly irritating (Urbach & Forbes, 1973). Tested at 4% in petrolatum, two samples of costus oil (RIFM nos 72–4–109 & 72–4–109AR) produced no irritation after 48-hr closed-patch tests on human subjects (Kligman, 1973). Neither costus concrete nor costus absolute (RIFM no. 38–4–76) tested in each case at 4% in petrolatum produced any irritation after a 48-hr closed-patch test on human subjects (Epstein, 1973).

Sensitization. Maximization tests (Kligman, 1966) were carried out on groups of volunteers. Costus oil (RIFM no. 72–4–109) tested at a concentration of 4% in petrolatum produced 25 sensitization reactions in 25 volunteers (Kligman, 1972). Costus oil (RIFM no. 72–4–109AR), tested on 25 volunteers at a concentration of 4% in petrolatum, produced such severe irritation reactions in eight subjects that they were subsequently not challenged (Kligman, 1973). Costus oil (RIFM no. C24–2–98ORD), tested at a concentration of 2% in petrolatum, produced 16 sensitization reactions in 26 volunteers (Epstein, 1974). Costus concrete (RIFM no. 14–4–88), tested at a concentration of 4% in petrolatum, produced six sensitization reactions in 21 volunteers (Epstein, 1973). Costus absolute (RIFM no. 38–4–76), tested at a concentration of 4% in petrolatum, produced 18 sensitization reactions in 24 volunteers and had to be reduced to 25% of the original concentration for the study to be completed (Epstein, 1973).

A preparation made of a lactone-rich fraction (74-2-259) from sample 74-109AR produced one sensitization reaction in 24 subjects in a maximization test. It produced severe

reactions in costus-sensitized individuals. A lactone-free sample from the same oil was prepared (74-2-258) and a maximization procedure produced no sensitization reaction in seven subjects nor did the sample cause responses in subjects previously sensitized to the costus oil (74-109AR). When the same sample of costus oil was hydrogenated (74-2-262) and tested by the maximization procedure, it produced no sensitization reactions in 20 subjects.

Phototoxicity. No phototoxic effects were reported for undiluted costus oil (Urbach & Forbes, 1973).

Additional published data

There have been reports of strong positive sensitization reactions to costus oil (Mitchell, 1974). The author attributed the reactions to the sesquiterpene lactones in the oil.

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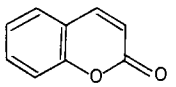
COUMARIN

Synonyms: 2-Oxo-1,2-benzopyran; 1,2-benzopyrone; *cis-o*-coumaric acid lactone; coumarinic anhydride; tonka bean camphor.

Structure:



Description and physical properties: EOA Spec. no. 201.
Occurrence: Found in many plants and essential oils such as cassia, melilot, orchid, lavender and balsam of Peru (Späth, 1937; Gildemeister & Hoffman, 1966).
Preparation: From salicylaldehyde by suitable chemical reaction and purification (Bedoukian, 1967).
Uses: In public use since the 1900s. Use in fragrances in the USA amounts to about 250,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·015	0·3
Maximum	0·2	0·02	0·1	0·8

Status

The FDA has prohibited the use of coumarin in food (21 CFR 121.106).

Biological data

Acute toxicity. The acute oral LD_{50} was reported to be 196 mg/kg in mice (Kitagawa & Iwaki, 1963), 293–680 mg/kg in rats (Hazleton, Tusing, Zeitlin, Thiessen & Murer, 1956; Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964) and 202 mg/kg in guinea-pigs (Jenner *et al.* 1964). The sc LD_{50} was reported as 310–342 mg/kg in mice (Kitagawa & Iwaki, 1963).

Chronic toxicity (oral route). In a 90-day rat study, coumarin at 50 or 250 ppm in the diet had no effect on weight gain, efficiency of food utilization or organ pathology, but a dietary level of 2500 ppm impaired food efficiency and produced liver enlargement and liver damage (Hazleton *et al.* 1956). In a 2-yr rat study, no effects were seen with 1000 ppm coumarin in the diet, but growth retardation and liver damage (bile-duct proliferation, cholangiofibrosis and focal necrosis) were seen with 2500 and 5000 ppm fed for 2 yr and also with 10,000 ppm fed for up to 8 wk (Hagan, Hansen, Fitzhugh, Jenner, Jones, Taylor, Long, Nelson & Brouwer, 1967). In another 2-yr rat study, feeding of 5000 ppm for 18 months was reported to produce bile-duct carcinomas, predominantly in males; extrahepatic metastasis was low (Bär & Griepentrog, 1967). The diagnosis of bile-duct carcinomas has been questioned however (*Food and Cosmetics Toxicology*, 1969).

In a 3-wk dog study, eight daily oral doses of 100 mg/kg produced liver damage and kidney changes compatible with a bile nephrosis (Hazleton *et al.* 1956).

In a 1-yr dog study, daily oral doses of 25, 50 and 100 mg/kg body weight given for 130–330, 35–277 and 9–16 days, respectively, caused emaciation, jaundice, liver damage (focal necrosis, fibrosis, and bile-duct proliferation) and pathological changes in the spleen, bone marrow and gall bladder, but no effect was seen with 10 mg/kg/day given for 297–350 days (Hagan *et al.* 1967).

Chronic toxicity (dermal route). A single application of 15% coumarin in acetone to mouse skin failed to produce epidermal hyperplasia within 3 days of dosage and no tumour-initiating activity was seen after either a single dose of 45 mg coumarin (15% in acetone) or a total dose of 150 mg coumarin (one dose of 10% in acetone followed by 12 weekly doses of 3·3% in acetone) to mouse skin followed in both cases by treatment with the tumour promoter, croton oil (Roe & Salaman, 1955).

Chronic toxicity (sc route). Twice-weekly sc injections of 2 mg coumarin in 0·5 ml arachis oil given for 65 wk to rats did not induce sarcomas at the injection site over 2 yr (Dickens & Jones, 1965).

Teratogenicity. The offspring of mice fed dietary levels of 0·05–0·25% coumarin on days 6–17 of pregnancy exhibited no malformations but increased stillbirths and delayed ossification were seen at the 0·25% level and increased mortality up to 3 wk of life was seen at all levels (Roll & Bär, 1967).

Sensitization. A maximization test (Kligman, 1966) carried out on 25 human volunteers using an 8% concentration in petrolatum produced no sensitization reactions (Greif, 1967).

Percutaneous absorption. Rabbits dosed dermally or orally with coumarin showed a similar pattern in the urinary excretion of coumarin metabolites (Pekker & Schäfer, 1969).

Metabolism. There is a striking difference in the metabolism of coumarin between man and other mammalian species. In man, coumarin is metabolized mainly to 7-hydroxycoumarin (Shilling, Crampton & Longland, 1969) but this metabolic transformation assumes lesser importance in the rat (Kaighen & Williams, 1961; Van Sumere & Teuchy, 1971) and rabbit (Kaighen & Williams, 1961), in which two species the excretion of 2-hydroxyphenylacetic acid is more marked than in man.

In man, 68–92% of an oral dose of coumarin is excreted in the urine as 7-hydroxycoumarin and 1–6% as 2-hydroxyphenylacetic acid (Shilling *et al.* 1969).

In the rat, about 55% of an oral dose of [3-^{14}C]coumarin is excreted in the urine, 3% of the dose as hydroxycoumarins, including 7-hydroxycoumarin, and 20% as 2-hydroxyphenylacetic acid; about 36% of the dose is eliminated in the faeces, partly as 2-hydroxyphenylacetic acid (Kaighen & Williams, 1961). Feuer, Golberg & Gibson (1966) found that 48 hr after administration of an oral dose of [3-^{14}C]coumarin to rats, 70% of the dose was excreted in the urine and 10% in the faeces. The major metabolites in 24-hr urine were 2-hydroxyphenylacetic acid and 2-hydroxyphenyllactic acid. In a more recent study in rats (Van Sumere & Teuchy, 1971), 37% of an ip dose of [2-^{14}C]coumarin was excreted in the urine, 30% in the expired air and 14% in the faeces. Metabolites identified in the urine included 5-, 7- and 8-hydroxycoumarins, *o*-coumaric acid, melilotic acid (2-hydroxyphenylpropionic acid) and 2-hydroxyphenylacetic acid together with unchanged coumarin, but only 0·7% of the dose was excreted as 7-hydroxycoumarin.

In the rabbit, benzene-ring hydroxylation and conjugation was more marked than in the rat and 90% of an oral dose of [3-^{14}C]coumarin was excreted in the urine as 3-hydroxycoumarin (21·7% of the dose), 7-hydroxycoumarin (12%), 4-, 5-, 6- and 8-hydroxycoumarins (0·4–3·4%), 2-hydroxyphenylacetic acid (20%) and 2-hydroxyphenyllactic acid (3%) (Kaighen & Williams, 1961). Following application of coumarin as a 5% ointment to the shaved skin of rabbits, the urinary metabolites included mainly 7-hydroxycoumarin and smaller amounts of 3- and 4-hydroxycoumarin, 2-hydroxyphenylacetic acid, 6,7-dihydroxycoumarin and unchanged coumarin, as judged by the intensity of the thin-layer chromatographic spots (Pekker & Schäfer, 1969). However the claim for 7-hydroxycoumarin as a major urinary metabolite following oral or dermal dosage of coumarin to rabbits needs to be confirmed (*Food and Cosmetics Toxicology*, 1970).

Other species such as the ferret, guinea-pig and mouse metabolize coumarin to 3-, 5-, 7- and 8-hydroxycoumarins, which are excreted in the urine (Mead, Smith & Williams, 1958).

On incubation with rat-liver microsomes, [3-^{14}C]coumarin is transformed into 3- and 7-hydroxycoumarins, 2-hydroxyphenylacetic acid and 2-hydroxyphenyllactic acid (Gibbs, Janakidevi & Feuer, 1971).

Biochemical assays on liver microsomes of various species have revealed coumarin-7-hydroxylase activity in rabbits, guinea-pigs, coypu, cats and pigeons, but not in mice or rats (Creaven, Parke & Williams, 1965) but more recently coumarin 7-hydroxylase has been demonstrated in rat-liver microsomes although its activity was lower than that of coumarin 3-hydroxylase (Feuer, 1970; Gibbs *et al.* 1971). Human liver can also 7-hydroxylate coumarin *in vitro* (*Food and Cosmetics Toxicology*, 1966).

The species difference in the metabolism of coumarin requires important toxicological

consideration. Coumarin and other hepatotoxic agents inhibit liver glucose-6-phosphatase and this effect is regarded as being indicative of liver damage (Feuer, Golberg & Le Pelley, 1965a,b). 2-Hydroxyphenylacetic acid strongly inhibits rat-liver glucose-6-phosphatase *in vitro* and to a lesser extent *in vivo*, whereas neither coumarin nor 7-hydroxycoumarin (the major metabolite in man) causes inhibition *in vitro* (Feuer *et al.* 1966). It is thus conceivable that the hepatotoxicity of coumarin in the rat is attributable to 2-hydroxyphenylacetic acid, the major urinary metabolite in the rat but minor metabolite in man. Consequently man could be less susceptible than the rat to the hepatotoxic action of coumarin.

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p-CRESOL

Synonyms: 4-Hydroxytoluene; 1-methyl-4-hydroxybenzene.

Structure: $CH_3 \cdot C_6H_4 \cdot OH$.

Description and physical properties: White crystals with a phenolic odour (*Merck Index*, 1968).

Occurrence: Has been found in a score of essential oils including ylang ylang and oil of jasmine (Gildemeister & Hoffman, 1966).

Preparation: By alkali fusion of *p*-toluenesulphonic acid (Arctander, 1969).

Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 2000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·001	0·001	0·04
Maximum	0·2	0·02	0·005	0·4

Analytical data: Gas chromatogram, RIFM no. 72–110; infra-red curve, RIFM no. 72–110.

Status

p-Cresol was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included *p*-cresol in the list of artificial flavouring substances not admissible at present.

Biological data

Acute toxicity. The acute oral LD_{50} was reported as 1·8 g/kg in the rat (*Merck Index*, 1968). The acute dermal LD_{50} in rabbits was reported as 3·6 (2·67–4·86) g/kg (Denine, 1973).

Irritation. *p*-Cresol applied full strength on intact or abraded rabbit skin was irritating (Denine, 1973). *p*-Cresol tested at 4% in petrolatum produced no irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at 4% concentration in petrolatum and produced no sensitization reactions (Kligman, 1972).

Threshold Limit Value. The TLV for *p*-cresol has been set at 5 ppm, at which level prolonged use may cause reddening and itching of the skin and, in time, dermatitis, eczema and even ulceration. Inhalation of the vapour has caused headache, nausea and vomiting, and tremor (American Conference of Governmental Industrial Hygienists, 1970).

Metabolism. *p*-Cresol is oxidized at the methyl group in both dogs and rabbits to yield *p*-hydroxybenzoic acid. In the rabbit up to 10% of oral doses of 0·25–0·5 g is excreted as free and conjugated *p*-hydroxybenzoic acid (Williams, 1959).

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p-CRESYL ACETATE

Synonyms: *p*-Tolyl acetate; 4-methylbenzoic acid methyl ester.
Structure: $CH_3 \cdot C_6H_4 \cdot CO_2 \cdot CH_3$
Description and physical properties: EOA Spec. no. 223.
Occurrence: Found in oils of cananga, wallflower and ylang ylang (Gildemeister & Hoffman, 1966).
Preparation: By acetylation of *p*-cresol.
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·12
Maximum	0·1	0·01	0·05	0·4

Analytical data: Gas chromatogram, RIFM no. 72–233; infra-red curve, RIFM no. 72–233.

Status

p-Cresyl acetate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included *p*-cresyl acetate in the list of admissible artificial flavouring substances at a level of 4 ppm. The *Food Chemicals Codex* (1972) has a monograph on *p*-cresyl acetate.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 1·9 (1·12–3·23) g/kg (Denine, 1973). The acute dermal LD_{50} in rabbits was reported as 2·1 (1·24–3·57) g/kg (Denine, 1973).

Irritation. *p*-Cresyl acetate applied full strength on intact or abraded rabbit skin produced no irritation (Denine, 1973). *p*-Cresyl acetate tested at 4% in petrolatum produced no irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at 4% concentration in petrolatum and produced no sensitization reactions (Kligman, 1972).

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Kligman, A. M. (1972). Report to RIFM, 22 November.

p-CRESYL ISOBUTYRATE

Synonym: *p*-Tolyl isobutyrate.
Structure: $CH_3 \cdot C_6H_4 \cdot OCO \cdot CH(CH_3)_2$.
Description and physical properties: EOA Spec. no. 232.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: From *p*-cresol and isobutyric acid by esterification.
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·0005	0·0025	0·04
Maximum	0·03	0·003	0·01	0·25

Analytical data: Gas chromatogram, RIFM no. 74–64; infra-red curve, RIFM no. 74–64.

Status

p-Cresyl isobutyrate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included *p*-cresyl isobutyrate at a level of 0·15 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health. The *Food Chemicals Codex* (1972) has a monograph on *p*-cresyl isobutyrate.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 4 ml/kg (3·53–4·58 ml/kg) and the acute dermal LD_{50} value in rabbits as 3·97 ml/kg (Levenstein, 1974).

Irritation. *p*-Cresyl isobutyrate applied full strength to the intact or abraded skin of rabbits for 24 hr under occlusion was mildly irritating (Levenstein, 1974). Tested on human subjects by a 48-hr occluded-patch test at 4% in petrolatum, the material was not irritating (Kligman, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers using 4% *p*-cresyl isobutyrate in petrolatum and produced no sensitization reactions (Kligman, 1974).

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Levenstein, I. (1974). Report to RIFM, 18 March.

p-CRESYL METHYL ETHER

Synonyms: Methyl *p*-cresol; *p*-methylanisole; 4-methylphenol methyl ether; 4-methyl-1-methoxybenzene.

Structure: $CH_3 \cdot C_6H_4 \cdot OCH_3$.

Description and physical properties: EOA Spec. no. 224.

Occurrence: Found in oil of ylang ylang, cananga and others (Gildemeister & Hoffman, 1966).

Preparation: By methylation of *p*-cresol.

Uses: In public use since the 1920s. Use in fragrances in the USA amounts to less than 10,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·01	0·2
Maximum	0·15	0·015	0·05	0·2

Analytical data: Gas chromatogram, RIFM no. 72–193; infra-red curve, RIFM no. 72–193.

Status

p-Cresyl methyl ether was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included *p*-cresyl methyl ether in the list of admissible artificial flavouring substances at a level of 5 ppm. The *Food Chemicals Codex* (1972) has a monograph on *p*-cresyl methyl ether.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 1·92 (1·51–2·45) g/kg (Hart, 1971). The acute dermal LD_{50} in rabbits was reported as >5 g/kg (Hart, 1971).

Irritation. *p*-Cresyl methyl ether applied full strength on intact or abraded rabbit skin was moderately irritating (Hart, 1971). *p*-Cresyl methyl ether tested at 2% in petrolatum produced no irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1971).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 human volunteers. The material was tested at a concentration of 2% in petrolatum and produced no sensitization reactions (Kligman, 1971).

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Kligman, A. M. (1971). Report to RIFM, 9 June.

p-CRESYL PHENYLACETATE

Synonym: *p*-Tolyl phenylacetate.
Structure: $CH_3 \cdot C_6H_4 \cdot OCO \cdot CH_2 \cdot C_6H_5$.
Description and physical properties: EOA Spec. no. 231.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: From *p*-cresol and phenylacetic acid by esterification.
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to less than 2000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·08
Maximum	0·1	0·01	0·03	0·3

Analytical data: Gas chromatogram, RIFM no. 72-111.

Status

p-Cresyl phenylacetate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included *p*-cresyl phenylacetate at a level of 5 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. *p*-Cresyl phenylacetate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1973). Tested at 4% in petrolatum in a 48-hr occluded-patch test in human subjects, it was not irritating (Kligman, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1974).

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CUBEB OIL

Description and physical properties: EOA Spec. no. 89. Cubeb oil has been reported to contain 33% sabinene, cineole, 17% sesquiterpene alcohols and 14% cadinene (Appell, 1968). In a chromatographic study, cubeb oil was found to contain 9.5% monoterpene hydrocarbons including 47% sabinene, 12–13% of α-thujene, of β-phellandrene and of α-pinene, and small amounts of myrcene, *p*-cymene, terpinolene, β-pinene, α-phellandrene, α- and γ-terpinene, *d*-limonene and ocimene (Ikeda, Stanley, Vannier & Spitler, 1962). The β-phellandrene fraction was separated and characterized by Wrolstad & Jennings (1964). The sesquiterpene hydrocarbons α- and β-cubebene have been isolated from oil of cubeb (Ohta, Sakai & Hirose, 1966).

Occurrence: Found in the fruit of *Piper cubeba* L. (Fam. Piperaceae).

Preparation: By steam distillation of the mature, unripe, sun-dried fruit of *P. cubeba* after crushing or coarse grinding.

Uses: In public use since before the 1850s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·2
Maximum	0·2	0·02	0·05	0·8

Status

Cubeb oil was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1163). The Council of Europe (1974) included cubeb in the list of substances, spices and seasonings deemed admissible for use with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on cubeb oil.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Levenstein, 1976).

Irritation. Undiluted cubeb oil applied to the backs of hairless mice and swine produced hyperkeratosis and dry desquamation (Urbach & Forbes, 1976). Applied full strength to intact or abraded rabbit skin for 24 hr under occlusion it was irritating (Levenstein, 1976). Tested at 8% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1976).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1976).

Phototoxicity. No phototoxic effects were reported for undiluted cubeb oil on hairless mice and swine (Urbach & Forbes, 1976).

Viruses. The death rate of rats receiving influenza virus dropped into the nostrils was significantly decreased by simultaneous administration of volatile oil from *P. cubeba* (Wang, 1958 & 1959).

Micro-organisms. Cubeb oil possessed no *in vitro* antifungal activity against 12 phytopathogenic fungi (Maruzzella & Balter, 1959) and three wood-destroying fungi (Maruzzella, Scrandis, Scrandis & Grabon, 1960), and only weak activity against four out of 15 pathogenic and non-pathogenic fungi (Maruzzella & Liguori, 1958) when tested by the filter-paper-disc method.

Cubeb oil possessed only weak *in vitro* antibacterial activity against *Bacillus brevis* and none against four other bacteria, and diminished the activity of other oils when tested in combination (Maruzzella & Henry, 1958). The vapour of cubeb oil inhibited the growth of *Bacillus subtilis* but not that of five other bacteria (Maruzzella & Sicurella, 1960).

The essential oil of *P. cubeba* inhibited the growth of 14 out of 15 bacteria tested by the filter-paper-disc method, showing the greatest antibacterial activity of six oils studied. In tests of combined oils, a 1:1 mixture of oils of *P. cubeba* and *Litsea chinensis* showed the maximum inhibitory response (Kar & Jain, 1971).

Medicinal uses. It was formerly used as a urinary antiseptic (*Merck Index*, 1968).

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CUMINALDEHYDE

Synonyms: Cuminic aldehyde; *p*-isopropylbenzaldehyde; 4-isopropylbenzaldehyde.
Structure: $CH_3{\cdot}CH(CH_3){\cdot}C_6H_4{\cdot}CHO$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Found in at least 50 essential oils such as cumin, Eucalyptus species, cinnamon, boldo and rue, and as the main constituent in oil of *Pectis papposa* Harn and Gray (Gildemeister & Hoffman, 1963).
Preparation: From *p*-isopropylbenzyl chloride and hexamethylenetetramine (Arctander, 1969).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 3000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·002	0·05
Maximum	0·05	0·05	0·02	0·4

Analytical data: Gas chromatogram, RIFM no. 72–114; infra-red curve, RIFM no. 72–114.

Status

Cuminaldehyde was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included cuminaldehyde in the list of admissible artificial flavouring substances, at 15 ppm.

Biological data

Acute toxicity. The acute oral LD_{50} was reported as 1·39 g/kg in the rat (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964). The acute dermal LD_{50} in rabbits was reported as 2·8 (2·24–3·50) g/kg (Denine, 1973).

Irritation. Cuminaldehyde applied undiluted to the backs of hairless mice produced no irritating effects (Urbach & Forbes, 1972), but was irritating when applied full strength to intact or abraded rabbit skin (Denine, 1973). Cuminaldehyde tested at 4% in petrolatum produced no irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at 4% concentration in petrolatum and produced no sensitization reactions (Kligman, 1972).

Phototoxicity. No phototoxic effects were reported for cuminaldehyde (Urbach & Forbes, 1972).

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CUMIN OIL

Description and physical properties: EOA Spec. no. 115. The main constituent of cumin oil is cuminaldehyde (Gildemeister & Hoffman, 1961; Guenther, 1950).
Occurrence: Found in the seeds of *Cuminum cyminum* L. (Fam. Umbelliferae).
Preparation: By steam distillation of the crushed dried fruit of *Cuminum cyminum* L.
Uses: In public use before the 1900s. Use in fragrances in the USA amounts to less than 2000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	—	—	0·003	0·05
Maximum	—	—	0·02	0·4

Analytical data: Gas chromatogram, RIFM no. 72–112; infra-red curve, RIFM no. 72–112.

Status

Cumin oil was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) included cumin oil in the list of substances, spices and seasonings deemed admissible for use with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on cumin oil.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 2·5 ml/kg (2·0–3·1 ml/kg) (Shelanski, 1972). The acute dermal LD_{50} value in rabbits was reported as 3·56 ml/kg (2·92–4·35 ml/kg) (Shelanski, 1972).

Irritation. Cumin oil applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Shelanski, 1972). Applied undiluted to the backs of hairless mice, it was not irritating (Urbach & Forbes, 1972). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1972).

Phototoxicity. Distinct phototoxic effects were reported for undiluted cumin oil, but none for its principal ingredient, cuminaldehyde (Urbach & Forbes, 1972).

Percutaneous absorption. Cumin oil was rapidly absorbed through the skin of the mouse (Meyer & Meyer, 1959).

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CUMINYL ALCOHOL

Synonyms: *p*-Isopropylbenzyl alcohol; cuminic alcohol.

Structure: $CH_3 \cdot CH(CH_3) \cdot C_6H_4 \cdot CH_2OH$.

Description and physical properties: A colourless liquid with a spicy odour (Arctander, 1969).

Occurrence: Found in the oil from fruits of *Cuminum cyminum* and *Carum carvi* L. and also in the oils of *Eucalyptus bakeris* (esterified) and French lavender (*Fenaroli's Handbook of Flavor Ingredients*, 1971; Gildemeister & Hoffman, 1962).

Preparation: By reduction of cuminaldehyde (Arctander, 1969).

Uses: In public use since the 1950s. Use in fragrances in the USA amounts to less than 2000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·15
Maximum	0·1	0·01	0·03	0·4

Analytical data: Gas chromatogram, RIFM no. 72–113; infra-red curve, RIFM no. 72–113.

Status

Cuminyl alcohol was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included cuminyl alcohol in the list of admissible artificial flavouring substances at a level of 15 ppm.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 1·02 g/kg (0·9–1·14 g/kg) (Moreno, 1973). The acute dermal LD_{50} in rabbits was reported as 2·5 g/kg (0·5–3·0 g/kg) (Moreno, 1973).

Irritation. Cuminyl alcohol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1973). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 24 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Epstein, 1973).

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CYCLAMEN ALDEHYDE

Synonyms: *p*-Isopropyl-α-methylhydrocinnamaldehyde; 2-methyl-3-(*p*-isopropylphenyl)-propionaldehyde.

Structure: $CH_3{\cdot}CH(CH_3){\cdot}C_6H_4{\cdot}CH_2{\cdot}CH(CH_3){\cdot}CHO$.

Description and physical properties: EOA Spec. no. 149.

Occurrence: Apparently has not been reported to occur in nature.

Preparation: By the condensation of cuminic aldehyde and propionaldehyde followed by hydrogenation in the presence of a catalyst (Bedoukian, 1967).

Uses: In public use since the 1920s. Use in fragrances in the USA amounts to about 150,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·02	0·01	0·12
Maximum	0·2	0·03	0·03	0·3

Analytical data: Gas chromatogram, RIFM no. 70–65; infra-red curve, RIFM no. 70–65.

Status

Cyclamen aldehyde was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included cyclamen aldehyde in the list of admissible artificial flavouring substances, at a level of 1 ppm. The *Food Chemicals Codex* (1972) has a monograph on cyclamen aldehyde.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 3·81 g/kg (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964).

Irritation. Cyclamen aldehyde tested at 3% in petrolatum produced a mild irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1971).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 human volunteers. The material was tested at a concentration of 3% in petrolatum and produced no sensitization reactions (Kligman, 1971).

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Kligman, A. M. (1971). Report to RIFM, 25 March.

CYCLAMEN ALDEHYDE DIETHYL ACETAL

Synonym: α-Methyl-*p*-isopropylhydrocinnamic aldehyde diethyl acetal.
Structure: $(CH_3)_2CH \cdot C_6H_4 \cdot CH_2 \cdot CH(CH_3) \cdot CH(OC_2H_5)_2$.
Description and physical properties: A colourless liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By the interaction of cyclamen aldehyde with triethyl orthoformate.
Uses: Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·005	0·025	0·3
Maximum	0·45	0·045	0·15	2·4

Analytical data: Gas chromatogram, RIFM no. 75–IFRA–22.

Status

Cyclamen aldehyde diethyl acetal is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974) or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1976).

Irritation. Cyclamen aldehyde diethyl acetal applied undiluted to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1976). Tested at 24% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 24% in petrolatum and produced no sensitization reactions (Kligman, 1975).

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CYCLAMEN ALDEHYDE PROPYLENEGLYCOL ACETAL

Synonym: α-Methyl-*p*-isopropylhydrocinnamic aldehyde propyleneglycol acetal.
Structure: $(CH_3)_2CH \cdot C_6H_4 \cdot CH_2 \cdot CH(CH_3) \cdot CH \cdot O \cdot CH(CH_3) \cdot CH_2$ (O)

Description and physical properties: A colourless liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By reacting cyclamen aldehyde with propylene glycol in the presence of a catalyst and with azeotropic removal of water.
Uses: Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·05	0·005	0·025	0·3
Maximum	0·45	0·045	0·15	2·4

Analytical data: Gas chromatogram, RIFM no. 75–IFRA–25.

Status

Cyclamen aldehyde propyleneglycol acetal is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974) or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1976).

Irritation. Cyclamen aldehyde propyleneglycol acetal applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1976). Tested at 24% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 24% in petrolatum and produced no sensitization reactions (Kligman, 1975).

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CYCLOHEXANOL

Synonyms: Hexalin; hexahydrophenol.
Structure: $C_6H_{11}OH$.
Description and physical properties: Colourless crystal needles.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By reduction of cyclohexanone or by hydrogenation of phenol in the presence of a catalyst (Arctander, 1969).
Uses: In public use since the 1920s.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·015	0·15
Maximum	0·2	0·024	0·08	0·4

Analytical data: Gas chromatogram, RIFM no. 74–71; infra-red curve, RIFM, no. 74–71.

Status

The Council of Europe (1974) included cyclohexanol in the list of artificial flavouring substances that may be added temporarily to foodstuffs without hazard to public health. Browning (1965) has an extensive monograph on cyclohexanol.

Biological data

Acute toxicity. The acute oral LD_{50} of cyclohexanol in rats was reported as 2·06 g/kg (Bär & Griepentrog, 1967; Smyth, Carpenter, Weil, Pozzani & Striegel, 1962). The acute oral minimum lethal dose (MnLD) for rabbits was 2·2–2·6 g/kg, with narcosis (Treon, Crutchfield & Kitzmiller, 1943a); lethal doses caused severe vascular damage and extreme toxic effects, with massive coagulation necrosis of the myocardium, lung, liver, kidney and brain, while sublethal doses caused much less severe degenerative lesions and vascular damage. The MnLD by single cutaneous application was 12·4–22·7 g/kg, with tremors, narcosis and hypothermia (Treon *et al.* 1943a). The acute sc LD_{50} of cyclohexanol (as sodium cyclohexyl succinate) in mice was 2·48 g/kg (Custode, Utreras & Naranjo, 1967). Also in mice, the acute im LD_{50} of cyclohexanol was 1·0 g/kg (Northover & Verghese, 1962) and the acute iv LD_{50} was 0·272 g/kg. Tubifex worms, 2–3 cm long, were immobilized by immersion in a 0·048 M (4·8 g/litre) solution of cyclohexanol, a determination which was found to give rapid results directly comparable to those in mice (Zagradnik, Chvapil, Vostal & Teisinger, 1962).

Toxic doses of cyclohexanol injected into mice and rats caused inhibition of motor activity, flaccidity, lateral position, clinico-tonic spasms and death, and cyclohexanol injected into mice intensified the sedative effect of phenobarbitone and sodium pentobarbitone and decreased the intensity of spasms caused by strychnine and Corazole (Myasoedova, 1968). Vasodilation by direct action on the blood vessels was demonstrated by Northover & Verghese (1962). In the anaesthetized dog, an iv dose of 18·4 mg/kg was required to produce a fall in systolic arterial pressure of 25% of the pre-injection value. A dose of 0·05 g in the fluid used to perfuse the leg of a dog or the isolated ear of a rabbit produced a maximum increase in venous outflow of 80 or 70%, respectively, over pre-injection values. Injection iv caused a transient decrease in the blood pressure of rabbits (Treon, 1963). Cyclohexanol decreased the arterial pressure in anaesthetized cats and inhibited the activity of isolated frog heart (Myasoedova, 1968).

Toxicity studies in rats showed cyclohexanol to possess very low toxicity and to have a depressive action on the central nervous system (Nannelli & Vallecchi, 1960).

Subacute and chronic toxicity. Repeated application of 10 ml cyclohexanol on the intact skin of a rabbit for 1 hr/day for 10 days induced narcosis, tumours, athetoid movements and hypothermia, together with local skin changes (Treon *et al.* 1943a). Long-term oral administration to rats of doses in cyclohexanol 5–10 times the maximum permissible concentration in water produced distinct changes in the central nervous system, as demonstrated by a method using conditioned reflexes; at doses corresponding to the maximum permissible concentration, only a slight increase in phase states was detected (Savelova & Sergeev, 1970). When rats received daily for 7 months an oral dose including cyclohexane, cyclohexanol, cyclohexanone and cyclohexanone oxime, each at the maximum permissible concentration or 25% of this level or at the minimum effective concentration (actual dosages not stated), it was found that all levels disturbed the conditioned reflex in all experimental animals and produced microscopic degenerative changes in the central nervous system, with a total toxic effect greater than was to be expected from the effects of the separate substances

(Savelova & Sergeev, 1970). When given as a 1·0% solution as a dietary additive to pregnant mice, cyclohexanol caused increases in the mortality rate of the young during the first 21 days of life and also inhibited their growth, to a greater extent in the females than the males (Gondry, 1973).

Inhalation toxicity. Cyclohexanol irritates the upper respiratory tract and has a narcotic effect intermediate between the effects of benzene and chloroform (Bernard, Pallade, London, Popovich, Gol'dshtein, Mikhail, Mandrik & Vancha, 1962). Exposure of rabbits to high concentrations of cyclohexanol in air for 6 hr/day on 5 days/wk induced an intoxication characterized by conjunctival congestion and irritation, lachrymation, salivation, lethargy, incoordination, narcosis and mild convulsions, and caused 50% mortality at a level of 997–1229 ppm (4·00–4·93 mg/litre) in air (Treon, Crutchfield & Kitzmiller, 1943b). Degenerative changes were found in the brain, heart, liver and kidneys of rabbits exposed repeatedly to 997–1229 ppm in air and similar but less severe changes were seen in the myocardium, liver and kidneys with 272 ppm (1·09 mg/litre) in air, while slight degenerative changes were barely demonstrable in the liver and kidneys at 145 ppm (0·58 mg/litre) (Treon *et al.* 1943b).

A decrease of 1–2% was found in the reduced glutathione of the blood of rabbits that inhaled vapours of cyclohexanol for 10–15 min on alternate days over a period of 21 days (Treon, 1963). Smyth *et al.* (1962) found that 8 hr was the maximum time for inhalation of concentrated cyclohexanol vapour by rats with no deaths.

In a more prolonged study (Dobrinskii, 1964), rats were exposed to cyclohexanol vapour for 24 hr/day for 87 days, followed by a 6-day starvation period (20% of normal rations). At a concentration of 0·61 mg/m^3, changes were noted in the interrelationship of the chronaxie of the extensor and flexor muscles (decreased after wk 7), in cholinesterase activity (increased time needed for hydrolysis of acetylcholine) and in the ascorbic acid content of liver (increased by 30% by the end of month 2). No changes were noted in health and weight gain, reactive (sulphydryl) groups of serum protein, or ascorbic acid content of the brain. At a concentration of 0·059 mg/m^3, all properties studied remained normal. It was concluded that the permissible average daily concentration in atmospheric air is 0·06 mg/m^3, the same as the level for maximum single permissible concentrations.

In a very early study, no effects were observed when a dog was exposed to air saturated with cyclohexanol for 10 min/day on 7 successive days (Treon, 1963). Lethargy and conjunctival irritation were observed in one monkey exposed to 693 ppm (2·78 mg/litre) in air for a total of 300 hr (Treon *et al.* 1943b).

The effect on cerebral electrical activity was determined by two methods in five human subjects. On the basis of the most sensitive electro-encephalographic method (electrocortical conditioned reflex), the maximum single permissible concentration recommended was 0·06 mg/m^3 (Dobrinskii, 1964). The threshold of action of inhaled cyclohexanol vapour on the electrical activity of the brain was found to be 0·06 mg/m^3 (Dobrinskii, 1966).

Threshold limit value. The threshold limit value for cyclohexanol has been set at 50 ppm (American Conference of Governmental Industrial Hygienists, 1973). In connexion with the production of plastics, a provisional maximum permissible concentration of 0·3 mg/litre [*sic*] was proposed by Bernard *et al.* (1962). On the basis of changes in cerebral electrical activity (electrocortical conditioned reflex) in man, the maximum single permissible concentration of cyclohexanol vapour recommended by Dobrinskii (1964 & 1966) was 0·06 mg/m^3. Following chronic exposure of rats to low concentrations of cyclohexanol vapour, Dobrinskii (1964) concluded that the permissible average daily concentration of cyclohexanol in atmospheric air was 0·06 mg/m^3, the same as the maximum single permissible concentration.

Exposure of human subjects for 3–5 min caused objectionable irritation of eyes, nose and throat in all subjects, and it was generally considered that the highest permissible concentration for an 8-hr exposure, should, from the standpoint of comfort, be less than 100 ppm (Nelson, Ege, Ross, Woodman & Silverman, 1943). The olfactory threshold in man was found to be 0·24 mg/m^3 (Dobrinskii, 1964).

Standards for a maximum permissible concentration of cyclohexanol in water have been established experimentally on the basis of toxicological criteria (levels not given) (Savelova & Sergeev, 1970).

Irritation. Cyclohexanol tested at a concentration of 4% in petrolatum produced no irritation after a 48-hr closed-patch test in human subjects (Epstein, 1974).

Cyclohexanol has been reported to have local irritating effects on the skin and the mucous membranes (Myasoedova, 1968). It caused slight irritation on uncovered rabbit belly and moderately severe corneal injury in rabbits (Smyth *et al.* 1962). Repeated application of 10 ml cyclohexanol to the intact skin of a rabbit for 1 hr/day for 10 days induced local necrosis, exudative ulceration, and thickening of the skin, in addition to narcosis and other systemic effects (Treon *et al.* 1943a). Only temporary erythema and superficial sloughing of the skin of rabbits resulted from application for 1 hr/day for 15 days of 5-g portions of a soap consisting of 5, 10 or 15% (w/w) cyclohexanol in potassium oleate (Treon *et al.* 1943a). There was considerable lachrymation at the higher concentrations, presumably from absorption through the skin.

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 26 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Epstein, 1974).

Skin penetration. Cyclohexanol is one of a number of alcohols that increase the penetration of externally applied drugs (Meyer, 1966). In an evaluation of skin-penetrating agents, cyclohexanol aided somewhat in the deep penetration of Rhodamine B into the corium of guinea-pig skin (Meyer, 1965). Intracutaneous injection of cyclic alcohols, including cyclohexanol dissolved in isopropyl myristate, increased local capillary permeability in rabbit skin, as measured by extravasal leakage of iv-injected Evans blue (Suzuki & Arai, 1966).

Metabolism. Cyclohexanol and its derivatives are generally not aromatized *in vivo*; large amounts of cyclohexanol may be excreted as urinary glucuronides (Williams, 1959), without prolonged retention in the organism (Browning, 1965). No urinary metabolites were detected when cyclohexanol was given to dogs by Bernhard (1937), who administered an sc dose of 0·29 g/kg, or by Weitzel (1950). Glucuronic acid was found in the urine of a dog following oral administration of cyclohexanol (Treon, 1963). Following administration to rabbits orally or by inhalation, cyclohexanol was excreted in the urine in conjugation with sulphuric and glucuronic acids. When 1·2 g cyclohexanol/kg (half the minimum lethal dose) was given orally to rabbits, 45–50% was excreted conjugated with glucuronic acid, with a decreased ratio of urinary inorganic sulphates to total sulphates. No cyclohexanone was recovered from the urine of a rabbit given 33% of the minimum lethal dose orally (Treon *et al.* 1943a,b). Elliott, Parke & Williams (1959) reported that more than 65% of a dose of 0·25 g cyclohexanol/kg was excreted by rabbits as glucuronides, chiefly cyclohexyl glucuronide, and an additional 6% was excreted as conjugated *trans*-cyclohexane-1,2-diol.

Cyclohexanol is of interest as a metabolite of sodium cyclamate, having been identified as a metabolite in the urine of rats (Kojima & Ichibagase, 1968), rabbits (Ichibagase, Kojima, Inoue & Suenaga, 1972; Kojima & Ichibagase, 1968), guinea-pigs (Asahina, Yamaha, Sarrazin & Watanabe, 1972) and human subjects (Kojima & Ichibagase, 1969) given sodium cyclamate orally. When rabbits received 50 mg cyclohexanol as a single oral dose, the urine contained 25% of the unchanged alcohol and $<1\%$ of the glucuronide. When rabbit-liver homogenate was incubated with cyclohexanol, 28% of the alcohol remained unchanged and 7% was metabolized. Almost no change occurred in the metabolism of cyclohexanol when the animal was pretreated with tolbutamide, which accelerates the metabolism of sodium cyclamate in the rabbit (Ichibagase *et al.* 1972).

Cyclohexanol was not utilized to any significant extent by a number of endocrine tissues from human placenta, rat ovary, rat testis and rat adrenal gland (Ferguson, Baillie, Calman & Hart, 1966). It was oxidized by horse-liver alcohol dehydrogenase in a preparative-scale process (Jones & Taylor, 1973) and was fermented in a process for the treatment of waste waters from caprolactam production (Kolesov, 1973).

Cyclohexanol was identified as a metabolite in the urine (free and glucuronide-conjugated) in the expired air of rats receiving *n*-heptyl cyclohexylboronate as a single ip, iv or oral dose of 0·1 mg/kg (Caujolle, Mariotti, Oustrin & Pitet, 1970).

Effect on insects. Cyclohexanol inhibited the wing vibration response of the male Mediterranean flour moth, *Ephestia kuehniella*, to sex pheromone from the female over a 30-sec period (Traynier & Wright, 1973).

Effect on enzymes. Cyclohexanol exerts an inhibiting effect on anaerobic glycolysis by aiding lactic acid synthesis, and inhibits the mitotic activity of neoplastic cells (Custode *et al.* 1967). Interference with glycolysis was studied as a factor influencing the radiation sensitivity of tumour cells. Of several alcohols studied, cyclohexanol showed the strongest inhibitory effect on glucose fermentation by yeast (Nannelli & Vallecchi, 1960). Cyclohexanol inhibits an enzyme in hog ascaris muscle which produces succinate from fumarate in the presence of reduced diphosphopyridine nucleotide as hydrogen donor and requires Mn^{++} or Mg^{++} (Obo & Nomura, 1961). It also has an inhibitory effect, dependent on its concentration, on the rate of butyrylcholine hydrolysis by horse-plasma cholinesterase (Patocka, 1970). The reversible association of an active centre of α-chymotrypsin with cyclohexanol and other enzyme inhibitors was studied by Martinek, Levashov & Berezin (1971) and by Levashov, Martinek & Berezin (1972). There was a positive correlation between the effectiveness of cyclohexanol as a chymotrypsin inhibitor and as an inhibitor of collagen-induced platelet aggregation in human platelet-rich plasma (Jobin, Tremblay & Morissette, 1970). The activity of cyclohexanol in the denaturation of T4-phage DNA was found to be dependent on its lipophilic character, as measured by the octanol–water coefficient, which closely paralleled the hydrophobic bonding of cyclohexanol to bovine serum albumin (Helmer, Kiehs & Hansch, 1968). Cyclohexanol was one of the inhibitors used in a kinetic study of the inhibition of peptic hydrolysis of *N*-acetyl-L-phenyl alanyl-L-tyrosine, which indicated that the inhibitors are bound to pepsin principally by hydrophobic forces (Schlamowitz, Shaw & Jackson, 1968).

In *in vitro* studies, cyclohexanol in concentrations of 0·1–0·01 M did not inhibit any of eight enzymes tested (Vogel, Snyder & Schulman, 1964).

Radiation. The radiosensitizing effect of cyclohexanol, an antagonist of glucose (in the form of sodium cyclohexyl succinate) was investigated in mice. The LD_{50} (30 days) of radiotherapy (655 R) and its effect on depilation (none at 2000 R but reduced hair regeneration at 600 R, with erythema

and skin ulcers in pre-depilated animals) were not changed by treatment with cyclohexanol (Custode *et al.* 1967). Irradiated pregnant mice treated with cyclohexanol (0·5–1·5 g/kg) delivered litters containing 21–54% live offspring, which soon died, while animals receiving only irradiation or only cyclohexanol delivered, respectively, 90% live offspring with 53% survival or 100% live offspring with 87% survival (Custode *et al.* 1967). When the ears of rabbits treated for 6 days with cyclohexanol were irradiated with X-rays in a single exposure, depilation of treated rabbits occurred 8 days after irradiation, compared with 15 days for the untreated controls (Nannelli & Vallecchi, 1960). Mortality in the irradiated treated rats was 80% compared with 0% in the irradiated controls.

In clinical trials, 40 patients with skin epithelioma received 2 g cyclohexanol/day by mouth or 1 g/day parenterally during therapy. Nineteen of 26 patients treated by radium implantation showed complete recovery, while recovery occurred in only eight of 20 patients given the same radium treatment without cyclohexanol. Five of 14 cyclohexanol-treated patients receiving X-ray therapy showed complete recovery. It was concluded that cyclohexanol exerts a radiation-sensitizing power which may be used with advantage in the radiological therapy of skin tumours (Nannelli & Vallecchi, 1960).

Genetic effects. The frequency of lethal mutations in male fruit flies (*Drosophila melanogaster*) was not affected by treatment with cyclohexanol at 0·1 ml/100 ml for 3 days (Goncharova, 1970). The recessive lethal mutation frequency after γ- and X-ray (1500 R) irradiation was not affected by pretreatment with cyclohexanol at 0·1 ml/100 ml for 3 days (Goncharova & Laryutina, 1970). In a study of the cytogenetic effects of cyclamate metabolites, achromatic regions, breaks and deletions were observed in karyograms of human leucocytes grown on media containing 0·01, 0·001 or 0·0001 M-cyclohexanol (Collin, 1971).

Additional published data

Of a group of 279 men and 174 women exposed daily to less than the permitted concentrations of benzene, cyclohexane, cyclohexanone, cyclohexanol, cyclohexanone oxime and caprolactam during caprolactam production, 114 individuals showed non-specific disturbances of the autonomic nervous system during a 2-yr period, as compared to eight out of 100 individuals in a non-exposed control group (Pestrii, 1970). It is apparent that headache and conjunctival irritation have resulted from prolonged exposure to excessive concentrations (Treon, 1963).

The only case of suspected intoxication was reported to the Home Office in Great Britain in 1932. A worker engaged in spraying leather with a preparation that contained butyl acetate and cyclohexanol complained of vomiting, coated tongue and slight tremors, which could not be attributed definitely to cyclohexanol (Browning, 1965).

Animal experiments have indicated that cyclohexanol is narcotic in high concentrations, with the possibility of damage to kidneys, liver, and blood vessels (Sax, 1968). Acute or chronic inhalation or skin contact may cause slight and reversible local effects, while moderate but non-lethal systemic effects may result from acute inhalation or ingestion (Sax, 1968).

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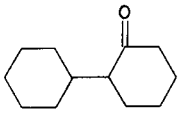
2-CYCLOHEXYL CYCLOHEXANONE

Synonyms: Bicyclohexanone; 2-cyclohexyl cyclohexan-1-one.
Structure:



Description and physical properties: A colourless liquid with a comparatively sweet odour (Arctander, 1969).
Occurrence: Apparently has not been reported to occur in nature.
Preparation: By self-condensation of cyclohexanone followed by reduction.
Uses: Use in fragrances in the USA amounts to about 35,000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·05	0·01	0·10	0·1
Maximum	0·30	0·03	0·15	2·0

Analytical data: Gas chromatogram, RIFM no. 72–116; infra-red curve, RIFM no. 72–116.

Status

Cyclohexyl cyclohexanone is not listed by the Council of Europe (1970), the *Food Chemicals Codex* (1972), FEMA (1965) or the FDA.

Biological data

Acute toxicity. The acute oral LD_{50} was reported as >5 g/kg in the rat (Denine, 1973). The acute dermal LD_{50} was reported as >5 g/kg in the rabbit (Denine, 1973).

Irritation. Cyclohexyl cyclohexanone applied full strength to intact or abraded rabbit skin was not irritating (Denine, 1973). Tested at 20% in petrolatum, it produced no irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at 20% concentration in petrolatum and produced no sensitization reactions (Kligman, 1972).

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CYCLOHEXYLETHYL ACETATE

Synonyms: Cyclohexane ethyl acetate; ethylcyclohexyl acetate; hexahydrophenyl ethyl acetate.
Structure: $C_6H_{11} \cdot CH_2 \cdot CH_2 \cdot OCO \cdot CH_3$.
Description and physical properties: A colourless oily liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By esterification of cyclohexylethanol with acetic acid or acetic anhydride (Arctander, 1969).
Uses: In public use since the 1950s.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·015	0·15
Maximum	0·2	0·024	0·08	0·4

Analytical data: Gas chromatogram, RIFM no. 74-75; infra-red curve, RIFM no. 74-75.

Status

Cyclohexylethyl acetate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included cyclohexylethyl acetate, at a level of 5 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 3·2 g/kg and the acute dermal LD_{50} value in rabbits as 5 g/kg (Wohl, 1974).

Irritation. Cyclohexylethyl acetate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Wohl, 1974). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 24 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Epstein, 1974).

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Wohl, A. J. (1974). Report to RIFM, 2 April.

CYCLOHEXYLETHYL ALCOHOL

Synonyms: 2-Cyclohexylethanol; hexahydrophenylethyl alcohol.
Structure: $C_6H_{11} \cdot CH_2 \cdot CH_2OH$.
Description and physical properties: A colourless oily liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By catalytic hydrogenation of phenylethyl alcohol under pressure (Arctander, 1969).
Uses: Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·015	0·15
Maximum	0·2	0·024	0·08	0·4

Analytical data: Gas chromatogram, RIFM no. 74–76; infra-red curve, RIFM no. 74–76.

Status

Cyclohexylethyl alcohol is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974), or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 0·94 g/kg (Wohl, 1974). The acute dermal LD_{50} value in rabbits was reported as 1·22 g/kg (Wohl, 1974).

Irritation. Cyclohexylethyl alcohol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Wohl, 1974). Tested at 4% in petrolatum in human subjects in a 48-hr closed-patch test, it produced no irritation (Kligman, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers using 4% cyclohexylethyl alcohol in petrolatum without producing sensitization reactions (Kligman, 1974).

Additional published data

β-Cyclohexylethyl alcohol was found to be a strong inhibitor of mitochondrial monoamine oxidase (Severina, 1969).

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Wohl, A. J. (1974). Report to RIFM, 2 April.

CYCLOPENTADECANOLIDE

Synonyms: Pentadecanolide; ω-pentadecalactone; 15-hydroxypentadecanoic acid lactone.
Structure: $CH_2 \cdot [CH_2]_{13} \cdot CO$ (O-bridged).

Description and physical properties: *Givaudan Index* (1961).
Occurrence: Found in angelica root oil (*Givaudan Index*, 1961).
Preparation: By cyclization of 15-hydroxypentadecanoic acid (Bedoukian, 1967).
Uses: Use in fragrances in the USA amounts to less than 3000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·0005	0·003	0·08
Maximum	0·03	0·003	0·01	1·0

Analytical data: Gas chromatogram, RIFM no. 74–77; infra-red curve, RIFM no. 74–77.

Status

Cyclopentadecanolide was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Levenstein, 1974).

Irritation. No irritation was produced by cyclopentadecanolide applied full strength to intact or abraded rabbit skin for 24 hr under occlusion (Levenstein, 1974) or to the backs of hairless mice and swine (Urbach & Forbes, 1974). Tested at 10% in petrolatum, cyclopentadecanolide produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1974).

Phototoxicity. No phototoxic effects were reported for cyclopentadecanolide (Urbach & Forbes, 1974).

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Levenstein, I. (1974). Report to RIFM, 15 March.

Urbach, F. & Forbes, P. D. (1974). Report to RIFM, 18 September.

CYCLOPENTADECANONE

Synonym: Normuscone.
Structure: $CH_2 \cdot [CH_2]_{13} \cdot CO$.

Description and physical properties: Colourless crystal needles.
Occurrence: Reported to be found in the scent glands of the Louisiana muskrat, *Ondatra zibethicus rivalicius* (Guenther, 1949).
Preparation: By the cyclization of dinitriles in high dilution (Bedoukian, 1967).
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to less than 1000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·0005	0·0025	0·04
Maximum	0·06	0·006	0·01	1·0

Analytical data: Gas chromatogram. RIFM no. 75–20; infra-red curve, RIFM no. 75–20.

Status

The Council of Europe (1974) included cyclopentadecanone in the list of artificial flavouring substances not fully evaluated.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1975). The acute ip LD_{100} of cyclopentadecanone was not reached but was estimated to be >35 mmol/kg for mice; an ip dose of 11·25 mmol/kg caused no deaths in 24 hr and one of 8·92 mmol/kg caused no deaths in 4 days (the length of the study). An oral dose of ⩾45 mmol/kg caused no deaths in mice. Intense agitation accompanied by catatonia of the tail was caused by low doses of cyclopentadecanone; gross examination of the mice revealed no specific pathology but occasionally degenerative hepatitis, proximal tubular nephritis and, rarely, pancreatic necrosis were found following dosing with cycloalkanones (Caujolle & Caujolle, 1965).

Irritation. Cyclopentadecanone applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was slightly irritating (Moreno, 1975). Tested at 10% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1975).

Metabolism. Ketones are not readily metabolized, although most of them probably undergo appreciable reduction to the corresponding secondary alcohols, which are excreted in the urine as glucuronic acid conjugates (Williams, 1959). Cyclopentadecanone was hydroxylated in cultures of four steroid-hydroxylating fungi (*Calonectria decora, Rhizopus nigricans, Daedalea rufescens* and *Ophiobolus herpotrichus*), but was not affected by *Aspergillus ochraceus.* Initial attack occurred at the most remote carbon atom, with yields of up to 26% of 8-hydroxycyclopentadecanone, plus dihydroxy compounds and more polar products (Ashton, Bailey & Jones, 1974).

Physiology. Following 4–7-wk exposure of rats from the age of 2 wk to an odorous environment containing a constant level of $1{\cdot}6 \times 10^{-12}$ M cyclopentadecanone, a distinctive and specific pattern of mitral cell "selective degeneration" (not cell death) was observed in the olfactory bulb (Pinching & Doving, 1974).

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p-CYMENE

Synonyms: Cymene; *p*-methyl-isopropylbenzene; 4-isopropyl-1-methylbenzene.
Structure: $CH_3{\cdot}C_6H_4{\cdot}CH(CH_3){\cdot}CH_3$.
Description and physical properties: A colourless mobile liquid with a 'gassy', kerosene-like odour (Arctander, 1969).
Occurrence: Found in nearly 100 volatile oils, including lemon, sage, thyme, coriander, star anise and cinnamon (Gildemeister & Hoffman, 1960).
Preparation: By catalytic disproportionation of dipentene (Arctander, 1969). It can also be obtained by dehydration of camphor and is an important by-product in the sulphite process for paper manufacture (Gerarde, 1960).
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to less than 9000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·01	0·1
Maximum	0·1	0·01	0·1	0·4

Analytical data: Gas chromatogram, RIFM no. 72–117; infra-red curve, RIFM no. 72–117.

Status

p-Cymene was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included *p*-cymene in the list of artificial flavouring substances not admissible at present. Browning (1965) provided an extensive monograph on *p*-cymene.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 4·75 g/kg (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964). The lethal dose by ip administration is 2·162 g/kg in the guinea-pig (Chassevant & Garnier, 1903). The acute dermal LD_{50} in rabbits was reported as >5 g/kg (Moreno, 1973).

Skin absorption. *p*-Cymene is well absorbed through the skin. In studies with ^{14}C-labelled *p*-cymene, the penetration observed was 254 $\mu g/cm^2$ in 60 min (Wepierre, Cohen & Valette, 1968). Absorption by the skin is more rapid than with toluene, *p*-xylene or ethylbenzene (Valette & Cavier, 1954).

Irritation. *p*-Cymene applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1973). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1972). *p*-Cymene is reported to be a primary skin irritant; contact with the undiluted liquid can produce erythema, dryness and defatting, the intensity depending on the dose and duration of contact (Gerarde, 1960). In an effort to explore the possible effects of vehicle and concentration on cutaneous irritation the Kligman & Wooding (1967) method was used to test the following formulations, applied under occlusion daily for 10 days to the same spot on the backs of ten subjects: Diethyl phthalate; diethyl phthalate containing 0·4% *p*-cymene; diethyl phthalate containing 4% *p*-cymene; petrolatum; petrolatum containing 0·4% *p*-cymene; petrolatum containing 4% *p*-cymene. There were no instances of marginal irritation and no differences between the groups (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at 4% concentration in petrolatum and produced no sensitization reactions (Kligman, 1972).

Threshold Limit Value. The TLV for *p*-cymene has been set at 100–200 ppm (by analogy with toluene), at which level it may be expected to have irritative and narcotic properties (*Handbook of Organic Industrial Solvents*, 1961).

Metabolism. In this compound both an isopropyl and a methyl group occur together and the available evidence shows that only the methyl group is oxidized, cumic acid (*p*-isopropylbenzoic acid) and its conjugate (cuminuric acid) being the main metabolites in dogs and in sheep (Williams, 1959). Following inhalation, only a small part is excreted unchanged, the remainder being oxidized to water-soluble metabolites. As early as 1873, Ziegler suggested that the readily oxidized propyl side-chain formed a –COOH group (Browning, 1965): The ultimate product in the case of dogs and sheep is cumic acid, which is probably excreted as a conjugate with glycine (Gerarde, 1960).

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CYSTE ABSOLUTE

Synonym: Ciste absolute.

Description and physical properties: A greenish alcoholic extract of the plant *Cistus ladaniferus* with a sweet amber-like odour (Naves & Mazuyer, 1947).

Occurrence: Found in the leaves, stems and flowering tops of the plant *Cistus ladaniferus* L. (Fam. Cistaceae) (Naves & Mazuyer, 1947).

Preparation: By alcoholic extraction of the concrete from the plant (Naves & Mazuyer, 1947).

Uses: In public use since the 1940s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·01	0·1
Maximum	0·1	0·01	0·04	0·4

Analytical data: Infra-red curve, RIFM no. 72–118.

Status

The FDA approves cyste absolute for food use (21 CFR 121.1163). The Council of Europe (1970) listed cyste absolute (*Cistus incanus* Ladaniferus) in the list of substances, spices and seasonings whose use is deemed admissible, with a possible limitation of the active principle in the final product.

Biological data

Acute toxicity. The acute oral LD_{50} was reported as >5 g/kg in the rat (Shelanski & Moldovan, 1973). The acute dermal LD_{50} was reported as >5 g/kg in the rabbit (Shelanski & Moldovan, 1973).

Irritation. Undiluted cyste absolute applied to the backs of hairless mice produced no irritating effects (Urbach & Forbes, 1973). It was also non-irritating when applied full strength to intact or abraded rabbit skin (Shelanski & Moldovan, 1973). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at 4% concentration in petrolatum and produced no sensitization reactions (Kligman, 1973).

Phototoxicity. No phototoxic effects were reported for cyste absolute (Urbach & Forbes, 1973).

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DAVANA OIL

Description and physical properties: A brownish, viscous liquid. The chemical composition of davana oil is unreported, but davanone, a sesquiterpenoid ketone, has been isolated from it (Sipma & Van der Wal, 1968).

Occurrence: Found in the plant of *Artemisia pallens* Wall. (Fam. Compositae) (Guenther, 1952).

Preparation: By steam distillation of the plant *A. pallens* Wall. (Guenther, 1952).

Uses: In public use since the 1940s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·08
Maximum	0·1	0·01	0·03	0·4

Analytical data: Gas chromatogram, RIFM no. 76–62; infra-red curve, RIFM no. 76–62.

Status

Davana oil was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1163). The Council of Europe (1974) included davana in the list of substances, spices and seasonings deemed admissible for use, with a possible limitation of the active principle in the final product.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1976).

Subacute toxicity. In a 90-day feeding study (Oser, Carson & Oser, 1965), male and female rats were given commercial-grade davana oil diluted with cottonseed oil and added to the diet at a level expected to provide approximately 18·7 mg/kg body weight/day, at least 100 times the maximum estimated daily dietary intake in man. No adverse effects were observed on growth, food consumption, haematology, blood chemistry, liver and kidney weights or the gross and microscopic appearance of major organs at autopsy.

Irritation. Undiluted davana oil applied to the backs of hairless mice and swine was not irritating (Urbach & Forbes, 1976), but applied to intact or abraded rabbit skin for 24 hr under occlusion it was moderately irritating (Moreno, 1976). Tested at 4% in petrolatum, the oil produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1976).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 33 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Epstein, 1976).

Phototoxicity. No phototoxic effects were reported for undiluted davana oil on hairless mice and swine (Urbach & Forbes, 1976).

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DECAHYDRO-β-NAPHTHOL

Synonyms: Decahydronaphthol-2; *trans*-decahydro-β-naphthol; 2-decalol.
Structure: $C_{10}H_{17} \cdot OH$.
Description and physical properties: EOA Spec. no. 235.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By hydrogenation of β-naphthol.
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 4000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·002	0·005	0·2
Maximum	0·2	0·025	0·05	0·25

Analytical data: Gas chromatogram, RIFM no. 72–119; infra-red curve, RIFM no. 72–119.

Status

Decahydro-β-naphthol is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1970), nor in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. Decahydro-β-naphthol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1973). Tested at 2% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 23 volunteers. The material was tested at a concentration of 2% in petrolatum and produced no sensitization reactions (Epstein, 1973).

Metabolism. Decahydro-β-naphthol is largely oxidized in the dog, only about a third of the dose appearing unchanged in the urine. A small amount, however, is excreted as a crystalline dihydroxydecalin (Williams, 1959).

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δ-DECALACTONE

Synonyms: Decanolide-1,5; amyl-δ-valerolactone.
Structure: $CH_3 \cdot [CH_2]_4 \cdot CH \cdot [CH_2]_3 \cdot CO$ (O bridge)

Description and physical properties: *Food Chemicals Codex* (1972).
Occurrence: Reported to be found in coconut and raspberry (*Fenaroli's Handbook of Flavor Ingredients*, 1975).
Preparation: By conversion of amyl cyclopentanone to 5-hydroxydecylic acid and subsequent lactonization (Arctander, 1969).
Uses: In public use since the 1960s. Use in fragrances in the USA amounts to less than 1000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·001	0·0001	0·0005	0·02
Maximum	0·03	0·003	0·005	0·1

Status

δ-Decalactone was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164; tolerance 10 ppm in margarine). The Council of Europe (1974) included δ-decalactone at a level of 20 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health. The *Food Chemicals Codex* (1972) has a monograph on δ-decalactone.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Levenstein, 1975).

Irritation. δ-Decalactone applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was slightly irritating (Levenstein, 1975). Tested at 1% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 1% in petrolatum and produced no sensitization reactions (Kligman, 1975).

Metabolism. Glucuronide and sulphate conjugates of δ-decalactone have been identified in cows' milk (Brewington, Parks & Schwartz, 1973), and δ-decalactone and other δ-lactones and δ-lactone precursors have been identified in cows' milk fat (Parliment, Nawar & Fagerson, 1966), butterfat (van Beers & van der Zijden, 1966), and beef fat located around the kidneys (Nakanishi & Watanabe, 1966). Weekly determination of the concentrations of δ-lactones, including δ-decalactone, in cows' milk during a 310-day lactation supported the hypothesis that the lactone precursors are biological in origin and may be involved in fatty acid synthesis (Dimick & Harner, 1968).

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γ-DECALACTONE

Synonyms: γ-*n*-Decalactone; decanolide-1,4; γ-*n*-hexyl-γ-butyrolactone.
Structure: $CH_3 \cdot [CH_2]_5 \cdot CH \cdot [CH_2]_2 \cdot CO$ (lactone ring: O)

Description and physical properties: A colourless liquid.
Occurrence: Reported to be found in peach and apricot aroma, as well as strawberry aroma (*Fenaroli's Handbook of Flavor Ingredients*, 1975).
Preparation: Isomerization and lactonization of α,β-decenoic acid.
Uses: In public use since the 1940s. Use in fragrances in the USA amounts to less than 1000 lb/yr. Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·001	0·0001	0·0005	0·02
Maximum	0·03	0·003	0·005	1·0

Analytical data: Gas chromatogram, RIFM no. 74–182; infra-red curve, RIFM no. 74–182.

Status

γ-Decalactone was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included γ-decalactone at a level of 10 ppm in the list of artificial flavouring substances that may be added temporarily to foodstuffs without hazard to public health.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1975).

Irritation. γ-Decalactone applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1975). Tested at 10% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1975).

Micro-organisms. γ-Decalactone at minimum concentrations of 2–4 mg/ml inhibited the growth of five fungi (Sakurai, Matsumoto & Adachi, 1968). It also inhibited the growth of three wood-destroying fungi in tests using the filter-paper-disc method (Maruzzella, Scrandis, Scrandis & Grabon, 1960). Decalactone in a 1:500 dilution did not inhibit *in vitro* growth of four Gram-positive and Gram-negative bacteria (Maruzzella & Bramnick, 1961), but the vapour of γ-decalactone inhibited *in vitro* growth of one out of four Gram-positive and Gram-negative bacteria (Maruzzella, Garofalo & Chiaramonte, 1961) and two out of four fungi (Maruzzella, Chiaramonte & Garofalo, 1961).

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DECYLENIC ALCOHOL

Synonyms: 9-Decenol-1; ω-decenol.

Structure: $CH_2{:}CH{\cdot}[CH_2]_7{\cdot}CH_2OH$.

Description and physical properties: A colourless oily liquid with a rose-like odour (Arctander, 1969).

Occurrence: Apparently has not been reported to occur in nature.

Preparation: From 1,10-decamethylene glycol (Arctander, 1969).

Uses: In public use since the 1950s. Use in fragrances in the USA amounts to less than 20,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·005	0·01	0·05
Maximum	0·09	0·009	0·04	0·2

Analytical data: Gas chromatogram, RIFM no. 71–73; infra-red curve, RIFM no. 71–73.

Status

Decylenic alcohol is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1970) or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1972).

Irritation. Decylenic alcohol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1972). Tested at 2% in petrolatum, it produced no irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 human volunteers. The material was tested at a concentration of 2% in petrolatum and produced no sensitization reactions (Kligman, 1972).

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DEERTONGUE INCOLORE

Synonym: Liatrix oleoresin.

Description and physical properties: *Merck Index* (1968). Coumarin is one of the ingredients of deertongue (*Merck Index*, 1968). Lupeol, α-amyrin, their palmitates and acetates, and lupenone were isolated from hexane extracts of dried deertongue leaves. A low-boiling fraction distilled from the total ether extract contained only 2,3-benzofuran, dihydrocoumarin and coumarin in the ratio of 1:3:20 (Appleton & Enzell, 1971).

Occurrence: Found in the leaves of *Liatris odoratissima* (Walt.) Willd. (Fam. Compositae) (*Merck Index*, 1968).

Preparation: By extraction of the dried leaves of *L. odoratissima* with a volatile solvent, followed usually by decolorization with charcoal and evaporation of the solvent.

Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·04
Maximum	0·1	0·01	0·03	0·5

Status

The Council of Europe (1974) included deertongue in the list of currently used flavouring substances for which the toxicological and technological data were deemed insufficient, their use being temporarily admitted, possibly with a limitation on the active principle in the final product.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 0·73 g/kg (0·47–0·99 g/kg) and the acute dermal LD_{50} value in rabbits as 3·67 g/kg (2·11–5·23 g/kg) (Moreno, 1975).

Irritation. Deertongue incolore was not irritating when applied full strength to intact or abraded rabbit skin for 24 hr under occlusion (Moreno, 1975) or when applied in a concentration of 1% in methanol to the backs of hairless mice and swine (Urbach & Forbes, 1975). Deertongue incolore (2% in methanol) was non-irritating when applied to the shaved back skin of the guinea-pig in a closed-patch test (Urbach & Forbes, 1976). Tested at 5% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 5% in petrolatum and produced no sensitization reactions (Kligman, 1975).

Phototoxicity. No phototoxic effects were reported for deertongue incolore (1% in methanol) on hairless mice and swine (Urbach & Forbes, 1975).

Photallergenicity. Deertongue incolore (2% in methanol) did not produce any photoallergic effects in a test involving application, on three alternate days, of a non-irritating dose (20 $\mu l/cm^2$) under a large occlusive patch (10 cm × 5 cm) to the shaved neck of guinea-pigs, removal of the patch after 1 hr and irradiation of the area with a solar simulator for 45 min to produce a mild erythema, a procedure followed 18 days after the last treatment by a further application and subsequent exposure to light filtered to remove UV-B; daily examination of the animals for 1 wk revealed no photoallergic reactions (Harber, Targovnik & Baer, 1967, modified by Urbach & Forbes, 1976).

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DIETHYLENE GLYCOL MONOETHYL ETHER

Synonym: Ethyl diethylene glycol.
Structure: $CH_2(OH)\cdot CH_2O\cdot[CH_2]_2\cdot OCH_2\cdot CH_3$.
Description and physical properties: A colourless hygroscopic liquid with a faint ethereal odour with a musty undertone (Arctander, 1969).
Occurrence: Has apparently not been reported to occur in nature.
Preparation: From ethyl alcohol plus ethylene oxide (Arctander, 1969).
Uses: Use in fragrances in the USA amounts to less than 5000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·05	0·005	0·025	0·5
Maximum	0·3	0·03	0·1	2·0

Analytical data: Gas chromatogram, RIFM no. 72–17; infra-red curve, RIFM no. 72–17.

Status

Browning (1965) has an extensive monograph on diethylene glycol monoethyl ether.

Biological data

Acute toxicity. The acute oral LD_{50}s in rats, mice and guinea-pigs were reported as 5·54, 6·58 and 3·87 g/kg, respectively (Laug, Calvery, Morris & Woodard, 1939). The LD_{50}s in mice, rats and rabbits from iv injection were reported as 3·9, 2·9 and 0·9 ml/kg, respectively, and the sc LD_{50}s in rats and rabbits were reported as 3·4 and 2·0 ml/kg, respectively (Stenger, Aeppli, Lislott, Müller, Peheim & Thomann, 1971). The acute dermal LD_{50} value in rabbits was reported as 10·3 g/kg (Carpenter, 1947).

Short-term toxicity. The no-effect level for diethylene glycol monoethyl ether administered to five rats in the drinking-water for 30 days was 0·49 g/kg, while 0·87 g/kg caused reduction in appetite and 1·77 g/kg caused some organic injury (Smyth & Carpenter, 1948).

In a 4-wk sc study in rats, doses of 100–400 μl/kg/day produced no deaths, although at 200–400 μl/kg/day, dyspnoea, somnolence and mild ataxia appeared, with some growth retardation in females. Doses of 800 μl/kg/day had similar effects and, in addition, growth was depressed also in males following some reduction in food intake. Changes in liver, kidney and testes were also seen in rats given 200 μl/kg/day orally (Stenger *et al.* 1971).

Diethylene glycol monoethyl ether containing less than 0·4% ethylene glycol was given for 90 days to rats at dietary levels of 0·5 or 5·0%, to mice at dietary levels of 0·2, 0·6, 1·8 or 5·4% and to pigs in daily oral doses of 167, 500 or 1500 mg/kg (Gaunt, Colley, Grasso, Lansdown & Gangolli, 1968). Three pigs given 1500 mg/kg/day for 14–21 days died with symptoms of uraemia and six out of 20 male mice fed the 5·4% diet died with signs of advanced renal damage. There was reduction of growth in rats and mice fed the highest dietary concentrations. Oxaluria was found in rats and mice at the highest feeding level and a reduction in haemoglobin concentration was seen in all three species at the highest level of administration. The no-effect levels were approximately 250 mg/kg/day in rats, 850–1000 mg/kg/day in mice and 167 mg/kg/day in pigs.

Long-term toxicity. Purified diethylene glycol monoethyl ether fed to rats at approximately 1·0 g/kg/day for 2 yr produced a few oxalate concretions in the kidney of one animal and caused slight liver damage and some interstitial oedema in the testes (Morris, Nelson & Calvery, 1942).

Irritation. Diethylene glycol monoethyl ether is not irritant to the skin of rabbits even upon prolonged and repeated contact (Rowe, 1963). Tested at 20% in petrolatum, it produced no irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The

material was tested at a concentration of 20% in petrolatum and produced no sensitization reactions (Kligman, 1972).

Metabolism. The major part of an administered dose of diethylene glycol monoethyl ether is oxidized in the body or excreted as the glucuronate, administration to rabbits orally or by sc injection being followed by a marked increase in the urinary content of glucuronic acid (Fellows, Luduena & Hanzlik, 1947).

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DIETHYLENE GLYCOL MONOMETHYL ETHER

Structure: $CH_2(OH) \cdot CH_2O \cdot [CH_2]_2 \cdot OCH_3$.

Description and physical properties: A colourless liquid with a faint musty odour (Arctander, 1969).

Occurrence: Has apparently not been reported to occur in nature.

Preparation: A by-product in the manufacture of ethylene glycol monomethyl ether (Arctander, 1969).

Uses: Use in fragances in the USA amounts to about 5000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·05	0·005	0·025	0·5
Maximum	0·3	0·03	0·1	2·0

Analytical data: Gas chromatogram, RIFM no. 72–18; infra-red curve, RIFM no. 72–18.

Status

Browning (1965) has an extensive monograph on diethylene glycol monomethyl ether.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 6·31 g/kg (Weil, 1972), while with a 50% aqueous solution the LD_{50} values were 9·2 ml/kg for rats and 4·16 ml/kg for guinea-pigs (Smyth, Seaton & Fischer, 1941). The acute dermal LD_{50} in rabbits was reported as 20 ml/kg (Browning, 1965).

Short-term toxicity. The maximum dose having no effect in rats given diethylene glycol monomethyl ether for 30 days in their drinking-water was less than 0·19 g/kg (Smyth & Carpenter, 1948). The highest dosage level survived was 1·83 g/kg.

Irritation. Diethylene glycol monomethyl ether is not appreciably irritating to the skin, but on extensive and prolonged contact, it can be absorbed in toxic and even lethal amounts (Rowe, 1963). Tested at 20% in petrolatum, it produced no irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 20% in petrolatum and produced no sensitization reactions (Kligman, 1972).

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DIETHYL MALEATE

Synonym: Ethyl maleate.
Structure: $C_2H_5 \cdot OCO \cdot CH{:}CH \cdot OCO \cdot C_2H_5$.
Description and physical properties: A colourless liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By direct esterification of maleic acid with ethyl alcohol (Arctander, 1969).
Uses: Use in fragrances in the USA amounts to less than 1000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·0033	0·01	0·1
Maximum	0·06	0·005	0·04	0·4

Status

Diethyl maleate is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974), or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 3·2 g/kg (Fassett, 1963). The actue dermal LD_{50} value in rats was reported as >2·5 g/kg (Moreno, 1975) and as 5 ml/kg (Fassett, 1963).

Inhalation toxicity. No death occurred in rats exposed to saturated vapours of diethyl maleate for 8 hr (Fassett, 1963).

Irritation. Diethyl maleate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1975). The ester was reported to be slightly irritating to rabbit skin and eye (Fassett, 1963). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced sensitization reactions in all 25 (Kligman, 1975). Diethyl maleate was reported to be a sensitizer in patch tests performed on four men working with unsaturated polyester resins (Malten & Zielhuis, 1964).

Metabolism. α,β-Unsaturated compounds, such as diethyl maleate, react enzymically with glutathione. The reaction has been demonstrated in fractions of rat liver (Boyland & Chasseaud, 1967) and avian liver (Wit & Snel, 1968). The enzyme differs from other known *S*-alkyl, *S*-aryl and *S*-epoxide transferase enzymes responsible for glutathione-conjugate formation (Boyland & Chasseaud, 1967). Diethyl maleate, administered parenterally to rats, reduced the hepatic glutathione content (Boyland & Chasseaud, 1970; Varga, Fischer & Szily, 1974). The latter workers also showed that diethyl maleate pretreatment of rats inhibited the glutathione conjugation of subsequently-administered bromsulphthalein.

Studying this ester's effect on the metabolism of parathion and methyl parathion, Mirer, Levine & Murphy (1975) showed that pretreatment of mice with diethyl maleate (1 mg/kg), 1 hr before challenge, depleted liver glutathione and potentiated parathion and methyl parathion toxicity. *In vivo*, diethyl maleate potentiated the inhibition of brain cholinesterase by parathion and methyl parathion. Diethyl maleate pretreatment caused a twofold increase in the brain concentrations of parathion and methyl parathion and a large increase in the activation of methyl parathion to methyl paraoxon, and also decreased total degradation. Diethyl maleate inhibited the activation and degradation of parathion.

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DIETHYL MALONATE

Synonyms: Ethyl malonate; malonic ester.
Structure: $CH_3 \cdot CH_2 \cdot OCO \cdot CH_2 \cdot OCO \cdot CH_2 \cdot CH_3$.
Description and physical properties: *Merck Index* (1968).
Occurrence: Reported to be found in several natural products (*Fenaroli's Handbook of Flavor Ingredients*, 1975).
Preparation: From chloroacetic acid and sodium cyanide followed by esterification with ethanol and sulphuric acid (*Merck Index*, 1968).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to approximately 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·04
Maximum	0·1	0·01	0·03	0·4

Analytical data: Gas chromatogram, RIFM no. 75–30; infra-red curve, RIFM no. 75–30.

Status

Diethyl malonate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included it in the list of artificial flavouring substances that may be added temporarily to foodstuffs without hazard to public health. The *Food Chemicals Codex* (1972) has a monograph on diethyl malonate.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as $>1{\cdot}6$ g/kg by Fassett (1963) and as 14·9 ml/kg by Smyth, Carpenter, Weil, Pozzani, Striegel & Nycum (1969). The acute dermal LD_{50} value in rabbits was reported as >5 g/kg by Moreno 1975) and as >16 ml/kg by Smyth *et al.* (1969). The acute dermal LD_{50} value for guinea-pigs was reported to be >10 ml/kg (Fassett, 1963).

Subacute toxicity. Diethyl malonate fed to rats for 90 days at more than 100 times the equivalent of the human daily dietary intake (averaging 35·93 mg/kg body weight/day for males and 41·14 mg/kg/day for females) had no adverse effects (Posternak, Linder & Vodoz, 1969). A diet containing 5% diethyl malonate was palatable and did not cause death when fed to chicks (Yoshida, Morimoto & Oda, 1970).

Inhalation. The maximum time for inhalation of the concentrated vapour of diethyl malonate by rats without deaths was found to be 8 hr (Smyth *et al.* 1969).

Irritation. Diethyl malonate in doses of 10 ml/kg caused no local irritation to guinea-pig skin (Fassett, 1963). Applied full strength to intact or abraded rabbit skin for 24 hr under occlusion, it was very slightly irritating (Moreno, 1975). Tested at 4% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1975). Smyth *et al.* (1969) also reported only very slight irritation of rabbit skin after application of undiluted diethyl malonate, but application of 0·005 ml of undiluted diethyl malonate to the rabbit cornea caused severe burning.

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 23 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Epstein, 1975).

Metabolism. When the ester was fed to chicks at a level of 5% in the diet, 32% of the energy from diethyl malonate was available (Yoshida *et al.* 1970). Hydrolysis of diethyl malonate would produce ethanol and malonic acid, which is a relatively strong acid and acts as an inhibitor of enzymes, including succinic dehydrogenase (Fassett, 1963). Malonic acid injected into rats or rabbits is excreted largely unchanged, but also causes increased excretion of citric and α-ketoglutaric acids (Krebs, Salvin & Johnson, 1938). Some malonate may be metabolized through the tricarboxylic acid cycle, with decarboxylation to acetate followed by transformation to succinate, which has been detected in rat urine (Lee & Lifson, 1951). Diethyl malonate was hydrolysed by adipose-tissue lipase (Lynn & Perryman, 1960) and to the monoester by α-chymotrypsin (Cohen & Crossely, 1964). It was oxidized in 110 min to the extent of 34% by the homogenized mycelium of urethane-grown *Streptomyces nitrifica* (Schatz, Trelawny, Schatz & Mohan, 1957).

Insects. Because it inhibits dehydrochlorinase activity, diethyl malonate (10–40 ppm) increased the toxicity of DDT (2 ppm) to DDT-resistant mosquitoes, *Culex fatigans* (Bajpai, Srivastava, Perti & Agarwal, 1971).

Enzymes. A 3% solution of diethyl malonate caused a 38% inhibition of the proteolytic activity of enzymes of the fungus *Ctenomyces* (Agarwal & Agarwal, 1971). In a concentration of 2%, the ester completely inhibited cellulase activity in gut extracts of the termites *Termes obesus* and *Heterotermes indicola* (Misra & Vijayaraghavan, 1956). A 0·1 M concentration did not increase levels of maleate *cis–trans* isomerase in bacterial cultures of *Alcaligenes faecalis*, although hydrolysed malonate was a strong inducer of this enzyme and is known to be a potent inhibitor of succinic dehydrogenase (Takamura, Nakatani, Soejima & Aoyama, 1968).

Micro-organisms. Diethyl malonate at a level of 0·5–3% inhibited the growth and proteolytic activity of the fungus *Ctenomyces* (Agarwal & Agarwal, 1971; Agarwal & Puvathingal, 1965), while a 1:50,000 dilution showed *in vitro* tuberculostatic activity against *Mycobacterium tuberculosis* (Jeney & Zsolnai, 1956) and a concentration of 0·013 M inhibited sporulation of *Bacillus cereus* and a number of other bacteria (Gollakota & Halvorson, 1963). The maximum non-lethal concentration of diethyl malonate for saprophytic microflora and protozoa was found to be 1 g/litre, a concentration that was lethal for Infusoria (Chekhovskaya, Nazarenko & Mikhailovskaya, 1973).

Because diethyl malonate increased biological oxygen demand, slowed mineralization of organic matter and decreased the level of initial ammonium nitrogen, the maximum allowable limit in reservoirs should be 0·002 mg/litre (Rudenko, 1972).

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DIHYDROANETHOLE

Synonym: *p-n*-Propyl anisole.
Structure: $CH_3 \cdot O \cdot C_6H_4 \cdot [CH_2]_2 \cdot CH_3$.
Description and physical properties: EOA Spec. no. 219.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By hydrogenation of the propenyl group in anethole.
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·05	0·005	0·05	0·2
Maximum	0·1	0·01	0·1	1·0

Analytical data: Gas chromatogram, RIFM no. 74–79; infra-red curve, RIFM no. 74–79.

Status

Dihydroanethole was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included dihydroanethole in the list of artificial flavouring substances that may be added temporarily to foodstuffs without hazard to public health. The *Food Chemicals Codex* (1972) has a monograph on dihydroanethole.

Biological data

Acute toxicity. The acute oral LD_{50} value was reported as 4·4 g/kg (3·38–5·72 g/kg) in the rat and as 7·30 g/kg (5·93–9·00 g/kg) in the mouse (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964). The acute dermal LD_{50} value in rabbits was reported as >5 g/kg (Levenstein, 1974).

Chronic toxicity. In feeding studies, 1000, 2500 and 10,000 ppm fed to rats in the diet for 19 wk produced bone changes (Hagan, Hansen, Fitzhugh, Jenner, Jones, Taylor, Long, Nelson & Brouwer, 1967). Of 20 male rats given dihydroanethole in doses of 2000 mg/kg increasing gradually to 5000 mg/kg for 32 days, seven of the animals survived the full 32 days of treatment and 16 lived long enough to receive the maximal daily dose of 5000 mg/kg. A moderate degree of osteoporosis in the bone was produced, along with macroscopic and microscopic changes in the stomach (Hagan *et al.* 1967).

Irritation. Dihydroanethole applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Levenstein, 1974). Tested at 10% in petrolatum on two different panels of subjects, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced one questionable sensitization reaction (Kligman, 1974; see Preface Note no. 1). The material was retested by the same test on a different panel of 25 subjects at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1974).

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Jenner, P. M., Hagan, E. C., Taylor, Jean M., Cook, E. L. & Fitzhugh, O. G. (1964). Food flavourings and compounds of related structure. I. Acute oral toxicity. *Fd Cosmet. Toxicol.* **2,** 327.

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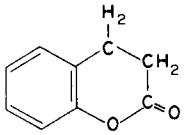
Levenstein, I. (1974). Report to RIFM, 20 March.

DIHYDROCOUMARIN

Synonyms: 3,4-Dihydrocoumarin; hydrocoumarin; 1,2-benzodihydropyrone.

Structure:



Description and physical properties: *Givaudan Index* (1961).
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By reduction of coumarin with a nickel catalyst (Arctander, 1969).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 10,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·2
Maximum	0·1	0·01	0·03	2·0

Analytical data: Infra-red curve, RIFM no. 72–19.

Status

Dihydrocoumarin was granted GRAS status by FEMA (1965). The Council of Europe (1970) included dihydrocoumarin in the list of admissible artificial flavouring substances, giving a level of 25 ppm.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 1·65 g/kg (1·47–1·83 g/kg) (Moreno, 1972a). The acute dermal LD_{50} value in rabbits was reported as >5 g/kg (Moreno, 1972b).

Subacute and long-term toxicity. In feeding studies, 1000 and 10,000 ppm fed to rats in the diet for 14 wk produced no effects (Hagan, Hansen, Fitzhugh, Jenner, Jones, Taylor, Long, Nelson & Brouwer, 1967). In a 2-yr study, dogs dosed daily with 50 and 150 mg/kg produced no effects (Hagan *et al.* 1967).

Irritation. Dihydrocoumarin applied full strength on intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1972b). Tested at 20% in petrolatum, it produced no irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 20% in petrolatum and produced sensitization reactions in all 25 test subjects (Kligman, 1972).

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Council of Europe (1970). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List A(1), Series 1, no. 557, p. 78. Strasbourg.

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Hagan, E. C., Hansen, W. H., Fitzhugh, O. G., Jenner, P. M., Jones, W. I., Taylor, Jean M., Long, Eleanor L., Nelson, A. A. & Brouwer, J. B. (1967). Food flavourings and compounds of related structure. II. Subacute and chronic toxicity. *Fd Cosmet. Toxicol.* **5**, 141.

Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.

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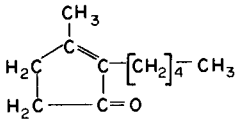
DIHYDROJASMONE

Synonyms: 2-Pentyl-3-methyl-2-cyclopenten-1-one; 3-methyl-2-(*n*-pentanyl)-2-cyclopentene-1-one.

Structure:



Description and physical properties: A colourless, slightly oily liquid with a floral-like odour (Arctander, 1969).
Occurrence: Has apparently not been reported to occur in nature.
Preparation: Hexyl bromide plus laevulinic ester yields a lactone, which is reacted with polyphosphoric acid or phosphorus pentoxide to produce hydrojasmone (Bedoukian, 1967).
Uses: In public use since the 1940s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·0005	0·002	0·04
Maximum	0·03	0·003	0·01	0·4

Analytical data: Gas chromatogram, RIFM no. 72–20; infra-red curve, RIFM no. 72–20.

Status

Dihydrojasmone is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1970), nor in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 2·5 g/kg (1·79–3·50 g/kg) (Keating, 1972). The acute dermal LD_{50} value in rabbits was reported as 5 g/kg (Keating, 1972).

Irritation. Dihydrojasmone applied full strength on intact or abraded rabbit skin for 24 hr under occlusion was irritating (Keating, 1972). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1972).

References

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Keating, J. W. (1972). Report to RIFM, 7 June.

Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.

Kligman, A. M. (1972). Report to RIFM, 19 July.

DIHYDROMYRCENOL

Synonym: 2,6-Dimethyl-7-octen-2-ol.
Structure: $CH_3 \cdot COH(CH_3) \cdot [CH_2]_3 \cdot C(CH_3):CH \cdot CH_3$.
Description and physical properties: A colourless, somewhat viscous oil (Arctander, 1969).
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By controlled, partial hydrogenation of myrcenol (Arctander, 1969).
Uses: Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·005	0·01	0·2
Maximum	0·1	0·01	0·03	0·4

Analytical data: Gas chromatogram, RIFM no. 72–122; infra-red curve, RIFM no. 72–122.

Status

Dihydromyrcenol is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1970), nor in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 3·6 g/kg (3·0–4·2 g/kg) (Moreno, 1973). The acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. Dihydromyrcenol applied full strength on intact or abraded rabbit skin for 24 hr under occlusion was mildly irritating (Moreno, 1973). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1973).

References

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Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.

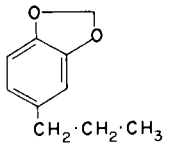
Kligman, A. M. (1973). Report to RIFM, 13 August.

Moreno, O. M. (1973). Report to RIFM, 4 June.

DIHYDROSAFROLE

Synonym: 1,2-Methylenedioxy-4-propylbenzene.

Structure:



Description and physical properties: *Givaudan Index* (1961).
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By catalytic hydrogenation of safrole (Arctander, 1969).
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to less than 2000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·005	0·1
Maximum	0·3	0·03	0·05	1·2

Analytical data: Gas chromatogram, RIFM no. 72–123; infra-red curve, RIFM no. 72–123.

Status

The FDA does not permit dihydrosafrole to be used in foods (21 CFR 121.106).

Biological data

Acute toxicity. The acute oral LD_{50} was reported as 2·26 g/kg (1·84–2·78 g/kg) in rats and as 4·30 g/kg in the mouse (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964). The acute dermal LD_{50} in rabbits was reported as >5 g/kg (Shelanski & Moldovan, 1973). Daily dosage for 4 days with 770 mg dihydrosafrole/kg caused macroscopic liver lesions and one death in six treated rats (Taylor, Jenner & Jones, 1964).

Subacute and long-term toxicity. In a feeding study, 1000 ppm fed to rats in the diet for 2 yr retarded growth in females and caused macroscopic and microscopic liver changes (Hagan, Hansen, Fitzhugh, Jenner, Jones, Taylor, Long, Nelson & Brouwer, 1967). In another feeding study, 250 and 500 mg/kg fed to rats in the diet for 34 and 46 days, respectively, produced no deaths (Hagan, Jenner, Jones, Fitzhugh, Long, Brouwer & Webb, 1965), while 750 mg/kg fed to rats in the diet for 26 days produced three deaths in ten animals.

The tumorigenicity of selected pesticides and industrial compounds was tested by continuous oral administration to both sexes of two hybrid strains of mice, starting at the age of 7 days (Innes, Ulland, Valerio, Petrucelli, Fishbein, Hart, Pallotta, Bates, Falk, Gart, Klein, Mitchell & Peters, 1969). Maximal tolerated doses were given for 18 months. Among the 120 test compounds, seven materials were included as positive controls. Dihydrosafrole which was one of these controls produced tumours of the liver in male mice.

Irritation. Dihydrosafrole applied full strength on intact or abraded rabbit skin was mildly irritating (Shelanski & Moldovan, 1973). Tested at 12% in petrolatum, it produced no irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 12% in petrolatum and produced no sensitization reactions (Kligman, 1973).

References

Arctander, S. (1969). *Perfume and Flavor Chemicals (Aroma Chemicals)*. Vol. 1, p. 968. S. Arctander, Montclair, New Jersey.

Givaudan Index (1961). *Specifications of Synthetics and Isolates for Perfumery*. 2nd ed., p. 133. Givaudan-Delawanna, Inc., New York.

Hagan, E. C., Hansen, W. H., Fitzhugh, O. G., Jenner, P. M., Jones, W. I., Taylor, Jean M., Long, Eleanor L., Nelson, A. A. & Brouwer, J. B. (1967). Food flavourings and compounds of related structure. II. Subacute and chronic toxicity. *Fd Cosmet. Toxicol.* **5,** 141.

Hagan, E. C., Jenner, P., Jones, W. I., Fitzhugh, O. G., Long, Eleanor L., Brouwer, J. G. & Webb, W. K. (1965). Toxic properties of compounds related to safrole. *Toxic. appl. Pharmac.* **7,** 18.

Innes, J. R. M., Ulland, B. M., Valerio, M. G., Petrucelli, L., Fishbein, L., Hart, E. R., Pallotta, A. J., Bates, R. R., Falk, H. L., Gart, J. J., Klein, M., Mitchell, I. & Peters, J. (1969). Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: A preliminary note. *J. natn. Cancer Inst.* **42,** 1101.

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Shelanski, M. V. & Moldovan, M. (1973). Report to RIFM, 2 February.

Taylor, Jean M., Jenner, P. M. & Jones, W. I. (1964). A comparison of the toxicity of some allyl, propenyl, and propyl compounds in the rat. *Toxic. appl. Pharmac.* **6,** 378.

DIHYDRO-α-TERPINEOL

Synonyms: *p*-Menthan-8-ol; 1-methyl-4-isopropylcyclohexane-8-ol.
Structure: $CH_3 \cdot C_6H_{10} \cdot C(CH_3)_2 \cdot OH$.
Description and physical properties: A liquid with a more woody pine-like odour than terpineol (Bedoukian, 1967).
Occurrence: Found in American wood turpentine pine oil (Guenther, 1949).
Preparation: By hydrogenation of α-terpineol using a platinum catalyst (Arctander, 1969).
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·05	0·005	0·03	0·4
Maximum	0·3	0·03	0·1	1·0

Analytical data: Gas chromatogram, RIFM no. 71–45; infra-red curve, RIFM no. 71–45.

Status

Dihydro-α-terpineol is not included in the listings of the FDA, FEMA (1965) or Council of Europe (1970), nor in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. Dihydro-α-terpineol applied full strength on intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1973). Tested at 10% in petrolatum, it produced no irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1972).

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Arctander, S. (1969). *Perfume and Flavor Chemicals (Aroma Chemicals)*. Vol. 1, p. 970. S. Arctander, Montclair, New Jersey.

Bedoukian, P. Z. (1967). *Perfumery and Flavoring Synthetics*. 2nd ed., p. 369. Elsevier Publishing Co., New York.

Council of Europe (1970). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. Strasbourg.

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Guenther, E. (1949). *The Essential Oils*. Vol. II, p. 186. D. Van Nostrand, Inc., Princeton, New Jersey.

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Kligman, A. M. (1972). Report to RIFM, 13 October.

Moreno, O. M. (1973). Report to RIFM, 5 July.

DIHYDROTERPINYL ACETATE

Synonym: *p*-Menthan-8-yl acetate.

Structure: $CH_3 \cdot C_6H_{10} \cdot C(CH_3)_2 \cdot OCO \cdot CH_3$.

Description and physical properties: A colourless liquid with a somewhat herbaceous-like odour (Arctander, 1969).

Occurrence: Has apparently not been reported to occur in nature.

Preparation: By hydrogenation of terpinyl acetate (Arctander, 1969; Bedoukian, 1967).

Uses: In public use since the 1950s. Use in fragrances in the USA amounts to about 10,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·4
Maximum	0·3	0·03	0·05	1·2

Analytical data: Gas chromatogram, RIFM nos 70–26, 71–49; infra-red curve, RIFM nos 70–26, 71–49.

Status

Dihydroterpinyl acetate is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1970), nor in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. The acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. Dihydroterpinyl acetate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was slightly irritating (Moreno, 1973). Tested at 12% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1974).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 12% in petrolatum and produced no sensitization reactions (Kligman, 1974).

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DILL WEED OIL

Synonyms: Dill oil; dill herb oil.

Description and physical properties: *Merck Index* (1968). The constituents of dill weed oil have been reported as predominantly *d*-α-phellandrene and carvone (Guenther, 1950), as mainly phellandrene together with limonene or dipentene, *d*-carvone (in much smaller quantities than in dill seed oil), and myristicin (Appell, 1968) and, in the case of the oil from *Anethum graveolens*, as *d*-α-phellandrene, limonene, terpinene and α-pinene with small amounts of carvone, dillapiole, myristicin and isomyristicin (Karow, 1969). The oil from the tops of Indian *A. graveolens* was found by Baslas & Baslas (1972) to contain (in ml/100 ml) limonene (12), α-terpinene (14), α-phellandrene (9), methyl benzoate (2·5), dihydrocarvone (7), carvone (13), carveol (4), safrole (2·4), dihydrocarveol (2·7), carvacrol (3), eugenol (5), sesquiterpenes (10) and dillapiole 2·5. Dill greens (American *A. graveolens*) contained *d*-carvone and myristicin, but not apiole and dillapiole, which were present in the roots (Lichtenstein, Liang, Schultz, Schnoes & Carter, 1974). Dill weed oil contains sizeable amounts of the psychotropic substance myristicin; isomyristicin and dillapiole are present with myristicin in *A. graveolens* (Shulgin, 1966). The fatty acid composition of the essential oils from the above-ground parts and from the fruit of *A. graveolens* was studied by Narzieva, Stepanenko, Umarov & Maksudov (1974), and seasonal changes in the quantity and composition of the essential oil from *A. graveolens* flowers, leaves and stems were studied by Zlatev & Balinova-Tsvetkova (1974).

Occurrence: Found in the plant of *A. graveolens*, L. (Fam. Umbelliferae) (Guenther, 1950).

Preparation: By steam distillation of the freshly cut plants of *A. graveolens* L. (Guenther, 1950).

Uses: In public use before the 1870s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·04
Maximum	0·1	0·01	0·03	0·4

Analytical data: Gas chromatogram, RIFM no. 75–36; infra-red curve, RIFM no. 75–36.

Status

Dill oil was given GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1974) included dill in the list of substances, spices and seasonings deemed admissible for use with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on dill oil.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 4·04 ml/kg and the acute dermal LD_{50} value in rabbits as > 5 g/kg (Levenstein, 1975).

Irritation. Undiluted dill weed oil was not irritating when applied to the backs of hairless mice and swine (Urbach & Forbes, 1975), or to intact or abraded rabbit skin for 24 hr under occlusion (Levenstein, 1975). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1975). The dill plant has been reported to be a photosensitizing agent (Stempel & Stempel, 1973).

Phototoxicity. No phototoxic effects were reported for undiluted dill weed oil on hairless mice and swine (Urbach & Forbes, 1975).

Medicinal uses. Used as an aromatic carminative in medicines (*Merck Index*, 1968).

Pharmacology. Dill oil from parts of the *A. graveolens* plant at concentrations of 50–100 μg/ml had a spasmolytic effect on smooth muscle (isolated rabbit and guinea-pig intestine and guinea-pig lung) and a 5% emulsion in physiological saline given iv to cats at 5–10 mg/kg increased respiratory volume and depressed blood pressure (Shipochliev, 1968). The spasmolytic effect was considered to be chiefly myotropic.

In nearly 100 haemorrhoidal patients, one-third of whom were young, repeated oral doses and nightly enemas of an aqueous infusion prepared from 20–25 g dill plant (*A. graveolens*) in 200–250 g water caused complete and lasting reduction of venous knots in 2–3 wk (Freise, 1938).

Insects. Crude dill green extracts from *A. graveolens* were active as insecticides and insecticide synergists because of their content of *d*-carvone and myristicin (Lichtenstein *et al.* 1974).

Micro-organisms. Oil from dill plants, *A. graveolens*, inhibited the growth of *Bacillus subtilis* in a 1:320 dilution and of *Staphylococcus aureus* in a 1:160 dilution, but did not affect the growth

of *Escherichia coli*. It also inhibited the growth of *Aspergillus oryzae* but not of two other fungi (Dovgich, 1971). In tests using the filter-paper-disc method, dill weed oil inhibited the *in vitro* growth of all of a group of three wood-destroying fungi (Maruzzella, Scrandis, Scrandis, & Grabon, 1960) and all of a group of 12 phytopathogenic fungi (Maruzzella & Balter, 1959), but only one of a group of ten pathogenic and non-pathogenic bacteria was affected (Maruzzella & Lichtenstein, 1956). The vapour of dill weed oil inhibited the *in vitro* growth of one of a group of four bacteria (Maruzzella & Sicurella, 1960).

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DIMETHYL ANTHRANILATE

Synonyms: Methyl *n*-methylanthranilate; methyl methylaminobenzoate.
Structure: $CH_3 \cdot OCO \cdot C_6H_4 \cdot NH \cdot CH_3$.
Description and physical properties: EOA Spec. no. 35.
Occurrence: Found as the main constituent in oil of mandarin leaves, and as a minor constituent in oils of mandarin, petitgrain, hyacinth and rue (*Givaudan Index*, 1961).
Preparation: By reacting anthranilic acid with methyl iodide in the presence of alkali or with methyl sulphate in acetic acid solution and then esterifying the acid in the usual manner (Bedoukian, 1967).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·2
Maximum	0·25	0·025	0·1	1·0

Analytical data: Gas chromatogram, RIFM no. 74–81; infra-red curve, RIFM no. 74–81.

Status

Dimethyl anthranilate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included dimethyl anthranilate in the list of flavouring substances that may be added temporarily to foodstuffs without hazard to public health. The *Food Chemicals Codex* (1972) has a monograph on dimethyl anthranilate.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 3·7 ml/kg (Levenstein, 1974). The acute oral LD_{50} in female rats was reported to be between 2·25 g/kg (no deaths) and 3·38 g/kg (100% deaths) (Gaunt, Sharratt, Grasso & Wright, 1970). The acute dermal LD_{50} value in rabbits was reported as >5 g/kg (Levenstein, 1974). The LC_{50} for larvae of *Tribolium destructor* was found to be 0·1151 mg/cm^3 (Vasechko, Kuznetsov, Smelyanets & Guznenok, 1970).

Chronic toxicity. In a feeding study, rats were given 0, 300, 1200 or 3600 ppm in the diet for 90 days (Gaunt *et al.* 1970). No adverse effects on body weight or food and water consumption were noted at any level of dosage. At 1200 and 3600 ppm, slight but significant leucocytopenia and anaemia occurred at wk 6 but not at wk 13. The kidney weights were also elevated at these two dosage levels but there were no associated changes in kidney function or renal histopathology. Other organ weights and histopathology showed no abnormalities. A level of 300 ppm was demonstrated to be without adverse effect, and the true no-effect level was considered to lie somewhere between 300 and 1200 ppm.

In another feeding study, male and female rats received approximately 20 mg/kg body weight/day for 90 days, as a commercial-grade sample diluted in cottonseed oil and added to the diet at about 100 times the estimated daily intake of 10·13 mg/day for a 50-kg man (Oser, Carson & Oser, 1965). There was no adverse effect on growth, food consumption, haematology, blood chemistry, liver and kidney weights, or gross and microscopic appearance of major organs at autopsy.

The no-effect level for rats given dimethyl anthranilate for 12 wk was 20·3 mg/kg (Bär & Griepentrog, 1967).

Irritation. Dimethyl anthranilate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Levenstein, 1974). Tested at 10% in petrolatum on two different panels of human subjects, it produced no irritation after a 48-hr closed-patch test (Kligman, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced two questionable sensitization reactions (Kligman, 1974; see Preface Note no. 1). When the material was retested (Kligman, 1966) on a different panel of 25 volunteers at a concentration of 10% in petrolatum, it produced no sensitization reactions (Kligman, 1974).

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DIMETHYLBENZYL CARBINOL

Synonyms: α,α-Dimethylphenethyl alcohol; 1,1-dimethyl-2-phenylethanol.
Structure: $C_6H_5 \cdot CH_2 \cdot C(CH_3)_2 \cdot OH$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By Grignard synthesis from benzyl magnesium chloride and acetone (Bedoukian, 1967).
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to less than 2000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·3
Maximum	0·15	0·015	0·1	0·8

Analytical data: Gas chromatogram, RIFM no. 72–130; infra-red curve, RIFM no. 72–130.

Status

Dimethylbenzyl carbinol was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included dimethylbenzyl carbinol in the list of admissible artificial flavouring substances, at a level of 5 ppm. The *Food Chemicals Codex* (1972) has a monograph on dimethylbenzyl carbinol.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 1·35 g/kg (1·02–1·68 g/kg) (Moreno, 1973). The acute dermal LD_{50} in rabbits was reported as >5 g/kg (Moreno, 1973).

Subacute toxicity. In feeding studies in rats, neither 10,000 ppm fed in the diet for 16 wk nor 1000 ppm fed in the diet for 28 wk had any effects (Hagan, Hansen, Fitzhugh, Jenner, Jones, Taylor, Long, Nelson & Brouwer, 1967).

Irritation. Dimethylbenzyl carbinol applied full strength on intact or abraded rabbit skin was not irritating (Moreno, 1973). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1973).

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Moreno, O. M. (1973). Report to RIFM, 1 February.

DIMETHYLBENZYL CARBINYL ACETATE

Synonyms: α,α-Dimethylphenethyl acetate; benzyldimethyl carbinyl acetate.
Structure: $C_6H_5 \cdot CH_2 \cdot C(CH_3)_2 \cdot O_2C \cdot CH_3$.
Description and physical properties: EOA Spec. no. 186.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By acetylation of dimethylbenzyl carbinol (Bedoukian, 1967).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to about 50,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·02	0·3
Maximum	0·2	0·02	0·10	0·40

Analytical data: Gas chromatogram, RIFM no. 70–35; infra-red curve, RIFM no. 70–35.

Status

Dimethylbenzyl carbinyl acetate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included dimethylbenzyl carbinyl acetate in the list of temporarily admissible artificial flavouring substances. The *Food Chemicals Codex* (1972) has a monograph on dimethylbenzyl carbinyl acetate.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 3·30 g/kg (2·55–4·05 g/kg) (Moreno, 1971). The acute dermal LD_{50} in rabbits was reported as >3 g/kg (Moreno, 1971).

Irritation. Dimethylbenzyl carbinyl acetate applied full strength on intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1971). Tested at 4% in petrolatum, it produced mild irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1971).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1971).

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Kligman, A. M. (1971). Report to RIFM, 2 April.

Moreno, O. M. (1971). Report to RIFM, 24 March.

DIMETHYL CITRACONATE

Synonym: Dimethyl methyl maleate.
Structure: $CH_3 \cdot OCO \cdot C(CH_3):CH \cdot OCO \cdot CH_3$.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By the reaction of methanol with citraconic anhydride in the presence of a catalyst.
Uses: Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	—	—	—	—
Maximum	—	—	—	1·2

Analytical data: Gas chromatogram, RIFM no. 74–185; infra-red curve, RIFM no. 74–185.

Status

Dimethyl citraconate is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974) or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1974).

Irritation. Dimethyl citraconate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was slightly irritating (Moreno, 1974). Tested at 12% in petrolatum it produced no irritation after a 48-hr closed-patch test on two different panels of human subjects (Epstein, 1974; Kligman, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 19 volunteers. The material was tested at a concentration of 12% in petrolatum and produced a questionably positive reaction in one of the 19 subjects (Epstein, 1974). In a second maximization test, the material was retested at a concentration of 12% in petrolatum and produced three sensitization reactions in 25 test volunteers (Kligman, 1975).

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DIMETHYLHEPTENAL

Synonyms: 2,6-Dimethyl-5-hepten-1-al; 2,6-dimethyl-2-heptenal-(7).
Structure: $CH_3 \cdot C(CH_3):CH \cdot [CH_2]_2 \cdot CH(CH_3) \cdot CHO$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By condensation of isobutyric aldehyde with α-methylcrotonaldehyde, followed by partial hydrogenation; also from methylheptenone through Darzen's reaction.
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to less than 3000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·1
Maximum	0·12	0·012	0·04	0·4

Analytical data: Gas chromatogram, RIFM no. 74–82; infra-red curve, RIFM no. 74–82.

Status

Dimethylheptenal was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included dimethylheptenal in the list of artificial flavouring substances that may be added temporarily to foodstuffs without hazard to public health.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Levenstein, 1974).

Irritation. Dimethylheptenal applied full strength to intact or abraded rabbit skin produced a mild erythema lasting 24 hr (Levenstein, 1974). Tested at 4% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 22 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Epstein, 1974).

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DIMETHYLHEPTENOL

Synonym: 2,6-Dimethyl-2-hepten-6-ol.
Structure: $CH_3 \cdot COH(CH_3) \cdot [CH_2]_2 \cdot CH:C(CH_3)_2$.
Description and physical properties: A colourless liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: A by-product in the manufacture of lavandulol.
Uses: In public use since the 1960s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·015	0·3
Maximum	0·2	0·02	0·07	1·0

Analytical data: Gas chromatogram, RIFM no. 74–186; infra-red curve, RIFM no. 74–186.

Status

Dimethylheptenol is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974), or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1974).

Irritation. Dimethylheptenol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was very irritating (Moreno, 1974). Tested at 10% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1974).

Metabolism. Tertiary alcohols tend to resist oxidation and not be metabolized readily, but they are usually highly conjugated as glucuronic acids which can be isolated from the urine (Williams, 1959).

References

Council of Europe (1974). Natural Flavouring Substances, Their Sources, and Added Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. Strasbourg.

Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. *Fd Technol., Champaign* **19** (2), part 2, 155.

Food Chemicals Codex (1972). 2nd ed. Prepared by the Committee on Specifications, Food Chemicals Codex, of the Committee on Food Protection. National Academy of Sciences–National Research Council Publ. 1406, Washington, D.C.

Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47,** 393.

Kligman, A. M. (1974). Report to RIFM, 12 September.

Kligman, A. M. & Epstein, W. (1975). Updating the maximization test for identifying contact allergens. *Contact Dermatitis* **1,** 231.

Moreno, O. M. (1974). Report to RIFM, 23 August.

Williams, R. T. (1959). *Detoxication Mechanisms. The Metabolism and Detoxication of Drugs, Toxic Substances and Other Organic Compounds.* 2nd ed., p. 67. Chapman & Hall Ltd., London.

3.6-DIMETHYL-3-OCTANOL

Structure: $CH_3 \cdot CH_2 \cdot CH(CH_3) \cdot [CH_2]_2 \cdot (CH_3)C(OH) \cdot CH_2 \cdot CH_3$.
Description and physical properties: A clear colourless liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By ethynilation of methyl ethyl ketone followed by dehydration and then hydrogenation.
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to more than 200,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·04	0·004	0·02	0·5
Maximum	0·3	0·03	0·1	1·0

Status

3,6-Dimethyl-3-octanol is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974), or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. 3,6-Dimethyl-3-octanol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1973). Tested at 20% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972; RIFM no. 72–20–69). Tested in petrolatum, it again produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 20% in petrolatum and produced four sensitization reactions in the 25 subjects (Kligman, 1972; RIFM no. 72–20–69; see Preface Note no. 1). The material was retested in petrolatum in a maximization test on 25 new volunteers and produced no sensitization reactions (Kligman, 1973).

References

Council of Europe (1974). Natural Flavouring Substances, Their Sources, and Added Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. Strasbourg.

Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. *Fd Technol., Champaign* **19** (2), part 2, 155.

Food Chemicals Codex (1972). 2nd ed. Prepared by the Committee on Specifications, Food Chemicals Codex, of the Committee on Food Protection. National Academy of Sciences–National Research Council Publ. 1406, Washington, D.C.

Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.

Kligman, A. M. (1972). Report to RIFM, 25 August.

Kligman, A. M. (1973). Report to RIFM, 27 August.

Kligman, A. M. & Epstein, W. (1975). Updating the maximization test for identifying contact allergens. *Contact Dermatitis* **1**, 231.

Moreno, O. M. (1973). Report to RIFM, 19 July.

3,7-DIMETHYL-1-OCTANOL

Synonym: Tetrahydrogeraniol.
Structure: $CH_3 \cdot CH(CH_3) \cdot [CH_2]_3 \cdot CH(CH_3) \cdot [CH_2]_2 \cdot OH$.
Description and physical properties: *Food Chemicals Codex* (1972).
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By reduction of geraniol or by reduction of citronellol, citronellal or citral (Arctander, 1969).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 10,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·02	0·2
Maximum	0·2	0·02	0·1	0·8

Analytical data: Gas chromatogram, RIFM no. 72–129; infra-red curve, RIFM no. 72–129.

Status

3,7-Dimethyl-1-octanol was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) listed 3,7-dimethyl-1-octanol (tetrahydrogeraniol), giving an ADI of 5 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on 3,7-dimethyl-1-octanol.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as >5 g/kg (Shelanski & Moldovan, 1973a). The acute dermal LD_{50} in the rabbit was reported as 2·4 g/kg (1·7–3·4 g/kg) (Shelanski & Moldovan, 1973a).

Irritation. 3,7-Dimethyl-1-octanol applied full strength on intact or abraded rabbit skin produced irritation (Shelanski & Moldovan, 1973b). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at 8% concentration in petrolatum and produced no sensitization reactions (Kligman, 1973).

References

Arctander, S. (1969). *Perfume and Flavor Chemicals (Aroma Chemicals)*. Vol. 1, p. 1032. S. Arctander, Montclair, New Jersey.

Council of Europe (1970). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List A(1), Series 1, no. 76, p. 52. Strasbourg.

Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. No. 2391. *Fd Technol., Champaign* **19** (2), part 2, 155.

Food Chemicals Codex (1972). 2nd ed. Prepared by the Committee on Specifications, Food Chemicals Codex, of the Committee on Food Protection. p. 254. National Academy of Sciences–National Research Council Publ. 1406, Washington, D.C.

Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.

Kligman, A. M. (1973). Report to RIFM, 12 February.

Shelanski, M. V. & Moldovan, M. (1973a). Report to RIFM, 30 January.

Shelanski, M. V. & Moldovan, M. (1973b). Report to RIFM, 16 February.

3,6-DIMETHYLOCTAN-3-YL ACETATE

Structure: $CH_3 \cdot CH_2 \cdot CH(CH_3) \cdot [CH_2]_2 \cdot (CH_3)C(OCO \cdot CH_3) \cdot CH_2 \cdot CH_3$.
Description and physical properties: A colourless liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By direct esterification of 3,6-dimethyl-3-octanol with acetic anhydride or with acetic acid under azeotropic conditions or by any other suitable methods.
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to approximately 30,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·015	0·3
Maximum	0·25	0·03	0·08	2·0

Status

3,6-Dimethyloctan-3-yl acetate is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974), or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. 3,6-Dimethyloctan-3-yl acetate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1973). Tested at 20% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 20% in petrolatum and produced no sensitization reactions (Kligman, 1972).

References

Council of Europe (1974). Natural Flavouring Substances, Their Sources, and Added Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. Strasbourg.

Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. *Fd Technol., Champaign* **19** (2), part 2, 155.

Food Chemicals Codex (1972). 2nd ed. Prepared by the Committee on Specifications, Food Chemicals Codex, of the Committee on Food Protection. National Academy of Sciences–National Research Council Publ. 1406, Washington, D.C.

Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.

Kligman, A. M. (1972). Report to RIFM, 23 August.

Kligman, A. M. & Epstein, W. (1975). Updating the maximization test for identifying contact allergens. *Contact Dermatitis* **1**, 231.

Moreno, O. M. (1973). Report to RIFM, 18 July.

DIMETHYLPHENYLETHYL CARBINOL

Synonyms: α,α-Dimethyl-γ-phenylpropyl alcohol; 1,1-dimethyl-3-phenylpropanol.
Structure: $C_6H_5 \cdot [CH_2]_2 \cdot C(CH_3)_2 \cdot OH$.
Description and physical properties: EOA Spec. no. 277.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By reaction of phenylethyl magnesium chloride with acetone (Bedoukian, 1967).
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to less than 7000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·3
Maximum	0·1	0·01	0·03	0·4

Analytical data: Gas chromatogram, RIFM no. 72–131; infra-red curve, RIFM no. 72–131.

Status

Dimethylphenylethyl carbinol is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1970), nor in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 2·2 ml/kg (1·8–2·7 ml/kg) (Shelanski, 1973). The acute dermal LD_{50} in rabbits was reported as 3·5 ml/kg (2·6–4·3 ml/kg) (Shelanski, 1973).

Irritation. Dimethylphenylethyl carbinol applied full strength on intact or abraded rabbit skin produced a moderate to severe irritation (Shelanski, 1973). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1973).

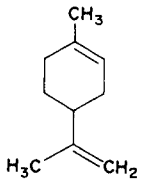
Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1973).

References

Bedoukian, P. Z. (1967). *Perfumery and Flavoring Synthetics*. 2nd ed., p. 77. Elsevier Publishing Co., New York.
Council of Europe (1970). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. Strasbourg.
Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. *Fd Technol., Champaign* **19** (2), part 2, 155.
Food Chemicals Codex (1972). 2nd ed. Prepared by the Committee of Specifications, Food Chemicals Codex, of the Committee on Food Protection. National Academy of Sciences–National Research Council Publ. 1406, Washington, D.C.
Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.
Kligman, A. M. (1973). Report to RIFM, 25 May.
Shelanski, M. V. (1973). Report to RIFM, 16 February and 20 February.

DIPENTENE

Synonyms: 1-Methyl-4-isopropenyl-1-cyclohexene; *d,l*-limonene; 1,8(9)-*p*-menthadiene.
Structure:



Description and physical properties: A colourless mobile liquid with a citrus-like odour (Arctander, 1969).
Occurrence: Found in a very large number of oils, including oils of lemongrass, citronella, palmarosa, cardamon and bergamot, Siberian pine needle oil and several other essential oils including turpentine oils of various origin (Guenther, 1949).
Preparation: As a by-product in the manufacture of terpineol and in various synthetic products made from α-pinene or turpentine oil (Arctander, 1969).
Uses: In public use since the 1940s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·05	0·05		0·5
Maximum	0·75	0·075	0·25	2·0

Analytical data: Gas chromatogram, RIFM no. 72-21; infra-red curve, RIFM no. 72-21.

Status

Dipentene (*d,l*-limonene) was granted GRAS status by FEMA (1965) and is approved by the FDA as GRAS for food use. The Council of Europe (1970) included dipentene (*d,l*-limonene) in the list of admissible artificial flavouring substances, with a technological limit except for chewing gum.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 5·3 g/kg (4·6–6·0 g/kg) (Moreno, 1972a). The acute dermal LD_{50} value for *d*-limonene was reported as >5 g/kg (Moreno, 1972b).

Irritation. d-Limonene applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1972b). Dipentene tested at 20% in petrolatum produced no irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 20% in petrolatum and produced no sensitization reactions (Kligman, 1972).

Additional published data

The autoxidation products of oil of turpentine (of Δ^3-carene) are eczematogenic (Pirilä, 1971).

References

Arctander, S. (1969). *Perfume and Flavor Chemicals (Aroma Chemicals)*. Vol. 1, p. 1074. S. Arctander, Montclair, New Jersey.

Council of Europe (1970). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List A(1), Series 1, no. 493, p. 75. Strasbourg.

Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. No. 2633. *Fd Technol., Champaign* **19** (2), part 2, 155.
Guenther. E. (1949). *The Essential Oils.* Vol. II. p. 27. C. Van Nostrand, Inc.. Princeton, New Jersey.
Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.
Kligman, A. M. (1972). Report to RIFM, 25 August.
Moreno, O. M. (1972a). Report to RIFM, 5 May.
Moreno, O. M. (1972b). Report to RIFM, 31 May.
Pirilä, V. (1971). Pyhän Laurin tie IB, Helsinki 34 (Finland).

DIPHENYLMETHANE

Synonym: Benzylbenzene.
Structure: $C_6H_5 \cdot CH_2 \cdot C_6H_5$.
Description and physical properties: EOA Spec. no. 129.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By interaction of benzyl chloride and benzene in the presence of an acid catalyst.
Uses: In public use since the 1940s. Use in fragrances in the USA amounts to less than 4000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·005	0·01	0·05
Maximum	0·2	0·02	0·1	0·8

Analytical data: Gas chromatogram, RIFM no. 72-132; infra-red curve RIFM 72-132.

Status

The Council of Europe (1970) included diphenylmethane in the list of temporarily admissible artificial flavouring substances.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 2·25 g/kg (1·76–2·74 g/kg) (Moreno, 1973). The acute dermal LD_{50} value in rabbits was reported as >5 g/kg (Moreno, 1973).

Irritation. Diphenylmethane applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Moreno, 1973). Tested at 8% in petrolatum it produced no irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1973).

Metabolism. Diphenylmethane is hydroxylated in the rabbit and some 15% of the dose is excreted as 4-hydroxydiphenylmethane, which is largely (80–90%) in the free state. Neither the hydrocarbon nor its metabolite is oestrogenic. This reaction also occurs in the dog (Williams, 1959).

References

Council of Europe (1970). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List A(1), Series 2, no. 121, p. 99. Strasbourg.
Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.
Kligman, A. M. (1973). Report to RIFM, 27 August.
Moreno, O. M. (1973). Report to RIFM, 1 February.
Williams, R. T. (1959). *Detoxication Mechanisms. The Metabolism and Detoxication of Drugs, Toxic Substances and Other Organic Compounds.* 2nd ed., p. 226. Chapman & Hall Ltd., London.

DIPHENYL OXIDE

Synonyms: Diphenyl ether; phenyl ether.
Structure: $C_6H_5 \cdot O \cdot C_6H_5$.
Description and physical properties: EOA Spec. no. 43.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By heating potassium phenolate with bromobenzene or with chlorobenzene at elevated temperatures (Bedoukian, 1967).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to about 100,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·05	0·005	0·05	0·15
Maximum	0·20	0·03	0·10	0·40

Status

The Council of Europe (1970) included diphenyl oxide in the list of temporarily admissible artificial flavouring substances.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 3·37 g/kg (2·59–4·37 g/kg) (Weir, 1971). The acute dermal LD_{50} value in rabbits was reported as >5 g/kg (Weir, 1971).

Irritation. Diphenyl oxide applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was slightly irritating (Weir, 1971). Applied to the eyes of rabbits, it produced negative results except for slight conjunctival irritation, which cleared in 72 hr (Weir, 1971).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1970).

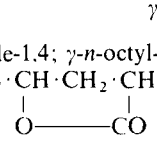
References

Bedoukian, P. Z. (1967). *Perfumery and Flavoring Synthetics*. 2nd ed., p. 153. Elsevier Publishing Co., New York.
Council of Europe (1970). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List A(1), Series 1, no. 215, p. 103. Strasbourg.
Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.
Kligman, A. M. (1970). Report to RIFM, 4 January.
Weir, R. J. (1971). Report to RIFM, 12 April.

γ-DODECALACTONE

Synonyms: Dodecanolide-1,4; γ-*n*-octyl-γ-*n*-butyrolactone.

Structure:



Description and physical properties: A colourless oily liquid.

Occurrence: Reported to be found in *Prunus persica* (*Fernaroli's Handbook of Flavor Ingredients*, 1975).

Preparation: From 4-hydroxydodecanoic acid by lactonization (Arctander, 1969).

Uses: In public use since the 1940s.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·001	0·001	0·0005	0·02
Maximum	0·03	0·003	0·005	0·2

Analytical data: Gas chromatogram. RIFM no. 74–189; infra-red curve. RIFM no. 74–189.

Status

γ-Dodecalactone was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included γ-dodecalactone at a level of 5 ppm in the list of artificial flavouring substances that may be added temporarily to foodstuffs without hazard to public health.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1974).

Irritation. γ-Dodecalactone applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1974). Tested at 12% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 12% in petrolatum and produced no sensitization reactions (Kligman, 1974).

Metabolism. γ-Dodecalactone was among compounds found to exist in cows' milk as conjugates (e.g. glucuronides and sulphates); they were identified after enzymatic hydrolysis of the isolated conjugated material (Brewington, Parks & Schwartz, 1973).

References

Arctander, S. (1969). *Perfume and Flavor Chemicals* (*Aroma Chemicals*). Vol. 1, no. 1102. S. Arctander, Montclair, New Jersey.

Brewington, C. R., Parks, O. W. & Schwartz, D. P. (1973). Conjugated compounds in cow's milk. *J. agric. Fd Chem.* **21**, 38.

Council of Europe (1974). Natural Flavouring Substances, Their Sources, and Added Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List 2, no. 2240, p. 333. Strasbourg.

Fenaroli's Handbook of Flavor Ingredients (1975). Edited by T. E. Furia and N. Bellanca. 2nd Ed. Vol. II, p. 154. CRC Press, Cleveland, Ohio.

Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. No. 2400. *Fd Technol., Champaign* **19**(2), part 2, 155.

Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.

Kligman, A. M. (1974). Report to RIFM, 19 November.

Kligman, A. M. & Epstein, W. (1975). Updating the maximization test for identifying contact allergens. *Contact Dermatitis* **1**, 231.

Moreno, O. M. (1974). Report to RIFM, 11 December.

EAU DE BROUTS ABSOLUTE

Description and physical properties: An orange-yellow to brownish-yellow liquid.
Occurrence: Found in the plant of petitgrain bigarde and orange flower, *Citrus aurantium* L. subspecies amara L. (Fam. Rutaceae).
Preparation: By extraction from a mixture of orange-flower water and petitgrain-bigarde water (Arctander, 1960).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to approximately 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·04
Maximum	0·1	0·01	0·03	0·4

Status

Eau de brouts is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974) or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1976).

Irritation. Undiluted eau de brouts absolute was not irritating when applied to the backs of hairless mice and swine (Urbach & Forbes, 1976), but was moderately irritating when applied to intact or abraded rabbit skin for 24 hr under occlusion (Moreno, 1976). Tested at 4% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1976).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1976).

Phototoxicity. No phototoxic effects were reported for undiluted eau de brouts absolute on hairless mice and swine (Urbach & Forbes, 1976).

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ELEMI OIL

Description and physical properties: A colourless to pale-yellow liquid. The main constituents of elemi oil are *d*-α-phellandrene and dipentene (Guenther, 1950). Manila elemi oleoresin from *Canarium commune* consists chiefly of triterpenic resin (65-75%) and an oil (15–25%) containing phellandrene, carvone, dipentene, elemicin, elemol and terpineol (Appell, 1968; Pernet, 1972; Summa, 1960).
Occurrence: As a pathological exudation of the tree *C. commune* L. or *C. luzonicum* Mig (Fam. Burseraceae) (Guenther, 1950).
Preparation: By steam distillation from the crude resin of *C. commune* L. or *C. luzonicum* Mig (*Fenaroli's Handbook of Flavor Ingredients*, 1975).
Uses: In public use before the 1900s. Use in fragrances in the USA amounts to approximately 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·1
Maximum	0·1	0·01	0·03	0·6

Analytical data: Infra-red curve, RIFM no. 74–191.

Status

Elemi was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1163). The Council of Europe (1974) included elemi in the list of substances, spices and seasonings deemed admissible for use with a possible limitation of the active principle in the final product.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 3·37 ± 0·405 g/kg and the acute dermal LD_{50} value in rabbits as approximately 5 g/kg (McGee, 1974). The oral LD_{50} of manila elemi in mice was > 5 g/kg (Toida, 1971).

Irritation. Undiluted elemi oil was not irritating when applied to the backs of hairless mice and swine (Urbach & Forbes, 1974) but was slightly irritating when applied to intact or abraded rabbit skin for 24 hr under occlusion (McGee, 1974). Tested at 4% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1975).

Phototoxicity. No phototoxic effects were reported for undiluted elemi oil on hairless mice and swine (Urbach & Forbes, 1974).

Additional published data

Elemi has been used as a stomach stimulant and as an expectorant (Pernet, 1972).

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Urbach, F. & Forbes, P. D. (1974). Report to RIFM, 6 December.

ESTRAGON OIL

Synonym: Tarragon oil.
Description and physical properties: EOA Spec. no. 121. The chief component of estragon oil is methyl chavicol (Guenther, 1952).
Occurrence: Found in the plant *Artemesia dracunculus* L. (Fam. Compositae).
Preparation: By steam distillation of the leaves, stems and flowers of the plant *Artemesia dracunculus* L.
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to less than 2000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·01	0·04
Maximum	0·1	0·01	0·1	0·4

Analytical data: Gas chromatogram, RIFM no. 72-134; infra-red curve, RIFM no. 72–134.

Status

Estragon oil was granted GRAS status by FEMA (1965) and is approved by the FDA as GRAS for food use. The Council of Europe (1970) included estragon oil (*Artemesia dracunculus*) in the list of substances, spices and seasonings whose use is deemed admissible with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on estragon oil.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 1·9 ml/kg (1·5–2·5 ml/kg) (Shelanski, 1973a). The acute dermal LD_{50} in rabbits exceeded 5 ml/kg (Shelanski, 1973b).

Irritation. Estragon oil applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was irritating (Shelanski, 1973b). It was also irritating when applied undiluted to the backs of hairless mice (Urbach & Forbes, 1973). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1972).

Phototoxicity. No phototoxic effects were reported for estragon oil (Urbach & Forbes, 1973).

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Urbach, F. & Forbes, P. D. (1973). Report to RIFM, 8 February.

ETHYL ACETATE

Synonym: Acetic ether.
Structure: $CH_3 \cdot CH_2 \cdot OCO \cdot CH_3$.
Description and physical properties: *Food Chemicals Codex* (1972).
Occurrence: Found in several essential oils (Gildemeister & Hoffman, 1966).
Preparation: From ethyl alcohol and acetic acid, usually in a multicolumnar distillation system (Arctander, 1969).
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to less than 2000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·01
Maximum	0·05	0·005	0·05	1·0

Analytical data: Gas chromatogram, RIFM no. 71-6; infra-red curve, RIFM no. 71-6.

Status

Ethyl acetate was granted GRAS status by FEMA (1965) and is approved by the FDA as GRAS for food use. The Council of Europe (1970) listed ethyl acetate, giving an ADI of 2·5 mg/kg and the *Food Chemicals Codex* (1972) has a monograph on ethyl acetate. The *National Formulary* (1970) has a monograph on ethyl acetate and the Joint FAO/WHO Expert Committee on Food Additives (1967) has published a monograph and specifications for ethyl acetate giving an unconditional ADI of 0–25 mg/kg. Browning (1965) published a monograph on ethyl acetate.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 5·6 g/kg while the inhalation LC_{50} in the rat was reported as 1600 ppm after 8 hr (Fassett, 1963).

Irritation. Ethyl acetate tested at 10% in petrolatum produced no irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1972).

Metabolism. Ethyl acetate is hydrolysed to ethyl alcohol, which is then partly excreted in the expired air and urine. The rest is metabolized, the acetate fraction becoming incorporated in the body pool (Fassett, 1963).

Threshold limit value. The threshold limit value for ethyl acetate has been set at 400 ppm at which point it produces nose and throat irritation and has a mild narcotic action (American Conference of Governmental Industrial Hygienists, 1973).

Additional published data

Eyeglass dermatitis limited to the nose occurred in a 58-yr-old woman. Patch testing revealed the offending agent to be a common solvent, ethylene glycol monomethyl ether acetate, used to weld the nosepads chemically to the eyeglass frame. The patient also had an unrevealed allergy to ethyl acetate (Jordan & Dahl, 1971).

When ethyl acetate was injected into the yolk sac of fresh fertile chicken eggs before incubation in a dose of 9, 22·5, 45 or 90 mg/egg, the hatchabilities were 85, 50, 35 and 15% respectively (McLaughlin, Marliac, Verrett, Mutchler & Fitzhugh, 1964).

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ETHYL ACETOACETATE

Synonyms: Acetoacetic ester; ethyl-3-oxobutanoate.
Structure: $CH_3 \cdot CO \cdot CH_2 \cdot OCO \cdot CH_2 \cdot CH_3$.
Description and physical properties: *Food Chemicals Codex* (1972).
Occurrence: Has apparently not been reported to occur in nature.
Preparation: From ethyl acetate by the action of sodium, sodium ethoxide, sodamide or calcium (*Merck Index*, 1968).
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to less than 8000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·1
Maximum	0·1	0·01	0·10	0·8

Analytical data: Gas chromatogram, RIFM no. 72-135; infra-red curve, RIFM no. 72-135.

Status

Ethyl acetoacetate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included ethyl acetoacetate in the list of admissible artificial flavouring substances, at a level of 500 ppm. The *Food Chemicals Codex* (1972) has a monograph on ethyl acetoacetate.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 3·98 g/kg (Smyth, Carpenter & Weil, 1949). The acute dermal LD_{50} in rabbits was reported as > 5 g/kg (Moreno, 1973).

Irritation. Ethyl acetoacetate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Moreno, 1973). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test in 26 human subjects (Epstein, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 26 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Epstein, 1973).

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ETHYL ACRYLATE

Synonym: Ethyl propenoate.
Structure: $CH_3 \cdot CH_2 \cdot OCO \cdot CH{:}CH_2$.
Description and physical properties: *Food Chemicals Codex* (1972).
Occurrence: Found in the fruits of *Ananas sativus* L. (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: By esterification of acrylic acid with ethanol.
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·01	0·04
Maximum	0·1	0·01	0·1	0·4

Status

Ethyl acrylate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) listed ethyl acrylate in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health, at a level of 1 ppm. The *Food Chemicals Codex* (1972) has a monograph on ethyl acrylate.

Biological data

Acute toxicity. The oral LD_{50} value was reported as 1000 mg/kg in rats and 400 mg/kg in rabbits (Fassett, 1963). The inhalation LC_{50} value in rats was reported as <1000 ppm (4 mg/litre) after 4 hr (Fassett, 1963).

Chronic toxicity. Rats were fed 6–7, 60–70 or 2000 ppm in the diet for 2 yr (Borzelleca, Larson, Hennigar, Huf, Crawford & Smith, 1964). At 2000 ppm, a decrease in fluid intake was observed in males and females; for the females decreases in food intake and body weight were recorded. Body weights of males were decreased only in yr 1. Body-weight ratios for heart, spleen, liver and testes were normal. Haemotological values were within normal ranges and semiquantitative tests for urinary concentrations of protein and reducing substances were negative. Histopathology, which was carried out on all groups except those given the lowest concentration, showed no abnormalities.

Dogs were fed 10, 100 or 300–1000 ppm in the diet for 2 yr (Borzelleca *et al.* 1964). The highest dose level (1000 ppm) was not tolerated at first (some dogs vomited). It was reduced to 300, therefore, and then raised gradually for 16 wk. No gross effects observed. At the highest dose, less food was consumed and less weight was gained. Organ weight/body weight ratios were normal at all dose levels. Histopathological examination revealed no lesions and haematological findings and urinary concentrations of reducing substances and proteins were within normal ranges.

Irritation. Ethyl acrylate tested at 4% in petrolatum produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 24 volunteers. The material was tested at a concentration of 4% in petrolatum and produced sensitization reactions in ten of the 24 (Epstein, 1974).

Threshold limit value. The threshold limit value for ethyl acrylate has been set at 25 ppm (American Conference of Governmental Industrial Hygienists, 1973).

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ETHYL AMYL KETONE

Synonym: 3-Octanone.
Structure: $CH_3 \cdot [CH_2]_4 \cdot CO \cdot CH_2 \cdot CH_3$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Found in oil of lavender (*Givaudan Index*, 1961).
Preparation: By heating propionic and caproic acids over thorium oxide or by oxidation of ethyl amyl carbinol (3-octanol) (Arctander, 1969).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 2000 lb/yr.

Concentrations in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·01	0·04
Maximum	0·05	0·02	0·05	0·2

Analytical data: Gas chromatogram, RIFM no. 72-136; infra-red curve, RIFM no. 72-136.

Status

Ethyl amyl ketone was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included ethyl amyl ketone in the list of temporarily admissible artificial flavouring substances.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Shelanski, 1973).

Irritation. Ethyl amyl ketone applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Shelanski, 1973). Tested at 2% in petrolatum, it produced no irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 2% in petrolatum and produced no sensitization reactions (Kligman, 1972).

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ETHYL ANISATE

Synonyms: Ethyl *p*-anisate; ethyl-*p*-methoxybenzoate.
Structure: $CH_3O \cdot C_6H_4 \cdot OCO \cdot CH_2 \cdot CH_3$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Reported to be found in guava (*Fenaroli's Handbook of Flavor Ingredients*, 1975).
Preparation: By direct esterification of ethyl alcohol with anisic acid under azeotropic conditions (Arctander, 1969).
Uses: In public use before the 1920s. Use in fragrances in the USA amounts to less than 1000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·04
Maximum	0·1	0·01	0·03	0·4

Status

Ethyl anisate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included ethyl anisate at a level of 8 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health. The *Food Chemicals Codex* (1972) has a monograph on ethyl anisate.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 2·04 ml/kg and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Levenstein, 1975).

Irritation. Ethyl anisate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Levenstein, 1975). Tested at 4% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1975).

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Kligman, A. M. & Epstein, W. (1975). Updating the maximization test for identifying contact allergens. *Contact Dermatitis* **1**, 231.

Levenstein, I. (1975). Report to RIFM, 19 May.

ETHYL ANTHRANILATE

Synonym: Ethyl *o*-aminobenzoate.
Structure: $NH_2 \cdot C_6H_4 \cdot OCO \cdot CH_2 \cdot CH_3$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Reported to be found in grapes (*Fenaroli's Handbook of Flavor Ingredients*, 1975).
Preparation: By interaction of isatoic anhydride with ethyl alcohol (Bedoukian, 1967).
Uses: In public use before the 1920s. Use in fragrances in the USA amounts to approximately 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·04
Maximum	0·2	0·02	0·05	0·6

Analytical data: Gas chromatogram, RIFM no. 75-IFRA-18; infra-red curve, RIFM no. 75-IFRA-18.

Status

Ethyl anthranilate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included ethyl anthranilate at a level of 20 ppm (except for chewing gum) in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health. The *Food Chemicals Codex* (1972) has a monograph on ethyl anthranilate.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 3·75 g/kg (3·32–4·18 g/kg) and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1975).

Irritation. Undiluted ethyl anthranilate was not irritating when applied to the backs of hairless mice and swine (Urbach & Forbes, 1976), but was moderately irritating when applied to intact or abraded rabbit skin for 24 hr under occlusion (Moreno, 1975). Tested at 4% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1975).

Phototoxicity. No phototoxic effects were reported for undiluted ethyl anthranilate on hairless mice and swine (Urbach & Forbes, 1976).

Photoallergenicity. Undiluted ethyl anthranilate did not produce any photoallergic effects in a test involving application, on three alternate days, of a non-irritating dose (20 $\mu l/cm^2$) under a large occlusive patch (10 cm × 5 cm) to the shaved neck of guinea-pigs, removal of the patch after 1 hr and irradiation of the area with a solar simulator for 45 min to produce a mild erythema, a procedure followed 18 days after the last treatment by a further application followed by exposure to light filtered to remove UV-B; daily examination of the animals for 1 wk revealed no photoallergic reactions (Harber, Targovnik & Baer, 1967, modified by Urbach & Forbes, 1976).

Pharmacology. Ethyl anthranilate behaved as a local anaesthetic, as measured by depression of muscle twitch, but was 50% less effective than the *m*- and *p*-aminobenzoate isomers. All three compounds potentiated the initial phase of caffeine-induced contracture of frog sartorius muscle, but the *o*-isomer had no effect on the peak tension of the contracture (Friedman, Bianchi & Weiss, 1974). It was proposed that the *o*-amino group has both steric and polar effects, its bulk preventing the inhibitory action of the carbonyl group on the caffeine-induced contracture of sartorius muscle, while the lone electron pair of the nitrogen atom induces a contracture on its own accord and potentiates a caffeine-induced contracture (Friedman, 1975).

Ethyl anthranilate (0·1 mmol/litre) decreased the frequency of the electric-organ discharges of the electric fish, *Gnathonemus moori*, but did not affect the individual pulse amplitudes, indicating that the compound acted on the pacemaker cells of the mesencephalic command nucleus (Walsh & Schopp, 1966).

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ETHYL BENZENE

Synonyms: Ethyl benzol; phenyl ethane.
Structure: $C_6H_5 \cdot CH_2 \cdot CH_3$.
Description and physical properties: A colourless mobile liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By Friedel-Crafts reaction on benzene, ethylbromide and aluminium chloride (Arctander, 1969).
Uses: Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual		(solvent uses for other materials)		0·1

Analytical data: Gas chromatogram, RIFM no. 74–194; infra-red curve, RIFM no. 74–194.

Status

Ethyl benzene is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974), or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 5·46 ml/kg (5·09–5·86 ml/kg) and the single skin penetration LD_{50} value for rabbits was reported as 17·8 ml/kg (Smyth, Carpenter, Weil, Pozzani & Striegel, 1962). The acture dermal LD_{50} value in rabbits was reported as >5 g/kg (Moreno, 1974).

Irritation. Ethyl benzene produced irritation when applied to the uncovered rabbit belly (Smyth *et al.* 1962). Applied full strength to intact or abraded rabbit skin for 24-hr under occlusion, it was moderately irritating (Moreno, 1974). Tested at 10% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1974).

Threshold limit value. The threshold limit value for ethyl benzene has been set at 100 ppm (American Conference of Governmental Industrial Hygienists, 1973).

Metabolism. The main oxidation of ethyl benzene occurs at the activated α-methylene group to yield methylphenylcarbinol which is also the precursor of hippuric and mandelic acids. Both optical isomers of methylphenylcarbinol are formed, probably in equal amounts, and these have been isolated from the urine of rabbits as the corresponding glucuronides. The two optical forms of mandelic acid have also been found (Williams, 1959).

In the rabbit, acetophenone is an intermediate in the major pathway of ethyl benzene metabolism to hippuric acid and is converted by the side reactions of *p*- and *m*-hydroxylation to *p*- and *m*-hydroxyacetophenones. The major pathway apparently involves its ω-oxidation to ω-hydroxyacetophenone, which is then converted successively to phenylglyoxal, phenylglyoxylic acid and (by a process of decarboxylation and conjugation) hippuric acid. Mandelic acid and 1-phenylethanol are also produced during the conversion of ethyl benzene to acetophenone, while an accessory metabolic pathway, identified by previous workers, involves ω-oxidation of ethyl benzene to phenylacetic acid and its conjugation to produce phenaceturic acid (Kiese & Lenk, 1974).

Skin penetration. Ethyl benzene was well absorbed on the skin of rats (Valette & Cavier, 1954).

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ETHYL BENZOATE

Structure: $CH_3 \cdot CH_2 \cdot OCO \cdot C_6H_5$.
Description and physical properties: EOA Spec. no. 210.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By esterification of ethyl alcohol and benzoic acid.
Uses: In public use since the 1940s. Use in fragrances in the USA amounts to less than 5000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·003	0·01	0·02
Maximum	0·1	0·01	0·1	0·8

Analytical data: Infra-red curve, RIFM no. 72-137.

Status

Ethyl benzoate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) listed ethyl benzoate, giving an ADI of 5 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on ethyl benzoate and Browning (1965) has published an extensive monograph on this ester.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 6·480 g/kg (Bär & Griepentrog, 1967). The acute dermal LD_{50} value in rabbits was reported as 1·94 g/kg (Graham & Kuizenga, 1945).

Irritation. Ethyl benzoate tested at 8% in petrolatum produced no irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1972).

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ETHYL BUTYRATE

Synonyms: Ethyl *n*-butanoate; butyric ether.
Structure: $CH_3 \cdot CH_2 \cdot OCO \cdot [CH_2]_2 \cdot CH_3$.
Description and physical properties: EOA Spec. no. 108.
Occurrence: Reported to occur in several oils (Gildemeister & Hoffman, 1966).
Preparation: By the esterification of normal butyric acid with ethyl alcohol.
Uses: In public use since the late 1800s. Use in fragrances in the USA amounts to less than 51,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	—	0·005	0·01
Maximum	0·05	0·001	0·05	0·5

Analytical data: Gas chromatogram, RIFM no. 71-46; infra-red curve, RIFM no. 71-46.

Status

Ethyl butyrate was granted GRAS status by FEMA (1965) and is approved as GRAS by the FDA for food use. The Council of Europe (1970) listed ethyl butyrate, giving an ADI of 1 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on ethyl butyrate. The Joint FAO/WHO Expert Committee on Food Additives (1967) has published a monograph and specifications for ethyl butyrate giving an unconditional ADI of 0–15 mg/kg, and Browning (1965) has also published a monograph on ethyl butyrate.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 13 g/kg (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964). The acute dermal LD_{50} value in rabbits was reported as >2 g/kg (Moreno, 1972).

Irritation. Ethyl butyrate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1972). Tested at 5% in petrolatum, it produced no irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 5% in petrolatum and produced no sensitization reactions (Kligman, 1972).

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ETHYL CAPROATE

Synonym: Ethyl hexanoate.
Structure: $CH_3 \cdot [CH_2]_4 \cdot OCO \cdot CH_2 \cdot CH_3$.
Description and physical properties: EOA Spec. no. 172.
Occurrence: Reported to be found in the fruits of *Ananas sativus* (*Fenaroli's Handbook of Flavor Ingredients*, 1975).
Preparation: By the direct esterification of caproic acid with ethyl alcohol.
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to approximately 3000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·04
Maximum	0·1	0·01	0·03	0·4

Analytical data: Gas chromatogram, RIFM no. 75–48; infra-red curve, RIFM no. 75–48.

Status

Ethyl caproate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included ethyl caproate at a level of 40 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health. The *Food Chemicals Codex* (1972) has a monograph on ethyl caproate.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1975).

Subacute and chronic toxicity. In a 1960 study, ethyl caproate fed to rats in the diet for 17 wk at 1000, 2500 and 10,000 ppm produced no pathological changes (Flavor and Extract Manufacturers' Association, 1974), and in a later study the no-effect level for rats fed ethyl caproate for 1 yr was 2500 ppm (Bär & Griepentrog, 1967). No deaths occurred and no severe fatty livers were observed when ethyl caproate was fed at a level of 35% in the diet for 2 wk to two young male rats receiving no choline (Stetten & Salcedo, 1945) and a diet containing 5% ethyl caproate was palatable and did not cause death when fed to four chicks (Yoshida, Morimoto & Oda, 1970).

Irritation. Ethyl caproate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1975). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 19 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Epstein, 1975).

Metabolism. Aliphatic esters, including ethyl caproate, are thought to be readily hydrolysed to the corresponding alcohol and acid, which are then further metabolized (Fassett, 1963). Ethyl caproate administered orally to rats produced a uniform ketonuria and it was considered probable that caproic acid was broken down chiefly by β-oxidation (Deuel, Hallman, Butts & Murray, 1936). When 2 g ethyl caproate dissolved in aqueous ethanol was fed directly into the rumen of a cow, 0·003% was transferred to the milk, reaching a maximum level of 60 μg/litre after 2–4 hr (Honkanen, Karvonen & Virtanen, 1964). The energy from ethyl caproate was 52% available when the ester was fed to four chicks at a level of 5% in the diet (Yoshida *et al.* 1970).

Skin absorption. In studies of absorption through the intact shaved abdominal skin of rats, ethyl caproate was found to be absorbed within 27 min (Valette & Cavier, 1954).

Insects. Ethyl caproate (0·3 μl/larva) reduced emergence and was somewhat toxic and melanogenic to larvae of the house fly *Musca domestica* (Quraishi, 1972). The ester was identified as a component of an aggregation pheromone secreted by the mandibular glands of the gregarious cockroach, *Blaberus craniifer* (Brossut, Dubois & Rigaud, 1974). It showed no alarm-releasing activity, as assayed in terms of attractiveness to guard bees, *Apis mellifera* (Boch & Shearer, 1971).

Micro-organisms. Microbial activity of the rumen of sheep and deer was promoted slightly with ethyl *n*-caproate (Oh, Sakai, Jones & Longhurst, 1967).

The vapours of ethyl caproate strongly inhibited the *in vitro* growth of five Gram-positive and Gram-negative bacteria (Maruzzella, Garofalo & Chiaramonte, 1961) and of four fungi (Maruzzella, Chiaramonte & Garofalo, 1961), but in a 1:500 dilution the ester did not inhibit the *in vitro* growth of four Gram-positive and Gram-negative bacteria (Maruzzella & Bramnick, 1961).

Plants. Ethyl caproate did not increase scald significantly in oil-wrapped stored apples (Huelin & Kennett, 1958).

Antileukaemic activity. Ethyl caproate (10 mmol/ml) showed antileukaemic activity when an *in vitro* mixture with AKR leukaemic cells was injected sc into mice of the AKR strain (Townsend, Brown, Felauer & Hazlett, 1961).

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ETHYL CAPRYLATE

Synonym: Ethyl octanoate.
Structure: $CH_3 \cdot [CH_2]_6 \cdot OCO \cdot CH_2 \cdot CH_3$.
Description and physical properties: EOA Spec. no. 173.
Occurrence: Reported to be found in cognac oil and other natural products.
Preparation: By the esterification of caprylic acid with ethanol.
Uses: In public use before the 1920s. Use in fragrances in the USA amounts to approximately 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·0005	0·0015	0·04
Maximum	0·06	0·006	0·02	0·2

Analytical data: Gas chromatogram, RIFM no. 75–49; infra-red curve, RIFM no. 75–49.

Status

Ethyl caprylate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included ethyl caprylate at a level of 40 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health. The *Food Chemicals Codex* (1972) has a monograph on ethyl caprylate.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 25·96 g/kg (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964) and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1975).

Subacute toxicity. In a feeding study, 1000, 2500 and 10,000 ppm fed to rats in the diet for 17 wk produced no macroscopic effects (Hagan, Hansen, Fitzhugh, Jenner, Jones, Taylor, Long, Nelson & Brouwer, 1967). When the ester was fed at a level of 35% in the diet for 2 wk to young male rats receiving no choline, renal haemorrhage and death occurred in four out of nine rats, but no severe fatty livers were observed (Stetten & Salcedo, 1945). Ethyl caprylate was palatable and caused no deaths when fed to 12 chicks at a level of 5% in the diet (Yoshida, Morimoto & Oda, 1970).

Irritation. Ethyl caprylate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1975). Tested at 2% in petrolatum, it produced no irritation after a 48-hr closed-patch test on two different panels of human subjects (Kligman, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 2% in petrolatum and produced two false sensitization reactions in the group of 25 (Kligman, 1975) (Spillover effect—Costus—See preface note no. 2). When the material was retested at the same concentration in another 25 volunteers, it produced no sensitization reactions (Kligman, 1975).

Metabolism. Aliphatic esters including ethyl caprylate are thought to be readily hydrolysed to the corresponding alcohol and acid, which are then further metabolized (Fassett, 1963). Oral administration of ethyl caprylate to rats produced a ketonuria twice as great as that from acetoacetate, indicating the formation of two fragments for the production of ketone bodies, and it was suggested that caprylic acid was probably broken down by a process involving multiple alternate oxidation (Deuel, Hallman, Butts & Murray, 1936).

The energy from ethyl carprylate was 43% available when the ester was fed to 12 chicks at a level of 5% in the diet (Yoshida *et al.* 1970). When 2 g ethyl caprylate dissolved in aqueous ethanol was fed directly into the rumen of a cow, 0·005% was transferred to the milk, reaching a maximum of 120 μg/litre after 2–4 hr (Honkanen, Karvonen & Virtanen, 1964).

Skin absorption. In studies of absorption through the intact shaved abdominal skin of the rat, ethyl caprylate was found to be absorbed within 38 min (Valette & Cavier, 1954).

Insects. Ethyl caprylate (0·3 μl/larva) reduced emergence and was toxic and somewhat melanogenic to larvae of the house fly *Musca domestica* (Quraishi, 1972). In tests with dipterous insects, ethyl caprylate was an attractant for Neophyllomyza but not for Siphonella (Sugawara & Muto, 1974).

Micro-organisms. Ethyl caprylate slightly inhibited the *in vitro* growth of two out of three wood-destroying fungi (Maruzzella, Scrandis, Scrandis & Grabon, 1960), but in a 1:500 dilution it did not inhibit the *in vitro* growth of four Gram-positive and Gram-negative bacteria (Maruzzella and Bramnick, 1961). Vapours of the ester inhibited the *in vitro* growth of two out of five Gram-positive and Gram-negative bacteria (Maruzzella, Garofalo & Chiaramonte, 1961), and all four of a group of fungi tested (Maruzzella, Chiaramonte & Garofalo, 1961).

Antileukaemic activity. Ethyl caprylate (5 mmol/ml) showed antileukaemic activity when an *in vitro* mixture with AKR leukaemic cells was injected sc into male mice of the AKR strain (Townsend, Brown, Felauer & Hazlett, 1961).

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ETHYL CINNAMATE

Synonyms: Ethyl β-phenylacrylate; ethyl 3-phenylpropenoate; ethyl *trans*-cinnamate.
Structure: $C_6H_5 \cdot CH{:}CH \cdot OCO \cdot CH_2 \cdot CH_3$.
Description and physical properties: *The Givaudan Index* (1961).
Occurrence: Found in storax oil, *Kaempferia galanga* and several other oils (Gildemeister & Hoffman, 1966).
Preparation: By direct esterification of ethanol with cinnamic acid under azeotropic conditions or by Claisen-type condensation of ethyl acetate and benzaldehyde in the presence of sodium metal (Bedoukian, 1967).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·02	0·08
Maximum	0·1	0·01	0·1	0·4

Status

Ethyl cinnamate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) listed ethyl cinnamate, giving an ADI of 1·25 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on ethyl cinnamate.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 7·8 g/kg (7·41–8·19 g/kg) (Russell, 1973). The acute dermal LD_{50} value in rabbits was reported as >5 g/kg (Russell, 1973).

Irritation. Ethyl cinnamate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Russell, 1973). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1973). A patch test using ethyl cinnamate at full strength for 24 hr produced one out of 22 irritation reactions (Katz, 1946). Tested on the forearms of volunteers, it was found to be free of irritating properties (Peterson & Hall, 1946).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1973).

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ETHYLENE BRASSYLATE

Synonyms: Ethylene undecane dicarboxylate.
Structure: $H_2C \cdot OCO \cdot [CH_2]_{11} \cdot OCO \cdot CH_2$.
Description and physical properties: EOA Spec. no. 188.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By depolymerization of the polyester of brassylic acid and ethylene glycol (Bedoukian, 1967).
Uses: In public use since the 1940s. Use in fragrances in the USA amounts to less than 2 million lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·01	0·2
Maximum	0·3	0·015	0·1	3·0

Analytical data: Gas chromatogram, RIFM no. 72–225; infra-red curve, RIFM no. 72–255.

Status

Ethylene brassylate is approved by the FDA for food use (21 CFR 121.1164).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1973).

Sub-acute toxicity. In a 20-day dermal study in New Zealand white rabbits, ethylene brassylate was applied at dosage levels of 30, 70 and 700 mg/kg/day. Dermal irritation was noted. Other than the dermal irritation and enlargement of regional lymph nodes at the 700 mg/kg/day dosage level, no compound related gross pathological lesions or organ weight variations were observed at autopsy or on study of the pathology (Goldenthal, 1974).

Irritation. Ethylene brassylate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1973). Tested at 30% in petrolatum, it produced no irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 30% in petrolatum and produced no sensitization reactions (Kligman, 1973).

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Kligman, A. M. (1973). Report to RIFM, 13 July.
Moreno, O. M. (1973) Report to RIFM, 14 May.

ETHYL HEXYL SALICYLATE

Structure: $HO \cdot C_6H_4 \cdot COO \cdot CH_2 \cdot CH(C_2H_5) \cdot C_4H_9$.

Description and physical properties: A colourless liquid.

Occurrence: Has apparently not been reported to occur in nature.

Preparation: From 2-ethylhexanol and salicylic acid by azeotropic-type esterification (Arctander, 1969).

Uses: In public use before the 1920s. Use in fragrances in the USA amounts to less than 1000 lb/yr. Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·1
Maximum	0·2	0·02	0·05	0·4

Analytical data: Gas chromatogram, RIFM no. 74–161; infra-red curve, RIFM no. 74–161.

Status

Ethyl hexyl salicylate is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974) or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Levenstein, 1974). The lowest lethal dose of 2-ethylhexyl salicylate given ip to mice was found to be 200 mg/kg (US National Institute for Occupational Safety and Health, 1975).

Irritation. Ethyl hexyl salicylate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was mildly irritating (Levenstein, 1974). Tested at 4% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 23 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Epstein, 1974).

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ETHYL LAURATE

Synonyms: Ethyl dodecanoate; ethyl dodecylate.
Structure: $CH_3 \cdot [CH_2]_{10} \cdot OCO \cdot CH_2 \cdot CH_3$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Reported to be found in nature (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: By direct esterification of ethanol with lauric acid under azeotropic conditions (Arctander, 1969).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·01	0·2
Maximum	0·3	0·03	0·005	1·2

Status

Ethyl laurate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) listed ethyl laurate, giving an ADI of 1 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on ethyl laurate and the Joint FAO/WHO Expert Committee on Food Additives (1967) has published a monograph and specifications for ethyl laurate giving a conditional ADI of 1 mg/kg.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. Ethyl laurate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Moreno, 1973). Tested at 12% in petrolatum, it produced no irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 12% in petrolatum and produced no sensitization reactions (Kligman, 1973).

Metabolism. Ethyl laurate is probably hydrolysed to ethyl alcohol and lauric acid, which then undergo normal metabolism (Fassett, 1963).

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Kligman, A. M. (1973). Report to RIFM, 12 August.

Moreno, O. M. (1973). Report to RIFM, 18 May.

ETHYL LINALOOL

Synonym: 3,7-Dimethyl-1,6-nonadien-3-ol.
Structure: $CH_3 \cdot CH_2 \cdot (CH_3)C{:}CH \cdot [CH_2]_2 \cdot (HO)C(CH_3) \cdot CH{:}CH_2$.
Description and physical properties: Colourless slightly oily liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: From methyl ethyl ketone and acetylene through a series of reactions (Bedoukian, 1967).
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to approximately 2000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·2
Maximum	0·2	0·02	0·1	2·4

Analytical data: Gas chromatogram, RIFM no. 75–54; infra-red curve, RIFM no. 75–54.

Status

Ethyl linalool is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974) or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1975).

Irritation. Ethyl linalool applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1975). Tested at 30% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 30% in petrolatum and produced no sensitization reactions (Epstein, 1975).

Metabolism. Tertiary alcohols are not readily metabolized and may be excreted in the urine both unchanged and highly conjugated with glucuronic acid. In rabbits, carbon–carbon double bonds make little difference to the extent of conjugation of *tert*-hexyl alcohols (Williams, 1959).

Insects. Ethyl linalool and other monoterpene alcohols possess moderate juvenile hormone activity for several insects (Levinson, 1966).

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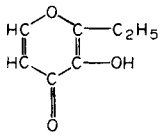
Williams, R. T. (1959). *Detoxication Mechanisms. The Metabolism and Detoxication of Drugs, Toxic Substances and Other Organic Compounds*. 2nd Ed., p. 67. Chapman & Hall Ltd., London.

ETHYL MALTOL

Synonym: 3-Hydroxy-2-ethyl-4-pyrone.
Structure:



Description and physical properties: *Food Chemicals Codex* (1972).
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By alkaline hydrolysis of streptomycin salts (Arctander, 1969).
Uses: In public use since the 1950s.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·001	0·002	0·04
Maximum	0·06	0·006	0·01	0·4

Analytical data: Infra-red curve, RIFM no. 74–195.

Status

Ethyl maltol is approved by the FDA for food use (21 CFR 121.1164) and was listed by the Council of Europe (1974) with an ADI of 2 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on ethyl maltol and the Joint FAO/WHO Expert Committee on Food Additives (1971) has given the compound an unconditional ADI of 0–2 mg/kg.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 1·22 g/kg (1·00–1·44 g/kg) (Moreno, 1974). The acute oral 7-day LD_{50}s in mice, rats and chicks were reported as 0·78, 1·2 and 1·27 g/kg, respectively (Gralla, Stebbins, Coleman & Delahunt, 1969). In a dermal LD_{50} study, the 5 g/kg could be applied only to one rabbit because of a lack of sample; this dosage in the one rabbit was not lethal (Moreno, 1974).

Short term toxicity. In 90-day studies involving the feeding of dietary levels providing 0–1000 mg ethyl maltol/kg body weight to groups of ten male and female rats, some kidney lesions were produced at the 1000-mg level but no gross pathological changes were observed (Gralla *et al.* 1969). In another 90-day study ethyl maltol was administered in oral doses of 0–500 mg/kg/day to groups of four male and female dogs. At the 500-mg level, there were transient signs of mild haemolytic anaemia and haemosiderin deposits were present in the Kupffer cells with small amounts of intracellular bilirubin (Gralla *et al.* 1969).

Long-term toxicity. No adverse effects were produced by 0–200 mg ethyl maltol/kg/day fed to 25 male and female rats for 2 yr. Eight male and female dogs similarly tolerated 2-yr oral dosage with 0–200 mg ethyl maltol/kg/day without adverse effects (Gralla *et al.* 1969).

Irritation. Ethyl maltol applied full strength to the intact or abraded skin of one rabbit was not irritating (Moreno, 1974). Tested at 10% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1974).

Metabolism. When orally administered, ethyl maltol was rapidly and extensively absorbed. Elimination was also extensive and rapid, involving conjugation as the glucuronide and ethereal sulphate, and excretion in the urine to the extent of 65–70% within 24 hr. Rate studies after iv dosage indicated that the bulk (86%) of the recovered conjugates was excreted within 6 hr (Rennhard, 1971).

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ETHYL METHYLPHENYLGLYCIDATE

Synonyms: Aldehyde C-16; strawberry aldehyde; ethyl α,β-epoxy-β-methylphenylpropionate; ethyl β-methylphenylglycidate.

Structure: $C_6H_5 \cdot C(CH_3) \cdot CH \cdot CO_2 \cdot CH_2 \cdot CH_3$.

Description and physical properties: EOA Spec. no. 109.

Occurrence: Has apparently not been reported to occur in nature.

Preparation: By the reaction of acetophenone and the ethyl ester of monochloracetic acid in the presence of an alkaline condensing agent (Bedoukian, 1967).

Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 5000 lb/yr.

Concentration in final product (%).

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·005	0·001	0·03
Maximum	0·05	0·05	0·01	0·05

Status

Ethyl methylphenylglycidate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) listed ethyl methylphenylglycidate among the artificial flavouring substances not admissible at present including it in the group "Biological Data Indicate Definite Toxicity". The *Food Chemicals Codex* (1972) has a monograph on ethyl methylphenylglycidate and that published by the Joint FAO/WHO Expert Committee on Food Additives (1967) gives a temporary ADI of 0–0·6 mg/kg.

Biological data

Acute toxicity. The acute oral LD_{50} was reported as 5470 mg/kg in the rat and as 4050 mg/kg in the guinea-pig (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964).

Chronic toxicity. In a feeding study in rats, a dietary level of 10,000 ppm given for 16 wk caused growth retardation, particularly in males, and marked testicular atrophy, while 2500 ppm fed to a similar group for 1 yr produced no effects (Hagan, Hansen, Fitzhugh, Jenner, Jones, Taylor, Long, Nelson & Brouwer, 1967). In a 2-yr feeding study, male and female rats fed a diet containing 5000 ppm ethyl methylphenylglycidate exhibited paralysis of the hindquarters as well as demyelinating degenerative changes in the sciatic nerve (Bär & Griepentrog, 1967). No effect was observed with a dietary level of 1000 ppm, but a subsequent paper (Griepentrog, 1969) reported the finding of effects at all levels when groups of rats were fed diets containing 1000, 3500, 5000 or 6000 ppm ethyl methylphenylglycidate for 2 yr. In these four groups the histological changes of the sciatic nerve were found in 22, 70, 65 and 60% respectively, the effects being marked in 17, 20, 40 and 40% respectively. No histological changes were found in the other organs studied, namely the liver, kidney, spleen and heart.

Irritation. Ethyl methylphenylglycidate tested at a 1% concentration in petrolatum produced no irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1971).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 1% in petrolatum and produced no sensitization reactions (Kligman, 1971).

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ETHYL OCTINE CARBONATE

Synonyms: Ethyl-2-nonynoate; ethyl octyne carboxylate.
Structure: $CH_3 \cdot [CH_2]_5 \cdot C \vdots C \cdot OCO \cdot CH_2 \cdot CH_3$.
Description and physical properties: A colourless liquid with an odour resembling that of violet leaves (Arctander, 1969).
Occurrence: Has apparently not been reported to occur in nature.
Preparation: From *n*-oct-l-yne via its sodium-derivative, with ethyl chlorocarbonate to the acetylenic ester (Bedoukian, 1967).
Uses: In public use since the 1920s.

Concentration in final product (%)

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·001	0·001	0·04
Maximum	0·05	0·01	0·01	0·2

Status

Ethyl octine carbonate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included ethyl octine carbonate in the list of admissible artificial flavouring substances, at a level of 1 ppm.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 2·85 g/kg (1·79–3·91 g/kg) (Moreno, 1973). The acute dermal LD_{50} in rabbits was reported as 5 g/kg (Moreno, 1973).

Irritation. Ethyl octine carbonate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Moreno, 1973). Tested at 2% in petrolatum, it produced no irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 2% in petrolatum and produced no sensitization reactions (Kligman, 1973).

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ETHYL PHENYLACETATE

Synonym: Ethyl α-toluate.
Structure: $C_6H_5 \cdot CH_2 \cdot OCO \cdot CH_2 \cdot CH_3$.
Description and physical properties: EOA Spec. no. 40.
Occurrence: Reported to be found in nature (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: By ethanolic esterification of the corresponding acid or nitrile.
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to less than 2000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·05	0·005	0·01	0·2
Maximum	0·2	0·02	0·05	0·8

Analytical data. Gas chromatogram, RIFM no. 72–140; infra-red curve, RIFM no. 72–140.

Status

Ethyl phenylacetate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included ethyl phenylacetate in its list of temporarily admissible artificial flavouring substances. The *Food Chemicals Codex* (1972) has a monograph on ethyl phenylacetate.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 3·30 g/kg (2·52–4·08 g/kg) (Moreno, 1973). The acute dermal LD_{50} in rabbits was reported as >5 g/kg (Moreno, 1973).

Irritation. Ethyl phenylacetate applied full strength on intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Moreno, 1973). When tested full strength for irritation on the forearms of volunteers, it had negative results (Peterson & Hall, 1945), and tested at 8% in petrolatum it produced no irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1973).

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ETHYL PHENYLGLYCIDATE

Synonyms: Ethyl 3-phenylglycidate; ethyl α,β-epoxy-α-phenylpropionate.
Structure: $C_6H_5 \cdot \underset{\diagdown O \diagup}{CH \cdot CH} \cdot OCO \cdot CH_2 \cdot CH_3$.

Description and physical properties: EOA Spec. no. 246.
Occurrence: Apparently has not been reported to occur in nature.
Preparation: By the reaction of benzaldehyde and the ethyl ester of monochloracetic acid in the presence of an alkaline condensing agent (Bedoukian, 1967).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 2000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·01	0·15
Maximum	0·1	0·01	0·05	0·4

Analytical data: Gas chromatogram. RIFM no. 72–141; infra-red curve, RIFM no. 72–141.

Status

Ethyl phenylglycidate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included ethyl phenylglycidate in its list of temporarily admissible artificial flavouring substances. The *Food Chemicals Codex* (1972) has a monograph on ethyl phenylglycidate.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 2·3 ml/kg (2·0–2·6 ml/kg) (Shelanski, 1973b). The acute dermal LD_{50} value in rabbits was reported as >5 g/kg (Shelanski, 1973a).

Irritation. Ethyl phenylglycidate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Shelanski, 1973a). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1973).

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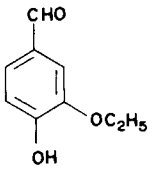
ETHYL VANILLIN

Synonyms: 3-Ethoxy-4-hydroxybenzaldehyde; protocatechuic aldehyde-3-ethyl ether.
Structure:



Description and physical properties: *Givaudan Index* (1961).
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By ethylation of protocatechualdehyde (Bedoukian, 1967).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 28,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·003	0·003	0·12
Maximum	0·10	0·025	0·06	0·20

Analytical data: Gas chromatogram, RIFM no. 70–11; infra-red curve, RIFM no. 70–11.

Status

Ethyl vanillin was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) listed ethyl vanillin, giving an ADI of 10 mg/kg. The *Food Chemicals Codex* (1972) and the *National Formulary* (1970) each has a monograph on ethyl vanillin and the Joint FAO/WHO Expert Committee on Food Additives (1967) has published a monograph and specifications for ethyl vanillin giving an unconditional ADI of 0–10 mg/kg.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as >2000 mg/kg (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964) and the acute oral LD in rabbits as 3000 mg/kg (Deichmann & Kitzmuller, 1940). The sc LD in rats was reported as 1800 mg/kg (Deichmann & Kitzmuller, 1940). The ip LD_{50} was reported as 750 mg/kg in mice and as 1140 mg/kg in guinea-pigs, while the iv LD in dogs was reported as 760 mg/kg (Caujolle & Meynier, 1954).

Long-term toxicity. In feeding studies, 20 mg/kg body weight/day fed to rats for 18 wk produced no effects, while rats fed 64 mg/kg/day for 10 wk showed a reduction in growth rate and myocardial, renal, hepatic, lung, spleen and stomach injuries (Deichmann & Kitzmuller, 1940).

Neither 20,000 and 50,000 ppm fed to male rats in the diet for 1 yr nor 5000, 10,000 and 20,000 ppm fed to male and female rats in the diet for 2 yr produced any effects (Hagan, Hansen, Fitzhugh, Jenner, Jones, Taylor, Long, Nelson & Brouwer, 1967).

Irritation. Ethyl vanillin tested at 2% in petrolatum produced a mild irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1970).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 2% in petrolatum and produced no sensitization reactions (Kligman, 1970).

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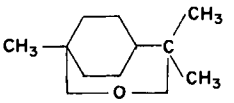
EUCALYPTOL

Synonyms: 1,8-cineole; 1,8-oxido-*p*-menthane; 1,8-epoxy-*o*-menthane.
Structure:



Description and physical properties: EOA Spec. no. 288.
Occurrence: Eucalyptol forms the main constituent of certain Eucalyptus species. It is found in several hundred oils, including cardamom, ginger root, spike lavender and rosemary (Gildemeister & Hoffman, 1966; Guenther, 1949).
Preparation: By separation from essential oils by freezing or by a combination of distilling and freezing.
Uses: In public use since the early 1900s. Use in fragrances in the USA amounts to less than 5000 lb/yr.

Concentration in final product (%)

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·005	0·02	0·2
Maximum	0·4	0·04	0·1	1·6

Analytical data: Infra-red curve, RIFM no. 72–143.

Status

Eucalyptol was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included eucalyptol in its list of admissible artificial flavouring substances, at a level of 15 ppm.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 2480 mg/kg (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964). The acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1972).

Irritation. Eucalyptol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Moreno, 1972). Tested at 16% in petrolatum, it produced no irritant effects after a 48-hr closed-patch test in 25 human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 16% in petrolatum and produced no sensitization reactions (Kligman, 1972).

Metabolism. Eucalyptol undergoes oxidation *in vivo* with the formation of hydroxycineole, which is excreted as hydroxycineoleglucuronic acid (Williams, 1959).

Additional published data

The administration of eucalyptol to rats (Jori, Bianchetti & Prestini, 1969; Jori, Bianchetti, Prestini & Garattini, 1970) increased the activity of drug-metabolizing enzymes in the liver. Furthermore, animals pretreated with eucalyptol showed a reduced sensitivity to pentobarbitone and lower plasma and brain concentrations of the barbiturate (Jori *et al.*, 1969 & 1970). Eucalyptol also increased the microsomal activity of rat liver after a single sc dose. Further doses did not enhance the effect. Eucalyptol did not affect the concentration of cytochrome *P*-450 in liver microsomes (Jori, Di Salle & Pescador, 1972).

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EUCALYPTUS OIL

Description and physical properties: *Food Chemicals Codex* (1972). The chief constituent of eucalyptus oil is eucalyptol* (Guenther, 1950).
Occurrence: Found in the leaves of *Eucalyptus globulus* Labill. and other species of Eucalyptus L'Heritier (Fam: Myrtaceae) (Guenther, 1950).
Preparation: By steam distillation of the leaves of *E. globulus* Labill. and other species of Eucalyptus L'Heritier (Gildemeister & Hoffman, 1961; Guenther, 1950).
Uses: In public use since before the 1900s. Use in fragrances in the USA amounts to less than 32,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·005	0·02	0·10
Maximum	0·3	0·04	0·1	1·0

Analytical data: Gas chromatogram, RIFM nos 70–14, 73–19; infra-red curve, RIFM nos 70–14, 73–19.

Status

Eucalyptus oil was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1163). The Council of Europe (1970) included eucalyptus oil in the list of substances, spices and seasonings whose use is deemed admissible with a possible limitation of the active principle in the final product. Monographs on eucalyptus oil have been published in the *Food Chemicals Codex* (1972) and in the *National Formulary* (1970).

Biological data

Acute toxicity. The acute oral LD_{50} value of eucalyptol was reported as 2480 mg/kg in the rat (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964). The acute dermal LD_{50} in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. Undiluted eucalyptus oil applied to the backs of hairless mice was not irritating (Urbach & Forbes, 1973). When applied full strength to intact or abraded rabbit skin for 24 hr under occlusion, it was moderately irritating (Moreno, 1973). Eucalyptus oil tested at 10% in petrolatum produced no irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1973), and a patch test using the full strength oil for 24 hr produced no reactions in 20 subjects (Katz, 1946).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1973).

Phototoxicity. No phototoxic effects were reported for eucalyptus oil (Urbach & Forbes, 1973).

Metabolism. 1,8-Cineole (eucalyptol), the chief constituent of eucalyptus oil, apparently undergoes oxidation *in vivo* with the formation of hydroxycineole which is excreted as hydroxycineoleglucuronic acid (Williams, 1959).

Additional published data

Eucalyptus oil has been reported to promote tumour formation on the skins of mice treated with the primary carcinogen 7,12-dimethylbenz[*a*]anthracene (Roe & Field, 1965). It has been shown to be rapidly absorbed through the skin of the mouse (Meyer & Meyer, 1959).

*See p.372.

Hypersensitivity from eucalyptus oil has been reported by Goodman & Gilman (1942), Löwenfeld (1932), Schwartz & Peck (1946) and Schwartz, Tulipan & Peck (1947).

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EUGENOL

Synonyms: 4-Allyl-2-methoxyphenol; 4-allylguaiacol; 2-methoxy-4-prop-2-enylphenol; 1-hydroxy-2-methoxy-4-allylbenzene.

Structure: $HO \cdot C_6H_3(OCH_3) \cdot CH_2 \cdot CH{:}CH_2$.

Description and physical properties: *Givaudan Index* (1961).

Occurrence: Eugenol is the main constituent of several important essential oils such as oil of clove, clove stem and leaf, pimenta berry and leaf, bay and cinnamon leaf. Eugenol also occurs in smaller quantities in numerous other oils, including cinnamon bark, cananga, calamus and ylang ylang (Gildemeister & Hoffman, 1966; Guenther, 1949).

Preparation: By isolation from clove-bud oil, clove-leaf oil, cinnamon-leaf oil or Brazilian oil of *Ocimum gratissimum* (Bedoukian, 1967).

Uses: In public use since before the 1900s. Use in fragrances in the USA amounts to less than 100,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·005	0·01	0·40
Maximum	0·50	0·03	0·30	0·80

Analytical data: Gas chromatogram, RIFM no. 2962; infra-red curve, RIFM no. 2962.

Status

Eugenol was granted GRAS status by FEMA (1965) and is approved by the FDA as GRAS for food use (21 CFR 121.101). The Council of Europe (1974) included eugenol in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health, giving an ADI of 5 mg/kg. The *Food Chemicals Codex* (1972) and the *United States Pharmacopeia* (1965) both have monographs on eugenol. The Joint FAO/WHO Expert Committee on Food Additives (1967) has published a monograph and specifications for eugenol giving a conditional ADI of 0–5 mg/kg.

Biological data

Acute toxicity. The acute oral LD_{50} has been reported as 2·68 g/kg in the rat, 3·00 g/kg in the mouse and 2·13 g/kg in the guinea-pig (Hagan, Jenner, Jones, Fitzhugh, Long, Brouwer & Webb, 1965; Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964). Elsewhere, the acute oral LD_{50} in rats was reported as 1·93 g/kg (Sober, Hollander & Sober, 1950). Rats given four daily oral doses of about 900 mg/kg showed minor liver damage consisting of discoloration, mottling and blunting of lobe edges (Taylor, Jenner & Jones, 1964).

Dogs given single oral doses of 250 or 500 mg eugenol/kg showed signs of intoxication including vomiting and two out of four dogs on the higher level died; no effect was seen at 200 mg/kg (Lauber & Hollander, 1950). Intravenous injection of eugenol, diluted 1–20 times, decreased transiently the systemic arterial blood pressure and myocardial contractile force, impaired motor activity and increased salivary flow. Large doses caused pulmonary oedema in some dogs given eugenol iv and produced rigidity of the hind limbs when given intra-arterially (Sticht & Smith, 1971). The stomachs of rats and guinea-pigs given oral doses of 150 mg eugenol/animal showed histological damage consisting of desquamation of the epithelium and punctate haemorrhages in the pyloric and glandular regions (Hartiala, Pulkkinen & Ball, 1966). Degenerative and reparative changes in the gastric mucous barrier were followed histologically after repeated application of a 5% eugenol emulsion to the mucosa of Heidenhain's pouch in dogs (Hollander & Goldfischer, 1949).

In tests on acute toxicity to mucous membranes, eugenol applied bilaterally to the ventral surface of the tongue of dogs for 5 min caused erythema and occasionally ulcers with a moderate diffuse inflammatory infiltration (Lilly, Cutcher & Jendresen, 1972).

Short-term toxicity. No liver damage was observed in rats fed eugenol at 1% in the diet for about 4 months (Taylor *et al.* 1964). Feeding of eugenol at 0, 0·1 or 1% in the diet to groups of ten male and ten female rats for 19 wk exerted no effect on growth, haematology or organ weights and histology (Hagan, Hansen, Fitzhugh, Jenner, Jones, Taylor, Long, Nelson & Brouwer, 1967). No adverse effect was observed in a group of 15 male and 15 female rats fed eugenol at 79·3 mg/kg body weight/day for 12 wk (Joint FAO/WHO Expert Committee on Food Additives, 1967).

In a group of 20 male rats given an initial oral dose of 1·40 g eugenol/kg which was gradually increased to 4·00 g/kg, eight rats survived 34 days and 15 rats lived long enough to receive the maximum dose. Slight enlargement of the liver and adrenals was observed and histological examination of the forestomach revealed moderately severe hyperplasia and hyperkeratosis of the stratified squamous epithelium with focal ulceration. A small degree of osteoporosis was also seen (Hagan *et al.* 1965 & 1967).

Irritation. Eugenol tested at 8% in petrolatum produced a mild irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1971). A patch test using undiluted eugenol for 24 hr produced no reactions in 20 subjects (Katz, 1946).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Greif, 1967; Kligman, 1971).

Metabolism. No absorption of eugenol occurred within 2 hr of application to the intact shaved skin of mice (Meyer & Meyer, 1959). Following ip injection of [^{14}C]eugenol into rats, radioactivity was distributed in various organs and the presence of $^{14}CO_2$ in the expired air indicated the demethylation of eugenol (Weinberg, Rabinowitz, Zanger & Gennaro, 1972). Over 70% of an oral dose of eugenol was

excreted in the urine of rabbits (Schröder & Vollmer, 1932).

Eugenol, administered ip to rats, had little or no effect on microsomal enzyme induction, as evidenced by measurements of pentobarbitone and ethanol sleeping times (Seto & Keup, 1969) and of hexobarbitone sleeping time, urinary ascorbic acid excretion and hepatic amidopyrine demethylation (Grübner, Klinger & Ankermann, 1972). The hydroxylation of dimethylamidopyrine and hexobarbitone by mouse-liver microsomes was weakly inhibited by eugenol *in vivo* (Jaffe, Fujii, Sengupta, Guerin & Epstein, 1968). Hexobarbitone narcosis and zoxazolamine paralysis were slightly prolonged in mice treated with eugenol (Fujii, Jaffe, Bishop, Arnold, Mackintosh & Epstein, 1970).

The inhibition by eugenol of glucuronic acid conjugation in the stomach of rats and guinea-pigs (Hartiala *et al.* 1966) and of dogs (Raussi & Hartiala, 1963) may have some bearing on the reported mucinogenic activity of eugenol and its beneficial effect on gastric-ulcer formation.

Additional published data

Eugenol showed weak tumour-promoting activity following its application to mouse skin subjected to initiating treatment with 7,12-dimethylbenz[*a*]anthracene (Van Duuren, Sivak, Segal, Orris & Langseth, 1966). Eugenol failed to potentiate gastric-tumour production by 20-methylcholanthrene in mice (Hitchcock, 1952).

In a test on 21 patients suffering from various dermatoses, several essential oils and their constituents, including eugenol, were tested and produced positive patch-test reactions (Woeber & Krombach, 1969).

Skin irritation and phototoxicity tests were carried out on various soap perfume preparations, including a preparation containing eugenol (Fujii, Furukawa & Suzuki, 1972).

Eugenol-containing preparations were tested for allergic skin reactions in guinea-pigs and in patients undergoing dental treatment with these preparations (Koch, Magnusson & Nyquist, 1971).

Eugenol showed weak cytotoxic activity against HeLa cells (Stoichev, Zolotovich, Nachev & Silyanovska, 1967).

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EUGENYL ACETATE

Synonyms: Eugenol acetate; 4-allyl-2-methoxyphenyl acetate; aceteugenol.
Structure: $CH_3 \cdot OCO \cdot C_6H_3(OCH_3) \cdot CH_2 \cdot CH{:}CH_2$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Found in the essentials oils of *Laurus nobilis* and clove buds and in clove leaves (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: From eugenol by acetylation (Arctander, 1969).
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to less than 5000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·1	0·01	0·005	0·25
Maximum	0·2	0·02	0·03	2·0

Analytical data: Gas chromatogram, RIFM no. 72–22; infra-red curve, RIFM no. 72–22.

Status

Eugenyl acetate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) listed eugenyl acetate, giving an ADI of 5 mg/kg.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 1·67 g/kg (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964) and as 2·6 g/kg (2·3–2·9 g/kg) (Moreno, 1972b). The acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1972a).

Chronic toxicity. In feeding studies, 1000, 2500 and 10,000 ppm fed to rats in the diet for 19 wk produced no macroscopic effect (Hagan, Hansen, Fitzhugh, Jenner, Jones, Taylor, Long, Nelson & Brouwer, 1967).

Irritation. Eugenyl acetate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1972a). Tested at 20% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 20% in petrolatum and produced no sensitization reactions (Kligman, 1972).

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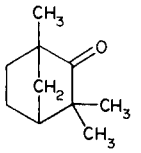
Moreno, O. M. (1972b). Report to RIFM, 5 May.

FENCHONE

Synonym: 1,3,3-Trimethyl-2-norbornanone.
Structure:



Description and physical properties: *Merck Index* (1968).
Occurrence: Reported to be found in many essential oils, including those of *Thuja plicata*, *T. occidentalis*, *T. standishii*, Russian anise, fennel, a few Artemisia varieties (*A. frigida*, *A. verlotorum* and *A. santolinaefolia*), *Lavandula stoechas* and *L. burmannii*. The highest levels (12–19%) are found in fennel oil (*Fenaroli's Handbook of Flavor Ingredients*, 1975; Gildemeister & Hoffman, 1963).
Preparation: By isolation from cedar leaf oil (Thuja oil) or by various synthetic methods (Arctander, 1969).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to approximately 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·005	0·05
Maximum	0·15	0·015	0·02	0·4

Analytical data: Gas chromatogram, RIFM no. 75–56.

Status

Fenchone was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included it at a level of 5 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 6·16 g/kg (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964) and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Levenstein, 1975).

Irritation. Fenchone applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was mildly irritating (Levenstein, 1975). Tested at 4% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1975).

Metabolism. Rimini (1901 & 1909) showed that, in the dog, fenchone was probably oxidized to 4-hydroxyfenchone. Reinartz & Zanke (1936) showed that there were other products. They separated, as lead salts, the glucuronides from the urine of dogs receiving *d*-fenchone. The lead was removed with sulphuric acid and the resulting solution was hydrolysed. In the resulting mixture of hydroxyfenchones, the presence of 4- and 5-hydroxyfenchones and π-apofenchone-3-carboxylic acid was demonstrated (Williams, 1959).

The (+) and (−) isomers of fenchone were hydroxylated by the mycelia of the pathogenic fungus *Absidia orchidis* to form a mixture of 5- and 6-exohydroxyfenchone (Pfrunder & Tamm, 1969). Fenchone was oxidized by Corynebacterium spp, strain T_1, to form the lactones 1,2-fencholide and 2,3-fencholide in a proportion of 9:1 (Chapman, Meerman & Gunsalus, 1965).

Inhalation. Steam inhalation of *d*-fenchone by urethanized rabbits produced a dose-dependent augmentation, which was greater in the autumn months, in the volume output of respiratory-tract fluid, with maximum effect at a level just detectable by odour (9 mg/kg added to the vaporizer). Inhalation of fenchone (1–27 mg/kg added to the vaporizer) produced a dose-dependent decline in the specific gravity of the respiratory-tract fluid (Boyd & Sheppard, 1971).

Pharmacology. In mice, fenchone injected sc in sesame oil produced clonic convulsions at non-lethal doses, with a median convulsive dose (CD_{50}) of 1133 mg/kg, and a dose of 500 mg/kg given sc was an effective arousal agent, reducing the hexobarbitone sleep time (Wenzel & Ross, 1957). In

rats, an ip dose of 500 mg/kg had no effect on pentobarbitone-depressed respiration, while ip doses of 50–400 mg/kg increased running activity but did not affect total activity (Wenzel & Ross, 1957). Fenchone showed some antispasmodic action on excised mouse intestine (Haginiwa, Harada & Morishita, 1963), and at 260 mmol/kg showed good choleretic properties of moderately long duration when given orally in olive oil to rats (Mörsdorf, 1966). Thomas (1958) reported that it acted as a central nervous system stimulant. Fenchone has been used medically as a counter-irritant (*Merck Index*, 1968).

Skin. In studies on the intact shaved abdominal skin of mice, absorption of fenchone was shown to be moderately rapid (45 min) (Meyer & Meyer, 1959). In an evaluation of skin-penetrating agents, fenchone did not aid the deep penetration of Rhodamine B into the corium or subcutis of guinea-pig skin (Meyer, 1965).

Insects. Fenchone (1–10 ppm) was found to be an attractant for the boll weevil, *Anthonomus grandis* (Gueldner, Thompson, Hardee & Hedin, 1970).

Worms. Applied to the tails of mice, fenchone provided no protection against infestation with cercariae of the trematode *Schistosoma mansoni* (Gilbert, DeSouza, Fascio, Kitagawa, Nascimento, Fortes, Seabra & Pellegrino, 1970). The 1-hr LC_{50} of fenchone for Enchytrae (oligochaete worms) was approximately 1:300; the 2-hr LPC_{50} (lethal or paralysing concentration) was 1:4000 (Göckeritz, Weuffen & Höppe, 1974).

Micro-organisms. Fenchone totally inhibited the growth of fungi and bacteria at dilutions of between 1:128 and 1:500 (Göckeritz *et al.* 1974). Certain fenchone-containing mixtures that inhibit the growth of bacteria and fungi have been patented as disinfecting compositions for use on skin and mucous surfaces,wounds and utensils (Gauvreau, 1974). At dilutions between 1:500 and 1:8000, fenchone totally inhibited the growth of ten out of 11 bacteria tested, and is liable to interfere with the success of commercial application of *Bacillus thuringiensis* to trees such as *Abies balsamea* (balm of Gilead fir) in which it is present (Smirnoff, 1972). It is an antimicrobial component of a patented washing composition (Noesler & Bloching, 1972).

Cells. Fenchone at concentrations of 1, 10 or 100 μg/ml was not toxic to HeLa cell cultures (Zolotovich, Nachev, Silyanovska & Stoichev, 1967; Zolotovitch, Siljanowska, Stojcev & Nachev, 1969).

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FENCHYL ACETATE

Synonym: 1,3,3-Trimethyl-2-norbornanyl acetate.
Structure: $C_{10}H_{17}\cdot OCO\cdot CH_3$ (for the structure of fenchone, $C_{10}H_{16}$:O, see p. 769).
Description and physical properties: A colourless liquid.
Occurrence: Reported to be found in the oil from the leaves and terminal branches of *Juniperus rigida*, in *Seseli sibiricum*, in rosemary and fennel oils and in the oil of hinoki leaves (*Fenaroli's Handbook of Flavor Ingredients*, 1975).
Preparation: By acetylation of fenchyl alcohol (Arctander, 1969).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 1000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·01	0·15
Maximum	0·3	0·03	0·05	0·5

Status

Fenchyl acetate was given GRAS status by FEMA (1973), and the Council of Europe (1974) included it in the list of artificial flavouring substances not fully evaluated.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1975).

Irritation. Fenchyl acetate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1975). Tested at 5% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 5% in petrolatum and produced no sensitization reactions (Kligman, 1975).

Skin. In studies on the intact shaved abdominal skin of mice, absorption of fenchyl acetate was moderately slow (54 min) (Meyer & Meyer, 1959). In an evaluation of skin penetrating agents, fenchyl acetate did not aid the deep penetration of Rhodamine B into the corium or subcutis of guinea-pig skin (Meyer, 1965).

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α-FENCHYL ALCOHOL

Synonyms: 1,3,3-Trimethyl-2-norbornanol; 2-fenchanol; α-fenchol.
Structure: $C_{10}H_{17}\cdot OH$ (for the structure of fenchone, $C_{10}H_{16}:O$, see p. 769).
Description and physical properties: A solid colourless crystalline mass.
Occurrence: Found in nature mixed with β-fenchyl alcohol in the essential oils of *Picea alba*, *Pinus silvestris*, pine oil, *Artemisia santolinaefolia* and others (*Fenaroli's Handbook of Flavor Ingredients*, 1975; Gildemeister & Hoffman, 1963).
Preparation: By reduction of fenchone (Arctander, 1969).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to approximately 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·005	0·05
Maximum	0·15	0·015	0·02	0·4

Status

Fenchyl alcohol was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included it at a level of 3 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1976).

Irritation. α-Fenchyl alcohol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1976). Tested at 4% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1976).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 24 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Epstein, 1976).

Metabolism. Both *l*-fenchyl and *l*-isofenchyl alcohols are excreted by rabbits as the corresponding glucuronides (Williams, 1959).

Insects. α-Fenchol was found to be a potent attractant for larvae of the New Zealand grass grub, *Costelytra zealandica* (Osborne & Boyd, 1974).

Micro-organisms. Fenchyl alcohol strongly inhibited the rumen microbial activity of both sheep and deer (Oh, Sakai, Jones & Longhurst, 1967). A commercial preparation containing borneol, methylchavicol, fenchyl alcohol and *Pinus silvestris* oil was found to possess bactericidal activity in dilutions between 1:100 and 1:500 against tubercle bacilli and *Staphylococcus aureus haemolyticus*, but not against *Escherichia coli* or *Bacterium pyocyaneus* (Ritzerfeld, 1959).

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FENNEL OIL, BITTER

Description and physical properties: *Food Chemicals Codex* (1972). The main constituent of bitter fennel oil is anethole (Guenther, 1950).
Occurrence: Found in the seeds of *Foeniculum vulgare* Mill. var. vulgare (Mill.) Thellung (Fam. Umbelliferae) (Guenther, 1950).
Preparation: By steam distillation of the crushed seeds of *Foeniculum vulgare* Mill. var. vulgare (Mill.) Thellung (Gildemeister & Hoffman, 1961; Guenther, 1950).
Uses: In public use before the 1900s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·04
Maximum	0·1	0·01	0·03	0·4

Analytical data: Gas chromatogram, RIFM no. 75-59; infra-red curve, RIFM no. 75-59.

Status

Bitter fennel oil is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974), or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 4·52 ml/kg (4·06–5·02 ml/kg) (Levenstein, 1975). The acute dermal LD_{50} value in rabbits was reported as >5 ml/kg (Levenstein, 1975).

Irritation. Fennel oil, bitter, applied undiluted to the backs of hairless mice and swine was not irritating (Urbach & Forbes, 1975), but applied full strength to intact or abraded rabbit skin for 24 hr under occlusion, it was irritating (Levenstein, 1975). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced sensitization reactions in three of the 25 test subjects (Kligman, 1975).

Phototoxicity. No phototoxic effects were reported for undiluted fennel oil, bitter, on hairless mice and swine (Urbach & Forbes, 1975).

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Urbach, F. & Forbes, P. D. (1975). Report to RIFM, 18 June.

FENNEL OIL

Description and physical properties: *Food Chemicals Codex* (1972).
Occurrence: Found in the plant *Foeniculum vulgare* Thellung (Fam. Umbelliferae) (Guenther, 1950).
Preparation: By steam distillation of the seeds of *Foeniculum vulgare* (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Uses: In public use before the 1900s. Use in fragrances in the USA amounts to less than 4000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·001	0·003	0·08
Maximum	0·07	0·007	0·02	0·4

Analytical data: Gas chromatogram, RIFM no. 72–145; infra-red curve, RIFM no. 72–145.

Status

Fennel oil was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) included fennel oil in the list of fruits and vegetables or parts thereof for which no restriction was proposed. Both the *Food Chemicals Codex* (1972) and the *United States Pharmacopeia* (1965) have a monograph on fennel oil.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 3·8 g/kg (3·43–4·17 g/kg) (Moreno, 1973). The acute dermal LD_{50} in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. Undiluted fennel oil applied to the backs of hairless mice was severely irritating (Urbach & Forbes, 1973). Applied full strength to intact or abraded rabbit skin for 24 hr under occlusion, it was moderately irritating (Moreno, 1973). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1973).

Sensitization. A maximzation test (Kligman, 1966) was carried out on 24 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Epstein, 1973).

Phototoxicity. No phototoxic effects were reported for fennel oil (Urbach & Forbes, 1973).

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FIR NEEDLE OIL, CANADIAN

Synonym: Balsam fir oil.

Description and physical properties: *Food Chemicals Codex* (1972). The chief constituent of Canadian fir needle oil is 1-α-pinene (Guenther, 1952).

Occurrence: Found in the leaves of *Abies balsamea* (L.) Mill. (Fam: Pinaceae) (Guenther, 1952).

Preparation: By steam distillation of the needles and twigs of *A. balsamea* (*Fenaroli's Handbook of Flavor Ingredients*, 1971).

Uses: In public use since the 1930s. Use in fragrance in the USA amounts to less than 35,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·005	0·1
Maximum	0·3	0·03	0·1	1·0

Status

Fir needle oil, Canadian was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1163). The Council of Europe (1974) included fir needle oil, Canadian in the list of flavouring substances temporarily admissible for use, possibly with a limitation on the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on fir needle oil, Canadian.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Wohl, 1974).

Irritation. Fir needle oil, Canadian applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Wohl, 1974). Applied undiluted to the backs of hairless mice, it was not irritating (Urbach & Forbes, 1974). Tested at 10% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966, modified) was carried out on 22 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Epstein, 1974).

Phototoxicity. No phototoxic effects were reported for fir needle oil, Canadian (Urbach & Forbes, 1974).

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Urbach, F. & Forbes, P. D. (1974). Report to RIFM, 12 April.

Wohl, A. S. (1974). Report to RIFM, 2 April.

FIR NEEDLE OIL, SIBERIAN

Description and physical properties: EOA Spec. no. 50. The chief constituent of fir needle oil, Siberian is *l*-bornyl acetate (Guenther, 1952).
Occurrence: Found in the needles and twigs of *Abies sibirica* Ledeb (Fam: Pinaceae).
Preparation: By steam distillation of the needles and twigs of *Abies sibirica* Ledeb.
Uses: In public use since the 1900s. Use in fragrances in the USA amounts to about 35,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·005	0·1
Maximum	0·3	0·03	0·1	0·25

Status

Fir needle oil, Siberian was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1163). The Council of Europe (1974) included fir needle oil, Siberian in the list of flavouring substances temporarily admitted for use, possibly with a limitation on the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on fir needle oil, Siberian.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 10·2 g/kg (6·7–13·7 g/kg) (Moreno, 1971). The acute dermal LD_{50} value in rabbits exceeded 3 g/kg (Moreno, 1971).

Irritation. Fir needle oil, Siberian applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1971). Tested at 2·5% in petrolatum, it produced a mild irritation after a 48-hr closed-patch test on human subjects (Kligman, 1971).

Sensitization. A maximization test (Kligman, 1966, modified) was carried out on 25 volunteers. The material was tested at a concentration of 2·5% in petrolatum and produced no sensitization reactions (Kligman, 1971).

References

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FOIN ABSOLUTE

Synonyms: Hay absolute; foin coupé.
Description and physical properties: A dark green to brownish green viscous liquid. Coumarin is a constituent of foin absolute (Poucher, 1974)).
Occurrence: Found in several common fodder grasses, including *Lolium perenne*, L. italicum, *Pheleum pratense*, *Poa pratense*, *Cynosurus cristatus* and *Anthoxanthum odoratum* (Naves, 1974; Poucher, 1974).
Preparation: By washing the concrete with alcohol (Arctander, 1960).
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to less than 1000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·0005	0·003	0·04
Maximum	0·05	0·005	0·02	0·3

Status

Foin absolute is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974) or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1976).

Irritation. Undiluted foin absolute was not irritating when applied to the backs of hairless mice and swine (Urbach & Forbes, 1976), but was slightly irritating when applied to intact or abraded rabbit skin for 24 hr under occlusion (Moreno, 1976). Tested at 4% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1976).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 24 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Epstein, 1976).

Phototoxicity. No phototoxic effects were reported for undiluted foin absolute on hairless mice and swine (Urbach & Forbes, 1976).

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GENET ABSOLUTE

Synonyms: Broom absolute; Spanish broom.
Description and physical properties: A viscous dark brown oil. The constituents of genet include free acids, phenols, terpenes, esters and aliphatic aldehydes (Guenther, 1952).
Occurrence: Found in the flowers of *Spartium junceum* L. (Fam. Leguminosae) (Guenther, 1952).
Preparation: By alcoholic extraction of the concrete (*Fenaroli's Handbook of Flavor Ingredients*, 1975).
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to less than 1000 lb/yr. Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·0005	0·003	0·04
Maximum	0·05	0·005	0·02	0·2

Status

Genet was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1163). The Council of Europe (1974) included genet in the list of currently used flavouring substances for which the toxicological and technological data are deemed insufficient; their use is temporarily admitted, possibly with a limitation on the active principle in the final product.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1975).

Irritation. Undiluted genet absolute was not irritating when applied to the backs of hairless mice and swine (Urbach & Forbes, 1975) but was moderately irritating when applied to intact or abraded rabbit skin for 24 hr under occlusion (Moreno, 1975). Tested at 12% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 12% in petrolatum and produced no sensitization reactions (Kligman, 1975).

Phototoxicity. No phototoxic effects were reported for undiluted genet absolute on hairless mice and swine (Urbach & Forbes, 1975).

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GERANIOL

Synonym: *trans*-3,7-Dimethyl-2,6-octadien-1-ol.
Structure: $CH_3 \cdot C(CH_3):CH \cdot [CH_2]_2 \cdot C(CH_3):CH \cdot CH_2OH$.
Description and physical properties: EOA Spec. no. 16.
Occurrence: Geraniol has been reported in over 250 essential oils (Bedoukian, 1967; Gildemeister & Hoffman, 1960).
Preparation: By fractional distillation from essential oils rich in geraniol, or synthetically from myrcene (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Uses: In public use before the 1900s. Use in fragrances in the USA amounts to about 800,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·02	0·3
Maximum	0·3	0·03	0·1	2·0

Analytical data: Gas chromatogram, RIFM nos 70–39 & 72–256; infra-red curve, RIFM nos 70–39 & 72–256.

Status

Geraniol was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) listed geraniol, giving an ADI of 5 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on geraniol.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 3·6 g/kg (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964) and as 4·8 g/kg, while the iv LD_{50} in rabbits was reported as 50 mg/kg (Yamawkai, 1962). The acute dermal LD_{50} value in rabbits was reported as >5 g/kg (Moreno, 1972).

Chronic toxicity. In two feeding studies in rats, neither 10,000 ppm fed in the diet for 16 wk nor 1000 ppm fed in the diet for 28 wk produced any effects (Hagan, Hansen, Fitzhugh, Jenner, Jones, Taylor, Long, Nelson & Brouwer, 1967).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 6% in petrolatum and produced no sensitization reactions (Greif, 1967). Hypersensitivity to geraniol may be encountered in certain individuals (Keil, 1947). Geraniol in a concentration of 10% in vaseline gave two positive reactions among 15 cases sensitive to balsams of Peru (Hjorth, 1961).

Metabolism. Geraniol is metabolized in the rabbit by ω-oxidation and by reduction of an $\alpha:\beta$-unsaturated bond (Parke, 1968). The products of geraniol metabolism are 'Hildebrandt acid' and 7-carboxy-3-methylocta-6-enoic acid. The latter acid is optically active (Williams, 1959).

Percutaneous absorption. Gerianol was not absorbed within 2 hr through the intact shaved abdominal skin of the mouse (Meyer & Meyer, 1959).

Antimicrobial properties. Antimicrobial effects have been reported for geraniol (Dabbah, Edwards & Moats, 1970).

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GERANIUM OIL ALGERIAN*

Synonym: Oil rose geranium Algerian.
Description and physical properties: EOA Spec. no. 53. The principal constituents of geranium oil Algerian are geraniol and geranyl tiglate (Poucher, 1974).
Occurrence: Found in the leaves of *Pelargonium graveolens* (Fam. Geraniaceae).
Preparation: By steam distillation of the leaves of *P. graveolens*.
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to approximately 100,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·3
Maximum	0·3	0·03	0·1	1·0

Status

Geranium oil was given GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1974) included geranium in the list of substances, spices and seasonings deemed admissible for use with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on geranium oil.

Biological data

Acute toxicity. The acute dermal LD_{50} value in guinea-pigs was reported as >5 g/kg (Moreno, 1974).

Irritation. Undiluted geranium oil Algerian was not irritating when applied to the backs of hairless mice and swine (Urbach & Forbes, 1974) but was slightly irritating when applied to intact or abraded rabbit and guinea-pig skin for 24 hr under occlusion (Moreno, 1974). Tested at 10% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1975). In closed patch tests on human skin, geranium oil in vaseline or ointment caused no primary irritation in 28 normal subjects at 20% concentration, in 30 normal subjects at 2% or in 43 subjects with dermatoses at 0·2% (Fujii, Furukawa & Suzuki, 1972).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1975).

Phototoxicity. No phototoxic effects were reported for undiluted geranium oil Algerian on hairless mice and swine (Urbach & Forbes, 1974).

Micro-organisms. Geranium oil Algerian showed *in vitro* antibacterial activity against each of five bacteria studied by Maruzzella & Henry (1958) and the vapour showed antibacterial activity against one of five bacteria studied by Maruzzella & Sicurella (1960). The bactericidal effect of geranium oil on three bacteria was studied by Abdullin (1962). Geranium oil Algerian showed *in vitro* antifungal activity against 12 of 15 fungi studied by Maruzzella & Liguori (1958) and fungistatic but not fungicidal activity was shown by geranium oil against *Trichophyton mentagrophytes* and *Candida albicans* (Korbely & Florian, 1971). The essential oil from the leaves of *P. roseum* was significantly fungistatic *in vitro* to several filamentous fungi pathogenic to man (Wollmann, Habicht, Lau & Schultz, 1973).

Cytotoxicity. The essential oil of *P. roseum* showed no cytotoxic effect in spite of the presence of significant amounts of geraniol and nerol, which are reported to be cytotoxic (Siljanowska, Stojcev, Zolotovitch & Nachev, 1969).

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* See related monographs on Geranium oil bourbon (*Fd Cosmet. Toxicol.* 1974, **12**, 883) and Geranium oil, Moroccan (*ibid* 1975, **13**, 451).

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GERANIUM OIL BOURBON

Synonyms: Oil geranium reunion; oil rose-geranium.

Description and physical properties: EOA Spec. no. 49. The chief constituents of geranium oil are geraniol and citronellol (Guenther, 1950).

Occurrence: Found in a variety or strain of the parent plant, *Pelargonium graveolens*, Ait. (Fam. Geraniaceae).

Preparation: By steam distillation of the fresh plants, harvested at the period of initial bloom.

Uses: In public use before the 1860s. Use in fragrances in the USA amounts to about 100,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·3
Maximum	0·3	0·03	0·1	1·0

Analytical data: Gas chromatogram, RIFM no. Y-42072; infra-red curve, RIFM no. Y-42072.

Status

Geranium oil was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) included geranium in the list of substances, spices and seasonings deemed admissible for use with a possible limitation of the active principle in the final product.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as >5 g/kg (Moreno, 1973). The acute dermal LD_{50} value in rabbits was reported as 2·5 g/kg (Moreno, 1973).

Irritation. Geranium oil bourbon applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1973), but applied undiluted to the backs of hairless mice, it was not irritating (Urbach & Forbes, 1972). Geranium oil reunion tested at a concentration of 10% in petrolatum produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1973). Contact with leaves of geranium has been reported to have caused a vesicular dermatitis (Anderson, 1923). Cosmetics containing oil of geranium may cause dermatitis in hypersensitive individuals (Flandin, Rabeau & Ukrainczyk, 1937; Schwartz & Peck, 1946; Schwartz, Tulipan & Peck, 1947; Sezary & Horowitz, 1937; Tulipan, 1938).

Phototoxicity. No phototoxic effects were reported for geranium oil bourbon (Urbach & Forbes, 1972).

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GERANIUM OIL MOROCCAN

Description and physical properties: EOA Spec. no. 160. The main constituents of geranium oil Moroccan are geraniol and citronellol (*Fenaroli's Handbook of Flavor Ingredients*, 1971).

Occurrence: Found in the leaves and stems of *Pelargonium roseum* wild and allied sorts (*P. graveolens* Ait and *P. graveolens* × *P. terebinthaceum*) (Fam.: Geraniaceae).

Preparation: By steam distillation of the leaves and stems of the fresh plant.

Uses: In public use since the 1920s. Use in fragrances in the USA amounts to approximately 100,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·002	0·005	0·05	0·3
Maximum	0·3	0·03	0·3	1·0

Status

Geranium oil was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1974) included geranium oil in the list of substances, spices and seasonings deemed admissible for use, with a possible limitation of the active principle in the final product.

Biological data

Acute toxicity. The acute dermal LD_{50} value in guinea-pigs was reported as >5 g/kg (Moreno, 1974).

Irritation. Undiluted geranium oil Moroccan applied to the backs of hairless mice was not irritating (Urbach & Forbes, 1974). Applied full strength to intact or abraded rabbit and guinea-pig skin for 24 hr under occlusion, it was slightly irritating (Moreno, 1974). Tested at 10% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966, modified) was carried out on 26 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Epstein, 1974).

Phototoxicity. No phototoxic effects were reported for geranium oil Moroccan (Urbach & Forbes, 1974).

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Urbach, F. & Forbes, P. D. (1974). Report to RIFM, 1 May.

GERANYL ACETATE

Synonyms: *trans*-3,7-Dimethyl-2,6-octadien-1-yl acetate; geraniol acetate.
Structure: $CH_3 \cdot C(CH_3):CH \cdot [CH_2]_2 \cdot C(CH_3):CH \cdot CH_2 \cdot OCO \cdot CH_3$.
Description and physical properties: EOA Spec. no. 11.
Occurrence: Found in over 80 essential oils including Ceylon citronella, palmarosa, lemongrass, petitgrain, neroli bigarade and others (*Fenaroli's Handbook of Flavor Ingredients*, 1971; Gildemeister & Hoffman, 1966).
Preparation: From geraniol by acetylation.
Uses: In public use before the 1920s. Use in fragrances in the USA amounts to about 100,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·2
Maximum	0·3	0·03	0·05	1·2

Status

Geranyl acetate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) listed geranyl acetate, giving an ADI of 5 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on geranyl acetate and the Joint FAO/WHO Expert Committee on Food Additives (1967) has published a monograph and specifications for the ester giving a conditional ADI of 0–5 mg/kg.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 6·33 g/kg (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964).

Chronic toxicity. In feeding studies, 1000, 2500 and 10,000 ppm fed to rats in the diet for 17 wk produced no effects (Hagan, Hansen, Fitzhugh, Jenner, Jones, Taylor, Long, Nelson & Brouwer, 1967).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Greif, 1967). Hypersensitivity has been encountered in some individuals (Keil, 1947).

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GERANYL BENZOATE

Synonym: *trans*-3,7-Dimethyl-2,6-octadien-1-yl benzoate.

Structure: $CH_3 \cdot C(CH_3):CH \cdot [CH_2]_2 \cdot C(CH_3):CH \cdot CH_2 \cdot OCO \cdot C_6H_5$.

Description and physical properties: *Givaudan Index* (1961).

Occurrence: Has been reported in ylang ylang oil (Gildemeister & Hoffman, 1960).

Preparation: From benzoyl chloride and geraniol with a pyridine catalyst (Arctander, 1969).

Uses: In public use before the 1920s. Use in fragrances in the USA amounts to about 2000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·08
Maximum	0·1	0·01	0·03	0·2

Analytical data: Gas chromatogram, RIFM no. 72–149; infra-red curve, RIFM no. 72–149.

Status

Geranyl benzoate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included geranyl benzoate in the list of artificial flavouring substances not admissible at present because of insufficient data. The *Food Chemicals Codex* (1972) has a monograph on geranyl benzoate.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. Geranyl benzoate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Moreno. 1973). Tested at 2% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1973).

Sensitization. A maximization test (Kligman. 1966) was carried out on 23 volunteers. The material was tested at a concentration of 2% in petrolatum and produced no sensitization reactions (Epstein, 1973).

References

Arctander, S. (1969). *Perfume and Flavor Chemicals (Aroma Chemicals)*. Vol. 1, no. 1434. S. Arctander, Montclair, New Jersey.

Council of Europe (1970). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List A(2), no. 82, p. 118. Strasbourg.

Epstein, W. L. (1973). Report to RIFM, 29 June.

Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. No. 2511. *Fd Technol., Champaign* **19**(2), part 2, 155.

Food Chemicals Codex (1972). 2nd ed. Prepared by the Committee on Specifications, Food Chemicals Codex, of the Committee on Food Protection. p. 338. National Academy of Sciences–National Research Council Publ. 1406, Washington, D.C.

Gildemeister, E. u. Hoffman, E. (1960). *Die Ätherischen Öle*. Vol. IIIa, p. 280. Akademie Verlag, Berlin.

Givaudan Index (1961). *Specifications of Synthetics and Isolates for Perfumery*. 2nd ed., p. 174. Givaudan-Delawanna, Inc., New York.

Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.

Moreno, O. M. (1973). Report to RIFM, 4 June.

GERANYL BUTYRATE

Synonym: *trans*-3,7-Dimethyl-2,6-octadien-1-yl butyrate.
Structure: $CH_3 \cdot C(CH_3):CH \cdot [CH_2]_2 \cdot C(CH_3):CH \cdot CH_2 \cdot OCO \cdot [CH_2]_2 \cdot CH_3$.
Description and physical properties: EOA Spec. no. 154.
Occurrence: Found in the essential oil of *Darwinia grandifolia*. It has been identified in lavender oil and in other essential oils (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: By the esterification of geraniol.
Uses: In public use before the 1920s. Use in fragrances in the USA amounts to about 2000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·12
Maximum	0·15	0·015	0·05	0·4

Analytical data: Gas chromatogram, RIFM no. 72–150; infra-red curve, RIFM no. 72–150.

Status

Geranyl butyrate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) listed geranyl butyrate, giving an ADI of 5 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on geranyl butyrate.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 10·6 g/kg (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964). The acute dermal LD_{50} in rabbits was reported as 5 g/kg (Shelanski, 1973).

Irritation. Geranyl butyrate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Shelanski, 1973). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1973).

References

Council of Europe (1970). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List A(1), Series 1, no. 275, p. 64. Strasbourg.

Fenaroli's Handbook of Flavor Ingredients (1971). Edited by T. E. Furia and N. Bellanca. p. 410. Chemical Rubber Co., Cleveland, Ohio.

Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. No. 2512. *Fd Technol., Champaign* **19**(2), part 2, 155.

Food Chemicals Codex (1972). 2nd ed. Prepared by the Committee on Specifications, Food Chemicals Codex, of the Committee on Food Protection. p. 339. National Academy of Sciences–National Research Council Publ. 1406, Washington, D.C.

Jenner, P. M., Hagan, E. C., Taylor, Jean M., Cook, E. L. & Fitzhugh, O. G. (1964). Food flavourings and compounds of related structure. I. Acute oral toxicity. *Fd Cosmet. Toxicol.* **2**, 327.

Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.

Kligman, A. M. (1973). Report to RIFM, 25 May.

Shelanski, M. V. (1973). Report to RIFM, 2 February.

GERANYL CAPROATE

Synonyms: Geranyl hexanoate; *trans*-3,7-dimethylocta-2,6-dien-1-yl *n*-hexanoate.
Structure: $CH_3 \cdot (CH_3)C{:}CH \cdot [CH_2]_2 \cdot C(CH_3){:}CH \cdot CH_2 \cdot OCO \cdot [CH_2]_4 \cdot CH_3$.
Description and physical properties: A colourless oily liquid.
Occurrence: Reported to be found in the essential oil of palmarosa and in the leaves of *Phebalium dentatum* (*Fenaroli's Handbook of Flavor Ingredients*, 1975).
Preparation. By an exchange reaction between methyl caproate and geraniol in the presence of a catalyst or sodium methylate.
Uses: In public use since the 1940s.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·002	0·05
Maximum	0·1	0·01	0·01	0·4

Analytical data: Gas chromatogram, RIFM no. 75–66; infra-red curve, RIFM no. 75–66.

Status

Geranyl caproate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) listed geranyl caproate giving an ADI of 5 mg/kg.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1975).

Irritation. Geranyl caproate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was slightly irritating (Moreno, 1975). Tested at 6% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 6% in petrolatum and produced no sensitization reactions (Kligman, 1975).

Insects. Geranyl caproate appeared as a major component of the Dufour's gland secretion of two species of Andrena bees (Bergstrom & Tengo, 1974). In a dose of 100 μg in acetone, it did not demonstrate activity mimicking the juvenile hormone when tested on the milkweed bug, *Oncopeltus fasciatus* (Brieger, 1971).

References

Bergstrom, G. & Tengo, J. (1974). Natural odoriferous compounds. IX. Farnesyl- and geranyl esters as main volatile constituent of the secretion from Dufour's gland in 6 species of *Andrena* (Hymenoptera, Apidae). *Chem. Scr.* **5**(1), 28.

Brieger, G. (1971). Juvenile hormone mimics. Structure–activity relations for *Oncopeltus fasciatus*. *J. Insect Physiol.* **17**, 2085.

Council of Europe (1974). Natural Flavouring Substances, Their Sources, and Added Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List 1, no. 317, p. 191. Strasbourg.

Fenaroli's Handbook of Flavor Ingredients (1975). 2nd Ed. Edited by T. E. Furia and N. Bellanca. Vol. II, p. 218. CRC Press, Cleveland, Ohio.

Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. No. 2515. *Fd Technol., Champaign* **19**(2), part 2, 155.

Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.

Kligman, A. M. (1975). Report to RIFM, 16 June.

Kligman, A. M. & Epstein, W. (1975). Updating the maximization test for identifying contact allergens. *Contact Dermatitis* **1**, 231.

Moreno, O. M. (1975). Report to RIFM, 25 June.

GERANYL CROTONATE

Synonyms: Geranyl-2-butenoate; *trans*-3,7-dimethyl-2,6-octadien-l-yl 2-butenoate.
Structure: $CH_3 \cdot C(CH_3):CH \cdot [CH_2]_2 \cdot C(CH_3):CH \cdot CH_2 \cdot OCO \cdot CH:CH \cdot CH_3$.
Description and physical properties: A colourless liquid with a warm-herbaceous, sweet odour (Arctander, 1969).
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By esterification of geraniol with crotonyl chloride.
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to over 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·2
Maximum	0·2	0·02	0·05	1·0

Analytical data: Gas chromatogram, RIFM no. 72–65; infra-red curve, RIFM no. 72–65.

Status

Geranyl crotonate is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1970), nor in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. Geranyl crotonate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1973). Tested at 10% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1972).

References

Arctander, S. (1969). *Perfume and Flavor Chemicals (Aroma Chemicals)*. Vol. 1, no. 1443. S. Arctander, Montclair, New Jersey.

Council of Europe (1970). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. Strasbourg.

Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. *Fd. Technol., Champaign* **19** (2), part 2, 155.

Food Chemicals Codex (1972). 2nd ed. Prepared by the Committee on Specifications, Food Chemicals Codex, of the Committee on Food Protection. National Academy of Sciences–National Research Council Publ. 1406, Washington, D.C.

Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.

Kligman, A. M. (1972). Report to RIFM, 23 August.

Moreno, O. M. (1973). Report to RIFM, 6 July.

GERANYL FORMATE

Synonym: *trans*-3,7-Dimethyl-2,6-octadien-1-yl formate.
Structure: $CH_3 \cdot C(CH_3):CH \cdot [CH_2]_2 \cdot C(CH_3):CH \cdot CH_2 \cdot OCO \cdot H$.
Description and physical properties: EOA Spec. no. 162.
Occurrence: Found in geranium oil, the oil of *Ledum palustre* and a dozen essential oils (*Fenaroli's Handbook of Flavor Ingredients*, 1971; Gildemeister & Hoffman, 1960).
Preparation: By the esterification of geraniol with formic acetic anhydride.
Uses: In public use before the 1920s. Use in fragrances in the USA amounts to about 10,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·1
Maximum	0·1	0·01	0·05	0·2

Status

Geranyl formate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) listed geranyl formate, giving an ADI of 5 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on geranyl formate.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as >6 g/kg (Weir, 1971). The acute dermal LD_{50} value in rabbits was reported as >5 g/kg (Weir, 1971).

Irritation. Geranyl formate produced slight conjunctival irritation, which disappeared within 72 hr in the rabbit eye (Weir, 1971). Applied full strength to intact or abraded rabbit skin for 24 hr under occlusion, it was not irritating (Weir, 1971). Tested at a concentration of 2% in petrolatum, it produced a mild irritation after a 48-hr closed-patch test on human subjects (Kligman, 1971).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 2% in petrolatum and produced no sensitization reactions (Kligman, 1971).

Percutaneous absorption. Geranyl formate was rapidly absorbed through the intact shaved abdominal skin of the mouse (Meyer & Meyer, 1959).

References

Council of Europe (1970). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List A(1), Series 1, no. 344, p. 67. Strasbourg.

Fenaroli's Handbook of Flavor Ingredients (1971). Edited by T. E. Furia and N. Bellanca. p. 411. Chemical Rubber Co., Cleveland, Ohio.

Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. No. 2514. *Fd Technol., Champaign* **19**(2), part 2, 155.

Food Chemicals Codex (1972). 2nd ed. Prepared by the Committee on Specifications, Food Chemicals Codex, of the Committee on Food Protection. p. 340. National Academy of Sciences–National Research Council Publ. 1406, Washington, D.C.

Gildemeister, E. u. Hoffman, F. (1960). *Die Ätherischen Öle*. Vol. IIIa, p. 242. Akademie Verlag, Berlin.

Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.

Kligman, A. M. (1971). Report to RIFM, 2 April.

Meyer, Fr. & Meyer, E. (1959). Percutaneous absorption of essential oils and their constituents. *Arzneimittel-Forsch.* **9**, 516.

Weir, R. J. (1971). Report to RIFM, 12 April.

GERANYL ISOBUTYRATE

Synonym: *trans*-3,7-Dimethyl-2,6-octadienyl isobutyrate.

Structure:

$CH_3 \cdot C(CH_3):CH \cdot [CH_2]_2 \cdot C(CH_3):CH \cdot CH_2 \cdot OCO \cdot CH(CH_3)_2$.

Description and physical properties: A colourless oily liquid.

Occurrence: Reported to be found in the essential oils of Japanese hops and valerian (*Fenaroli's Handbook of Flavor Ingredients*, 1971).

Preparation: From geraniol and isobutyric acid or by any other suitable means.

Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·01	0·12
Maximum	0·15	0·015	0·05	0·6

Analytical data: Gas chromatogram, RIFM no. 72-151; infra-red curve, RIFM no. 72-151.

Status

Geranyl isobutyrate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included geranyl isobutyrate, at a level of 15 ppm, in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Shelanski, 1973).

Irritation. Geranyl isobutyrate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was mildly irritating (Shelanski, 1973). Tested at 10% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966, modified) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1973).

References

Council of Europe (1974). Natural Flavouring Substances, Their Sources, and Added Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List 1, no. 306, p. 189, Strasbourg.

Fenaroli's Handbook of Flavor Ingredients (1971). Edited by T. E. Furia & N. Bellanca. p. 412. Chemical Rubber Co., Cleveland, Ohio.

Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. No. 2513. *Fd Technol., Champaign* **19**(2), part 2, 155.

Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.

Kligman, A. M. (1973). Report to RIFM, 12 February.

Shelanski, M. V. (1973). Report to RIFM, 30 January.

GERANYL ISOVALERATE

Synonym: *trans*-3,7-Dimethyl-2,6-octadienyl isopentanoate.
Structure: $CH_3 \cdot C(CH_3):CH \cdot [CH_2]_2 \cdot C(CH_3):CH \cdot CH_2 \cdot OCO \cdot CH_2 \cdot CH(CH_3) \cdot CH_3$.
Description and physical properties: A colourless oily liquid.
Occurrence: Reported to be found in *Eucalyptus citriodora* Hook (*Fenaroli's Handbook of Flavor Ingredients*, 1975).
Preparation: By direct esterification of geraniol with isovaleric acid under azeotropic conditions (Arctander, 1969).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to approximately 6000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·08
Maximum	0·05	0·005	0·02	0·3

Analytical data: Gas chromatogram, RIFM no. 75–67; infra-red curve, RIFM no. 75–67.

Status

Geranyl isovalerate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) listed geranyl isovalerate, giving an ADI of 5 mg/kg.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Levenstein, 1975).

Irritation. Geranyl isovalerate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was mildly irritating (Levenstein. 1975). Tested at 2% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein. 1975).

Sensitization. A maximization test (Kligman. 1966; Kligman & Epstein. 1975) was carried out on 24 volunteers. The material was tested at a concentration of 2% in petrolatum and produced no sensitization reactions (Epstein. 1975).

References

Arctander, S. (1969). *Perfume and Flavor Chemicals* (*Aroma Chemicals*), Vol. 1, no. 1461. S. Arctander, Montclair, New Jersey.

Council of Europe (1974). Natural Flavouring Substances, Their Sources, and Added Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List 1, no. 448, p. 217. Strasbourg.

Epstein, W. L. (1975). Report to RIFM. 15 August.

Fenaroli's Handbook of Flavor Ingredients (1975). 2nd Ed. Edited by T. E. Furia and N. Bellanca. Vol. II. p. 219. CRC Press. Cleveland, Ohio.

Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. No. 2518. *Fd Technol., Champaign* **19**(2), part 2, 155.

Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.

Kligman, A. M. & Epstein. W. (1975). Updating the maximization test for identifying contact allergens. *Contact Dermatitis* **1**, 231.

Levenstein, I. (1975). Report to RIFM, 16 May.

GERANYL NITRILE

Synonyms: Geranonitrile; 3,7-dimethyl-2,6-octadienenitrile.
Structure: $CH_3 \cdot C(CH_3):CH \cdot [CH_2]_2 \cdot C(CH_3):CH \cdot CN$.
Description and physical properties: A colourless or very pale yellow liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: From geranialoxime with acetic anhydride (Arctander, 1969).
Uses: In public use since the 1940s.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·1
Maximum	0·15	0·015	0·05	1·2

Analytical data: Gas chromatogram. RIFM no. 74-203; infra-red curve, RIFM no. 74-203.

Status

Geranyl nitrile is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974) or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 3·1 g/kg and the acute dermal LD_{50} value in rabbits as 4·3 g/kg (Wohl, 1974).

Irritation. Geranyl nitrile applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Wohl, 1974). Tested at 12% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 12% in petrolatum and produced no sensitization reactions (Kligman, 1974).

Metabolism. The toxicity of organic cyanides appears to depend, in almost every case, on whether they can be metabolized in the body to the free cyanide ion, CN^-, and on the rate and extent of this conversion and the rate of detoxication of cyanide to thiocyanate. Alkyl cyanides appear to be metabolized in the body chiefly by formation of hydrogen cyanide plus the acid with one less carbon atom (Williams, 1959).

References

Arctander, S. (1969). *Perfume and Flavor Chemicals (Aroma Chemicals)*. Vol. 1, no. 1451. S. Arctander, Montclair, New Jersey.

Council of Europe (1974). Natural Flavouring Substances, Their Sources, and Added Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. Strasbourg.

Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. *Fd Technol., Champaign* **19**(2), part 2, 155.

Food Chemicals Codex (1972). 2nd Ed. Prepared by the Committee on Specifications, Food Chemicals Codex, of the Committee on Food Protection. National Academy of Sciences–National Research Council Publ. 1406, Washington, D.C.

Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.

Kligman, A. M. (1974). Report to RIFM, 21 August.

Kligman, A. M. & Epstein, W. (1975). Updating the maximization test for identifying contact allergens. *Contact Dermatitis* **1**, 231.

Williams, R. T. (1959). *Detoxication Mechanisms. The Metabolism and Detoxication of Drugs, Toxic Substances and Other Organic Compounds*. 2nd Ed. pp. 390–409. Chapman & Hall Ltd., London.

Wohl, A. J. (1974). Report to RIFM, 19 August.

GERANYL PHENYLACETATE

Synonym: *trans*-3,7-Dimethyl-2,6-octadien-1-yl phenyl acetate.
Structure: $CH_3 \cdot C(CH_3):CH \cdot [CH_2]_2 \cdot C(CH_3):CH \cdot CH_2 \cdot OCO \cdot CH_2 \cdot C_6H_5$.
Description and physical properties: EOA Spec. no. 280.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By the esterification of geraniol with phenylacetyl chloride.
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 5000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·01	0·08
Maximum	0·15	0·015	0·1	0·4

Analytical data: Gas chromatogram, RIFM no. 72–153; infra-red curve, RIFM no. 72–153.

Status

Geranyl phenylacetate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included geranyl phenylacetate in the list of admissible artificial flavouring substances at a level of 5 ppm (except for chewing gum). The *Food Chemicals Codex* (1972) has a monograph on geranyl phenylacetate.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Russell, 1973).

Irritation. Geranyl phenylacetate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Russell, 1973). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1973).

References

Council of Europe (1970). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List A(1), Series 1, no. 232, p. 61. Strasbourg.

Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. No. 2516. *Fd Technol., Champaign* **19**(2), part 2, 155.

Food Chemicals Codex (1972). 2nd ed. Prepared by the Committee on Specifications, Food Chemicals Codex, of the Committee on Food Protection. p. 341. National Academy of Sciences–National Research Council Publ. 1406, Washington, D.C.

Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.

Kligman, A. M. (1973). Report to RIFM, 27 July.

Russell, T. J. (1973). Report to RIFM, 6 March.

GERANYL PROPIONATE

Synonym: *trans*-3,7-Dimethyl-2,6-octadien-l-yl propionate.
Structure: $CH_3 \cdot C(CH_3):CH \cdot [CH_2]_2 \cdot C(CH_3):CH \cdot CH_2 \cdot OCO \cdot CH_2 \cdot CH_3$.
Description and physical properties: EOA Spec. no. 144.
Occurrence: Found in *Fortunella margarita* (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: By the esterification of geraniol with propionic anhydride.
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to about 5000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·1
Maximum	0·15	0·015	0·05	0·4

Analytical data: Gas chromatogram, RIFM no. 72–155; infra-red curve, RIFM no. 72–155.

Status

Geranyl propionate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) listed geranyl propionate, giving an ADI of 1 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on geranyl propionate.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Russell, 1973).

Irritation. Geranyl propionate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Russell, 1973). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1973).

Percutaneous absorption. Geranyl propionate was rapidly absorbed through the intaet shaved abdominal skin of the mouse (Meyer & Meyer, 1959).

References

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Fenaroli's Handbook of Flavor Ingredients (1971). Edited by T. E. Furia and N. Bellanca. p. 413. Chemical Rubber Co., Cleveland, Ohio.

Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. No. 2517. *Fd Technol., Champaign* **19**(2), part 2, 155.

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Meyer, F. & Meyer, E. (1959). Percutaneous absorption of essential oils and their constituents. *Arzneimittel-Forsch.* **9**, 516.

Russell, T. J. (1973). Report to RIFM, 6 March.

GERANYL TIGLATE

Synonym: *trans*-3,7-Dimethyl-2,6-octadien-1-yl *cis*-α-β-dimethyl acrylate.
Structure: $CH_3 \cdot C(CH_3):CH \cdot [CH_2]_2 \cdot C(CH_3):CH \cdot CH_2 \cdot OCO \cdot C(:CH \cdot CH_3) \cdot CH_3$.
Description and physical properties: A colourless oily liquid with a geranium, fruit-like odour (Arctander, 1969).
Occurrence: Has been found in geranium oil.
Preparation: From geraniol and tiglyl chloride in an inert volatile solvent using a pyridine-type catalyst (Arctander, 1969).
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to about 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·2
Maximum	0·15	0·015	0·05	0·6

Analytical data: Gas chromatogram, RIFM no. 72–154; infra-red curve, RIFM no. 72–154.

Status

Geranyl tiglate is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1970), nor in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Shelanski, 1972).

Irritation. Geranyl tiglate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was mildly irritating (Shelanski, 1972). Tested at 6% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 6% in petrolatum and produced no sensitization reactions (Kligman, 1972).

References

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Council of Europe (1970). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. Strasbourg.
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Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.
Kligman, A. M. (1972). Report to RIFM, 19 October.
Shelanski, M. V. (1972). Report to RIFM, 14 July.

GINGER OIL

Description and physical properties: *Food Chemicals Codex* (1972). The principal constituent of ginger oil is zingiberene (Guenther, 1952).

Occurrence: Found in the plant *Zingiber officinale* Roscoe (Fam. Zingiberaceae) (Guenther, 1952).

Preparation: By steam distillation of the dried ground rhizomes (*Fenaroli's Handbook of Flavor Ingredients*, 1971).

Uses: In public use before the 1900s. Use in fragrances in the USA amounts to less than 2000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·08
Maximum	0·1	0·01	0·03	0·4

Analytical data: Gas chromatogram, RIFM no. 72–156; infra-red curve, RIFM no. 72–156.

Status

Ginger oil was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) included ginger oil in the list of substances, spices and seasonings deemed admissible for use with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on ginger oil.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Shelanski, 1972).

Irritation. Undiluted ginger oil applied to the backs of hairless mice was not irritating (Urbach & Forbes, 1972). Applied full strength to intact or abraded rabbit skin for 24 hr under occlusion, it was moderately irritating (Shelanski, 1972). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1972). Toilet preparations containing oil of the rhizomes of ginger may produce dermatitis in hypersensitive individuals (Tulipan, 1938).

Phototoxicity. Low-level phototoxic effects reported for ginger oil are not considered significant (Urbach & Forbes, 1972).

References

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Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.

Kligman, A. M. (1972). Report to RIFM, 13 October.

Shelanski, M. V. (1972). Report to RIFM, 14 July.

Tulipan, L. (1938). Cosmetic irritants. *Archs Derm. Syph.* **38**, 906.

Urbach, F. & Forbes, P. D. (1972). Report to RIFM, 26 July.

GRAPEFRUIT OIL EXPRESSED

Description and physical properties: EOA Spec. no. 30. The main constituent of grapefruit oil expressed is limonene (Gildemeister & Hoffman, 1959; Guenther, 1949).
Occurrence: Found in the fresh peel of the fruit *Citrus paradisi* Macfayden (Fam. Rutaceae).
Preparation: By expression of the fresh peel of the fruit.
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 18,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·05	0·005	0·03	0·5
Maximum	0·3	0·03	0·15	1·0

Analytical data: Gas chromatogram, RIFM nos 72-24 and 73-21; infra-red curve, RIFM nos 72-24 and 73-21.

Status

Grapefruit oil was granted GRAS status by FEMA (1965) and is approved by the FDA as GRAS for food use. The Council of Europe (1970) included grapefruit oil in the list of fruits and vegetables or parts thereof, parts for which no restriction is proposed. The *Food Chemicals Codex* (1972) has a monograph on grapefruit oil.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. Undiluted grapefruit oil applied to the backs of hairless mice was not irritating (Urbach & Forbes, 1972). Applied full strength to intact or abraded rabbit skin for 24 hr under occlusion it was slightly irritating (Moreno, 1973), and tested at 10% in petrolatum, it produced no irritation after a 48-hr closed-patch test in 24 human subjects (Kligman, 1971). A patch test using full strength grapefruit oil for 24 hr produced no reactions in 26 subjects (Katz, 1946).

Sensitization. A maximization test (Kligman, 1966) was carried out on 24 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1971). A repeated-insult patch test using a 4% concentration in petrolatum did not sensitize any of 40 subjects (Thomas, 1971).

Phototoxicity. No phototoxic effects were reported for grapefruit oil (Urbach & Forbes, 1972).

Additional published data

The presence and identity of terpenes, psoralens and coumarins in grapefruit oil has been reported (Kesterson, Hendrickson & Braddock, 1971). Antibacterial properties have been reported for grapefruit oil (Dabbah, Edwards & Moats, 1970), and the oil has been reported to promote tumour formation on the skins of mice treated with the primary carcinogen 7,12-dimethylbenz[*a*]anthracene (Roe & Field, 1965).

References

Council of Europe (1970). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List N(1), Series 1(a), no. 140, p. 18. Strasbourg.

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Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. No. 2530. *Fd Technol., Champaign* **19** (2), part 2, 155.

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Gildemeister, E. u. Hoffman, F. (1959). *Die Ätherischen Öle*. Vol. V. p. 603. Akademie Verlag, Berlin.

Guenther, E. (1949). *The Essential Oils*. Vol. III. p. 347. D. Van Nostrand, Inc., Princeton, New Jersey.

Katz, A. (1946). *Spice Mill* **69** (July), 46.

Kesterson, J. W., Hendrickson, R. & Braddock, R. J. (1971). Florida Citrus Oils. Agricultural Experiment Stations. Bulletin 749 (technical), University of Florida, Gainesville.

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Kligman, A. M. (1971). Report to RIFM, 23 March.

Moreno, O. M. (1973). Report to RIFM, 18 July.

Roe, F. J. C. & Field, Winifred E. H. (1965). Chronic toxicity of essential oils and certain other products of natural origin. *Fd Cosmet. Toxicol.* **3,** 311.

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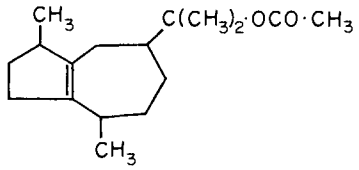
GUAIACWOOD ACETATE

Synonyms: Guaiac acetate; guaiol acetate.
Structure: Major component—



Description and physical properties: EOA Spec. no. 221.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By the acetylation of guaiacwood oil.
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to about 30,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·01	0·2
Maximum	0·2	0·02	0·05	0·8

Analytical data: Gas chromatogram, RIFM no. 72–157; infra-red curve, RIFM no. 72–157.

Status

Guaiacwood acetate is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included guaiacwood acetate (guaiyl acetate) in the list of admissible artificial flavouring substances at a level of 1 ppm.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. Guaiacwood acetate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Moreno, 1973). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1973).

References

Council of Europe (1970). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List A(1), Series 1, no. 554, p. 79. Strasbourg.
Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.
Kligman, A. M. (1973). Report to RIFM, 9 May.
Moreno, O. M. (1973). Report to RIFM, 1 February.

GUAIAC WOOD OIL

Description and physical properties: EOA Spec. no. 63. The main constituent of guaiac wood oil is guaiol (*Fenaroli's Handbook of Flavor Ingredients*, 1971).

Occurrence: Found in the tree *Bulnesia sarmienti* Lor. (Fam. Zygophyllaceae).

Preparation: By steam distillation of the chipped wood or sawdust of *Bulnesia sarmienti* Lor.

Uses: In public use before the 1900s. Use in fragrances in the USA amounts to about 50,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·01	0·3
Maximum	0·3	0·03	0·05	0·8

Status

Guaiac wood oil was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1163). The Council of Europe (1970) included guaiac wood in the list of currently used flavouring substances temporarily admitted for use with a possible limitation on the active principle in the final product.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1973).

Short-term toxicity. In a 90-day feeding study in rats the concentration without effect was 31·8 mg/kg (Bär & Griepentrog, 1967).

Irritation. Undiluted guaiac wood oil applied to the backs of hairless mice was not irritating (Urbach & Forbes, 1973). Applied full strength to intact or abraded rabbit skin for 24 hr under occlusion, it was moderately irritating (Moreno, 1973). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1971).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1971).

Phototoxicity. No phototoxic effects were reported for guaiac wood oil (Urbach & Forbes, 1973).

References

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Council of Europe (1970). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List N(1), Series 2, no. 97, p. 16. Strasbourg.

Fenaroli's Handbook of Flavor Ingredients (1971). Edited by T. E. Furia and N. Bellanca. p. 127. Chemical Rubber Co., Cleveland, Ohio.

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Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.

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Moreno, O. M. (1973). Report to RIFM, 5 July.

Urbach, F. & Forbes, P. D. (1973). Report to RIFM, 18 July.

GURJUN BALSAM*

Description and physical properties: *Merck Index* (1968). Gurjon balsam, an oleoresin exuded from trees of the Dipterocarpus species, is composed almost entirely of the essential oil gurjon balsam oil (60–80%) and gurjunic acid resin (Arctander, 1960; *Merck Index*, 1968). The overall composition of gurjon balsam and/or oil from various sources has been reported by Dutt (1961) studying *D. turbinatus*, by Diaz, Ehret, Ourisson, Palmade, Patil, Pesnelle & Streith (1966) studying Vietnamese Dipterocarpus, by Baslas (1968) studying *D. griffithi*, by Bisset, Diaz, Ehret, Ourisson, Palmade, Patil, Pesnelle & Streith (1966) and by Vrkoc, Krepinsky, Herout, & Sorm (1964). Specific components studied include γ-gurjunene (Ehret & Ourisson, 1969), sesquiterpenes (Wenninger, Yates & Dolinsky, 1966), sesquiterpenes and triterpenoids from *D. pilosus* (Gupta & Dev, 1971a,b), and apitonene-1 (Kitao & Ikeda, 1967) and terpenoids (Ikeda & Kitao, 1972) from *D. gracilis*.
Occurrence: As a pathological exudation of the wood of several species of Dipterocarpus (Fam. Dipterocarpaceae) (Guenther. 1952).
Preparation: By the collection of the exuding balsam of the wood of several species of Dipterocarpus (Guenther. 1952).
Uses: In public use before the 1920s. Use in fragrances in the USA amounts to approximately 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·1
Maximum	0·3	0·03	0·1	1·2

Analytical data: Gas chromatogram. RIFM no. 75–68; infra-red curve, RIFM no. 75–68.

Status

Gurjun balsam is not included in the listings of the FDA. FEMA (1965) or the Council of Europe (1974) or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1975).

Irritation. Gurjun balsam applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1975). Tested at 12% in petrolatum. it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1975).

Sensitization. A maximization test (Kligman. 1966; Kligman & Epstein. 1975) was carried out on 19 volunteers. The material was tested at a concentration of 12% in petrolatum and produced no sensitization reactions (Epstein, 1975).

Additional published data

In India, gurjun balsam and/or gurjun balsam oil have been used to treat a variety of diseases (Dutt, 1961).

References

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Bisset, N. G., Diaz, M. A., Ehret, C., Ourisson, G., Palmade, M., Patil, F., Pesnelle, P. & Streith, J. (1966). Chemotaxonomic studies in the Dipterocarpaceae. II. Constituents of the genus *Dipterocarpus*. A chemotaxonomic classification. *Phytochemistry* **5**, 865.

Council of Europe (1974). Natural Flavouring Substances. Their Sources. and Added Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. Strasbourg.

Diaz, M. A., Ehret, C., Ourisson, G., Palmade, M., Patil, F., Pesnelle, P. & Streith, J. (1966). Constituents of resins from Vietnamese *Dipterocarpus*. *Vietnamica Chim. Acta* p. 79.

Dutt. S. (1961). Indian oleo-resins and their essential oils. Part V. Liquid oleo-resins or balsams of Indian origin. *Indian Oil Soap J.* **27**(3). 53.

Ehret, C. & Ourisson, G. (1969). Structure and configuration of γ-gurjunene. Isomerization of γ-gurjunene. *Tetrahedron* **25**, 1785.

Epstein, W. L. (1975). Report to RIFM. 15 August.

*See following monograph on gurjun oil.

Flavouring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. *Fd Technol., Champaign* **19**(2), part 2. 155.

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Gupta, A. S. & Dev, S. (1971a). Sesquiterpenes. XLVI. Sesquiterpenes from the oleoresin of *Dipterocarpus pilosus*: humulene epoxide-III, caryophyllenol-I and caryophyllenol-II. *Tetrahedron* **27,** 635.

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GURJUN OIL*

Synonym: Gurjun balsam oil.

Description and physical properties: A yellow somewhat viscous liquid. The principal constituents of gurjun balsam oil are α- and β-gurjunene (Guenther, 1952).

Occurrence: As a pathological exudation of the wood of several species of Dipterocarpus (Fam. Dipterocarpaceae) (Guenther, 1952).

Preparation: By steam distillation of the balsam (Guenther, 1952).

Uses: In public use before the 1920s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·1
Maximum	0·3	0·03	0·1	0·8

Analytical data: Gas chromatogram, RIFM no. 74-205; infra-red curve, RIFM no. 74-205.

Status

Gurjun oil is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974) or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1974).

Irritation. Undiluted gurjun oil was not irritating when applied to the backs of hairless mice and swine (Urbach & Forbes, 1974) or to intact or abraded rabbit skin for 24 hr under occlusion (Moreno, 1974). Tested at 8% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 24 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Epstein, 1974).

Phototoxicity. No phototoxic effects were reported for undiluted gurjun oil on hairless mice and swine (Urbach & Forbes, 1974).

Additional published data

In India, gurjun balsam and/or gurjun balsam oil have been used to treat a variety of diseases (Dutt, 1961).

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*See preceding monograph on gurjun balsam.

HELIOTROPIN

Synonyms: Piperonal; 3,4-methylenedioxybenzaldehyde.
Structure: $O \cdot CH_2 \cdot O \cdot C_6H_3 \cdot CHO$.
Description and physical properties: EOA Spec. no. 6.
Occurrence: Reported to be found in a score of essential oils, including *Robina pseudoacacia* and *Eryngium poterium*, in the oils of *Spirea ulmaria* and the leaves of *Doryphora sassafras*. Also reported to be found in Tahitian vanilla, camphor wood oil and violet flowers concrete and absolute (*Fenaroli's Handbook of Flavor Ingredients*, 1971; Gildemeister & Hoffman, 1966).
Preparation: By the oxidation of isosafrole (Bedoukian, 1967).
Uses: In public use since the 1880s. Use in fragrances in the USA amounts to approximately 150,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·003	0·015	0·3
Maximum	0·3	0·025	0·07	0·8

Status

Heliotropin was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) listed heliotropin giving an ADI of 2·5 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on heliotropin and the Joint FAO/WHO Expert Committee on Food Additives (1967) has published a monograph and specifications for heliotropin giving an unconditional ADI of 0–2·5 mg/kg.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 2·7 g/kg (2·35–3·10 g/kg) (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964). The acute ip LD_{50} in mice was reported as >500 mg/kg (Fassett, 1963).

Subacute and long-term toxicity. In feeding studies, neither 1000 ppm fed to rats in the diet for 28 wk nor 10,000 ppm fed to rats in the diet for 15 wk had any effects (Hagan, Hansen, Fitzhugh, Jenner, Jones, Taylor, Long, Nelson & Brouwer, 1967). Groups of 20 male and 20 female rats were fed diets containing 0·1 or 0·5% heliotropin for 2 yr without any specific adverse effect (Bär & Griepentrog, 1967).

Irritation. A patch test using heliotropin full strength for 24 hr produced one irritation reaction in 20 subjects (Katz, 1946).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 6% in petrolatum and produced no sensitization reactions (Greif, 1967).

Metabolism. In the animal body heliotropin undergoes the expected metabolic reaction involving oxidation to the corresponding acid (Williams, 1959).

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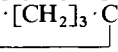
2-*n*-HEPTYL CYCLOPENTANONE

Synonym: α-Heptyl cyclopentanone.

Structure: 

Description and physical properties: *Givaudan Index* (1961).

Occurrence: Has apparently not been reported to occur in nature.

Preparation: By catalytic reduction of heptylidene cyclopentanone (Arctander, 1969).

Uses: In public use since the 1940s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·2
Maximum	0·1	0·01	0·03	1·0

Analytical data: Gas chromatogram, RIFM no. 72-147; infra-red curve, RIFM no. 72-147.

Status

2-*n*-Heptyl cyclopentanone is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974), nor in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as >5 g/kg (Shelanski, 1973). The acute dermal LD_{50} value in rabbits was reported as 5 g/kg (Shelanski, 1973).

Irritation. 2-*n*-Heptyl cyclopentanone applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was irritating (Shelanski, 1973). Tested at 10% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966, modified) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1973).

References

Arctander, S. (1969). *Perfume and Flavor Chemicals (Aroma Chemicals)*. Vol. I, no. 1534. S. Arctander, Montclair, New Jersey.

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Shelanski, M. V. (1973). Report to RIFM, 30 January.

HEXADECANOLIDE

Synonyms: Dihydroambrettolide; cyclohexadecanolide; 16-hydroxyhexadecanoic acid lactone.

Structure: $CH_2 \cdot [CH_2]_{14} \cdot C{:}O$ (O bridging the ring)

Description and physical properties: An opaque crystalline mass.

Occurrence: Has apparently not been reported to occur in nature.

Preparation: By the persulphuric acid (or other peracid) oxidation of cyclohexadecanone.

Uses: In public use since the 1950s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·001	–	0·001	0·04
Maximum	0·01	–	0·003	0·4

Analytical data: Gas chromatogram, RIFM no. 74-206; infra-red curve, RIFM no. 74-206.

Status

Hexadecanolide is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974), nor in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1974).

Irritation. Hexadecanolide applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1974). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1974).

Sensitization. A maximization test (Kligman, 1966, modified) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1974).

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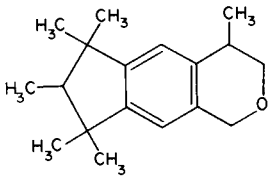
1,3,4,6,7,8-HEXAHYDRO-4,6,6,7,8,8-HEXAMETHYL-CYCLOPENTA-γ-2-BENZOPYRAN

Synonym: Galoxolide.
Structure:



Description and physical properties: Almost colourless viscous liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: From pentamethylindan and propylene oxide through the Friedel-Crafts reaction (Bedoukian, 1967).
Uses: In public use since the 1960s. Use in fragrances in the USA exceeds 50,000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·15	0·015	0·10	0·3
Maximum	0·5	0·05	0·15	2·5

Analytical data: Gas chromatogram, RIFM no. 74–202; infra-red curve, RIFM no. 74–202.

Status

1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-γ-2-benzopyran is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974), or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1975).

Irritation. When applied full strength to intact or abraded rabbit skin for 24 hr under occlusion, the material was moderately irritating (Moreno, 1975). Tested at 15% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 19 volunteers. The material was tested at a concentration of 15% in petrolatum and produced no sensitization reactions (Epstein, 1974).

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Moreno, O. M. (1975). Report to RIFM. 11 April.

HEXEN-2-AL

Synonyms: *trans*-2-Hexenal; β-propyl acrolein.

Structure: $CH_3 \cdot [CH_2]_2 \cdot C(H):C \cdot CHO$.

Description and physical properties: A colourless liquid.

Occurrence: Reported to be found in the distillation waters of numerous plants; also identified among the constituents of a dozen essential oils (Gildemeister & Hoffman, 1963).

Preparation: From interaction of butyraldehyde acetal with vinyl ether followed by hydrolysis or by any other suitable means.

Uses: In public use since the 1950s. Use in fragrances in the USA amounts to approximately 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·003	0·04
Maximum	0·1	0·01	0·02	0·4

Analytical data: Gas chromatogram, RIFM no. 72-159; infra-red curve, RIFM no. 72-159.

Status

Hexen-2-al was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included hexen-2-al in the list of artificial flavouring substances that may be added temporarily to foodstuffs without hazard to public health.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 0·85 g/kg (0·65–1·05 g/kg) (Moreno, 1973). The oral LD_{50} values for *trans*-2-hexenal were reported as 780–1130 and 1550–1750 mg/kg in rats and mice, respectively, and the ip LD_{50} values were reported as 100–200 mg/kg in both species (Gaunt, Colley, Wright, Creasey, Grasso & Gangolli, 1971). The acute dermal LD_{50} value in rabbits was reported as 0·60 g/kg (0·37–0·83 g/kg) (Moreno, 1973).

Subacute toxicity. *trans*-2-Hexenal was fed to rats at dietary levels of 0 (control), 260, 640, 1600 or 4000 ppm for 13 wk (Gaunt *et al.* 1971). The g given 4000 ppm showed a slight (but not statisti significant) reduction in growth rate associated a reduced intake of a diet shown to be less palat than the control diet. The treatments had no e on haematology or serum and urine analyses. only consistent abnormality was an increase in ovary weights of all treated female rats, but this unaccompanied by any change in ovarian histol This effect was not dose-related and in further stu (Gaunt *et al.* 1971), in which female rats were *trans*-2-hexenal at 4000 ppm of the diet for 13 wk female rabbits were given daily oral doses of 200 kg for 13 wk, no effect on ovary weight was fo A mild anaemia, increased stomach weights and a gastric ulceration were seen in the treated rabbits it was considered likely that these effects were to the high local concentrations of the test compo resulting from oral intubation. The no-untoward-e level for *trans*-2-hexenal in the rat study 1600 ppm of the diet (approximately 80 mg/kg/

Irritation. Hexen-2-al applied full strength to in or abraded rabbit skin for 24 hr under occlusion moderately irritating (Moreno, 1973). Tested at in petrolatum, it produced no irritation after a 4 closed-patch test on human subjects (Kligman, 1

Sensitization. A maximization test (Kligman, 1 modified) was carried out on 25 volunteers. material was tested at a concentration of 4% in p latum and produced no sensitization reactions (K man, 1973).

References

Council of Europe (1974). Natural Flavouring Substa Their Sources, and Added Artificial Flavouring stances. Partial Agreement in the Social and P Health Field. List 2, no. 2007, p. 281. Strasbourg.

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Gaunt, I. F., Colley, J., Wright, M., Creasey, Mar Grasso, P. & Gangolli, S. D. (1971). Acute and s term toxicity studies on *trans*-2-hexenal. *Fd Cosmet. ocol.*, **9**, 775.

Gildemeister, E. u. Hoffman, F. (1963). *Die Ätherischer* Vol. IIIc. p. 38. Akademie Verlag, Berlin.

Kligman, A. M. (1966). The identification of co allergens by human assay. III. The maximization A procedure for screening and rating contact sensit *J. invest. Derm.* **47**, 393.

Kligman, A. M. (1973). Report to RIFM, 9 October.

Moreno, O. M. (1973). Report to RIFM, 23 July.

cis-3-HEXENOL

Synonyms: *cis*-3-Hexen-1-ol; β-γ-hexenol; leaf alcohol.

Structure: $CH_3 \cdot CH_2 \cdot \underset{H}{C}:\underset{H}{C} \cdot [CH_2]_2 \cdot OH$.

Description and physical properties: EOA Spec. no. 270.

Occurrence: Reported to be found in several essential oils and in many fruit juices (Bedoukian, 1967; *Fenaroli's Handbook of Flavor Ingredients*, 1971).

Preparation: By the reaction of butyne-1 with ethylene oxide and subsequent selective reduction to the *cis* isomer (Bedoukian, 1967).

Uses: In public use since the 1940s. Use in fragrances in the USA amounts to less than 20,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·001	0·001	0·08
Maximum	0·1	0·01	0·02	0·4

Analytical data: Gas chromatogram, RIFM no. 72–160; infra-red curve, RIFM no. 72–160.

Status

cis-3-Hexenol was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included *cis*-3-hexenol (hex-3-en-1-ol) in the list of temporarily admissible artificial flavouring substances.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 4·70 g/kg (3·82–5·58 g/kg) (Moreno, 1973). The acute dermal LD_{50} value in rabbits was reported as >5 g/kg (Moreno, 1973).

Short-term toxicity. In a 90-day study, rats were given *cis*-3-hexenol at levels of 310, 1250 and 5000 ppm in the diet. No effects were seen at 310 and 1250 ppm but at 5000 ppm the relative kidney weight was increased in male rats and the urine collected was more concentrated (Gaunt, Colley, Grasso, Lansdown & Gangolli, 1969).

Irritation. cis-3-Hexenol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Moreno, 1973). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1973).

References

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Council of Europe (1970). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List A(1), Series 2, no. 23, p. 94. Strasbourg.

Fenaroli's Handbook of Flavor Ingredients (1971). Edited by F. E. Furia and N. Bellanca. p. 430. Chemical Rubber Co., Cleveland, Ohio.

Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. No. 2563. *Fd Technol., Champaign* **19**(2), part 2, 155.

Gaunt, I. F., Colley, J., Grasso, P., Lansdown, A. B. G. & Gangolli, S. D. (1969). Acute (rat and mouse) and short-term (rat) toxicity studies on *cis*-3-hexen-1-ol. *Fd Cosmet. Toxicol.* **7**, 451.

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Kligman, A. M. (1973). Report to RIFM, 2 July.

Moreno, O. M. (1973). Report to RIFM, 1 February.

trans-2-HEXENOL

Synonym: 2-Hexen-1-ol; 2-hexenol.

Structure: $CH_3 \cdot [CH_2]_2 \cdot \overset{H}{C}:\overset{}{C} \cdot CH_2OH$.

Description and physical properties: A colourless liquid with a powerful, fruity-green-like odour (Arctander, 1969).

Occurrence: Reported to be found as a constituent of fresh raspberry aroma; also identified in Valencia orange juice and apple aroma, probably occurring as an ester (*Fenaroli's Handbook of Flavor Ingredients*, 1971).

Preparation: By the reduction of 2-hexenal.

Uses: In public use since the 1950s. Use in fragrances in the USA amounts to less than 3000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·001	0·001	0·08
Maximum	0·1	0·01	0·02	0·4

Analytical data: Gas chromatogram, RIFM no. 72–25; infra-red curve, RIFM no. 72–25.

Status

trans-2-Hexenol was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included *trans*-2-hexenol in the list of admissible artificial flavouring substances at a level of 4 ppm.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 3·5 g/kg (2·94–4·17 g/kg) (Keating, 1972). The acute dermal LD_{50} value in rabbits was reported as 4·5 g/kg (4·02–5·04 g/kg) (Keating, 1972).

Irritation. trans-2-Hexenol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was irritating (Keating, 1972). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1972).

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Council of Europe (1970). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List A(1), Series 1, no. 70, p. 52. Strasbourg.

Fenaroli's Handbook of Flavor Ingredients (1971). Edited by T. E. Furia and N. Bellanca. p. 429. Chemical Rubber Co., Cleveland, Ohio.

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Keating, J. W. (1972). Report to RIFM, 7 June.

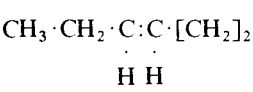
Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.

Kligman, A. M. (1972). Report to RIFM, 19 July.

cis-3-HEXENYL ACETATE

Synonym: *cis*-3-Hexen-1-yl acetate.

Structure:



Description and physical properties: EOA Spec. no. 269.

Occurrence: Reported to occur in tea leaves and *Achillea fragrantissima*.

Preparation: By the acetylation of *cis*-3-hexenol.

Uses: In public use since the 1950s. Use in fragrances in the USA amounts to approximately 2000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·05
Maximum	0·15	0·015	0·02	1·0

Status

cis-3-Hexenyl acetate was granted GRAS status by FEMA (1971).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Wohl, 1974).

Irritation. *cis*-3-Hexenyl acetate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Wohl, 1974). Tested at a concentration of 10% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966, modified) was carried out on 22 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Epstein, 1974).

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HEXYL ACETATE

Synonym: *n*-Hexyl acetate.
Structure: $CH_3 \cdot [CH_2]_5 \cdot OCO \cdot CH_3$.
Description and physical properties: A colourless liquid with a sweet fruit-like odour (Arctander, 1969).
Occurrence: Found in fruital aromas (e.g. of *Fragaria vesca*) and essential oils (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: By direct esterification of *n*-hexanol with acetic acid under azeotropic conditions, or with acetic anhydride (Arctander, 1969).
Uses: In public use since the 1940s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·08
Maximum	0·1	0·01	0·05	0·4

Analytical data: Gas chromatogram, RIFM no. 72–161; infra-red curve, RIFM no. 72–161.

Status

Hexyl acetate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) listed hexyl acetate, giving an ADI of 1 mg/kg, and Browning (1965) has an extensive monograph on this ester.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 6·16 g/kg (Browning, 1965). The acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Russell, 1973).

Irritation. Hexyl acetate tested at 4% in petrolatum produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1973).

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Kligman, A. M. (1973). Report to RIFM, 10 October.

Russell, T. J. (1973). Report to RIFM, 5 March.

HEXYL CINNAMIC ALDEHYDE

Synonym: α-*n*-Hexyl cinnamic aldehyde.
Structure: $C_6H_5 \cdot CH:C(CHO) \cdot [CH_2]_5 \cdot CH_3$.
Description and physical properties: EOA Spec. no. 189.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By condensation of octylaldehyde with benzaldehyde (Bedoukian, 1967).
Uses: In public use before the 1950s. Use in fragrances in the USA amounts to approximately 300,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·015	0·4
Maximum	0·3	0·03	0·1	1·2

Analytical data: Gas chromatogram, RIFM no. 73–3; infra-red curve, RIFM no. 73–3.

Status

Hexyl cinnamic aldehyde was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included hexyl cinnamic aldehyde in the list of admissible artificial flavouring substances at a level of 1 ppm. The *Food Chemicals Codex* (1972) has a monograph on hexyl cinnamic aldehyde.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 3·1 g/kg (2·45–3·75 g/kg) (Moreno, 1971). The acute dermal LD_{50} value in rabbits was reported as >3 g/kg (Moreno, 1971).

Irritation. Hexyl cinnamic aldehyde applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1971). Tested at 12% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 12% in petrolatum and produced no sensitization reactions (Kligman, 1973).

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Moreno, O. M. (1971). Report to RIFM, 24 March.

n-HEXYL ETHYL ACETOACETATE

Synonyms: Ethyl-2-hexyl acetoacetate; hexyl acetoacetic ester.
Structure:

$$CH_3 \cdot CO \cdot CH([CH_2]_5 \cdot CH_3) \cdot OCO \cdot CH_2 \cdot CH_3.$$

Description and physical properties: A colourless slightly oily liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By the alkylation of ethyl acetoacetate with hexyl bromide or by any other suitable method.
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to approximately 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·05
Maximum	0·1	0·01	0·02	0·4

Analytical data: Gas chromatogram, RIFM no. 72-148; infra-red curve, RIFM no. 72-148.

Status

n-Hexyl ethyl acetoacetate is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974), nor in the Food Chemicals Codex (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Shelanski, 1973).

Irritation. *n*-Hexyl ethyl acetoacetate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Shelanski, 1973). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966, modified) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1972).

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Shelanski, M. V. (1973). Report to RIFM, 30 January.

HEXYL SALICYLATE

Synonym: *n*-Hexyl *o*-hydroxybenzoate.
Structure: $CH_3 \cdot [CH_2]_5 \cdot OCO \cdot C_6H_4 \cdot OH$.
Description and physical properties: Colourless oily liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By methyl salicylate exchange with *n*-hexanol using a sodium methoxylate catalyst.
Uses: In public use since the 1940s.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·015	0·1
Maximum	0·3	0·03	0·05	0·3

Analytical data: Gas chromatogram, RIFM no. T-04477; infra-red curve, RIFM no. T-04477.

Status

Hexyl salicylate is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974), or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1975).

Irritation. Hexyl salicylate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1975), but applied undiluted to the backs of hairless mice and swine it was not irritating (Urbach & Forbes, 1975). Tested at 3% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 22 volunteers. The material was tested at a concentration of 3% in petrolatum and produced no sensitization reactions (Epstein, 1975).

Phototoxicity. No phototoxic effects were reported for undiluted hexyl salicylate on hairless mice and swine (Urbach & Forbes, 1975).

Metabolism. Because of the widespread medicinal use of salicyclic acid and its derivatives, there is an extensive literature on the metabolism and excretion of these compounds. Most esters of salicyclic acid hydrolyse to salicylic acid in the body, but this occurs more readily with the lower esters, little of the amyl ester being split. A large proportion of salicylic acid is excreted unchanged by most species; salicyluric acid, gentisic acid, and salicylglucuronides are also known to be excreted (Williams, 1959). Salicylic acid has been found to be teratogenic to rats (Koshakji, 1972).

Normal primary alcohols are, in general, readily oxidized in the body via aldehydes to the corresponding acids and to carbon dioxide. In rabbits, only 10·3% of an oral dose of n-hexanol of 25 mM/3 kg (0·85 g/kg) was excreted in the urine as the glucuronide, which was isolated (Kamil, Smith & Williams, 1953).

Micro-organisms. At 1:10.000 dilution in a liquid medium, hexyl salicylate showed fungistatic action against *Anchorion quinckeanum*, *Trichophyton gypseum* and *Epidermophyton Kaufam-Wolff* when incubated for 10 days at 30°C. No such action against four other fungi was observed using a 1:5000 dilution and incubation for 5 days at 30°C (Zsolnai, 1960).

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HO LEAF OIL

Description and physical properties: A colourless liquid with a sweet, floral odour reminiscent of linalool (*Fenaroli's Handbook of Flavor Ingredients*, 1971). The chief constituent of ho leaf oil is linalool (Guenther, 1950).

Occurrence: Found in the leaves of the tree *Cinnamomum camphora* L. Nees & Ebermeier (Fam. Lauraceae) (*Fenaroli's Handbook of Flavor Ingredients*, 1971).

Preparation: By steam distillation of the leaves of *Cinnamomum camphora* Sieb. (*Fenaroli's Handbook of Flavor Ingredients*, 1971).

Uses: In public use since the 1920s. Use in fragrances in the USA amounts to about 50,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·005	0·02	0·2
Maximum	0·25	0·025	0·05	1·0

Status

The Council of Europe (1970) included ho leaf oil (*Cinnamomum camphora*) in the list of flavouring substances temporarily admitted for use, possibly with a limitation on the active principle in the final product.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 3·27 g/kg (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964). The acute dermal LD_{50} value in rabbits was reported as >5 g/kg (Hart, 1971).

Irritation. Ho leaf oil applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Hart, 1971). Tested at 10% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1971).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1971).

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Jenner, P. M., Hagan, E. C., Taylor, Jean M., Cook, E. L. & Fitzhugh, O. G. (1964). Food flavourings and compounds of related structure. I. Acute oral toxicity. *Fd Cosmet. Toxicol.* **2**, 327.

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HYACINTH ABSOLUTE

Description and physical properties: A viscous reddish-brown liquid. The constituents of hyacinth absolute include benzyl benzoate, benzyl alcohol and esters of cinnamic alcohol (Naves, 1974; Poucher, 1974).

Occurrence: Found in the flowers of *Hyacinthus orientalis* L. (Fam. Liliaceae) and related species (Guenther. 1952).

Preparation: By alcoholic extraction of the concrete (*Fenaroli's Handbook of Flavor Ingredients*, 1975).

Uses: In public use since the 1900s. Use in fragrances in the USA amounts to approximately 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·0005	0·003	0·04
Maximum	0·05	0·005	0·02	0·4

Status

Hyacinth is approved by the FDA for food use (21 CFR 121.1163).

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported to be 4·2 g/kg (3·69–4·71 g/kg) and the acute dermal LD_{50} value in rabbits to be $>1·25$ g/kg (Moreno, 1976).

Irritation. Undiluted hyacinth absolute was not irritating when applied to the backs of hairless mice and swine (Urbach & Forbes, 1976) but was moderately irritating when applied to intact or abraded rabbit skin for 24 hr under occlusion (Moreno, 1976). Tested at 8% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1975).

The juice of hyacinth bulbs has powerful skin-irritating properties, and the effects are seen especially among packers and sorters in nursery gardens (Gafafer, 1943). In a reported case of acute generalized eczema, the eruption covered almost the entire skin; the patient had used perfume extract and carried it around in his breast pocket (von Varge, 1936). In another case there were dry, scaly and fissured lesions of the ends of the fingers with itching behind both ears, and a patch test with hyacinth oil was positive (Johnson, 1935).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 21 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Epstein, 1975). Dermatoses brought about by handling hyacinth bulbs have been reported all over the low countries (Huriez, Martin, Merveille & Blin, 1972).

Phototoxicity. No phototoxic effects were reported for undiluted hyacinth absolute on hairless mice and swine (Urbach & Forbes, 1976).

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HYDRATROPIC ACETATE

Synonyms: α-Methylphenylethyl acetate; 2-phenylpropyl acetate; hydratropyl acetate.
Structure: $C_6H_5 \cdot CH(CH_3) \cdot CH_2 \cdot OCO \cdot CH_3$.
Description and physical properties: A colourless liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By direct esterification of hydratropyl alcohol with acetic acid under azeotropic conditions, or with acetic anhydride (Arctander, 1969).
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to approximately 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·08
Maximum	0·15	0·015	0·05	1·2

Analytical data: Gas chromatogram, RIFM no. 75–73; infra-red curve, RIFM no. 75–73.

Status

Hydratropic acetate is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974) or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 4·3 g/kg (3·46–5·14 g/kg) and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1975).

Irritation. Hydratropic acetate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was slightly irritating (Moreno, 1975). Tested at 12% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 12% in petrolatum and produced no sensitization reactions (Kligman, 1975).

Metabolism. Racemic hydratropic acetate was asymmetrically hydrolysed by *Bacillus subtilis* var. *niger* to form (−)-2-phenylpropanol and (+)-2-phenylpropyl acetate (Oritani & Yamashita, 1973).

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HYDRATROPIC ALCOHOL

Synonyms: Hydratropyl alcohol; α-methyl phenylethyl alcohol; 2-phenylpropan-1-ol.
Structure: $C_6H_5 \cdot CH(CH_3) \cdot CH_2OH$.
Description and physical properties: A colourless liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By catalytic hydrogenation of the corresponding aldehyde.
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·01	0·1
Maximum	0·15	0·015	0·05	0·6

Analytical data: Gas chromatogram, RIFM no. 74-136; infra-red curve, RIFM no. 74–136.

Status

Hydratropic alcohol was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included hydratropic alcohol at a level of 1 ppm in the list of artificial flavouring substances that may be added temporarily to foodstuffs without hazard to public health.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 2·3 ± 0·407 g/kg (McGee, 1974). The acute dermal LD_{50} value in rabbits exceeded 5 g/kg (McGee, 1974).

Irritation. Hydratropic alcohol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (McGee, 1974). Tested at 6% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1974).

Sensitization. A maximization test (Kligman, 1966, modified) was carried out on 25 volunteers. The material was tested at a concentration of 6% in petrolatum and produced no sensitization reactions (Kligman, 1974).

Metabolism. Hydratropic alcohol is oxidized to hydratropic acid, which is excreted as a glucuronide, but some 10–20% of the alcohol is directly conjugated and excreted as hydratropyl glucuronide (Williams, 1959).

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McGee, G. (1974). Report to RIFM, 27 September.

Williams, R. T. (1959). *Detoxication Mechanisms. The Metabolism and Detoxication of Drugs, Toxic Substances and Other Organic Compounds.* 2nd ed., p. 47. Chapman & Hall Ltd., London.

HYDRATROPIC ALDEHYDE

Synonyms: Hydratropaldehyde; 2-phenylpropionaldehyde; α-methyl phenylacetaldehyde.
Structure: $C_6H_5 \cdot CH(CH_3) \cdot CHO$.
Description and physical properties: EOA Spec. no. 100.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By the alkaline condensation of acetophenone and ethyl chloroacetate followed by decomposition of the resulting glycidate (Bedoukian, 1967).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 25,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·08
Maximum	0·15	0·015	0·03	0·6

Analytical data: Gas chromatogram, RIFM no. 70–32; infra-red curve, RIFM no. 70–32.

Status

Hydratropic aldehyde was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included hydratropic aldehyde at a level of 1 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health. The *Food Chemicals Codex* (1972) has a monograph on hydratropic aldehyde.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 3·65 g/kg (2·71–4·91 g/kg) by Weir (1971) and as 2·8 g/kg by Jenner, Hagan, Taylor, Cook & Fitzhugh (1964). The acute dermal LD_{50} value in rabbits was reported as >5 g/kg (Weir, 1971).

Irritation. Hydratropic aldehyde applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was severely irritating (Weir, 1971). It was moderately irritating to rabbit skin in a primary skin irritation study (Weir, 1971). Tested at 2% in petrolatum, it produced a mild irritation after a 48-hr closed-patch test on human subjects (Kligman, 1971).

Conjunctival irritation produced by undiluted hydratropic aldehyde in the rabbit eye cleared by 24 hr (Weir, 1971).

Sensitization. A maximization test (Kligman, 1966, modified) was carried out on 25 volunteers. The material was tested at a concentration of 2% in petrolatum and produced no sensitization reactions (Kligman, 1971).

References

Bedoukian, P. Z. (1967). *Perfumery and Flavoring Synthetics.* 2nd ed., p.297. Elsevier Publishing Co., New York.

Council of Europe (1974). National Flavouring Substances, Their Sources, And Added Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List 1, no. 126, p. 150. Strasbourg.

Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. No. 2886. *Fd Technol., Champaign* 19(2), part 2, 155.

Food Chemicals Codex (1972). 2nd ed. Prepared by the Committee on Specifications, Food Chemicals Codex, of the Committee on Food Protection. p.612. National Academy of Sciences–National Research Council Publ. 1406, Washington, D.C.

Jenner, P. M., Hagan, E. C., Taylor, Jean M., Cook, E. L. & Fitzhugh, O. G. (1964). Food flavourings and compounds of related structure. I. Acute oral toxicity. *Fd Cosmet. Toxicol.* **2,** 327.

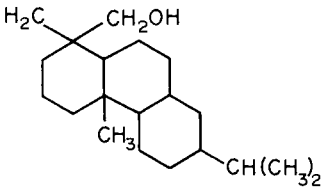
Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47,** 393.

Kligman, A. M. (1971). Report to RIFM, 2 April.

Weir, R. J. (1971). Report to RIFM, 12 April.

HYDROABIETYL ALCOHOL

Structure: Main component—



Description and physical properties: A colourless viscous liquid with a very faint wood-like odour (Arctander, 1969).
Occurrence: Has apparently not been reported to occur in nature.
Preparation: From hydrogenated rosin acids (Arctander, 1969).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 9000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·1	0·01	0·03	0·5
Maximum	0·5	0·05	0·2	1·0

Analytical data: Infra-red curve, RIFM no. 72–92 (72–79A).

Status

Hydroabietyl alcohol is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1970) nor in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Shelanski, 1972).

Irritation. Hydroabietyl alcohol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Shelanski, 1972). Tested at 10% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced sensitization in three of those tested (Kligman, 1972).

References

Arctander, S. (1969). *Perfume and Flavor Chemicals (Aroma Chemicals)*. Vol. 1, no. 2. S. Arctander, Montclair, New Jersey.

Council of Europe (1970). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. Strasbourg.

Flavouring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. *Fd Technol., Champaign* **19** (2), part 2, 155.

Food Chemicals Codex (1972). 2nd ed. Prepared by the Committee on Specifications, Food Chemicals Codex, of the Committee on Food Protection. National Academy of Sciences–National Research Council Publ. 1406, Washington, D.C.

Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.

Kligman, A. M. (1972). Report to RIFM, 19 October.

Shelanski, M. V. (1972). Report to RIFM, 14 July.

HYDROXYCITRONELLAL

Synonym: 7-Hydroxy-3,7-dimethyloctan-1-al.
Structure: $CH_3 \cdot (HO)C(CH_3) \cdot [CH_2]_3 \cdot CH(CH_3) \cdot CH_2 \cdot CHO$.
Description and physical properties: EOA Spec. no. 5.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By hydration of citronellal (Bedoukian, 1967).
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to about 500,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·02	0·2
Maximum	0·3	0·03	0·2	0·5

Analytical data: Gas chromatogram, RIFM no. 70–15; infra-red curve, RIFM no. 70–15.

Status

Hydroxycitronellal was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) listed hydroxycitronellal, giving an ADI of 2·5 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on hydroxycitronellal.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as >5 g/kg (Moreno, 1973). The acute dermal LD_{50} value in rabbits was reported as >2 g/kg (Moreno, 1973).

Irritation. Hydroxycitronellal applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Moreno, 1973). A patch test using full strength hydroxycitronellal for 24 hr produced two irritation reactions in 22 subjects (Katz, 1946). Tested at 5% in petrolatum, hydroxycitronellal produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. Two maximization tests (Kligman, 1966) were carried out, each on 25 volunteers. The material, tested at concentrations of 5% (Kligman, 1973) and 12% (Greif, 1967) in petrolatum produced no sensitization reactions.

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Bedoukian, P. Z. (1967). *Perfumery and Flavoring Synthetics.* 2nd ed., p. 182. Elsevier Publishing Co., New York.
Council of Europe (1970). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List A(1), Series 1, no. 101, p. 54. Strasbourg.
Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. No. 2583. *Fd Technol., Champaign* **19**(2), part 2, 155.
Food Chemicals Codex (1972). 2nd ed. Prepared by the Committee on Specifications, Food Chemicals Codex, of the Committee on Food Protection. p. 380. National Academy of Sciences–National Research Council Publ. 1406, Washington, D.C.
Greif, N. (1967). Cutaneous safety of fragrance materials as measured by the maximization test. *Am. Perfumer Cosmet.* **82** (June), 54.
Katz, A. (1946). *Spice Mill* **69** (July), 46.
Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.
Kligman, A. M. (1973). Report to RIFM, 13 June.
Moreno, O. M. (1973). Report to RIFM, 1 February.

HYDROXYCITRONELLAL DIMETHYLACETAL

Synonym: 1,1-Dimethoxy-3,7-dimethyl-octan-7-ol.
Structure:

$$CH_3 \cdot (OH)C(CH_3) \cdot [CH_2]_3 \cdot CH(CH_3) \cdot CH_2 \cdot CH(OCH_3) \cdot OCH_3.$$

Description and physical properties: EOA Spec. no. 148.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: From hydroxycitronellal and methyl alcohol in the presence of a catalyst (Bedoukian, 1967).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 4000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·05	0·005	0·03	0·5
Maximum	0·25	0·025	0·2	2·0

Analytical data: Gas chromatogram, RIFM no. 72–163; infra-red curve, RIFM no. 72–163.

Status

Hydroxycitronellal dimethylacetal was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) listed hydroxycitronellal dimethylacetal, giving an ADI of 1 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on hydroxycitronellal dimethylacetal.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Shelanski, 1973).

Irritation. Hydroxycitronellal dimethylacetal applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was mildly irritating (Shelanski, 1973). Tested at 10% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966, modified) was carried out on 25 volunteers. The material was tested at a 10% concentration in petrolatum and produced no sensitization reactions (Kligman, 1972).

References

Bedoukian, P. Z. (1967). *Perfumery and Flavoring Synthetics*. 2nd ed., p.190. Elsevier Publishing Co., New York.

Council of Europe (1974). Natural Flavouring Substances, Their Sources, and Added Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List 1, no. 45, p.133. Strasbourg.

Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. No. 2585. *Fd Technol., Champaign* 19(2), part 2, 155.

Food Chemicals Codex (1972). 2nd ed. Prepared by the Committee on Specifications, Food Chemicals Codex, of the Committee on Food Protection. p. 381. National Academy of Sciences–National Research Council Publ. 1406, Washington, D.C.

Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.

Kligman, A. M. (1972). Report to RIFM, 1 November.

Shelanski, M. V. (1973). Report to RIFM, 30 January.

HYDROXYCITRONELLAL-METHYL ANTHRANILATE

Synonyms: Methyl-*N*-3,7-dimethyl-7-hydroxyoctylidene anthranilate; hydroxycitronellylidene-methyl anthranilate Schiff base.

Structure: $CH_3 \cdot (OH)C(CH_3) \cdot [CH_2]_3 \cdot CH(CH_3) \cdot CH_2 \cdot CH{:}N \cdot C_6H_4 \cdot OCO \cdot CH_3$.

Description and physical properties: *Givaudan Index* (1961).

Occurrence: Has apparently not been reported to occur in nature.

Preparation: By condensation using methyl anthranilate and hydroxycitronellal (Arctander, 1969).

Uses: In public use since the 1920s. Use in fragrances in the USA amounts to approximately 20,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·1
Maximum	0·1	0·01	0·03	0·6

Analytical data: Infra-red curve, RIFM no. 71–32.

Status

Hydroxycitronellal-methyl anthranilate is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974), nor in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as >5 ml/kg (Lynch, 1971). The acute dermal LD_{50} value in rabbits was reported as >10 ml/kg (Lynch, 1971).

Irritation. Hydroxycitronellal-methyl anthranilate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Lynch. 1971). Tested at 6% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1971).

Sensitization. A maximization test (Kligman, 1966, modified) was carried out on 25 volunteers. The material was tested at a concentration of 6% in petrolatum and produced no sensitization reactions (Kligman, 1971).

References

Arctander, S. (1969). *Perfume and Flavor Chemicals (Aroma Chemicals)*. Vol. 1, no. 1735. S. Arctander, Montclair, New Jersey.

Council of Europe (1974). Natural Flavouring Substances, Their Sources, and Added Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. Strasbourg.

Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. *Fd Technol., Champaign* **19** (2), part 2, 155.

Food Chemicals Codex (1972). 2nd ed. Prepared by the Committee on Specifications, Food Chemicals Codex, of the Committee on Food Protection. National Academy of Sciences–National Research Council Publ. 1406, Washington, D.C.

Givaudan Index (1961). *Specifications of Synthetics and Isolates for Perfumery*. 2nd ed., p. 64. Givaudan-Delawanna, Inc., New York.

Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.

Kligman, A. M. (1971). Report to RIFM, 21 June.

Lynch, T. A. (1971). Report to RIFM, 16 June.

HYDROXYCITRONELLOL

Synonym: 7-Hydroxy-3,7-dimethyloctan-1-ol.
Structure: $CH_3 \cdot (HO)C(CH_3) \cdot [CH_2]_3 \cdot CH(CH_3) \cdot [CH_2]_2 \cdot OH$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Has apparently not been reported to occur in nature.
Preparation: From myrcene via its dihydrochloride to chlorodihydrogeranyl acetate, followed by saponification and hydrogenation to subject alcohol (Bedoukian, 1967).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·01	0·3
Maximum	0·15	0·015	0·05	1·0

Analytical data: Gas chromatogram, RIFM no. 72–128; infra-red curve, RIFM no. 72–128.

Status

Hydroxycitronellol was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included hydroxycitronellol in the list of admissible artificial flavouring substances at a level of 3 ppm.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Levenstein, 1973).

Irritation. Hydroxycitronellol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was mildly irritating (Levenstein, 1973). Tested at 10% in petrolatum, it produced no irritating effects after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at 10% in petrolatum and produced no sensitization reactions (Kligman, 1972).

References

Bedoukian, P. Z. (1967). *Perfumery and Flavoring Synthetics.* 2nd ed., p. 188. Elsevier Publishing Co., New York.
Council of Europe (1970). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List A(1), Series 1, no. 561, p. 79. Strasbourg.
Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. No. 2586. *Fd Technol., Champaign* **19**(2), part 2, 155.
Givaudan Index (1961). *Specifications of Synthetics and Isolates for Perfumery.* 2nd ed., p. 192. Givaudan-Delawanna, Inc., New York.
Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.
Kligman, A. M. (1972). Report to RIFM, 1 February.
Levenstein, I. (1973). Report to RIFM, 9 January & 16 February.

INDOLE

Synonyms: Benzopyrrole; 1-benzazole.
Structure: $C_6H_4 \cdot NH \cdot CH:CH$.
Description and physical properties: EOA Spec. no. 21.
Occurrence: Reported to occur in over two dozen essential oils including neroli oil and in the oils extracted from the flowers of *Jasminum grandiflorum*, bitter orange and *Jasminum odoratissinium* L. (Gildemeister & Hoffman, 1966).
Preparation: By the reduction of indoxyl, indoxyl carboxylic acid or indigo (Bedoukian, 1967).
Uses: In public use since the early 1900s. Use in fragrances in the USA amounts to about 4000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·001	0·0001	0·0005	0·03
Maximum	0·01	0·001	0·003	0·1

Analytical data: Gas chromatogram, RIFM no. 70–71; infra-red curve, RIFM no. 70–71.

Status

Indole was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included indole in the list of admissible artificial flavouring substances at a level of 1 ppm. The *Food Chemicals Codex* (1972) has a monograph on indole.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 1 ml/kg (0·64–1·57 ml/kg) (Smyth, Carpenter, Weil, Pozzani & Striegel, 1962). The single skin-penetration LD_{50} for rabbits was reported as 0·79 ml/kg (0·59–1·07 ml/kg) and 8 hr was the maximum period of concentrated vapour inhalation that caused no deaths in rats (Smyth *et al.* 1962).

Irritation. Indole was reported not to be irritating to the uncovered rabbit belly (Smyth *et al.* 1962).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 1% in petrolatum and produced no sensitization reactions (Kligman, 1970).

Metabolism. Indole is oxidized to 3-hydroxyindole (indoxyl) which is conjugated with glucuronic and sulphuric acids before excretion. The sulphate conjugate seems to be the main product in rabbits and, even with relatively large doses of indole, the sulphate conjugation always exceeds that of glucuronic acid (Williams, 1959).

References

Bedoukian, P. Z. (1967). *Perfumery and Flavoring Synthetics*. 2nd ed., p. 192. Elsevier Publishing Co., New York.

Council of Europe (1970). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List A(1), Series 1, no. 562, p. 79. Strasbourg.

Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. No. 2593. *Fd Technol., Champaign* **19**(2), part 2, 155.

Food Chemicals Codex (1972). 2nd ed. Prepared by the Committee on Specifications, Food Chemicals Codex, of the Committee on Food Protection. p. 389. National Academy of Sciences–National Research Council Publ. 1406, Washington, D.C.

Gildemeister, E. u. Hoffman, F. (1966). *Die Ätherischen Öle*. Vol. IIId, p. 812. Akademie Verlag, Berlin.

Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.

Kligman, A. M. (1970). Report to RIFM, 4 January.

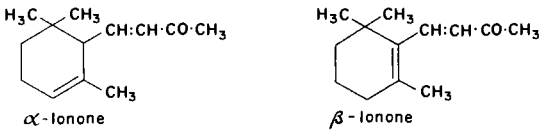
Smyth, H. F. Jr., Carpenter, C. P., Weil, C. S., Pozzani, U. C. & Striegel, Jean A. (1962). Range-finding toxicity data: List VI. *Am. ind. Hyg. Ass. J.* **23**, 95.

Williams, R. T. (1959). *Detoxication Mechanisms. The Metabolism and Detoxication of Drugs, Toxic Substances and Other Organic Compounds*. 2nd ed., p. 668. Chapman & Hall Ltd., London.

IONONE

Synonym: A mixture of α and β-isomers of cyclocitrylidenacetone.

Structure:



Description and physical properties: EOA Spec. no. 61.

Occurrence: The α-isomer has been reported in the essential oil of *Sphaeranthus inducus* L. and in the absolute essence of *Acacia farnesiana*. The β-isomer has been reported to be found in raspberry, in the distillate from flowers of *Boronia megatisma* Nees., and in a few other essences (*Fenaroli's Handbook of Flavor Ingredients*, 1971). α-Ionone occurs in the essential oils of orange and *Ligusticum elatum*, in extract of *Osmanthus fragrans* Lour., in the flavour of tea, and in the essential oil of tangelo (*Citrus reticulata* Blanco × *C. paradisi* MacFayden). β-Ionone is an important constituent of essential oils of *Cunila lythrifolia* Benth., and *Siparuna nicaraguensis* Heml.; it has also been found in tomatoes (Naves, 1971).

Preparation: By chemical synthesis or by condensing citral with acetone to form pseudo-ionone which is then cyclized by acid-type reagents (Bedoukian, 1967).

Uses: In public use since the 1900s. Use in fragrances in the USA amounts to approximately 200,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·015	0·3
Maximum	0·3	0·03	0·08	1·5

Status

Both α- and β-ionone were granted GRAS status by FEMA (1965) and are approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) listed α- and β-ionone, giving ADIs of 0·1 mg/kg for both. The *Food Chemicals Codex* (1972) has monographs on α- and β-ionone and the Joint FAO/WHO Expert Committee on Food Additives (1967) has published monographs and specifications for both isomers, giving conditional ADIs of 0–0·1 mg/kg.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 4·59 g/kg (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964). The ip LD_{50} value in mice was reported as 2·27 g/kg (Sporn, Schoebesch, Marin, Panaitescu & Runcanu, 1963).

Subacute toxicity. In feeding studies, 1000, 2500 and 10,000 ppm fed to rats in the diet for 17 wk produced microscopic liver changes, ranging from very slight swelling of the parenchymal cells at the lowest level to moderate swelling at the highest level (Hagan, Hansen, Fitzhugh, Jenner, Jones, Taylor, Long, Nelson & Brouwer, 1967). Rats fed 13–115 mg of α- and β-ionone for 5–9 days produced fatty infiltration of liver parenchymal cells (Shillinger, 1950). In a 12-wk feeding study in rats the concentration without effect was reported as 10·6 mg/kg for α-ionone and as 11·4 mg/kg for β-ionone (Bär & Griepentrog, 1967).

Irritation. A patch test using ionone full strength for 24 hr produced no reactions in eleven subjects (Katz, 1946). Mendelsohn (1946) reported ionone to be non-irritating.

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Greif, 1967).

Metabolism. Ionones are metabolized mainly by oxidation of the ring system at the carbon atom alpha to the ring double bond and by reduction of the carbonyl group (Williams, 1959). On administration to dogs α-ionone is hydroxylated in the ring at the carbon atom which is alpha to the ring double bond to yield 5-hydroxy-α-ionone (Prelog, Wursch & Meier, 1951). Rabbits dosed orally with β-ionone excreted in the urine unchanged β-ionone, 3-oxo-β-ionone, 3-oxo-β-ionol, dihydro-3-oxo-β-ionol and 3-hydroxy-β-ionol. Excretion products were isolated as 2,4-dinitrophenylhydrazone derivatives and as *p*-nitrobenzoate derivatives. The glucuronides of 3-oxo-β-ionol and dihydro-3-oxo-β-ionol were also detected in the urine (Ide & Toki, 1970).

References

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Bedoukian, P. Z. (1967). *Perfumery and Flavoring Synthetics*. 2nd ed., p. 192. Elsevier Publishing Co., New York.

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Fenaroli's Handbook of Flavor Ingredients (1971). Edited by T. E. Furia & N. Bellanca. p. 442. Chemical Rubber Co., Cleveland, Ohio.

Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. No. 2594 & 2595. *Fd Technol., Champaign* 19(2), part 2, 155.

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Greif, N. (1967). Cutaneous safety of fragrance materials as measured by the maximization test. *Am. Perfumer Cosmet.* **82** (June), 54.

Hagan, E. C., Hansen, W. H., Fitzhugh, O. G., Jenner, P. M., Jones, W. I., Taylor, Jean M., Long, Eleanor L., Nelson, A. A. & Brouwer, J. B. (1967). Food flavourings and compounds of related structure. II. Subacute and chronic toxicity. *Fd Cosmet. Toxicol.* **5**, 141.

Ide, H. & Toki, S. (1970). Metabolism of β-ionone. Isolation, characterization and identification of the metabolites in the urine of rabbits. *Biochem. J.* **119**, 281.

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α-IRONE

Synonyms: 6-Methyl-α-ionone; *cis*-(2,6)-*cis*-(2^1,2^2)-α-irone.

Structure: $HC_3 \cdot C_9H_{15} \cdot CH{:}CH \cdot CO \cdot CH_3$.

(For the structure of the α isomer of ionone, $C_9H_{15} \cdot CH{:}CH \cdot CO \cdot CH_3$, see monograph thereon, p. 549.)

Description and physical properties: *Givaudan Index* (1961).

Occurrence: Found in orris root oil, where the β- and γ-isomers also occur as well as several stereo-isomers (*Givaudan Index*, 1961). It is also found in raspberry and some flowers of Pittosporum sp. (*Fernaroli's Handbook of Flavor Ingredients*, 1971).

Preparation: Synthetically from dimethylheptenone.

Uses: In public use since the 1920s. Use in fragrances in the USA amounts to approximately 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·0005	0·002	0·04
Maximum	0·03	0·003	0·01	0·5

Analytical data: Gas chromatogram, RIFM no. 72–26; infra-red curve, RIFM no. 72–26.

Status

α-Irone was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) listed α-irone, giving an ADI of 0·1 mg/kg.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Shelanski, 1972).

Subacute toxicity. In a 12-wk feeding study on rats, the concentration without effect was reported as 5·2 mg/kg (Bär & Griepentrog, 1967).

Irritation. α-Irone applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was mildly irritating (Shelanski, 1972). Tested at 10% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966, modified) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1972).

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ISOAMYL ACETATE

Synonyms: Amyl acetate; β-methyl butyl acetate.
Structure: $CH_3 \cdot CH(CH_3) \cdot [CH_2]_2 \cdot OCO \cdot CH_3$.
Description and physical properties: EOA Spec. no. 110.
Occurrence: Reported to be found in a number of naturally occurring products, including apple, banana, cocoa bean, coffee, cognac, grape, peach, pear, pineapple and strawberry (FEMA, 1974).
Preparation: By the esterification of commercial isoamyl alcohol with acetic acid.
Uses: In public use before the 1900s. Use in fragrances in the USA amounts to about 10,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·05	0·005	0·003	0·05
Maximum	0·2	0·02	0·02	0·3

Analytical data: Gas chromatogram, RIFM no. 72–164; infra-red curve, RIFM no. 72–164.

Status

Isoamyl acetate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) listed isoamyl acetate, giving an ADI of 1 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on isoamyl acetate and Browning (1965) has an extensive monograph on amyl acetate.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1973). The oral (by stomach tube) LD_{50} value in rabbits was reported as 57 mmol/kg (Munch, 1972).

Irritation. Isoamyl acetate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Moreno, 1973). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966, modified) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1973).

Threshold limit value. The threshold limit value for isoamyl acetate has been set at 100 ppm (American Conference of Governmental Industrial Hygienists, 1973).

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ISOAMYL PROPIONATE

Synonym: Isopentyl propionate.
Structure: $CH_3 \cdot CH(CH_3) \cdot [CH_2]_2 \cdot OCO \cdot CH_2 \cdot CH_3$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Reported to have been found in cocoa bean and Bulgarian peppermint (*Fenaroli's Handbook of Flavor Ingredients*. 1971).
Preparation: From isoamyl alcohol and propionic acid by direct esterification under azeotropic conditions (Arctander, 1969).
Uses: In public use since the early 1900s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·1
Maximum	0·1	0·015	0·03	0·4

Status

Isoamyl propionate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) listed isoamyl propionate, giving an ADI of 1 mg/kg (except for chewing gum).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 ml/kg (Levenstein, 1975). The acute ip LD_{50} for rats was found to be approximately 2·3 g/kg (Selisko, Ackermann & Kupke, 1962).

In rabbits, the narcotic dose (ND_{50}) and the lethal dose (LD_{50}) of isoamyl propionate given by stomach tube were found to be 36 and 48 mmol/kg (5·18 and 6·91 g/kg), respectively, indicating a narrow margin of safety between the two doses (Munch, 1972). The threshold narcotic concentration of isoamyl propionate to tadpoles was found to be 5 mmols/litre (0·72 g/litre) water (Munch, 1972).

Irritation. Isoamyl propionate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Levenstein, 1975). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1975).

Metabolism. Esters such as propionates are hydrolysed to materials that are normally in the diet or are readily converted to such materials (Fassett, 1963a). The lower toxicities of the higher propionate esters (isoamyl < *n*-butyl < *n*-propyl < ethyl) and of the higher isoamyl esters (isovalerate < *n*-butyrate < propionate < acetate) were attributed to their slower rates of hydrolysis, which made less free alcohol available (Selisko, Ackermann & Kupke, 1962). The metabolism of propionic acid is known to proceed by conversion to succinic acid and oxidation through the citric acid cycle (Fassett, 1963b).

In rats, the primary amyl alcohols are mainly metabolized by oxidation, the primary oxidation apparently occurring chiefly in the liver. The effects of these alcohols appear to be explicable in terms of the aldehydes (irritation of the peritoneum and redness of the lungs) and fatty acids (sedation) formed as intermediates during their metabolism. When injected into rats at 1 g/kg, isoamyl alcohol disappeared from the blood in about 5 hr with excretion of only 0·97% in the expired air and 0·27% in the urine (Haggard, Miller & Greenberg, 1945). In rabbits, only 9% of an isoamyl alcohol dose of 25 mmol/3 kg (0.73 g/kg) was excreted in the urine as the glucuronide, which was isolated (Kamil, Smith & Williams, 1953).

Antispasmodic action. Isoamyl propionate was found to possess some atropine-like and papaverine-like activity (Takagi, Fujii & Takayanagi, 1958).

Insects. Isoamyl propionate showed moderate alarm-releasing activity, as assayed in terms of attractiveness to guard bees, *Apis mellifera* (Boch & Shearer, 1971). The relation of choice of oviposition sites by *Aedes aegypti* (mosquito) to the chemical and physical properties of fatty acid esters, including pentyl propionate, was studied by Perry, Fay & Johnson (1967), who found that the choice was determined primarily by stimulation of olfactory chemoreceptors.

Micro-organisms: The vapour of isoamyl propionate strongly inhibited the growth of four fungi (Maruzzella, Chiaramonte & Garofalo, 1961), but when tested by the filter-paper disk method isoamyl propionate did not inhibit the growth of three wood-destroying fungi (Maruzzella, Scrandis, Scrandis & Grabon, 1960). "Amyl propionate" at 1:500 dilution had no inhibitory effect *in vitro* on growing cultures of four bacteria (Maruzzella & Bramnick, 1961).

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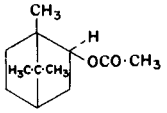
ISOBORNYL ACETATE

Synonyms: 2-Camphanyl acetate; bicyclo[2,2,1]-1,7,7-trimethylheptanyl-2-acetate.

Structure:



Description and physical properties: EOA Spec. no. 74.

Occurrence: Has apparently not been reported to occur in nature.

Preparation: By reaction of camphene with acetic acid under acid catalysis or by any other suitable means.

Uses: In public use since the 1930s. Use in fragrances in the USA amounts to approximately 200,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·05	0·005	0·005	0·2
Maximum	0·4	0·04	0·05	1·0

Analytical data: Gas chromatogram, RIFM no. 70–16; infra-red curve, RIFM no. 70–16.

Status

Isobornyl acetate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included isobornyl acetate in the list of artificial flavouring substances that may be added temporarily to foodstuffs without hazard to public health. The *Food Chemicals Codex* (1972) has a monograph on isobornyl acetate.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as > 10 g/kg (Fogleman, 1970). The acute dermal LD_{50} value in rabbits exceeded 20 g/kg (Fogleman, 1970).

Short-term toxicity. Isobornyl acetate dissolved in corn oil was administered daily to rats by stomach tube in doses of 0 (control), 15, 90 or 270 mg/kg body weight/day for 13 wk. There were no differences between treated and control animals in the rate of body-weight gain, the food intake or the results of haematological investigations. Male rats given 270 mg/kg/day showed a decrease in renal concentrating ability, an increase in water intake, exfoliation of renal tubular cells, increased kidney weight and vacuolation of the renal tubular cells. Signs of nephrotoxicity were also seen with daily doses of 90 mg/kg. Vacuolation of the epithelium of the intrahepatic bile-duct and an increase in liver weights were found at 270 mg/kg. The caeca were also enlarged at this dosage level. The no-effect level found was 15 mg/kg/day, more than 100 times the calculated maximum intake by man (Gaunt, Agrelo, Colley, Lansdown & Grasso, 1971).

Irritation. Isobornyl acetate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was mildly irritating (Fogleman, 1970).

Sensitization. A maximization test (Kligman, 1966, modified) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1970).

References

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Fogleman, R. W. (1970). Report to RIFM, 25 August.

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Kligman, A. M. (1970). Report to RIFM, 7 October.

ISOBORNYL PROPIONATE

Structure: $C_{10}H_{17}\cdot OCO\cdot CH_2\cdot CH_3$ (for structure of isobornyl radical, $C_{10}H_{17}$, see monograph on isobornyl acetate, p. 552).

Description and physical properties: A colourless oily liquid.

Occurrence: Has apparently not been reported to occur in nature.

Preparation: By the reaction of camphene with propionic acid using an acid catalyst.

Uses: In public use since the 1930s. Use in fragrances in the USA amounts to approximately 2000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·05	0·005	0·005	0·2
Maximum	0·4	0·04	0·05	1·0

Analytical data: Gas chromatogram, RIFM no. 72–166; infra-red curve, RIFM no. 72–166.

Status

Isobornyl propionate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included isobornyl propionate, at a level of 2 ppm, in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. Isobornyl propionate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Moreno, 1973). Tested at 10% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966, modified) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1973).

References

Council of Europe (1974). Natural Flavouring Substances, Their Sources, and Added Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List 1, no. 412, p. 209. Strasbourg.

Flavoring Extract Manufacturers' Association (1965). Survey of flavouring ingredient usage levels. No. 2163. *Fd Technol., Champaign* **19** (2), part 2, 155.

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Kligman, A. M. (1973). Report to RIFM, 21 May.

Moreno, O. M. (1973). Report to RIFM, 1 February.

ISOBUTYL BENZOATE

Structure: $C_6H_5 \cdot COO \cdot CH_2 \cdot CH(CH_3) \cdot CH_3$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By direct esterification of isobutyl alcohol with benzoic acid, under azeotropic conditions (Arctander, 1969).
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to approximately 2000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·015	0·3
Maximum	0·3	0·03	0·05	1·0

Analytical data: Gas chromatogram, RIFM no. 72–167; infra-red curve, RIFM no. 72–167.

Status

Isobutyl benzoate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) listed isobutyl benzoate, giving an ADI of 5 mg/kg.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 3·7 mg/kg (3·19–4·29 mg/kg) (Levenstein, 1973). The acute dermal LD_{50} value in rabbits was reported as > 5 ml/kg (Levenstein, 1973).

Irritation. Isobutyl benzoate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Levenstein, 1973). Tested at 2% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966, modified) was carried out on 25 volunteers. The material was tested at a concentration of 2% in petrolatum and produced no sensitization reactions (Kligman, 1973).

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Kligman, A. M. (1973). Report to RIFM, 9 May.

Levenstein, I. (1973). Report to RIFM, 10 January and 16 February.

ISOBUTYL CINNAMATE

Structure: $C_6H_5 \cdot CH{:}CH \cdot OCO \cdot CH_2 \cdot CH(CH_3) \cdot CH_3$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By direct esterification of isobutanol with cinnamic acid under azeotropic conditions (Arctander, 1969).
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to approximately 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·005	0·2
Maximum	0·15	0·025	0·05	0·8

Status

Isobutyl cinnamate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) listed isobutyl cinnamate giving an ADI of 1·25 mg/kg, and the *Food Chemicals Codex* (1972) has a monograph on this ester.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Levenstein, 1975).

Irritation. Isobutyl cinnamate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was mildly irritating (Levenstein, 1975). Tested at 8% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 24 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Epstein, 1975).

Metabolism. Since the hydrolysis of ester linkages in foreign compounds may be catalysed by many different esterases, which are to be found in all animals and bacteria and have, for the most part, a low degree of substrate specificity (Parke, 1968), it seems probable that isobutyl cinnamate, like other esters, would be hydrolysed to form the corresponding acid and alcohol.

Micro-organisms. Growth of *Bacillus subtilis*, *Escherichia coli* and *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant) was not inhibited by isobutyl cinnamate in a dilution of 1:500 (Maruzzella & Bramnick, 1961). The vapour of isobutyl cinnamate had no inhibitory effect on growing cultures of *Candida albicans*, *Phoma betae*, *Geotrichum candidum* and *Oospora lactis* (Maruzzella, Chiaramonte & Garofalo, 1961).

Plants. Isobutyl cinnamate applied at 0·02% to apple foliage provided <10% protection against powdery apple mildew (Kirby, Frick & Moore, 1965).

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ISOBUTYL PHENYLACETATE

Synonym: Isobutyl α-toluate.
Structure: $CH_3 \cdot CH(CH_3) \cdot CH_2 \cdot OCO \cdot CH_2 \cdot C_6H_5$.
Description and physical properties: EOA Spec. no. 104.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By esterification of phenylacetic acid with isobutyl alcohol.
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·08
Maximum	0·1	0·01	0·03	0·4

Status

Isobutyl phenylacetate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included isobutyl phenylacetate in the list of artificial flavouring substances that may be added temporarily to foodstuffs without hazard to public health. The *Food Chemicals Codex* (1972) has a monograph on isobutyl phenylacetate.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. Isobutyl phenylacetate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was mildly irritating (Moreno, 1973). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1973).

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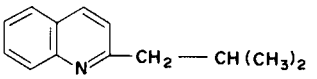
Moreno, O. M. (1973). Report to RIFM, 18 May.

ISOBUTYL QUINOLINE

Synonyms: 2-Isobutylquinoline; α-isobutylquinoline.
Structure:



Description and physical properties: *Givaudan Index* (1961).
Occurrence: Has apparently not been reported to occur in nature.
Preparation: From acrolein and secondary butylaniline followed by dehydration and oxidation (Bedoukian, 1967).
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to less than 2000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·0005	0·0015	0·04
Maximum	0·05	0·005	0·02	0·2

Analytical data: Gas chromatogram, RIFM no. 72-169; infra-red curve, RIFM no. 72-169.

Status

Isobutyl quinoline is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974), or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 1·02 g/kg (0·78–1·26 g/kg) (Moreno, 1973). The acute dermal LD_{50} value in rabbits was reported as >5 g/kg (Moreno, 1973).

Irritation. Isobutyl quinoline applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Moreno, 1973). Tested at 2% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 2% in petrolatum and produced no sensitization reactions (Kligman, 1973). Applied full strength for 48 hr in the standard occluded aluminium patch test used by the North American Contact Dermatitis Research Group, it did not produce any irritation in a 62-yr-old subject with a perfume dermatitis (Larsen, 1975).

References

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Kligman, A. M. & Epstein, W. (1975). Updating the maximization test for identifying contact allergens. *Contact Dermatitis* **1**, 231.

Larsen, W. G. (1975). Cosmetic dermatitis due to a perfume. *Contact Dermatitis* **1**, 142.

Moreno, O. M. (1973). Report to RIFM, 1 February.

ISOBUTYL SALICYLATE

Synonym: Isobutyl *o*-hydroxybenzoate.
Structure: $CH_3 \cdot CH(CH_3) \cdot CH_2 \cdot OCO \cdot C_6H_4 \cdot OH$.
Description and physical properties: EOA Spec. no. 208.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By esterification of isobutyl alcohol and salicylic acid.
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to approximately 3000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·015	0·4
Maximum	0·3	0·03	0·05	1·2

Analytical data: Gas chromatogram, RIFM no. 73–23; infra-red curve, RIFM no. 73–23.

Status

Isobutyl salicylate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included isobutyl salicylate at a level of 5 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health. The *Food Chemicals Codex* (1972) has a monograph on isobutyl salicylate.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 1·56 g/kg (1·32–1·80 g/kg) and the acute dermal LD_{50} value in rabbits as >5 g/kg (Moreno, 1973).

Irritation. Isobutyl salicylate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was slightly irritating (Moreno, 1973). Tested at 10% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1975).

References

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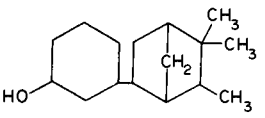
Moreno, O. M. (1973). Report to RIFM, 18 July.

ISOCAMPHYL CYCLOHEXANOL (MIXED ISOMERS)

Synonym: 3-(Isocamphyl-5)-cyclohexanol; indisan.
Structure:



(a typical isomer)

Description and physical properties: A colourless material.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By reaction of camphene with guaiacol and subsequent hydrogenation and hydrogenolysis of the methoxy group.
Uses: Use in fragrances in the USA amounts to over 25,000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·015	0·5
Maximum	0·45	0·005	0·1	2·0

Analytical data: Gas chromatogram, RIFM no. 74–213; infra-red curve. RIFM no. 74–213.

Status

Isocamphyl cyclohexanol (mixed isomers) is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974) or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno. 1975).

Irritation. Applied full strength to intact or abraded rabbit skin for 24 hr under occlusion it was moderately irritating (Moreno, 1975). Tested at 20% in petrolatum it produced irritant reactions in two out of 25 human subjects in a 48-hr closed-patch test (Epstein, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 20% in petrolatum and produced no sensitization reactions (Epstein, 1975).

References

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Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.

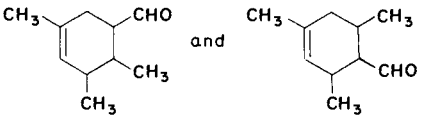
Kligman, A. M. & Epstein, W. (1975). Updating the maximization test for identifying contact allergens. *Contact Dermatitis* **1**, 231.

Moreno. O. M. (1975). Report to RIFM, 3 February.

ISOCYCLOCITRAL

Synonyms: 1,3,5-Trimethyl-3-cyclohexene-1-carboxaldehyde; 2,3,5-trimethyl-4-cyclohexene-1-carboxaldehyde.

Structure:



Description and physical properties: The *Givaudan Index* (1961).

Occurrence: Has apparently not been reported to occur in nature.

Preparation: By a Diels–Alder-type condensation of 2-methyl-1,3-pentadiene with crotonaldehyde (Bedoukian, 1967).

Uses: In public use since the 1950s. Use in fragrances in the USA amounts to approximately 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·08
Maximum	0·1	0·01	0·03	0·4

Analytical data: Gas chromatogram, RIFM no. 72-170; infra-red curve, RIFM no. 72-170.

Status

Isocyclocitral is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974), or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported to be 4·5 ml/kg (4·16–4·86 ml/kg) (Levenstein, 1973a). The acute dermal LD_{50} value was reported to be >5 ml/kg in the rabbit (Levenstein, 1973b).

Irritation. Isocyclocitral applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was mildly irritating (Levenstein, 1973b). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1972).

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Kligman, A. M. (1972). Report to RIFM, 1 November.

Kligman, A. M. & Epstein, W. (1975). Updating the maximization test for identifying contact allergens. *Contact Dermatitis* **1**, 231.

Levenstein, I. (1973a). Report to RIFM, 9 January.

Levenstein, I. (1973b). Report to RIFM, 16 February.

ISOEUGENOL

Synonyms: 4 Propenylguaiacol; 2-methoxy-4-propenylphenol.
Structure: $HO \cdot (OCH_3)C_6H_3 \cdot CH{:}CH \cdot CH_3$.
Description and physical properties: EOA Spec. no. 202.
Occurrence: Reported to be found in clove, ylang ylang, tuberose, jonquil and other oils.
Preparation: By the alkaline isomerization of eugenol from oils with a high eugenol content.
Uses: In public use since the 1900s. Use in fragrances in the USA amounts to approximately 40,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·015	0·4
Maximum	0·3	0·03	0·1	0·8

Status

Isoeugenol was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) listed isoeugenol, giving an ADI of 5 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on isoeugenol.

Biological data

Acute toxicity. The acute oral LD_{50} of isoeugenol for rats was found to be 1·56 g/kg, the animals remaining comatose with scrawny appearance for several days, and death occurring within 1 hr–7 days (Taylor, Jenner & Jones, 1964) (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964). The acute oral LD_{50} of isoeugenol for guinea-pigs was found to be 1·41 g/kg (Jenner *et al.* 1964). The acute ip LD_{50} for mice was reported to be 0·365 g/kg for the *cis* and 0·54 g/kg for the *trans* isomer. The highest doses causing no deaths were 0·10 and 0·20 g/kg and the lowest doses causing the death of all animals were 0·60 and 0·80 g/kg for *cis*- and *trans*-isoeugenol, respectively (Caujolle & Meynier, 1960a,b). The acute ip LD_{50} (within 4 days) was found to be 600 mg isoeugenol/kg in mice that were also receiving hexobarbitone or zoxazolamine (Fujii, Jaffe, Bishop, Arnold, Mackintosh & Epstein, 1970). The LD_{50} in mice treated by an unidentified route was reported to be about 10–20 mg (Rotmistrov, Gendenshtein & Matveenko, 1957). Isoeugenol injected ip into mice promptly produced a distinct hypothermia, the maximum lowering of rectal temperature for a dose of 0·10 g/kg being 4°C at 30 min for *cis*-isoeugenol and 1·5°C at 20 min for *trans*-isoeugenol (Caujolle & Meynier, 1960b).

Isoeugenol did not affect rope-climbing performance of rats at 80 mg/kg, but at 160 mg/kg, climbing performance was impaired by depression and hindquarter paralysis (de Mello & Carlini, 1973). It did not produce catatonic effects and did not affect spontaneous motor activity in mice at 100 mg/kg (de Mello & Carlini, 1973). In mice, isoeugenol prolonged pentobarbitone and ethanol sleeping times when given in ip doses of 50 and 100 mg/kg, respectively (Seto & Keup, 1969), but injected ip in doses of 2·5–640 mg/kg, it caused no significant inhibition of hepatic microsomal enzyme function, as measured by prolongation of hexobarbitone narcosis and of zoxazolamine paralysis (Fujii *et al.* 1970). Injected ip into mice at 160 mg/kg, isoeugenol did not appreciably inhibit liver microsomal hydroxylation of dimethylaminopyrine and hexobarbitone substrates (Jaffe, Fujii, Sengupta, Guerin & Epstein, 1968).

Subacute toxicity. When isoeugenol was given orally to rats at 520 mg/kg (33% of the LD_{50}) daily for 4 days, one out of six animals died, and no macroscopic liver lesions were observed (Taylor *et al.* 1964). Rats receiving 10,000 ppm of isoeugenol in the diet for 16 wk showed no effect on growth or haematology and no macroscopic or microscopic changes in the tissues (Hagan, Hansen, Fitzhugh, Jenner, Jones, Taylor, Long, Nelson & Brouwer, 1967).

Irritation. Isoeugenol tested at 8% in petrolatum produced a mild irritation after a 48-hr closed-patch test on human subjects (Kligman, 1971). In closed-patch tests on human skin, isoeugenol in vaseline or ointment caused primary irritation (erythema) in three of 35 normal subjects and in one of 30 normal subjects when applied in concentrations of 5 and 2%, respectively, while erythema resulted in one of 54 subjects with dermatoses tested with a concentration of 0·1% in 99% ethanol or a cream base (Fujii, Furukawa & Suzuki, 1972). Moderate skin reactions in guinea-pigs resulted when 1% isoeugenol in peanut oil was applied to the injection site 3 wk after a 10-day course of daily intradermal injections of a 0.1% suspension of isoeugenol (Griepentrog, 1961).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1971).

Metabolism. Phenols are usually conjugated with glucuronic acid to form aryl glucosiduronic acids and with sulphuric acid to form ethereal sulphates. Hydroxylation and methylation of the phenolic hydroxyl group may also occur as minor reactions (Williams, 1959).

Percutaneous absorption. Isoeugenol was not absorbed within 2 hr by the intact shaved abdominal skin of the mouse (Meyer & Meyer, 1959). In an evaluation of skin-penetrating agents, it did not aid penetration of Rhodamine B into guinea-pig skin (Meyer, 1965).

Daily intake. The maximum possible intake of isoeugenol in the human diet was calculated to be 4·33 mg/day (age 2–65+ yr) or 0·19 mg/kg body weight/day (age 12–23 months) (Federation of American Societies for Experimental Biology, 1973).

Insects. Isoeugenol was not attractive to the termite, *Reticulitermes flavipes* (Watanabe & Casida, 1963).

Micro-organisms. Growth of *Bacillus subtilis, Escherichia coli* and two strains of *Staphylococcus aureus* was not inhibited by isoeugenol at 1:500 dilution (Maruzzella & Bramnick, 1961), but dilutions of 1:1000–1:6400 were reported to be bactericidal to pure and mixed cultures of staphylococci and various intestinal bacteria (Bobchenko, Baisheva & Nikitina, 1956). While isoeugenol in solution had little or no inhibitory activity against four bacteria, the vapour caused moderate inhibition (Mashimo, Serisawa & Kuroda, 1953). Its reportedly high bactericidal activity was attributed to molecular structure, increased activity being associated with decreased stability (Soldatova & Voroshin, 1962).

Isoeugenol inhibited *in vitro* growth of the wood-destroying fungi *Lenzites trabea, Polyporus versicolor* and *Lentinus lepideus* (Maruzzella, Scrandis, Scrandis & Grabon, 1960), and its vapour inhibited *in vitro* growth of the fungi *Candida albicans, Phoma betae, Geotrichem candidum* and *Oospora lactis* (Maruzzella, Chiaramonte & Garofalo, 1961). Hyphal growth and sporulation of the fungus *Choanephora trispora* were completely inhibited by 0·03–0·06% isoeugenol but were not inhibited by 0·001–0·006% (Zajic & Kuehn, 1961). Isoeugenol was not significantly toxic to powdery mildews of apple and barley at 0·02–0·05% (Kirby, Frick & Moore, 1965). Its toxicity to *Paramecium caudatum, Trichomonas vaginalis* and infusoria was tested by Rotmistrov *et al.* (1957).

Dental use. Isoeugenol is a component of a patented dental cement which is claimed to inhibit inflammatory cells and promote calcific bridge formation (Biorex Laboratories Ltd., 1966).

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ISOEUGENYL ACETATE

Synonyms: Isoeugenol acetate; 2-methoxy-4-propenyl phenyl acetate; acetisoeugenol.
Structure: $CH_3 \cdot CH{:}CH \cdot C_6H_3(OCH_3) \cdot OCO \cdot CH_3$.
Description and physical properties: EOA Spec. no. 276.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: From isoeugenol and acetic acid by esterification.
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·3
Maximum	0·2	0·02	0·05	1·0

Analytical data: Gas chromatogram, RIFM no. 72–28; infra-red curve, RIFM no. 72–28.

Status

Isoeugenyl acetate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) listed isoeugenyl acetate, giving an ADI of 5 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on isoeugenyl acetate.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 3·45 g/kg (3·16–3·74 g/kg) while the acute dermal LD_{50} in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. Isoeugenyl acetate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was slightly irritating (Moreno, 1973). Tested at 10% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1973).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 23 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Epstein, 1973).

Metabolism. The hydrolysis of ester linkages of foreign compounds may be catalysed by many different esterases, which are to be found in all animals and bacteria and which generally have a low degree of substrate specificity (Parke, 1968).

Daily intake. The maximum possible daily intake of isoeugenyl acetate in the human diet was calculated to be 4·39 mg/day (age 2–65+ yr) or 0·19 mg/kg/day (age 12–23 months) (Federation of American Societies for Experimental Biology, 1973).

Insects. Termites, *Reticulitermes flavipes*, were rapidly attracted by and remained on discs treated with isoeugenyl acetate (Watanabe & Casida, 1963).

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Parke, D. V. (1968). *The Biochemistry of Foreign Compounds*. p. 125. Pergamon Press, Oxford.

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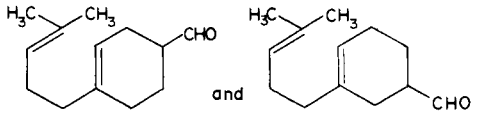
ISOHEXENYL CYCLOHEXENYL CARBOXALDEHYDE

Synonyms: 4-(4-Methyl-3-penten-1-yl)-3-cyclohexene-1-carboxaldehyde; myrac aldehyde.
Structure:



Description and physical properties: Colourless oily liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: From myrcene and acrolein (Arctander, 1969).
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to approximately 12,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·1
Maximum	0·1	0·01	0·015	0·3

Analytical data: Gas chromatogram, RIFM no. 74–137; infra-red curve, RIFM no. 74–137.

Status

Isohexenyl cyclohexenyl carboxaldehyde is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974) or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1974).

Irritation. Isohexenyl cyclohexenyl carboxaldehyde applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1974). Tested at 3% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 23 volunteers. The material was tested at a concentration of 3% in petrolatum and produced no sensitization reactions (Epstein, 1974).

References

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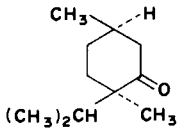
Moreno, O. M. (1974). Report to RIFM, 10 December.

ISOMENTHONE

Structure:



Description and physical properties: A colourless slightly oily liquid.
Occurrence: *d*-Isomenthone has been reported to have been isolated from *Micromeria abissinica* Benth., *Pelargonium tomentosum* Jacquin and others. *l*-Isomenthone has been identified in *Reunion geranium*, *Pelargonium capitatum* and others (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: By hydrogenation of piperitone.
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to less than 3000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·003	0·08
Maximum	0·2	0·02	0·05	0·8

Analytical data: Gas chromatogram, RIFM no. 72-172; infra-red curve, RIFM no. 72-172.

Status

The Council of Europe (1974) included isomenthone at a level of 0·5 ppm in the list of artificial flavouring substances that may be added temporarily to foodstuffs without hazard to public health.

Biological data

Acute toxicity. The acute dermal LD_{50} in rabbits was reported as >5 ml/kg (Levenstein, 1973).

Irritation. Isomenthone applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was mildly irritating (Levenstein, 1973). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1973).

Metabolism. *d*-Isomenthone undergoes reduction in the rabbit, since *d*-isomethylglucuronide is excreted in the urine. The other possible reduction product, *d*-neoisomenthol is not excreted (Williams, 1959).

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Kligman, A. M. (1973). Report to RIFM, 9 May.

Kligman, A. M. & Epstein, W. (1975). Updating the maximization test for identifying contact allergens. *Contact Dermatitis.* **1**, 231.

Levenstein, I. (1973). Report to RIFM, 16 February.

Williams, R. T. (1959). *Detoxication Mechanisms. The Metabolism and Detoxication of Drugs, Toxic Substances and Other Organic Compounds.* 2nd Ed., p. 526. Chapman & Hall, Ltd., London.

2-ISOPROPYL-5-METHYL-2-HEXENE-1-AL

Synonym: Isodihydrolavandulyl aldehyde.
Structure: $CH_3 \cdot CH(CH_3) \cdot CH_2 \cdot CH{:}C(CH \cdot (CH_3)_2) \cdot CHO$.
Description and physical properties: A colourless oily liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By aldol condensation of isovaleraldehyde.
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·1
Maximum	0·15	0·015	0·04	1·0

Analytical data: Gas chromatogram, RIFM no. 72-68; infra-red curve, RIFM no. 72-68.

Status

2-Isopropyl-5-methyl-2-hexene-1-al was given GRAS status by FEMA (1973).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. 2-Isopropyl-5-methyl-2-hexene-1-al applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1973). Tested at 10% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1972).

References

Flavoring Extract Manufacturers' Association (1973). Survey of flavoring ingredient usage levels. No. 3406. *Fd Technol., Champaign* **27** (11), 56.

Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.

Kligman, A. M. (1972). Report to RIFM, 23 August.

Kligman, A. M. & Epstein, W. (1975). Updating the maximization test for identifying contact allergens. *Contact Dermatitis* **1**, 231.

Moreno, O. M. (1973). Report to RIFM, 23 July.

2-ISOPROPYL-5-METHYL-2-HEXENE-1-OL

Synonym: Isodihydrolavandulol.
Structure: $CH_3 \cdot CH(CH_3) \cdot CH_2 \cdot CH{:}C(CH \cdot (CH_3)_2) \cdot CH_2OH$.
Description and physical properties: A colourless liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By reduction of isodihydrolavandulyl aldehyde.
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to approximately 5000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·2
Maximum	0·25	0·025	0·05	1·0

Analytical data: Gas chromatogram, RIFM no. 72-66; infra-red curve, RIFM no. 72-66.

Status

2-Isopropyl-5-methyl-2-hexene-1-ol is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974), or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. 2-Isopropyl-5-methyl-2-hexene-1-ol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1973). Tested at 10% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1972).

References

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Moreno, O. M. (1973). Report to RIFM, 16 July.

2-ISOPROPYL-5-METHYL-2-HEXENE-1-YL ACETATE

Synonym: Isodihydrolavandulyl acetate.
Structure: $CH_3 \cdot CH(CH_3) \cdot CH_2 \cdot CH{:}C(CH \cdot (CH_3)_2) \cdot CH_2 \cdot OCO \cdot CH_3$.
Description and physical properties: A colourless liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By acetylation of isodihydrolavandulol (Arctander, 1969).
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to approximately 20,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·01	0·2
Maximum	0·25	0·025	0·05	1·0

Analytical data: Gas chromatogram, RIFM no. 72-67; infra-red curve, RIFM no. 72-67.

Status

2-Isopropyl-5-methyl-2-hexene-1-yl acetate is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974), or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. 2-Isopropyl-5-methyl-2-hexene-1-yl acetate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was mildly irritating (Moreno, 1973). Tested at 10% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1972).

References

Arctander, S. (1969). *Perfume and Flavor Chemicals (Aroma Chemicals)*. Vol. 1, no. 958. S. Arctander, Montclair, New Jersey.

Council of Europe (1974). Natural Flavouring Substances, Their Sources, and Added Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. Strasbourg.

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Food Chemicals Codex (1972). 2nd Ed. Prepared by the Committee on Specifications, Food Chemicals Codex, of the Committee on Food Protection. National Academy of Sciences–National Research Council Publ. 1406, Washington, D.C.

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Kligman, A. M. & Epstein, W. (1975). Updating the maximization test for identifying contact allergens. *Contact Dermatitis* **1**, 231.

Moreno, O. M. (1973). Report to RIFM, 6 July.

ISOPROPYL MYRISTATE

Synonym: Isopropyl tetradecanoate.
Structure: $(CH_3)_2 \cdot CH \cdot OCO \cdot [CH_2]_{12} \cdot CH_3$.
Description and physical properties: A colourless oily liquid.
Occurrence: Apparently has not been reported to occur in nature.
Preparation: By conventional esterification of isopropanol with myristic acid (Arctander, 1969).
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to approximately 100,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·02	0·5
Maximum	0·3	0·03	0·2	2·0

Status

The Council of Europe (1974) included isopropyl myristate at a level of 5 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health. Isopropyl myristate is included in a provisional list of acceptable additives for use in hair-sprays compiled by the Federal Health Office of West Germany (Bundesgesundheitsamt, 1965).

Biological data

Acute toxicity. The acute oral LD_{50} value in mice was reported as >100 ml/kg (Fassett, 1963). The acute dermal LD_{50} in rabbits was reported as >5 g/kg (Moreno, 1974). When an ip dose of 100 ml/kg was given to two mice over a 4-hr period, both animals survived the 72-hr observation period (Platcow & Voss, 1954), and later the ip LD_{50} in mice was reported to be >50·2 ml/kg (Fitzgerald, Kurtz, Schardein & Kaump, 1968). Fitzgerald *et al.* (1968) also reported that the ip and sc LD_{50} values exceeded 79·5 ml/kg in rats.

Subacute toxicity. A mixture of 25% isopropyl myristate and 75% peanut oil produced only minor local damage without definitive systemic effects when injected repeatedly into rats, dogs and monkeys, or when given as single intramuscular injections to rabbits (Fitzgerald *et al.* 1968). Daily ip injection of 5 ml/kg in rats for 20 days caused three deaths after 5 days, but no growth depression or histopathological changes were observed in the surviving five rats (Platcow & Voss, 1954).

Irritation. Daily cutaneous application of isopropyl myristate to the skin of mice and rabbits for up to 28 days induced a prompt skin response (Fitzgerald *et al.* 1968). This was characterized at first by erythema, and later by lichenification and fissure formation. Histologically, acanthosis, para- and hyperkeratosis, focal erosion and focal haemorrhage were seen. In rabbits, the skin lesions regressed slowly after cessation of treatment, while in mice the lesions tended to regress during continued treatment. Similar reactions occurred with combinations of isopropyl myristate and peanut oil, but the intensities of the dermatoses were generally related to the proportion of isopropyl myristate in the mixture. Peanut oil alone produced only mild gross and microscopic changes (Fitzgerald *et al.* 1968). No signs of allergic or other types of sensitivity were observed in tests using intracutaneous injection in guinea-pigs (Platcow & Voss, 1954). Direct contact with the rabbit eye produced only mild, transient irritation (Platcow & Voss, 1954). No parenteral irritation was observed after injection of trypan blue solution following intracutaneous injection of isopropyl myristate into the abdominal skin of the rabbit (Platcow & Voss, 1954).

In a 48-hr occluded patch test using 20% isopropyl myristate in petrolatum on human subjects, no irritant effects were produced (Kligman, 1974), and isopropyl myristate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Moreno, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers using 20% isopropyl myristate in petrolatum. No sensitization reactions were produced (Kligman, 1974). Bergwein (1964) describes isopropyl myristate as being completely free of dermatological objections and possessing no sensitizing properties at all.

Metabolism. Higher molecular weight aliphatic esters are thought to be readily hydrolysed to the corresponding alcohols and acids which are then metabolized; isopropyl myristate is undoubtedly hydrolysed to normal metabolic products (Fassett, 1963). When myristic acid (as the ethyl ester) was fed to dogs, <2% of the amount fed was detected as unabsorbed material in the faeces, and no increased amount of ether-soluble acids was found in the urine (Weitzel, 1951).

Isopropyl myristate was found to be utilized as the sole source of carbon by micro-organisms (12 of 23 strains of bacteria, all of 25 strains of yeast and all of 17 strains of fungi) isolated from cosmetic products (Yanagi & Onishi, 1971).

Carcinogenesis. Isopropyl myristate (as a 50% solution in isopropyl alcohol) significantly accelerated the carcinogenic activity of 0·15% benzo[*a*]pyrene on the skin of C3H mice, and also significantly depressed the response of sensitized guinea pigs to 2,4-dinitrochlorobenzene challenge in the same way as known accelerators (Horton, Van Dreal & Bingham, 1966). No tumours were produced when isopropyl myristate as a 1% solution in acetone was painted once weekly for 18 months on the skin of mice (Giles & Byron, 1968). The potential carcinogenicity and toxicity of isopropyl myristate was studied in female Swiss mice by the administration of repeated applications on the skin for the life-span of the animals (Stenbäck & Shubik, 1974). Tumours seen in both control and treated animals were mainly lymphomas, haemangiomas of the liver and lung adenomas, but tumours of other organs also occurred. No statistically significant increase in tumour incidence was caused by isopropyl myristate. Skin lesions, slight inflammation and ulceration were seen, but no persistent cutaneous abnormalities occurred. A few skin tumours were seen in treated areas as well as in untreated areas and in control animals. Thus a carcinogenic or toxic potential which would affect the use of isopropyl myristate in man was not detected (Stenbäck & Shubik, 1974).

Skin penetration. Isopropyl myristate was used as a solvent in studying the effect of intracutaneously injected alcohol on capillary permeability in rabbit skin, by measuring the extravasal leakage of Evans blue injected iv (Suzuki & Arai, 1966; Suzuki & Motoyoshi, 1965). Gelled isopropyl myristate was found to exert a much greater effect than petrolatum USP on the penetration of dexamethasone through stripped human skin, although it apparently had little influence on penetration through intact skin (Dempski, Portnoff & Wase, 1969).

Micro-organisms. The toxicity of isopropyl myristate to micro-organisms has been studied because of the use of this ester as a solubilizing agent in sterility testing of ophthalmic ointments. Tsuji, Stapert, Robertson & Waiyaki (1970) found that isopropyl myristate was more toxic to gram-negative than to gram-positive micro-organisms, and that *Pseudomonas aeruginosa* was the most sensitive to isopropyl myristate of the gram-negative micro-organisms tested. The toxic compounds can be removed and the toxicity of both filter- and heat-sterilized isopropyl myristate can be reduced by basic alumina treatment. The toxic effect may be due to trace amounts of acidic catalysts remaining after production of isopropyl myristate (Tsuji & Robertson, 1973).

Pharmacology. Isopropyl myristate is used in pharmaceutical preparations because it improves solubility and increases absorption through the skin. External uses include a non-irritating iodine preparation for disinfecting the skin (Powers & Rieger, 1963) and aerosol bactericidal preparations for feminine hygiene use without irritation of the skin and mucous membranes (Geistlich, 1970; Watson, 1969). Preparations for internal use include oral steroid formulations (Hirata, 1970) and anaesthetic injection solutions (Davis, Pearce & Connor, 1972).

Veterinary medications containing isopropyl myristate include oral or parenteral compositions for lungworm infections (N. V. Philips' Gloielampenfabrieken, 1964) and a spray formulation for bovine udders to treat mastitis, combat infection and improve the general skin condition (Kraus, 1965). Isopropyl myristate has been found to be an effective repository vehicle for im injection of penicillin in rabbits and for sc administration of oestrogens in ovariectomized rats (Platcow & Voss, 1954).

In assays on human forearms, vasoconstrictor activity of ointment preparations containing 0·025% betamethasone 17-benzoate in white soft paraffin was increased by the presence of isopropyl myristate (Pepler, Woodford & Morrison, 1971). Donovan, Ohmart & Stoklosa (1954) noted that the good solvent properties of isopropyl myristate might increase the therapeutic activity of formulations by the apparent alteration in particle size of the active ingredients, so that further evaluation and clinical study would be necessary before its use in extemporaneous compounding could be recommended. Studies in which the antifungal activity of paraben esters solubilized by surfactants was decreased by isopropyl myristate (Matsumoto & Aoki, 1962) indicate that the effectiveness of medicinal substances may be influenced by the presence of surfactants and oily ingredients such as isopropyl myristate.

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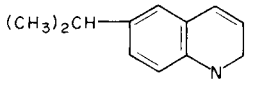
ISOPROPYL QUINOLINE

Synonyms: 6-Isopropyl quinoline; *p*-isopropyl quinoline.
Structure:



Description and physical properties: *Givaudan Index* (1961).
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By Skraup's reaction from *p*-isopropylaniline and acrolein (Arctander, 1969).
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·003	0·0003	0·001	0·04
Maximum	0·03	0·003	0·005	0·15

Analytical data: Gas chromatogram, RIFM no. 74–219; infra-red curve, RIFM no. 74–219.

Status

Isopropyl quinoline is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974), or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 0·94 g/kg (0·71–1·17 g/kg) and the acute dermal LD_{50} in rabbits as 0·16 g/kg (0·10–0·22 g/kg) (Moreno, 1974).

Irritation. Isopropyl quinoline applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was slightly irritating (Moreno, 1974). Tested at 2% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 24 volunteers. The material was tested at a concentration of 2% in petrolatum and produced no sensitization reactions (Epstein, 1974).

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ISOPULEGOL

Synonyms: *p*-Menth-8-en-3-ol; 1-methyl-4-isopropenylcyclohexan-3-ol.
Structure: $CH_3 \cdot C(CH_2) \cdot C_6H_9(CH_3) \cdot OH$.
Description and physical properties: EOA Spec. no. 282.
Occurrence: l-Isopulegol has been reported in the essences of lemongrass, East African geranium and *Eucalyptus citriodora*. *d*-Isopulegol is present in the oils of Backhousia and *Baeckea citriodorae*. *d*-Neoisopulegol is found in *Mentha rotundifolia* (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: By the isomerization and cyclization of citronellal.
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to approximately 3000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·01	0·12
Maximum	0·2	0·02	0·03	0·6

Analytical data: Gas chromatogram, RIFM no. 71–47; infra-red curve, RIFM no. 71–47.

Status

Isopulegol was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included isopulegol in the list of artificial flavouring substances that may be added temporarily to foodstuffs without hazard to public health. The *Food Chemicals Codex* (1972) has a monograph on isopulegol.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 1·03 $\pm$ 0·10 ml/kg and the acute dermal LD_{50} in rabbits as approximately 3 ml/kg (Lynch, 1971).

Irritation. Isopulegol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was severely irritating (Lynch, 1971). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1971).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1971).

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ISOPULEGOL ACETATE

Synonym: 1-Methyl-4-isopropenylcyclohexan-3-yl acetate.
Structure: $CH_3 \cdot C(CH_2) \cdot C_6H_9(CH_3) \cdot OCO \cdot CH_3$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Apparently has not been reported to occur in nature.
Preparation: By acetylation of isopulegol.
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 2000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·015	0·12
Maximum	0·2	0·02	0·05	0·8

Analytical data: Gas chromatogram, RIFM no. 72-173; infra-red curve, RIFM no. 72-173.

Status

Isopulegol acetate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included isopulegol acetate in the list of artificial flavouring substances that may be added temporarily to foodstuffs without hazard to public health.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Russell, 1973).

Irritation. Isopulegol acetate tested at 8% in petrolatum produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1973).

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ISOSAFROLE*

Synonyms: 3,4-Methylenedioxy-1-propenylbenzene; 4-propenylcatechol methylene ether.
Structure: $CH_3 \cdot CH{:}CH \cdot C_6H_3 \cdot O \cdot CH_2 \cdot O$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: The *trans* form occurs in the essential oil of ylang-ylang. It has also been identified in the oils of *Illicium religiosum* and *Ligusticum acutilobum* Sieb. and Zucc. (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: From safrole by treatment with potassium or sodium hydroxide in the dry state or alcoholic solution, under pressure or at atmospheric pressure (Arctander, 1969).
Uses: In public use before the 1920s. Use in fragrances in the USA amounts to approximately 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·015	0·12
Maximum	0·2	0·02	0·05	0·8

Analytical data: Gas chromatogram, RIFM no. 72-29; infra-red curve, RIFM no. 72-29.

Status

The FDA does not permit isosafrole to be used in foods (21 CFR 121.106).

Biological data

Acute toxicity. The acute oral LD_{50} value was reported as 1·34 g/kg in rats and as 2·47 g/kg in mice (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964). The acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1972). Four daily oral doses of 460 mg isosafrole/kg given to rats produced macroscopic liver lesions (Taylor, Jenner & Jones, 1964). Oral doses of 500 mg isosafrole/kg/day given as a 25% solution in corn oil to rats for 41 days killed eight of ten animals, while 250 mg/kg/day killed only two of ten in 34 days (Hagan, Jenner, Jones, Fitzhugh, Long, Brouwer & Webb, 1965).

Subacute toxicity. In a feeding study, 10,000 ppm fed to rats in the diet for 11 wk produced growth retardation in both sexes and macroscopic and microscopic liver changes. No rats on this dose survived beyond 11 wk of treatment (Hagan, Hansen, Fitzhugh, Jenner, Jones, Taylor, Long, Nelson & Brouwer, 1967).

Long-term toxicity. In a 2-yr feeding study in rats involving groups of ten males and ten females on 1000 or 2500 ppm and of 25 males and 25 females on 5000 ppm, slight liver damage occurred at the two lowest levels but no liver tumours were seen, while primary hepatic tumours appeared at the highest level. Growth retardation in both sexes occurred at the highest level, while at the two lower levels only slight growth retardation in females was observed. An increased number of interstitial-cell tumours in the testes and an increased incidence of chronic nephritis in the kidney were observed at the highest level. Slight thyroid damage was also observed at the 5000 and 2500 ppm level (Hagan *et al.*, 1965).

Irritation. Isosafrole applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1972). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1972).

Metabolism. On oxidation, isosafrole gives rise initially to an allyl alcohol and another, unidentified, conjugated alcohol, which are further oxidized to the vinyl ketone and piperonyl acrolein, respectively. Condensation of the vinyl ketone with an amine would then lead to the formation of tertiary aminomethylenedioxypropiophenones (Mannich bases) (McKinney, Oswald, Fishbein & Walker, 1972).

Enzyme induction. Rats pretreated ip with isosafrole showed an enhanced ring- and *N*-hydroxylation of 2-acetamidofluorene by rat-liver microsomes *in vitro*. In hamsters an injection of 200 mg isosafrole/kg inhibited all hydroxylating activities of 2-acetamidofluorene except for the 7-hydroxylation of 2-acetamidofluorene (Lotlikar & Wasserman, 1972).

*A monograph on safrole appeared on p. 983 of *Food and Cosmetics Toxicology* 1974, **12**.

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JASMINE ABSOLUTE

Description and physical properties: A viscous, clear, yellow-brown liquid having the characteristic odour of jasmine. The main constituent of jasmine absolute is benzyl acetate (Guenther, 1952).
Occurrence: Found in the flowers of *Jasminum officinale* L. and other species of Jasminum (Fam. Oleaceae) (Guenther, 1952).
Preparation: By extraction of the concrete with ethanol (*Fenaroli's Handbook of Flavor Ingredients*, 1971; Naves, 1974).
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to approximately 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	Rarely	—	0·002	0·1
Maximum	used	—	0·03	0·3

Analytical data: Gas chromatogram, RIFM no. 72-174; infra-red curve, RIFM no. 72-174.

Status

Jasmine absolute was given GRAS status by FEMA (1965) and jasmine is approved by the FDA for food use (GRAS). The Council of Europe (1974) included jasmine in the list of substances, spices and seasonings deemed admissible for use with a possible limitation of the active principle in the final product.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1972).

Irritation. Undiluted jasmine absolute applied to the backs of hairless mice and swine (Urbach & Forbes, 1973) or to intact or abraded rabbit skin for 24 hr under occlusion (Moreno, 1972) was not irritating. Tested at 3% in petrolatum, jasmine absolute produced no irritation after a 48-hr closed-patch test on two different panels of human subjects (Kligman, 1972 & 1973).

Sensitization. In a maximization test (Kligman, 1966; Kligman & Epstein, 1975) carried out on 25 volunteers, the material (RIFM no. 72-3-174), tested at a concentration of 3% in petrolatum, produced sensitization reactions in two of the test subjects (Kligman, 1972)*. In a second maximization test (Kligman, 1966; Kligman & Epstein, 1975), carried out on 25 new volunteers, the material (RIFM no. 72-3-174R) was again tested at a concentration of 3% in petrolatum and produced no sensitization reactions (Kligman, 1973).

Phototoxicity. No phototoxic effects were reported for undiluted jasmine absolute on hairless mice and swine (Urbach & Forbes, 1973).

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*'*Spillover effect*'. In maximization testing, four unrelated materials are tested on each of 25 human subjects. In the event that one of the four test materials turns out to be a potent sensitizer (in this case it was Costus oil, which sensitized 25/25 subjects), false weak positive results may occur with the other three materials. When these three materials are subsequently retested out of the context of the serious allergen, and in the same or different groups of subjects, they prove to be negative. We refer to this as the 'spillover effect' (Björnberg, 1968; Kligman & Epstein, 1975).

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JUNIPER BERRY OIL

Description and physical properties: EOA Spec. no. 113. The principal constituents of juniper berry oil include *d*-pinene, camphene, l-terpineol-4 and other oxygenated constituents (Guenther, 1952).
Occurrence: Found in the fruit (berries) of *Juniperus communis* L. (Fam. Cupressaceae).
Preparation: By steam distillation of the dried ripe fruit.
Uses: In public use before the 1900s. Use in fragrances in the USA amounts to approximately 2000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·1
Maximum	0·2	0·02	0·05	0·8

Analytical data: Gas chromatogram, RIFM no. 72-175; infra-red curve, RIFM no. 72-175.

Status

Juniper berry was given GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1974) included juniper berry in the list of substances, spices and seasonings deemed admissible for use with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on juniper berry.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as >5 g/kg (Shelanski, 1972) and as 8·0 g/kg (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964). The acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Shelanski, 1972).

Irritation. Undiluted juniper berry oil applied to the backs of hairless mice and swine was not irritating (Urbach & Forbes, 1972), but applied to intact or abraded rabbit skin for 24 hr under occlusion it was moderately irritating (Shelanski, 1972). A patch test using juniper berry full strength for 24 hr produced two irritation reactions in 20 subjects (Katz, 1946). Juniper berry oil tested at 8% in petrolatum produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1972).

Phototoxicity. No phototoxic effects were reported for undiluted juniper berry oil on hairless mice and swine (Urbach & Forbes, 1972).

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LABDANUM OIL

Description and physical properties: EOA Spec. no. 181. The main constituents of labdanum oil are acetophenone, 1,5,5-trimethyl-6-cyclohexanone and ladaniol (Guenther, 1952).
Occurrence: Found in the gum of the shrub *Cistus ladaniferus* L. (Fam. Cistaceae).
Preparation: By steam distillation of the crude gum.
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to approximately 5000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·12
Maximum	0·1	0·01	0·03	0·8

Status

Labdanum was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1163). The Council of Europe (1974) included labdanum in the list of substances, spices and seasonings deemed admissible for use with a possible limitation of the active principal in the final product. The *Food Chemicals Codex* (1972) has a monograph on labdanum.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 8·98 g/kg (5·40–12·56 g/kg) (Hart, 1971). The acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Hart, 1971).

Irritation. Labdanum oil applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Hart, 1971). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1971).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1971). Cistus labdanum applied full strength for 48 hr in the standard occluded aluminium patch test used by the North American Contact Dermatitis Research Group did not produce any irritation or sensitization in a 62-yr-old subject with a perfume dermatitis (Larsen, 1975).

Additional published data

An extensive review of the monoterpenes in the volatile leaf oil of *Cistus labdanum* has been reported (Gülz, 1974).

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Larsen, W. G. (1975). Cosmetic dermatitis due to a perfume. *Contact Dermatitis* **1**, 142.

LAUREL LEAF OIL

Description and physical properties: EOA Spec. no. 119. The main constituent of laurel leaf oil is cineole (Guenther, 1950).

Occurrence: Found in the leaves of *Laurus nobilis* L. (Fam. Lauraceae).

Preparation: By steam distillation of the leaves of *Laurus nobilis* (Gildemeister & Hoffman, 1959).

Uses: In public use before the 1900s. Use in fragrances in the USA amounts to approximately 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·04
Maximum	0·06	0·006	0·02	0·2

Analytical data: Gas chromatogram, RIFM no. 73-97; infra-red curve, RIFM no. 73-97.

Status

Laurel leaf oil was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.101). The Council of Europe (1974) included laurel leaf in the list of substances, spices and seasonings deemed admissible for use, with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on laurel leaf oil.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 3·95 g/kg (3·17–4·74 g/kg) (Moreno, 1974). The acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1974).

Irritation. Laurel leaf oil applied undiluted to the backs of hairless mice and swine was not irritating (Urbach & Forbes, 1974), but when applied full strength to intact or abraded rabbit skin for 24 hr under occlusion it was moderately irritating (Moreno, 1974). Laurel leaf oil (RIFM no. 73-2-97) tested at 2% in petrolatum produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974). Retested at 10% in petrolatum (RIFM no. 73-10-97R), it again produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1974). Laurel leaf oil European (RIFM no. M-10-R) tested at 10% in petrolatum produced no irritation after a 48-hr closed-patch test on two different panels of human subjects (Epstein, 1975; Kligman, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material (RIFM no. 73-2-97) was tested at a concentration of 2% in petrolatum and produced no sensitization reactions (Epstein, 1974). When retested on 25 new volunteers by the same maximization test at a concentration of 10% in petrolatum, the material (RIFM no. 73-10-97R) produced no sensitization reactions (Kligman, 1974). Laurel leaf oil European (RIFM no. M-10-R) at a concentration of 10% in petrolatum produced no sensitization reactions when subjected to this maximization test, either in a first group of 25 volunteers (Kligman, 1975) or in a second group of 24 new volunteers (Epstein, 1975). Laurel leaf oil (RIFM no. M-10-R(O)) patch-tested at 10% in petrolatum on costus-sensitized individuals produced sensitization reactions in all six test subjects (Epstein, 1975).

Contact allergy to *Laurus nobilis* L. is common in some European countries, with topical medicaments, occupational situations, clothing and food being the most common sources (Bandmann & Dohn, 1967; Foussereau, Benezra & Ourisson, 1970). Laurel leaf oil has been reported to cause hyperaemia and severe inflammation (Finkenrath, 1941; Flandin, Rabeau & Ukrainczyk, 1938; Zundel, 1936). Components of the essential oil from leaves of *Laurus nobilis* boiling above 70°C at 15 mm are said to cause an allergic reaction in human skin (Teisseire, 1966). Cross-sensitization between Frullania and *Laurus nobilis* (L.) has been demonstrated, with new results on laurel oil pointing to the possibility of a common denominator (the α-methylene-γ-butyrolactone moiety) between the laurel and Frullania (Foussereau, Muller & Benezra, 1975).

Laurel oil has been listed as a sensitizer by Fregert (1974).

Phototoxicity. No phototoxic effects were reported for undiluted laurel leaf oil on hairless mice and swine (Urbach & Forbes, 1974).

Antibacterial properties. The essential oil from laurel was found to have bactericidal and fungicidal properties against a number of organisms. The oil was more effective than the aqueous extract from the leaves (1:10), which was not effective against *Salmonella enteritidis*, *S. typhimurium* or *Staphylococcus aureus* (Lomsadze & Pruidze, 1967).

Pharmacology. Pharmacological effects on circulation, such as the action on excised toad heart, rabbit heart, respiration and blood pressure, and on blood vessels of the hind legs of the toad were studied for various essential oils, including leaf oil from *Laurus nobilis*. The oils generally depressed the heart rate and decreased blood pressure (Haginiwa, Harada, Nakajima & Sakai, 1962).

Additional published data

Using an allergologic functional analysis, laurel leaf oil allergen has been shown to be an unsaturated ketone which can be isolated (as a mixture) with Girard reagent P (Foussereau *et al.* 1970). Formulations including laurel oil and leaves are claimed to have antidandruff properties (Czira, 1970; Mina, 1971).

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OIL LAVANDIN ACETYLATED

Description and physical properties: The main constituent of oil lavandin acetylated is linalyl acetate (Arctander, 1960).
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By acetylation of lavandin oil (Arctander, 1960).
Uses: In public use since the 1950s. Use of fragrances in the USA amounts to approximately 20,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·015	0·03
Maximum	0·3	0·03	0·1	1·2

Analytical data: Gas chromatogram, RIFM nos 72-31, 72-176; infra-red curve, RIFM nos 72-31, 72-176.

Status

Oil lavandin acetylated is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974), or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeds 5 g/kg (Keating, 1972).

Irritation. Undiluted oil lavandin acetylated applied to the backs of hairless mice and swine was not irritating (Urbach & Forbes, 1972). Tested at 10% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1972).

Phototoxicity. No phototoxic effects were reported for undiluted oil lavandin acetylated on hairless mice and swine (Urbach & Forbes, 1972).

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LAVANDIN OIL

Description and physical properties: EOA Spec. no. 41. The main constituent of lavandin oil is linalool (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Occurrence: Found in the plant *Lavandula hybrida* Reverchon (Fam. Labiatae).
Preparation: By steam distillation of the flowering stalks of *Lavandula hybrida* Reverchon (Gildemeister & Hoffman, 1961).
Uses: In public use since the 1900s. Use in fragrances in the USA amounts to approximately 500,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·015	0·3
Maximum	0·3	0·03	0·1	1·2

Analytical data: Gas chromatogram, RIFM no. 242981; infra-red curve, RIFM nos 242981, 73-24.

Status

Lavandin oil was given GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. Undiluted lavandin oil applied to the backs of hairless mice and swine was not irritating (Urbach & Forbes, 1973). Applied full strength to intact or abraded rabbit skin for 24 hr under occlusion, it was slightly irritating (Moreno, 1973). Tested at 5% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1971).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 26 volunteers. The material was tested at a concentration of 5% in petrolatum and produced no sensitization reactions (Kligman, 1971).

Phototoxicity. No phototoxic effects were reported for undiluted lavandin oil on hairless mice and swine (Urbach & Forbes, 1973).

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LAVENDER ABSOLUTE

Description and physical properties: A dark green liquid. The main constituent of lavender absolute is linalyl acetate (Guenther, 1949).
Occurrence: Found in the flowers of *Lavandula officinalis* chaix (Fam. Labiatae) (Guenther, 1949).
Preparation: From an alcoholic extract of the concrete which is extracted from the plant material using an organic solvent.
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to approximately 5000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·2
Maximum	0·15	0·015	0·03	1·0

Analytical data: Gas chromatogram, RIFM no. NAK-3; infra-red curve, RIFM no. NAK-3.

Status

Lavender absolute was given GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS).

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 4·25 g/kg (3·82–4·68 g/kg) (Moreno, 1975). The acute dermal LD_{50} value in guinea-pigs was reported at >5 g/kg (Moreno, 1975).

Irritation. Lavender absolute applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was slightly irritating (Moreno, 1975). Tested at 10% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1975). Lavender absolute (referred to as lavender oil) has been listed as a sensitizer (Nakayama, Hanaoka & Ohshiro, 1974).

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LAVENDER OIL

Description and physical properties: *Food Chemicals Codex* (1972). The main constituent of lavender oil is linalyl acetate (Guenther, 1949).
Occurrence: Found in the plant *Lavandula officinalis* chaix (Fam. Labiatae) (Guenther, 1949).
Preparation: By steam distillation of the flowering stalks of *Lavandula officinalis* chaix (Guenther, 1949).
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to approximately 100,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·015	0·3
Maximum	0·3	0·03	0·1	1·2

Analytical data: Gas chromatogram, RIFM no. 73-25; infra-red curve, RIFM no. 73-25.

Status

Lavender oil was given GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1974) included lavender oil in the list of substances, spices and seasonings deemed admissible for use, with a possible limitation of the active principle in the final product. Both the *Food Chemicals Codex* (1972) and the *National Formulary* (1970) have monographs on lavender oil.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. Undiluted lavender oil applied to the backs of hairless mice and swine was not irritating (Urbach & Forbes, 1973). Applied full strength to intact or abraded rabbit skin for 24 hr under occlusion, it was slightly irritating (Moreno, 1973). Tested at 16% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1971).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 16% in petrolatum and produced no sensitization reactions (Kligman, 1971).

Phototoxicity. No phototoxic effects were reported for undiluted lavender oil on hairless mice and swine (Urbach & Forbes, 1973).

Percutaneous absorption. Lavender oil was not absorbed within 2 hr of application to the intact shaved abdominal skin of the mouse (Meyer & Meyer, 1959).

Additional published data

The chemistry of lavender oil has been reviewed extensively (de La Torre, 1974), and a study of lavender oils and their constitution has been published (Staicov, Chingova & Kalaidjiev, 1969).

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SPIKE LAVENDER OIL

Description and physical properties: EOA Spec. no. 4. The main constituents of spike lavender oil are linalool and cineole.
Occurrence: Found in the plant *Lavandula latifolia* Vill. (L. Spica D. C.) (Fam. Labiatae).
Preparation: By steam distillation of the sun-dried flowers.
Uses: In public use before the 1860s. Use in fragrances in the USA amounts to approximately 100,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·03	0·01	0·2
Maximum	0·3	0·03	0·1	0·8

Analytical data: Gas chromatogram, RIFM no. 72-30; infra-red curve, RIFM no. 72-30.

Status

Spike lavender oil was given GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1974) included spike lavender oil in the list of substances, spices and seasonings deemed admissible for use, with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on spike lavender oil.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 3·8 g/kg (3·3–4·3 g/kg) (Moreno, 1972a). The acute dermal LD_{50} value in rabbits was reported as >2 g/kg (Moreno, 1972b).

Irritation. Spike lavender oil applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1972b). A patch test using spike lavender oil full strength for 24 hr produced no reactions in 15 human subjects (Katz, 1946). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1972).

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LEMONGRASS OIL EAST INDIAN

Description and physical properties: EOA Spec. no. 7. The main constituent of lemongrass oil is citral (Guenther, 1950). The non-citral portion has been described by Aggar, Kamath & Rao (1968).
Occurrence: Found in the grasses of *Cymbopogon flexuosus* (Stapf) and *Andropogon nardus* var. flexuosus (Fam. Graminae).
Preparation: By steam distillation of the freshly cut and partially dried grasses (Gildemeister & Hoffman, 1956).
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to approximately 50,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·003	0·08
Maximum	0·25	0·025	0·02	0·7

Analytical data: Gas chromatogram, RIFM no. 71-48; infra-red curve, RIFM no. 71-48.

Status

Lemongrass oil was given GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council for Europe (1974) included lemongrass in the list of substances, spices and seasonings deemed admissible for use, with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on lemongrass oil

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 5·6 g/kg (5·1–6·1 g/kg) (Moreno, 1972a). The acute dermal LD_{50} value in rabbits exceeded 2 g/kg (Moreno, 1972b).

Irritation. Undiluted lemongrass oil E.I. applied to the backs of hairless mice and swine was mildly irritating (Urbach & Forbes, 1972). Applied full strength to intact or abraded rabbit skin for 24 hr under occlusion, it was moderately irritating (Moreno, 1972b). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1972).

Phototoxicity. No phototoxic effects were reported for undiluted lemongrass oil E.I. on hairless mice and swine (Urbach & Forbes, 1972).

References

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LEMONGRASS OIL WEST INDIAN

Description and physical properties: EOA Spec. no. 7. The main constituent of lemongrass oil W.I. is citral (Guenther, 1950).

Occurrence: Found in the grasses of *Cymbopogon citratus* (Stapf) and *Andropogon nardus* var. ceriferus (Hack).

Preparation: By steam distillation of the freshly cut and partially dried grasses (Gildemeister & Hoffman, 1956).

Uses: In public use since the 1920s. Use in fragrances in the USA amounts to approximately 250,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·003	0·08
Maximum	0·25	0·025	0·02	0·7

Analytical data: Gas chromatogram, RIFM no. 71-4; infra-red curve, RIFM no. 71–4.

Status

Lemongrass oil was given GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1974) included lemongrass in the list of substances, spices and seasonings deemed admissible for use, with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on lemongrass oil.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Hart, 1971).

Irritation. Lemongrass oil W.I. applied undiluted to the backs of hairless mice and swine was mildly irritating (Urbach & Forbes, 1972). Applied full strength to intact or abraded rabbit skin for 24 hr under occlusion, it was moderately irritating (Hart, 1971). Tested at 4% in petrolatum, the material (RIFM no 71-4-4) produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1971). Lemongrass oil W.I. (RIFM no. DL-5-01) tested at 5% in petrolatum similarly produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material (RIFM no. 71-4-4) was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1971). In a further maximization test on 25 volunteers, the material (RIFM no. DL-5-01) was tested at a concentration of 5% in petrolatum and produced no sensitization reactions (Kligman, 1972).

Phototoxicity. No phototoxic effects were reported for undiluted lemongrass oil W.I. on hairless mice and swine (Urbach & Forbes, 1972).

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LEMON OIL EXPRESSED

Description and physical properties: *Food Chemicals Codex* (1972). The main constituent of lemon oil is *d*-limonene (Gildemeister & Hoffman, 1959; Guenther, 1949).
Occurrence: Found in the peel of the fruit *Citrus limon* (Linn.) Burm. F., (Fam. Rutaceae) (Guenther, 1949).
Preparation: By expression of the ripe peel of the fruit (Arctander, 1960).
Uses: In public use since the early 1800s. Use in fragrances in the USA amounts to about 150,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·05	0·005	0·25	0·50
Maximum	0·4	0·004	0·15	1·0

Analytical data: Gas chromatogram, RIFM nos 72-32 and 72-61; infra-red curve, RIFM nos 72-32 and 72-61.

Status

Lemon oil was granted GRAS status by FEMA (1965) and is approved by the FDA as GRAS for food use. The Council of Europe (1970) included lemon oil in the list of substances, spices and seasonings whose use is deemed admissible, with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) and the *United States Pharmacopeia* (1965) have monographs on lemon oil.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Hart, 1971).

Irritation. Lemon oil applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Hart, 1971). Three samples of lemon oil (RIFM nos 72-32, 72-61 and 72–241) applied undiluted to the backs of hairless mice were mildly irritating (Urbach & Forbes, 1972), but three other samples of lemon oil (RIFM nos 72-249, 72-230 and 72–251) similarly applied undiluted to the backs of hairless mice were not irritating (Urbach & Forbes, 1972). Lemon oil tested at 10% in petrolatum produced no irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1971). A patch test using full strength lemon oil for 24 hr produced no reactions in 24 human subjects (Katz, 1946).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1971).

Phototoxicity. Distinct phototoxic effects were reported by Urbach & Forbes (1972) for five samples of lemon oil—RIFM nos 72-61, 72-249, 72-250 (Italian), 72-241 (Greek) and 72-251 (Ivory Coast). Low-level phototoxic effects were reported for lemon oil (California; RIFM no. 72-32) (Urbach & Forbes, 1972).

Additional published data

The presence and identity of coumarins and psoralens in lemon oil has been reported (Kesterson, Hendrickson & Braddock, 1971; Stanley & Vannier, 1957). Antibacterial properties have been reported for lemon oil (Dabbah, Edwards & Moats, 1970), which has also been reported to promote tumour formation on the skins of mice treated with the primary carcinogen, 7,12-dimethylbenz[*a*]anthracene (Roe & Field, 1965).

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Urbach, F. & Forbes, P. D. (1972). Report to RIFM, 26 May; 22 September and 19 December.

LEMON OIL DISTILLED*

Preparation: By steam distillation of chopped lemon peel under partial vacuum (Arctander, 1960).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Hart, 1971).

Irritation. Lemon oil applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Hart, 1971). Lemon oil distilled (RIFM no. 72-240) applied undiluted to the backs of hairless mice was slightly irritating (Urbach & Forbes, 1972). Lemon oil FCF applied undiluted to the backs of hairless mice was not irritating (Urbach & Forbes, 1974). Lemon oil tested at 10% in petrolatum produced no irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1971).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1971).

Phototoxicity. No phototoxic effects were reported for lemon oil distilled, RIFM no. 72-240 (Urbach & Forbes, 1972) or for lemon oil FCF (Urbach & Forbes, 1974).

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*See also preceding monograph on Lemon Oil Expressed.

LIME OIL DISTILLED

Description and physical properties: EOA Spec. no. 78. The main constituent of lime oil distilled is *d*-limonene (Gildemeister & Hoffman, 1959; Guenther, 1949).
Occurrence: Found in the fruit *Citrus aurantifolia* Swingle formerly classified as *Citrus medica* L., var acida Brandis (Fam. Rutaceae).
Preparation: By distillation of the whole crushed fruit.
Uses: In public use before the 1900s. Use in fragrances in the USA amounts to about 50,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·05	0·005	0·03	0·4
Maximum	0·25	0·025	0·1	1·5

Analytical data: Gas chromatogram, RIFM no. S-2276.

Status

Lime oil was granted GRAS status by FEMA (1965) and is approved as GRAS by the FDA for food use. The Council of Europe (1970) included lime oil in the list of substances, spices and seasonings whose use is deemed admissible, with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on lime oil distilled.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Hart, 1971).

Irritation. Lime oil applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was slightly irritating (Hart, 1971). Tested at 15% in petrolatum, it produced no irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1971). A patch test using full strength lime oil for 24 hr produced no reactions in 20 subjects (Katz, 1946).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 15% in petrolatum and produced no sensitization reactions (Kligman, 1971).

Phototoxicity. No phototoxic effects were reported for lime oil distilled (Urbach & Forbes, 1972).

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Urbach, F. & Forbes, P. D. (1972). Report to RIFM, 23 March.

LIME OIL EXPRESSED

Description and physical properties: EOA Spec. no. 88. The chief constituent of lime oil expressed is *d*-limonene (Gildemeister & Hoffman, 1959; Guenther, 1949).
Occurrence: Found in the peel of the fruit *Citrus aurantifolia* Swingle, formerly classified as *Citrus medica* L., var acida Brandis (Fam. Rutaceae).
Preparation: By expression from the fresh peel of the fruit.
Uses: In public use since the 1800s. Use in fragrances in the USA amounts to about 50,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·05	0·005	0·03	0·5
Maximum	0·25	0·025	0·1	1·5

Status

Lime oil was granted GRAS status by FEMA (1965) and is approved by the FDA as GRAS for food use. The Council of Europe (1970) included lime oil in the list of substances, spices and seasonings whose use is deemed admissible, with a possible limitation of the active principle in the final product.

Biological data*

Phototoxicity. Lime oil expressed was found to have phototoxic properties when tested on hairless mice, pigs and man (Urbach & Forbes, 1972).

Additional published data

Lime oil has been reported as a tumour promoter on the skin and in the forestomach epithelium of mice treated with the primary carcinogen, 7,12-dimethylbenz[*a*]anthracene (Roe & Field, 1965). Eleven cases of photodermatitis due to oil of Persian lime have been reported and a photodynamic reaction was experimentally produced by oil from the Persian lime on the skin and subsequent solar irradiation (Sams, 1941). The presence and identity of coumarins and psoralens in lime oil has been reported (Kesterson, Hendrickson & Braddock, 1971; Stanley & Vannier, 1967).

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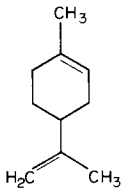
*See also preceding monograph on Lime Oil Distilled.

d-LIMONENE

Synonyms: 1,8(9)-*p*-Methadiene; 1-methyl-4-isopropenyl-1-cyclohexene.
Structure:



Description and physical properties: EOA Spec. no. 253.
Occurrence: *d*-Limonene is the main constituent of orange oil and occurs in lemon, mandarin, lime, grapefruit, bergamot, neroli, petitgrain, elemi, caraway, dill, fennel, celery, erigeron and orthodon oils and a very large number of other essential oils (Gildemeister & Hoffman, 1960; Guenther, 1949).
Preparation: By steam distillation after alkali treatment of citrus peels and pulp, and also by the fractionation of orange oil.
Uses: In public use before the 1900s. Use in fragrances in the USA amounts to approximately 150,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·05	0·005	0·03	0·3
Maximum	0·25	0·025	0·2	1·0

Analytical data: Gas chromatogram, RIFM nos 70–27, 72–62; infra-red curve, RIFM nos 70–27, 72–62.

Status

d-Limonene was given GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1974) included *d*-limonene with a technological limit, except for chewing gum, in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health. The *Food Chemicals Codex* (1972) has a monograph on *d*-limonene. An extensive review of the chemistry of limonene and its derivatives has been published by Verghese (1969).

Biological data

Acute toxicity. Both the acute oral LD_{50} in rats and the acute dermal LD_{50} in rabbits exceeded 5 g/kg (Moreno, 1972).

Irritation. *d*-Limonene applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1972). The *Merck Index* (1968) reported limonene to be a skin irritant.

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Greif, 1967). One case of hypersensitivity to oil of lemon due to its content of limonene has been reported (Keil, 1947). Allergic eczemas from orange peel are considered to be due usually to sensitization to limonene, but it appears that other constituents may be the cause, since among cases of sensitivity to orange peel, two showed negative reactions to limonene and not all were sensitive to lemon peel, as would have been expected if limonene were the cause of the sensitivity (Hjorth, 1961).

On auto-oxidation of the four most frequently occurring constituents of Swedish turpentine (i.e. Δ^3-carene, α-pinene, β-pinene and limonene), Δ^3-carene yields the most eczematogenic products, while limonene required more oxygen to be a reactor (Hellerstrom, Thyresson & Widmark, 1957). Limonene cannot be made to produce dermatitis; any reaction observed with limonene from turpentine is a result of contamination with Δ^3-carene (Pirilä, Veiko & Siltanen, 1958) or its oxidation products (Opdyke, 1973). Limonene has been reported to be a sensitizer (*Merck Index*, 1968), but the reported cases of sensitization have probably been caused by auto-oxidation products of the oils.

Percutaneous absorption. Limonene was well absorbed on to the skin of rats (Valette & Cavier, 1954).

Antibacterial activity. Antibacterial properties have been reported for *d*-limonene (Dabbah, Edwards & Moats, 1970).

Carcinogenesis. *d*-Limonene exerts anticarcinogenic or chemophylactic effects against the carcinogenic effects of sc-injected dibenzopyrene (Homburger, Treger & Boger, 1971). The hydroperoxide derivatives of *d*-limonene have produced carcinogenic and cocarcinogenic effects (Homburger & Boger, 1968).

Additional published data

Limonene administered orally has a weak psycholeptic effect in the mouse, and an effective dose was of the order of 50–150 mg/kg; the psychotropic action of limonene is a transient one and it is unlikely that the compound would have any effect of this kind in man at the concentrations in which it occurs in food or drinks (Le Bourhis & Soenen, 1973).

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LINALOOL

Synonyms: 3,7-Dimethyl-1,6-octadien-3-ol; 2,6-dimethyl-octadien-2,7-ol-6.
Structure: $CH_3 \cdot C(CH_3):CH \cdot [CH_2]_2 \cdot (CH_3)C(OH) \cdot CH:CH_2$.
Description and physical properties: EOA Specs nos 48 & 226.
Occurrence: The optically active forms (*d*- and *l*-) and the optically inactive form occur naturally in more than 200 oils from herbs, leaves, flowers and wood. The *l*-form is present in the largest amounts (80–85%) in the distillates from leaves of *Cinnamomum camphora* var. *orientalis* and *C. camphora* var. *occidentalis* and in the distillate from Cajenne rosewood. It has also been reported in champaca, ylang-ylang, neroli, Mexican linaloe, bergamot, lavandin and others. A mixture of *d*- and *l*-linalool has been reported in Brazil rosewood (85%). The *d*-form has been found in palmarosa, mace, sweet orange-flower distillate, petitgrain, coriander (60–70%), marjoram, *Orthodon linaloolíferum* (80%) and others. The inactive form has been reported in clary sage, jasmine and *Nectandra elaiophora* (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: By fractionation of Bois de Rose oil or by chemical synthesis.
Uses: In public use before the 1900s. Use in fragrances in the USA amounts to approximately 200,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·04	0·004	0·02	0·5
Maximum	0·3	0·03	0·1	1·5

Analytical data: Gas chromatogram, RIFM no. 70–66; infra-red curve, RIFM no. 70–66.

Status

Linalool was given GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1974) listed linalool giving an ADI of 0.25 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on linalool and the Joint FAO/WHO Expert Committee on Food Additives (1967) has published a monograph and specifications for linalool giving a conditional ADI of 0–0.25 mg/kg.

Biological data

Acute toxicity. The acute ip LD_{50} of linalool was found to be 340 mg/kg for male albino mice and 307 mg/kg for male albino rats (Atanassova-Shopova, Roussinov & Boycheva, 1973). In tests using 75–800 mg/kg, animals rapidly developed an ataxic gait, obviously reduced spontaneous motor activity and depression while higher doses caused the assumption of a lateral position and development of respiratory disturbances leading to death. Narcotic effects were obtained with a dose equivalent to approximately half of the LD_{50}.

The acute oral LD_{50} of linalool for rats was found to be 2790 mg/kg, with ataxia soon after treatment and death within 4–18 hr (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964). The acute intramuscular LD_{50} for mice was found to be 8 g/kg (Northover & Verghese, 1962). The acute dermal LD_{50} in rabbits was reported as 5610 (3578–8374 mg/kg) Fogleman, 1970).

Subacute toxicity. The maximum tolerated dose (MTD) of linalool for mice was found to be 0·125 g/kg, determined as the maximum single dose tolerated by all of a group of five mice given six ip injections over a 2-wk period (Stoner, Shimkin, Kniazeff, Weisburger, Weisburger & Gori, 1973). The effects of linalool on hepatic drug-metabolizing enzymes in the rat were studied by Parke and co-workers. Pretreatment of rats for 3 days with 150 mg linalool/kg ip caused no increase in the activities of biphenyl 4-hydroxylase, glucuronyl transferase, or cytochrome *P*-450 in liver homogenates, but increased the activity of 4-nitrobenzoate reductase by 25–50% (Parke & Rahman, 1969).

In a longer study, intragastric administration of 500 mg linalool/kg/day for up to 64 days indicated that effects on liver proteins and drug-metabolizing enzymes developed slowly and might represent physiological adaptation to linalool. Thus linalool may be involved in the induction of drug-metabolizing enzymes in neonatal rats (from 4 wk old). Over the 64-day period, body weight was not affected, while liver weight and relative liver weight were slightly increased after day 30. Microsomal-protein concentration was increased after day 14. Cytochrome concentrations were decreased on day 7 but had increased by 50–70% by day 64. 4-Methylumbelliferone-glucuronyl transferase activity increased from 17% on day 3 to 150% by day 64, while alcohol-dehydrogenase activity was depressed by 33% on day 3, but was normal between days 14 and 64 (Parke, Rahman & Walker, 1974b).

Irritation. Linalool applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Fogleman, 1970). Tested at 20% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1970). In other closed-patch tests on human skin, linalool caused no primary irritation in 28 normal subjects when applied as a 20% concentration in vaseline or ointment, in 30 normal subjects when applied at 2%, or in 84 subjects with dermatoses when tested in 0·4% concentration in ethanol or a cream base (Fujii, Furukawa & Suzuki, 1972).

In tests of acanthogenic activity, daily application of a 20% solution of linalool in absolute alcohol to guinea-pig skin for 8–10 days caused some epidermal thickening, with a mean acanthosis factor of 4·6 (solvent = 1) (Schaaf, 1961).

The effect of linalool and other alcohols on local capillary permeability was studied in rabbits by the intracutaneous injection of various concentrations dissolved in isopropyl myristate and the measurement of the resulting extravasal leakage of Evans blue injected iv. Tertiary alcohols showed lower responses than other types of alcohols, while responses were enhanced for unsaturated alcohols (Suzuki & Arai, 1966).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 20% in petrolatum and produced no sensitization reactions (Kligman, 1970). In another maximization test (Kligman, 1966) on 25 volunteers, the material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Greif, 1967).

Metabolism. The metabolism of ^{14}C-labelled linalool in the rat was studied by Parke, Rahman & Walker (1974a). An intragastric dose of 500 mg linalool/kg body weight was largely (93%) excreted within 72 hr in the urine (55%), faeces (23%) and expired air (15%). The radioactivity remaining after 72 hr was located mainly in the liver (0·5%), gut (0·6%), skin (0·8%) and skeletal muscle (1·2%). Rapid urinary excretion indicated that linalool was rapidly absorbed from the gut, while delay in excretion in the expired air suggested that linalool might enter intermediary metabolism and also be metabolized by conjugation in the bile and urine. Ip administration of 20 mg linalool indicated that enterohepatic circulation occurred, resulting in a short-term metabolic load on the liver and delayed faecal excretion. The metabolism of large doses in the rat, with rapid excretion of linalool and its metabolites, suggests no long-term hazard from tissue accumulation on chronic exposure to concentrations normally encountered in foods, although enterohepatic circulation might prolong the metabolic load on the liver over a relatively short period.

A study of the effects of linalool and other terpenoids on hepatic drug-metabolizing enzymes suggested that these compounds induce the enzymes involved in their own metabolism. Linalool, which is metabolized by reduction and conjugation with glucuronic acid, increased the activity of 4-nitrobenzoate reductase but did not increase other enzymes studied (Parke & Rahman, 1969).

Linalool can be metabolized by micro-organisms. *l*-Linalool was partially oxidized by incubation with *Aspergillus niger* (Goto, 1967). The linalool content of grape essential oil decreased during must fermentation and wine formation (Rodopulo, Egorov, Bezzubov, Kormakova & Megrelidze, 1972). A strain of *Pseudomonas pseudomallei*, isolated from soil, metabolized linalool with the formation of camphor, 4-methyl-4-vinylbutyrolactone, 4-methyl-*trans*-3-hexenoic acid, and 2,6-dimethyl-6-hydroxy-*trans*-2,7-octadienoic acid (Mizutani, Hayashi, Ueda & Tatsumi, 1971).

Percutaneous absorption. Linalool was not absorbed within 2 hr on the intact shaved abdominal skin of the mouse (Meyer & Meyer, 1959). In an evaluation of skin penetrating agents, linalool as a 50% solution did not aid penetration of Rhodamine B into guinea-pig skin (Meyer, 1965).

Carcinogenicity. When mice received ip injections of the maximum tolerated dose (MTD) or 0·2 MTD (total dose 3·00 and 0·60 g/kg, respectively) 3 times/wk for 8 wk, 9–11 mice/group of 15 survived 24 wk, with no increase in primary lung-tumour induction compared with untreated controls (Stoner *et al.* 1973). Linalool as a 20% solution in acetone was reported to be a weak tumour-promoter on the skins of mice treated with the primary carcinogen, 9,10-dimethyl-1,2-benzanthracene (Roe & Field, 1965). Linalool and other terpenic compounds present in tobacco leaves or added during processing may be precursors of carcinogenic hydrocarbons formed during smoking by breakdown to isoprene, which is converted to an aromatic tar containing benzo[a]pyrene (Gil-Av & Shabtai, 1963).

Pharmacology. l-Linalool showed no sedative action in the mouse motility test when injected ip at a dose of 100 mg/kg (Binet, Binet, Miocque, Roux & Bernier, 1972), but Wagner & Sprinkmeyer (1973) reported that linalool depressed spontaneous motility of mice at doses of 31·6 and 100 mg/kg.

Linalool showed spasmolytic action against carbachol-, histamine- and barium chloride-induced contractions in isolated guinea-pig ileum, the ED_{50} being about 100–200 mg/litre (Wagner & Sprinkmeyer, 1973), and in the isolated rat duodenum, contractions caused by 0.05 μg acetylcholine/ml were inhibited by 50% by 10 μg *l*-linalool/ml (Binet *et al.* 1972). Linalool showed slight papavarine-like and very slight atropine-like antispasmodic action on small intestine isolated from the mouse (Imaseki & Kitabatake, 1962).

In studies carried out by Atanassova-Shopova *et al.* (1973), the ED_{50} for preventing tonic hyperextension of the hind limbs of rats from electric shock was found to be 135 mg/kg given ip. Linalool had a marked anticonvulsive and protective effect on pentylenetetrazol convulsions in mice at 150,

175 and 200 mg/kg and in rats at 200 and 300 mg/kg. It showed a slight antistrychnine effect in mice at high and toxic doses (300 mg/kg), reduced motor activity of mice at 100 mg/kg, and at 50 mg/kg slightly decreased the motor activity of amphetamine- or caffeine-stimulated mice. The TD_{50} (neurotoxic dose) of linalool for influencing motor co-ordination of mice in the Rota-rod test was found to be 178 mg/kg. Linalool at doses of 50 or 100 mg/kg prolonged the narcotic effects of hexobarbitone, alcohol and chloral hydrate.

The equilibrium and spontaneous or reflex activity of the goldfish, *Carassium auratus*, was disturbed by exposure to aquarium water containing a 0·1–3 ml/litre concentration of a suspension containing 1 ml linalool plus 9 ml of a 10% aqueous solution of Tween 80, and the agressiveness of the male fighting fish, *Betta splendens*, was only very slightly inhibited by exposure to aquarium water containing 0·3 ml of the same suspension of linalool/litre (Binet, 1972).

Linalool and other terpene alcohols were found to be useful in man as sedatives and spasmolytics when administered in doses of 0·01–1 g, the effects having been tested in mice, goldfish, and rats (Laboratoires Meram, 1966).

Linalool depressed frog-heart activity in doses above 0·2 mg/g (Lysenko, 1962). Vasodilation by direct action of linalool upon the blood vessels was demonstrated by Northover & Verghese (1962). An iv dose of 9·2 mg/kg was required to produce a 25% fall in systolic arterial blood pressure in the anaesthetized dog and a hypotensive response was also observed in the decerebrated and despinalized dog. A dose of 0·05 g in fluid perfusing the leg of an anaesthetized dog or the isolated ear of a rabbit produced a maximum increase of 120% or 90%, respectively, in venous outflow over pre-injection values. Linalool dilated the small blood vessels of the exposed mesorchium of the anaesthetized mouse, lowering the threshold for electronic stimulation. Incubation of human, bovine and canine aortae in 0·15 M-linalool failed to stabilize the structure of the aortic wall proteins against hydrothermal shrinkage (Milch, 1965). Linalool inhibited incorporation of acetic acid or mevalonic acid into total or digitonin-precipitable nonsaponifiable lipids by rat-liver homogenates (Gey, Pletscher, Isler, Rüegg, Saucy & Würsch, 1960).

Micro-organisms. Linalool inhibited the *in vitro* growth of all three wood-destroying fungi studied by Maruzzella, Scrandis, Scrandis & Grabon (1960), and the vapour of linalool inhibited the growth of all four fungi tested by Maruzzella, Chiaramonte & Garofalo (1961). Linalool at 1:10,000 dilution showed moderate stimulatory action on the germination of uredospores of the wheat stem rust organism *Puccinia graminis* (French, 1961). Linalool strongly inhibited the rumen microbial activity of sheep and deer (Oh, Sakai, Jones & Longhurst, 1967) and at 1:500 dilution inhibited *in vitro* growth of *Escherichia coli* but not of three gram-positive bacteria, *Bacillus subtilis* and two strains of *Staphylococcus aureus* (Maruzzella & Bramnick, 1961). Münzing & Schels (1972) reported, however, that at 1:500 dilution it inhibited the growth of *Staph. aureus* and *Escherichia coli* but not of *Proteus vulgaris* and *Pseudomonas aeruginosa*, all found in contaminated cosmetics.

The relative bactericidal action of linalool was reported to be seven times that of phenol (Führer, 1972). It showed no antibacterial activity *in vitro* on tubercle bacilli, but enhanced the effectiveness of small (5 mg) daily doses of dihydrostreptomycin when given im in weekly doses of 10 mg to guinea-pigs infected with tuberculosis (Kato & Gözsy, 1958). It exhibited only weak therapeutic activity in experimental tuberculosis of guinea-pigs and slightly induced a local India-ink and trypan blue accumulation in rat skin, but did not stimulate the phagocytic activity of guinea-pig macrophages (Gözsy & Kato, 1958).

Linalool strongly inhibited the growth of all nine bacteria tested by Kellner & Kober (1956) and caused moderate to strong inhibition of the growth of most of 34 bacterial strains tested by Möse & Lukas (1957). In *in vitro* tests, it inhibited the production of spores and parasporal crystals by *Bacillus thuringiensis* (Morris, 1972).

In rabbits, linalool delayed the development of experimental gas gangrene, acted as a therapeutic agent and lowered mortality (Chuiko, Lavrushina & Pavlotskaya, 1957). The presence of linalool increased the bactericidal effectiveness of certain patented betaine compositions (Hofmann, 1971) and patented compositions containing linalool and a cetylpyridinium halide inhibit the growth of bacteria and fungi and may be used to disinfect skin and mucous surfaces, wounds and various articles and utensils (Gauvreau, 1971).

Viruses. Linalool in daily doses of 1 mg, given as a single oral dose or in the drinking-water, protected chicks against avian lymphomatosis virus strain ES4, and was proposed as an antineoplastic and antiviral agent for veterinary administration (Baranger, 1971).

Cytotoxicity. Linalool was found to be moderately cytotoxic to Chang, HeLa, and KB cells (Nachev, Zolotovich, Silyanovska & Stojcev, 1967). When tested against HeLa cells in monolayer culture, linalool was cytotoxic at 100 μg/litre, weakly active at 10 μg/litre, and inactive at 1 μg/litre (Nachev, Zolotovitch, Siljanowski & Stojcev, 1968).

Odour sensing. d-Linalool ($1–5 \times 10^{-4}$ M) stimulated $Na^+–K^+$ ATPase in rabbit olfactory preparations and in nerve-ending-particle fractions from rat olfactory endoturbinals, but caused approximately 20% inhibition of activity of this enzyme in rat brain. It was proposed that perturbation of this enzyme may be important in the initiation of odour sensing (Koch & Desaiah, 1974). Linalool decreased the 267 nm spectral absorption of rabbit olfactory epithelium preparations. The change was attributed to the formation of a complex involving stimulant and olfactory protein, rather

Insects. Linalool was found to be attractive to the honeybee, *Apis mellifera* (Waller, Loper & Berdel, 1973) and to larvae of the cotton leafworm, *Spodoptera littoralis* (Khalifa, Rizk, Salama & El-Sharaby, 1973), and the silkworm, *Bombyx mori* (Hamamura & Naito, 1961). It was found to be relatively ineffective as a repellent for the mosquito, *Aedes aegypti* (Burton, 1969). Linalool decreased the wing vibration response of male Mediterranean flour moths, *Ephestia kuehniella*, to sex pheromone from females over a 30-sec period, but increased the number of males attracted to the pheromone source (Traynier & Wright, 1973). Epoxidation of linalool produced a product with sex pheromone activity for the male codling moth, *Carpocapsa pomonella* (McDonough, George & Butt, 1969). Pure linalool possessed no juvenile-hormone activity against *Galleria mellonella* pupae, but a commercial sample of linalool showed slight activity (Schneiderman, Krishnakumaran, Kulkarni & Friedman, 1965).

Trematodes. Linalool applied to the tails of mice provided no protection against infestation with cercariae of *Schistosoma mansoni* (Gilbert, De Souza, Fascio, Kitagawa, Nascimento, Fortes, Seabra & Pellergrino, 1970).

Plants. The inhibiting effects of linalool on the growth of *Lepidium sativum* seedlings and the germination of *Raphanus sativus* seeds were studied by Garshtya & Koval'chuk (1972).

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LINALYL ANTHRANILATE

Synonym: Linalyl *o*-aminobenzoate.
Structure: $CH_3 \cdot C(CH_3):CH \cdot [CH_2]_2 \cdot (CH_3)C(CH:CH_2) \cdot OCO \cdot C_6H_4 \cdot NH_2$.
Description and physical properties: A pale straw-coloured oily liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: From linalyl formate plus methyl anthranilate with sodium linalool or from linalool plus isatoic anhydride with a trace of sodium hydroxide as starter catalyst, or by any other suitable means.
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 1000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·01	0·005	0·12
Maximum	0·2	0·02	0·2	0·8

Analytical data: Gas chromatograms, RIFM no. 72-178; infra-red curve, RIFM no. 72-178.

Status

Linalyl anthranilate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included linalyl anthranilate at a level of 8 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 4·25 g/kg (4·0–4·5 g/kg) (Russell, 1973). The acute dermal LD_{50} value in rabbits was reported as >5 g/kg (Russell, 1973).

Irritation. Linalyl anthranilate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Russell, 1973). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman. 1973).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1973).

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Kligman, A. M. (1973). Report to RIFM, 27 July.
Kligman, A. M. & Epstein, W. (1975). Updating the maximization test for identifying contact allergens. *Contact Dermatitis* **1**, 231.
Russell, T. J. (1973). Report to RIFM, 6 March.

LINALYL BENZOATE

Synonym: 3,7-Dimethyl-1,6-octadien-3-yl benzoate.
Structure: $CH_3 \cdot C(CH_3):CH \cdot [CH_2]_2 \cdot (CH_3)C(CH:CH_2) \cdot OCO \cdot C_6H_5$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Reported to be found in the essential oils of ylang-ylang and tuberose (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: By esterification of dehydrolinalool with benzoic acid followed by hydrogenation of the dehydro ester, or by any other suitable means.
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to less than 3000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·01	0·12
Maximum	0·2	0·02	0·06	0·8

Status

Linalyl benzoate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included linalyl benzoate at a level of 1 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health. The *Food Chemicals Codex* (1972) has a monograph on linalyl benzoate.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. Linalyl benzoate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was mildly irritating (Moreni, 1973). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1973).

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Kligman, A. M. (1973). Report to RIFM, 9 October.

Kligman, A. M. & Epstein, W. (1975). Updating the maximization test for identifying contact allergens. *Contact Dermatitis* **1**, 231.

Moreno, O. M. (1973). Report to RIFM, 18 May.

LINALYL BUTYRATE

Synonym: Linalyl *n*-butyrate.
Structure: $CH_3 \cdot C(CH_3):CH \cdot [CH_2]_2 \cdot (CH_3)C(OCO \cdot [CH_2]_2 \cdot CH_3) \cdot CH:CH_2$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Reported to be found in the oil of *Artemisia porrecta* var. *coerulea* and in lavender oil (*Fenaroli's Handbook of Flavor Ingredients*, 1975).
Preparation: From dehydrolinalool by esterification and subsequent hydrogenation (Arctander, 1969).
Uses: In public use before the 1920s. Use in fragrances in the USA amounts to less than 1000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·12
Maximum	0·2	0·02	0·05	0·8

Analytical data: Gas chromatogram, RIFM no. 75-92; infra-red curve, RIFM no. 75-92.

Status

Linalyl butyrate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) listed linalyl butyrate giving an ADI of 0·25 mg/kg.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Levenstein, 1975). Linalyl butyrate strongly decreased the 267 nm spectral absorption of rabbit olfactory epithelium preparations (Ash & Skogen, 1970).

Irritation. Linalyl butyrate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Levenstein, 1975). Tested at 8% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 23 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Epstein, 1975).

Metabolism. The hydrolysis of ester linkages in foreign compounds may be catalysed by many different esterases, which are to be found in all animals and bacteria and which have, for the most part, a low degree of substrate specificity (Parke, 1968). No cumulative effects would be expected for most butyrates in view of their hydrolysis to materials that are either normally in the diet or readily converted to such materials (Fassett, 1963).

Pharmacology. Linalyl butyrate strongly decreased the spontaneous motility of mice at a dosage of 100 mg/kg (Wagner & Sprinkmeyer, 1973).

Insects. Linalyl butyrate possessed no juvenile hormone activity when injected into pupae of the wax moth, *Galleria mellonella* (Schneiderman, Krishnakumaran, Kulkarni & Friedman, 1965).

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LINALYL CINNAMATE

Structure: $CH_3 \cdot C(CH_3):CH \cdot [CH_2]_2 \cdot (CH_3)C(CH:CH_2) \cdot OCO \cdot CH:CH \cdot C_6H_5$.
Description and physical properties: An almost colourless oily or slightly viscous liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: From linalyl formate plus methyl cinnamate plus linalool sodium, or from dehydrolinalool and cinnamic acid via the dehydro ester, which is hydrogenated to the subject ester, or by any other suitable means.
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to less than 3000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·12
Maximum	0·1	0·01	0·03	0·8

Status

Linalyl cinnamate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) listed linalyl cinnamate giving an ADI of 1·25 mg/kg.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 9·96 g/kg (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964). The acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1973).

Subacute toxicity. In feeding studies, 1000, 2500 and 10,000 ppm linalyl cinnamate fed to rats in the diet for 17 wk produced no effects (Hagan, Hansen, Fitzhugh, Jenner, Jones, Taylor, Long Nelson & Brouwer, 1967).

Irritation. Linalyl cinnamate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was mildly irritating (Moreno, 1973). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1973).

References

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Moreno, O. M. (1973). Report to RIFM, 14 May.

LINALYL FORMATE

Synonym: 3,7-Dimethyl-1,6-octadien-3-yl formate.
Structure: $CH_3 \cdot C(CH_3):CH \cdot [CH_2]_2 \cdot (CH_3)C(OCOH) \cdot CH:CH_2$.
Description and physical properties: EOA Spec. no. 275.
Occurrence: Reported to be found in Lavandula, *Prunus armeniaca*, *P. persica*, and *Salvia sclarea* (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: By the esterification of linalool or by chemical synthesis.
Uses: In public use before the 1920s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·12
Maximum	0·15	0·015	0·03	0·8

Analytical data: Gas chromatogram, RIFM no. 72–127; infra-red curve, RIFM no. 72–127.

Status

Linalyl formate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) listed linalyl formate, giving an ADI of 0·25 mg/kg.

Biological data

Acute toxicity. Both the acute oral LD_{50} in rats and the acute dermal LD_{50} in rabbits exceeded 5 g/kg (Russell, 1973).

Irritation. Linalyl formate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Russell, 1973). Tested at 10% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1973).

References

Council of Europe (1974). Natural Flavouring Substances, Their Sources, and Added Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List 1, no. 347, p. 198. Strasbourg.

Fenaroli's Handbook of Flavor Ingredients (1971). Edited by T. E. Furia and N. Bellanca. p. 487. Chemical Rubber Co., Cleveland, Ohio.

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Kligman, A. M. (1973). Report to RIFM, 10 October.

Kligman, A. M. & Epstein, W. (1975). Updating the maximization test for identifying contact allergens. *Contact Dermatitis* **1**, 231.

Russell, T. J. (1973). Report to RIFM, 6 March.

LINALYL ISOBUTYRATE

Synonym: 3,7-Dimethyl-1,6-octadien-3-yl isobutyrate.
Structure: $CH_3 \cdot C(CH_3):CH \cdot [CH_2]_2 \cdot (CH_3)C(OCO \cdot CH(CH_3) \cdot CH_3) \cdot CH:CH_2$.
Description and physical properties: EOA Spec. no. 274.
Occurrence: Reported to be found in the essential oils of Ceylon cinnamon and lavender oil (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: By esterification of linalool with isobutyric anhydride or by other suitable means.
Uses: In public use before the 1920s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·015	0·2
Maximum	0·25	0·025	0·08	0·8

Analytical data: Gas chromatogram, RIFM no. 74–99; infra-red curve, RIFM no. 74–99.

Status

Linalyl isobutyrate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included linalyl isobutyrate at a level of 15 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health. The *Food Chemicals Codex* (1972) has a monograph on linalyl isobutyrate.

Biological data

Acute toxicity: In the rat, the acute oral LD_{50} was reported to be >36.3 g/kg (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964). At this dose, the highest tested, toxic signs included depression, wet fur and diarrhoea, but the surviving animals appeared normal after 1 wk. In the mouse, the acute oral LD_{50} was 15·1 g/kg (Jenner *et al.* 1964); animals were depressed soon after treatment and excitable after 1 hr, with rough fur, and death occurred between 4 hr and 3 days. The acute dermal LD_{50} in rabbits was reported as >5 g/kg (Moreno, 1974).

Chronic toxicity. Up to 10,000 ppm linalyl isobutyrate fed to rats in the diet for 18 wk produced no macroscopic effects (Hagan, Hansen, Fitzhugh, Jenner, Jones, Taylor, Long, Nelson & Brouwer, 1967).

Irritation. Linalyl isobutyrate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1974). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1974).

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LINALYL METHYL ETHER

Synonyms: Methyl linalyl ether; linalool methyl ether.
Structure: $CH_3 \cdot C(CH_3):CH:[CH_2]_2 \cdot (CH_3)C(OCH_3) \cdot CH:CH_2$.
Description and physical properties: A colourless, slightly oily liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By methylation of linalool.
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·12
Maximum	0·1	0·01	0·02	0·5

Status

Linalyl methyl ether is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974), or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} in rats and the acute dermal LD_{50} in rabbits exceeded 5 g/kg (Moreno, 1974).

Irritation. Linalyl methyl ether applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1974). Tested at 5% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 24 volunteers. The material was tested at a concentration of 5% in petrolatum and produced no sensitization reactions (Epstein, 1974).

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Moreno, O. M. (1974). Report to RIFM, 22 August.

LINALYL PHENYLACETATE

Synonym: Linalyl α-toluate.
Structure: $CH_3 \cdot C(CH_3):CH \cdot [CH_2]_2 \cdot (CH_3)C(CH:CH_2) \cdot OCO \cdot CH_2 \cdot C_6H_5$.
Description and physical properties: A colourless or pale straw-coloured viscous liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: From dehydrolinalool and methyl phenylacetate in the presence of sodium methylate catalyst, followed by hydrogenation of the ester, or by any other suitable means.
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 1000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·12
Maximum	0·1	0·01	0·01	0·4

Status

The Council of Europe (1974) has included linalyl phenylacetate at a level of 0·5 ppm in the list of artificial flavouring susbstances that may be added to foodstuffs without hazard to public health.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1974).

Irritation. Linalyl phenylacetate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Moreno, 1974). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1974).

Metabolism: Open-chain olefinic terpene esters are presumably hydrolysed to the alcohol and the acid (Fassett, 1963). Open-chain terpenes are metabolized in the rabbit by ω-oxidation and by reduction of an α,β-double bond (Williams, 1959).

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LINALYL PROPIONATE

Synonym: 3,7-Dimethyl-1,6-octadien-3-yl propionate.
Structure: $CH_3 \cdot C(CH_3):CH \cdot [CH_2]_2 \cdot (CH_3)C(OCO \cdot CH_2 \cdot CH_3) \cdot CH:CH_2$.
Description and physical properties: EOA Spec. no. 138.
Occurrence: Reported to be found in lavender and sage (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: By the esterification of linalool with propionic acid or propionic anhydride or by any other suitable means.
Uses: In public use before the 1920s. Use in fragrances in the USA amounts to approximately 10,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·0005	0·01	0·12
Maximum	0·07	0·005	0·2	0·8

Analytical data: Gas chromatogram, RIFM no. 72–181; infra-red curve, RIFM no. 72–181.

Status

Linalyl propionate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) listed linalyl propionate, giving an ADI of 0·25 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on linalyl propionate.

Biological data

Acute toxicity. Both the acute oral LD_{50} in rats and the acute dermal LD_{50} in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. Linalyl propionate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was mildly irritating (Moreno, 1973). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1973).

References

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Moreno, O. M. (1973). Report to RIFM, 14 May.

MALTOL

Synonym: 3-Hydroxy-2-methyl-4-pyrone.
Structure: $CH{:}CH\cdot CO\cdot C(OH){:}C(CH_3)$ (ring O)

Description and physical properties: *Food Chemicals Codex* (1972).
Occurrence: Reported to be found in the bark of young larch trees (*Pinus larix*), pine needles (*Abies alba*), chicory, wood tars and oils, and in roasted malt (Bedoukian, 1967; *Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: By alkaline hydrolysis of streptomycin salts (*Merck Index*, 1968).
Uses: In public use since the 1930s.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·0005	0·003	0·05
Maximum	0·06	0·006	0·15	0·4

Analytical data: Infra-red curve, RIFM no. 74-222.

Status

Maltol was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) listed maltol, giving an ADI of 1 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on maltol.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported to be 2·33 g/kg (1·57–3·09 g/kg) (Moreno, 1974). The acute oral 7-day LD_{50}s in mice, rats and chicks were reported to be 848, 1440 and 3720 mg/kg, respectively (Gralla, Stebbins, Coleman & Delahunt, 1969). Acute oral LD_{50} values were found to be 550 mg/kg in mice, 1620 mg/kg in rabbits and 1410 mg/kg in guinea-pigs (Dow Chemical Company, 1967). The acute sc LD_{50} in mice was found to be 820 mg/kg. Sc injection of 400 mg/kg resulted in decreased spontaneous activity, bradycardia, hypothermia, skeletal-muscle relaxation and diminution of pinna, corneal, and ipsilateral flexor reflexes (Aoyagi, Kimura & Murata, 1974). Because of a lack of sample, 5 g/kg could only be applied to one rabbit in the dermal LD_{50} study, but this dosage was not lethal in the one rabbit (Moreno, 1974).

Short-term toxicity. In rats receiving 1000 mg/kg/day for 90 days, maltol caused severe body weight depression from wk 3 in males and wk 9 in females, kidney damage with albuminuria and microscopic kidney lesions, and two deaths out of 20 animals, presumably as a result of renal failure (Gralla *et al.* 1969).

Maltol caused debilitation and death in four dogs given 500 mg/kg/day, with accompanying signs of acute haemolysis and altered hepatorenal function (Gralla *et al.* 1969). In the pathological evaluation of numerous tissues, damage held to be directly or indirectly related to maltol included pulmonary oedema, pericentral and midzonal hepatic necrosis, fatty degeneration of the myocardium, adrenal cortical and medullary necrosis and testicular degeneration. No deaths resulted from doses of 250 or 125 mg/kg/day given for 90 days.

Studies carried out at the Municipal Hospital of Basel and reported in 1947 by Firmenich & Cie. indicated that maltol ("Corps Praline") consumed daily at a dose of 1·5 g was completely harmless (Bohnsack, 1964). In a study reported by the Dow Chemical Co. in 1947, rats showed no recognizably harmful effects after consuming for 6 months a diet containing 1% maltol ("Palatone"), a dosage level equivalent to 0·5–1 g/kg/day and greatly exceeding the amount of maltol used in foodstuffs (Bohnsack, 1964). Young pigs (20–24 days old) given maltol at 25 or 200 g/ton in a nutritionally balanced animal feed for 3–5 wk remained healthy and gained more weight than did a control group receiving no maltol (Olson, 1967).

Irritation. Maltol applied full strength to the intact or abraded skin of one rabbit was moderately irritating (Moreno, 1974). Tested at 10% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1974).

Metabolism. Maltol is rapidly and extensively metabolized in the dog and excreted by the conjugation pathway common to phenolic compounds. Rennhard (1971) reported that 57% of an iv dose was recovered in 24 hr, 88% of the total excretion occurring in the first 6 hr and 65–70% of the dose administered being recovered as sulphate and glucuronide conjugates.

Pharmacology. In mice, spontaneous motor activity was depressed by sc injection of relatively low doses of maltol (75 mg/kg), hexobarbitone sleeping time was prolonged by sc or oral administration of 300 mg/kg, and convulsions induced by pentylenetetrazole or strychnine were inhibited by sc injection of toxic doses (500 mg/kg), but 1 mM concentrations of maltol had no effect on oxygen uptake by slices of the brain cortex of the rat (Aoyagi *et al.* 1974).

Insects. In a study of the molecular basis of odour perception, an olfactory mutant of *Drosophila melanogaster* (fruit fly) was attracted by maltol and certain other compounds, while the parent strain was repelled. The response was attributed to the presence and spacing of hydroxyl, carbonyl, aldehyde and carboxyl groups (Kikuchi, 1973).

Micro-organisms. Maltol has been reported to inhibit fungus growth at 0.1%, which is a higher concentration than will be found in finished consumer products (Arctander, 1969). Maltol was found by Wolf & Westveer (1950) to possess antimicrobial activity at or above 0.20–1.50% in water against two pathogenic bacteria (*Salmonella typhosa* and *Micrococcus pyogenes* var. *aureus*) and four food-spoilage bacteria, yeasts, and fungi (*Aerobacter aerogenes*, *Penicillium digitatum*, *Rhizopus nigricans* and *Saccharomyces cerevisiae*). In broth-dilution tests, maltol completely inhibited seven homofermentative and eight heterofermentative strains of Lactobacilli at concentrations above 4 mg/ml (Fitzgerald & Jordan, 1953). At 1·2% maltol did not prevent mould growth for 11 wk in hay containing 40% moisture (Schenk & Kennedy, 1955).

Plants. Maltol, like certain 6-substituted derivatives of kojic acid, stimulated the growth of *Lemna minor* (duckweed), possibly as a result of the formation of chelates (Nickell & Gordon, 1963). Maltol and other heterocyclic keto compounds accelerated and improved seed germination when mixed with dried blood or other metallic porphyrin complexes in seed coating, presumably by inducing nitrogen fixation, supplying easily assimilable protein-decomposition products and promoting the formation of hormones and enzymes in the sprouting seeds (Hale, 1954).

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MARJORAM OIL, SPANISH

Description and physical properties: EOA Spec. no. 143. The main constituent of marjoram oil, Spanish is cineole (Guenther, 1949).
Occurrence: Found in the shrub *Thymus mastichina* L. (Fam. Labiatae).
Preparation: By steam-distillation of the flowering plant material *Thymus mastichina* L.
Uses: In public use before the 1900s. Use in fragrances in the USA amounts to less than 2000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·003	0·005	0·12
Maximum	0·15	0·015	0·03	0·6

Analytical data: Gas chromatogram, RIFM no. 72-185; infra-red curve, RIFM, no. 72-185.

Status

The *Food Chemicals Codex* (1972) has a monograph on marjoram oil, Spanish.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. Marjoram oil, Spanish applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was mildly irritating (Moreno, 1973). Applied undiluted to the backs of hairless mice and swine, it was not irritating (Urbach & Forbes, 1973), and tested at 6% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1973).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 23 human volunteers. The material was tested at a concentration of 6% in petrolatum and produced no sensitization reactions (Epstein, 1973).

Phototoxicity. No phototoxic effects were reported for undiluted marjoram oil, Spanish on hairless mice and swine (Urbach & Forbes, 1973).

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MARJORAM OIL SWEET

Description and physical properties: A pale yellow mobile liquid. The main constituents of marjoram oil sweet include terpinene and terpineol (Guenther, 1949).
Occurrence: Found in the plant *Marjorana hortensis* Moench (*Origanum marjorana* L.; Fam. Labiatae) (Guenther, 1949).
Preparation: By steam-distillation of the leaves of the plant *Origanum marjorana* L. (Guenther, 1949).
Uses: In public use before the 1880s. Use in fragrances in the USA amounts to less than 1000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·003	0·005	0·12
Maximum	0·15	0·015	0·03	0·6

Analytical data: Gas chromatogram, RIFM no. 73-184; infra-red curve, RIFM no. 73-184.

Status

Marjoram oil sweet was given GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1974) included marjoram oil sweet in the list of substances, spices and seasonings deemed admissible for use, with a possible limitation of the active principle in the final product.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 2·24 g/kg (Wohl, 1974). The acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Wohl, 1974).

Irritation. Marjoram oil sweet applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Wohl, 1974). Tested at 6% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1973).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 23 human volunteers. The material was tested at a concentration of 6% in petrolatum and produced no sensitization reactions (Epstein, 1973).

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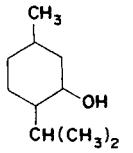
Wohl, A. J. (1974). Report to RIFM, 2 April.

l-MENTHOL

Synonyms: 3-*p*-Menthanol; *p*-menthan-3-ol; 4-isopropyl-1-methylcyclohexan-3-ol.
Structure:



Description and physical properties: *Givaudan Index* (1961).
Occurrence: Found in high concentrations in oils of peppermint (*Mentha piperita*) and Japanese mint oil (*Mentha arvensis*) and in lower concentrations in Réunion geranium oil, and also in a large number of essential oils (*Fenaroli's Handbook of Flavor Ingredients*, 1971; Guenther, 1949).
Preparation: By isolation from *Mentha arvensis* oils or synthetically from turpentine and from thymol.
Uses: In public use before the 1900s. Use in fragrances in the USA amounts to less than 50,000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·04
Maximum	0·2	0·02	0·05	0·3

Status

Menthol was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) listed menthol, giving an ADI of 2 mg/kg. The *Food Chemicals Codex* (1972) and the *United States Pharmacopeia* (1965) have monographs on menthol. The Joint FAO/WHO Expert Committee on Food Additives (1968) has published a monograph and specifications for menthol giving an unconditional ADI of 0–0·2 mg/kg.

Biological data

Acute toxicity. The acute oral LD_{50} values were reported as 3300 mg/kg in the rat (Herken, 1961) and as 800–1000 mg/kg in the cat (Flury, 1920). The sc LD_{50}s in mice and rats were reported at 5000–6000 and 1000–2500 mg/kg, respectively (Flury, 1920). The lethal sc dose in rats was reported as 2000 mg/kg (*Merck Index*, 1968). The lethal ip doses in mice, rats and guinea-pigs were reported as 2000, 1500 and 4000 mg/kg, respectively (Macht, 1939) while the ip LD_{50} in cats was reported as 800–1000 mg/kg (Flury, 1920) and that in rabbits as approximately 2000 mg/kg (Herken, 1961). The lethal iv dose in cats was reported at 34 mg/kg (Macht, 1939), and the acute dermal LD_{50} value in rabbits as >5 g/kg (Wohl, 1974).

Short-term toxicity. In a feeding study, groups of 40 male and 40 female rats received 0, 100 or 200 mg/kg body weight of either *l*- or *dl*-menthol in their diets for 5·5 wk. There were no adverse efffects on weight gain or excretion of glucuronide, water and electrolytes, nor was there any interference with CNS reactions to cardrazol or electric shock or with iv hexobarbitone sleeping-time compared with controls (Herken, 1961).

Menthol has a psycholeptic effect in the mouse. However, the psychotropic activity of this compound, particularly when administered orally, is weak. When administered ip, the effective dose is of the order of 100–600 mg/kg, according to the test used and the substance studied. The psychotropic action of this substance is always transient and it is unlikely that it would have any effects of this kind in man at the concentrations that occur in food or drinks (Le Bourhis & Soenen, 1973).

Menthol was studied to establish whether it could affect the metabolism of other drugs in rats and was found to be inactive with respect to pentobarbitone sleeping time (Jori, Bianchetti & Prestini, 1969).

Chronic urticaria with basophil leucopaenia on challenge has been reported after contact with menthol in toothpaste, mentholated cigarettes and peppermint sweets (McGowan, 1966). Bradycardia, ataxia, confusion and mental irritability were correlated with the inhalation of volatile menthol (from mentholated cigarettes) in a 58-yr-old woman (Luke, 1962). Two cases of idiopathic auricular fibrillation from excessive peppermint eating have been reported (Thomas, 1962), and a case of generalized urticaria in a young woman resulting from a predilection for peppermint candy, mint-flavoured toothpaste and mentholated cigarettes has been reported (Papa & Shelley, 1964). Strict avoid-

ance of peppermint and all other sources of menthol led to the prompt disappearance of effects, after which the patient reacted positively to challenge tests by menthol, both dermal and oral.

Irritation. *l*-Menthol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Wohl, 1974). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test in human subjects (Epstein, 1974), although it has been reported that menthol may act as a mild irritant in man (*Merck Index*, 1968).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 24 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Epstein, 1974).

Metabolism. *l*-Menthol conjugates readily in the rabbit forming *l*-menthyl-*β*-*d*-glucuronide. About half of the *l*-menthol fed to rabbits is excreted combined with glucuronic acid (Williams, 1938); the fate of the other half is not known, but it is possible that ring fission occurs with considerable degradation of the menthol molecule. In dogs, much oxidation of menthol takes place and only about 5% of the dose can be recovered in the urine as the glucuronide. According to Quick (1924) the percentage of a dose of *l*-menthol that is excreted combined with glucuronic acid in the rabbit depends on the magnitude of the dose; the larger the dose, the less is the conjugation (Williams, 1959).

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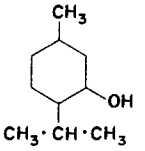
MENTHOL RACEMIC

Synonyms: *dl*-Menthol; 3-*p*-menthanol; 4-isopropyl-1-methylcyclohexan-3-ol.
Structure:



Description and physical properties: *Givaudan Index* (1961).
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By hydrogenation of thymol followed by separation from its other isomers.
Uses: In public use since the 1900s. Use in fragrances in the USA amounts to approximately 5000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·01	0·04
Maximum	0·2	0·02	0·05	0·3

Analytical data: Gas chromatogram, RIFM no. 72-187; infra-red curve, RIFM no. 72-187.

Status

Menthol was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) listed menthol, giving an ADI of 2 mg/kg. The *Food Chemicals Codex* (1972) and the *United States Pharmacopeia* (1965) have monographs on menthol. The Joint FAO/WHO Expert Committee on Food Additives (1967) has published a monograph and specifications for menthol, giving an unconditional ADI of 0–0·2 mg/kg.

Biological data

Acute toxicity. The acute oral LD_{50} in rats has been reported as 3180 mg/kg by Jenner, Hagan, Taylor, Cook & Fitzhugh (1964) and as 2900 mg/kg by Herken (1961). The acute oral LD_{50} in cats was reported to be 1500–1600 mg/kg (Flury & Seel, 1926). The sc LD_{50} in the mouse was reported as 1400–1600 mg/kg (Flury & Seel, 1926) and the ip LD_{50} as 750 mg/kg in the rat (Herken, 1961) and 1500–1600 mg/kg in the cat (Flury & Seel, 1926). In rabbits, the ip LD_{50} was reported to be approximately 2000 mg/kg (Herken, 1961), while the acute dermal LD_{50} exceeded 5000 mg/kg (Levenstein, 1973).

Short-term toxicity. In a feeding study, groups of 40 male and 40 female rats recieved 0, 100 or 200 mg/kg body weight of either *l*- or *dl*-menthol in their diets for 5·5 wk. There were no adverse effects on weight gain or excretion of glucuronide, water and electrolytes, nor was there any interference with CNS reactions to cardrazol or electric shock or with iv hexobarbitone sleeping-time compared with controls (Herken, 1961).

Irritation. Menthol racemic applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was mildly irritating (Levenstein, 1973). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test in human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1973).

Metabolism. Rabbits are said to eliminate 59% of *dl*-menthol as glucuronide (Williams, 1938).

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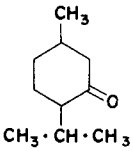
MENTHONE RACEMIC

Synonyms: 4-Isopropyl-1-methylcyclohexan-3-one; *p*-menthan-3-one.
Structure:



Description and physical properties: *Givaudan Index* (1961).
Occurrence: Several stereoisomers are reported to be found in nature. *l*-Menthone is a constituent of the essential oils of Russian and American peppermint, geranium, *Andropogon fragrans*, *Mentha timija*, *Mentha arvensis* and others. *d*-Menthone is present in the essential oils of *Barosma pulchellum*, *Nepeta japonica* Maxim. and others. *d*-Isomenthone has been reported to be isolated from *Micromeria abissinica* Benth., *Pelargonium tomentosum* Jacquin. and others. *l*-Isomenthone has been identified in Reunion geranium, *Pelargonium capitatum* and others (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: By oxidation of menthol or by partial hydrogenation of thymol.
Uses: In public use since the 1920s. Use of fragrances in the USA amounts to approximately 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·1
Maximum	0·2	0·02	0·05	0·8

Analytical data: Gas chromatogram, RIFM no. 72-188; intra-red curve, RIFM no. 72-188.

Status

Menthone was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included menthone in the list of artificial flavouring substances that may be added temporarily to foodstuffs without hazard to public health.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 2·18 ml/kg (1·82–2·62 ml/kg) (Levenstein, 1973a). The acute dermal LD_{50} in rabbits exceeded 5 g/kg (Levenstein, 1973b).

Irritation. Menthone racemic applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was mildly irritating (Levenstein, 1973b). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test in human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1973).

Metabolism. Hämäläinen (1912) claimed that menthone was probably oxidized in the rabbit to ketomenthone, since the glucuronide produced was converted by warm dilute H_2SO_4 to a substance which was probably $\Delta^{4(8)}$-*p*-menthen-3-one (pulegone). Williams (1940), however, showed that it underwent reduction in the rabbit with the production of *d*-neomenthol. The presence of *l*-menthol, the other possible reduction product, was not detected and it appeared that the biological reduction was asymmetric (Williams, 1959).

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l-MENTHYL ACETATE

Synonym: *l-p*-Menth-3-yl acetate.
Structure: $(CH_3)_2 \cdot CH \cdot C_6H_9(CH_3) \cdot OCO \cdot CH_3$.
Description and physical properties: *Merck Index* (1968).
Occurrence: Found in peppermint oil (Guenther, 1949).
Preparation: By direct esterification of *l*-menthol with acetic acid under azeotropic conditions (Arctander, 1969).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to approximately 3000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·2
Maximum	0·2	0·02	0·05	0·8

Analytical data: Gas chromatogram, RIFM no. 72-189; infra-red curve, RIFM no. 72-189.

Status

Menthyl acetate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR. 121.1164). The Council of Europe (1974) listed menthyl acetate giving an ADI of 2 mg/kg (therapeutic doses).

Biological data

Acute toxicity. Both the acute oral LD_{50} in rats and the acute dermal LD_{50} in rabbits exceeded 5 g/kg (Shelanski, 1972).

Irritation. *l*-Menthyl acetate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was mildly irritating (Shelanski, 1972). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1972).

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Guenther, E. (1949). *The Essential Oils*. Vol. II, p. 632. D. Van Nostrand, Inc., Princeton, New Jersey.

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MENTHYL ACETATE RACEMIC

Synonym: *dl*-Menthyl acetate.
Structure: $(CH_3)_2 \cdot CH \cdot C_6H_9(CH_3) \cdot OCO \cdot CH_3$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Reported to be found in peppermint oil (Guenther, 1949).
Preparation: By direct esterification of racemic menthol with acetic acid under azeotropic conditions (Arctander, 1969).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to approximately 3000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·2
Maximum	0·2	0·02	0·05	0·8

Analytical data: Gas chromatogram, RIFM no. 72-190; infra-red curve, RIFM no. 72-190.

Status

Menthyl acetate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) listed menthyl acetate, giving an ADI of 2 mg/kg (therapeutic doses).

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 7·62 ml/kg (5·95–9·75 ml/kg) (Levenstein, 1973a). The acute dermal LD_{50} in rabbits was reported as > 5 g/kg (Levenstein, 1973b).

Irritation. Racemic menthyl acetate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was mildly irritating (Levenstein, 1973b). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1973).

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Levenstein, I. (1973a). Report to RIFM, 10 January.

Levenstein, I. (1973b). Report to RIFM, 16 February.

p-METHOXYACETOPHENONE

Synonyms: Acetanisole; *p*-acetylanisole.
Structure: $CH_3 \cdot O \cdot C_6H_4 \cdot CO \cdot CH_3$.
Description and physical properties: EOA Spec. no. 151.
Occurrence: Found in castoreum (*Givaudan Index*, 1961).
Preparation: By a Friedel-Craft synthesis using anisole, acetic anhydride or acetyl chloride and aluminium chloride.
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to about 2000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·003	0·005	0·12
Maximum	0·15	0·015	0·03	0·6

Analytical data: Gas chromatogram, RIFM no. 72–191; infra-red curve, RIFM no. 72–191.

Status

p-Methoxyacetophenone was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) listed *p*-methoxyacetophenone giving an ADI of 1 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on *p*-methoxyacetophenone.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 1·72 g/kg (1·47–1·97 g/kg) (Moreno, 1973). The acute dermal LD_{50} value in rabbits was reported as >5 g/kg (Moreno, 1973).

Irritation. p-Methoxyacetophenone applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1973). Tested at 6% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 6% in petrolatum and produced no sensitization reactions (Kligman, 1973).

References

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Kligman, A. M. (1973). Report to RIFM, 13 August.

Moreno, O. M. (1973). Report to RIFM, 18 July.

o-METHOXYCINNAMIC ALDEHYDE

Synonym: β-(*o*-Methoxyphenyl)acrolein.
Structure: $CH_3O \cdot C_6H_4 \cdot CH:CH \cdot CHO$.
Description and physical properties: Pale-yellowish crystals or semi-solid mass, melting point 45–46°C.
Occurrence: Reported to be found in cinnamon essential oil (*Cinnamomum cassia* Nees et Bl.), from which it is separated as stearoptene (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: By condensation of salicylaldehyde methyl ether with acetaldehyde in alkaline solution (Arctander, 1969).
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·002	0·003	0·05
Maximum	0·2	0·03	0·03	0·3

Status

o-Methoxycinnamic aldehyde is approved by the FDA for food use (21 CFR 121.1164), and is listed by the Council of Europe (1974) with an ADI of 1·25 mg/kg.

Biological data

Acute toxicity. Both the acute oral LD_{50} in rats and the acute dermal LD_{50} in rabbits exceeded 5 g/kg (Levenstein, 1974).

Irritation. *o*-Methoxycinnamic aldehyde applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was mildly irritating (Levenstein, 1974). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 23 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Epstein, 1974).

Metabolism. In the animal body, aromatic aldehydes are oxidized to the corresponding acid; cinnamic aldehyde is oxidized to cinnamic acid which is then degraded to benzoic acid. In substituted anisoles with a carboxyl group or potential carboxyl group attached to the aromatic ring, the ether link is relatively stable. In rabbits, anisaldehyde (4-methoxybenzaldehyde) forms the corresponding ester glucuronide which appears in the urine (Williams, 1959).

Antitumour activity. *o*-Methoxycinnamaldehyde did not show significant activity against the tumour system leukaemia L-1210 (Billman & Tonnis, 1971).

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METHOXYCITRONELLAL

Synonyms: 3,7-Dimethyl-7-methoxy-1-octanal; hydroxycitronellal methyl ether.
Structure: $CH_3 \cdot (OCH_3)C(CH_3) \cdot [CH_2]_3 \cdot CH(CH_3) \cdot CH_2 \cdot CHO$.
Description and physical properties: A colourless liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By catalytic methylation of hydroxycitronellal (Arctander, 1969).
Uses: In public use since the 1930s.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·015	0·3
Maximum	0·45	0·045	0·1	2·0

Status

Methoxycitronellal is not included in the listings of the FDA. FEMA (1965) or the Council of Europe (1974) or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1975). Quistad, Staiger & Schooley (1974) described methoxycitronellal as non-toxic to mammals, giving the LD_{50} in rats again as >5 g/kg.

Irritation. Methoxycitronellal applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1975). Tested at 10% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 22 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Epstein, 1975). Methoxycitronellal was, however, listed as a sensitizer by Nakayama, Hanaoka & Ohshiro (1974). At 10% in a petrolatum base, it is included in a perfume-screening series being used in Japan (Larsen, 1975).

Metabolism. On rice and alfalfa, methoxycitronellal formed as a metabolite of the insect-growth regulator, methoprene, was converted to methoxycitronellic acid and hydroxycitronellic acid and their conjugates (Quistad *et al.* 1974).

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4-(*p*-METHOXYPHENYL)BUTAN-2-ONE

Synonyms: Anisyl acetone; *p*-methoxyphenylbutanone.
Structure: $CH_3 \cdot O \cdot C_6H_4 \cdot [CH_2]_2 \cdot CO \cdot CH_3$.
Description and physical properties: A colourless oily liquid with a sweet floral odour (Arctander, 1969).
Occurrence: Found in the odorous principle obtained by extraction from aloe wood (*Aquilaria agallocha* Roxb) and hydrolysis (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: By condensation of anisaldehyde with acetone, followed by hydrogenation (Arctander, 1969).
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to about 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·08
Maximum	0·1	0·01	0·03	0·5

Analytical data: Gas chromatogram, RIFM no. 72–192; infra-red curve, RIFM no. 72–192.

Status

4-(*p*-Methoxyphenyl)butan-2-one was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included 4-(*p*-methoxyphenyl)butan-2-one in the list of admissible artificial flavouring substances at a level of 25 ppm.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Russell, 1973).

Irritation. 4-(*p*-Methoxyphenyl)butan-2-one applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Russell, 1973). Tested at 5% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 5% in petrolatum and produced no sensitization reactions (Kligman, 1973).

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METHYL ABIETATE

Synonym: Methyl ester of wood rosin.

Description and physical properties: Methyl abietate is a colourless to yellow, almost odourless, thick liquid (*Merck Index*, 1968).

Occurrence: Wood rosin is found in the resinous residue of turpentine (Arctander, 1960).

Preparation: Prepared by esterification of wood rosin with methanol.

Uses: In public use since the 1930s. Use in fragrances in the USA amounts to about 25,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·1
Maximum	0·2	0·02	0·05	0·2

Analytical data: Infra-red curve, RIFM no. 72–71.

Status

Methyl abietate is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1970), nor in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1972).

Irritation. Methyl abietate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 2% in petrolatum and produced no sensitization reactions (Kligman, 1972).

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p-METHYLACETOPHENONE

Synonyms: 4-Methylacetophenone; methyl *p*-tolyl ketone.
Structure: $CH_3 \cdot C_6H_4 \cdot CO \cdot CH_3$.
Description and physical properties: EOA Spec. no. 38.
Occurrence: Found in the essential oil distilled from the wood of *Myrocarpus fastigiatus*, *Myrocarpus frondosus*, bois de rose and probably mimosa extracts (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: By the Friedel-Crafts synthesis using toluene, anhydrous aluminium chloride, and acetic anhydride or acetyl chloride.
Uses: In public use before the 1920s. Use in fragrances in the USA amounts to about 30,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·002	0·005	0·12
Maximum	0·15	0·015	0·05	0·60

Status

p-Methylacetophenone was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) listed *p*-methylacetophenone giving an ADI of 1 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on *p*-methylacetophenone.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 1·4 g/kg (Calandra, 1971). The acute dermal LD_{50} value in rabbits was reported as >2 g/kg (Calandra, 1971).

Irritation. *p*-Methylacetophenone applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was slightly irritating (Calandra, 1971). A patch test using full strength *p*-methylacetophenone for 24 hr produced one irritation reaction in 15 human subjects (Katz, 1946).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 6% in petrolatum and produced no sensitization reactions (Kligman, 1970).

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METHYL *n*-AMYL KETONE

Synonyms: 2-Heptanone; amyl methyl ketone.
Structure: $CH_3 \cdot CO \cdot [CH_2]_4 \cdot CH_3$.
Description and physical properties: *Food Chemicals Codex* (1972).
Occurrence: Reported to be found in clove oil and Ceylon cinnamon oil (Guenther, 1949).
Preparation: From ethylbutyl acetoacetate (Arctander, 1969).
Uses: In public use since the 1940s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·04
Maximum	0·1	0·01	0·04	0·4

Analytical data: Gas chromatogram, RIFM no. 74–103; infra-red curve, RIFM no. 74–103.

Status

Methyl amyl ketone was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included it at a level of 30 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health. The *Food Chemicals Codex* (1972) has a monograph on methyl amyl ketone.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 1670 mg/kg (Bär & Griepentrog, 1967) and in white mice as 0·73 g/kg (Srepel & Akacić, 1962). The acute dermal LD_{50} in rabbits exceeded 5 g/kg (Levenstein, 1974) and Smyth, Carpenter, Weil, Pozzani & Striegel (1962) reported the acute dermal LD_{50} to be 12·6 ml/kg.

Chronic toxicity. In a study in which rats received 0, 20, 100 or 500 mg/kg/day by oral intubation in oil solution for 13 wk, there were no statistically significant differences between treated and control rats in the rate of body-weight gain, food or water consumption, haematological findings or the results of renal concentration tests. The histological appearance of the tissues was unaffected by treatment. Ketone bodies found in the urine of a few male rats given 20 mg/kg were thought to be due to excretion of the unchanged compound. At 500 mg/kg/day, the liver weight was increased in both sexes and the kidney weight was increased in males only; some slight increases were also seen at the 100 mg/kg/day level. The excretion of cells in the urine was increased at the 100 and 500 mg/kg/day levels. The no-untoward-effect level was established as 20 mg/kg body weight/day, a level approximately 100 times the estimated maximum intake by man likely to result from its use as a flavouring (Gaunt, Carpanini, Wright, Grasso & Gangolli, 1972).

Irritation. Methyl amyl ketone applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Levenstein, 1974). It produced a degree of irritation on the uncovered rabbit belly rated as moderate and corneal injury in rabbits rated as mild (Smyth *et al.* 1962.

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 26 volunteers. The material was tested at a concentration of 4% petrolatum and produced no sensitization reactions (Epstein, 1974).

Inhalation. In single inhalation studies on guinea-pigs, a vapour concentration of 1500 ppm was irritating to the mucous membranes, 2000 ppm was strongly narcotic and 4800 ppm caused narcosis and death after exposure for 4–8 hr (Specht, Miller, Valaer & Sayers, 1940). Prolonged exposure to all of these concentrations caused varying degrees of irritation to the mucous membranes and a progressive general narcosis characterized by depression of rectal temperature, respiratory rate and heart rate, as well as the abolition of corneal, auditory and equilibratory reflexes. A 4-hr exposure of rats caused no deaths at 2000 ppm in air, but all six treated animals were killed by 4000 ppm (Smyth *et al.* 1962).

Threshold limit value. The threshold limit value for methyl amyl ketone has been set at 100 ppm (US Occupational Safety and Health Administration, 1972).

Metabolism. When 950 mg methyl amyl ketone/kg body weight was administered orally to rabbits, 40% was excreted as heptyl-2-glucuronide, and traces of the unchanged ketone were also found in the urine (Kamil, Smith & Williams, 1953). 2-Heptanone (methyl amyl ketone) was identified

as being among the approximately 300 compounds present in the volatile constituents of urine from male and female subjects (Zlatkis & Liebich, 1971).

Anthelmintic activity. No anthelmintic activity was observed against *Anguillula aceti, Tubiflex rivulorum, Hirudo medicinalis* and *Ascaris suilla* at concentrations of 200, 300, 200 and 200 mg %, respectively (Srepel & Akacić, 1962).

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METHYL ANISATE

Synonym: Methyl-*p*-methoxybenzoate.
Structure: $CH_3 \cdot O \cdot C_6H_4 \cdot OCO \cdot CH_3$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Reported to be found in the mushroom, *Trametes graveolens* (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: By direct esterification of anisic acid with methyl alcohol, e.g. under azeotropic conditions (Arctander, 1969).
Uses: In public use before the 1920s. Use in fragrances in the USA amounts to less than 1000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·12
Maximum	0·1	0·01	0·03	0·4

Status

Methyl anisate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included methyl anisate at a level of 8 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health.

Biological data

Acute toxicity. Both the acute oral LD_{50} in rats and the acute dermal LD_{50} in rabbits exceeded 5 g/kg (Levenstein, 1975).

Irritation. Methyl anisate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was mildly irritating (Levenstein, 1975). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1975).

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METHYL ANTHRANILATE

Synonyms: Methyl *o*-aminobenzoate; methyl 2-aminobenzoate.
Structure: $NH_2 \cdot C_6H_4 \cdot COO \cdot CH_3$.
Description and physical properties: EOA Spec. no. 34.
Occurrence: Reported to be found in nearly 50 essential oils, including neroli, orange, bergamot, lemon, mandarin, jasmine, tuberose, gardenia, champaca, ylang-ylang and others; also found in the juice and oil of *Vitis labrusca* (Gildemeister & Hoffman, 1966).
Preparation: By interaction of isatoic anhydride with methanol in the presence of alkali catalysts (Bedoukian, 1967).
Uses: In public use before the 1920s. Use in fragrances in the USA amounts to about 50,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·005	0·003	0·1
Maximum	0·2	0·03	0·03	1·0

Analytical data: Gas chromatogram, RIFM nos 2774, 73–26; infra-red curve, RIFM nos 2774, 73–26.

Status

Methyl anthranilate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) listed methyl anthranilate, giving an ADI of 1·5 mg/kg. It is the subject of a *Food Chemicals Codex* (1972) monograph and the Joint FAO/WHO Expert Committee on Food Additives (1967) has published a monograph and specifications for methyl anthranilate, giving a conditional ADI of 0–1·5 mg/kg.

Biological data

Acute toxicity. The acute oral LD_{50}s in mice, rats and guinea-pigs were reported as 3·9, 2·91 and 2·78 g/kg, respectively (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964). The acute dermal LD_{50} value in rabbits was reported as > 5 g/kg (Moreno, 1973).

Chronic toxicity. In feeding studies, 1000 and 10,000 ppm fed to rats in the diet for 13 wk produced no macroscopic effects (Hagan, Hansen, Fitzhugh, Jenner, Jones, Taylor, Long, Nelson & Brouwer, 1967).

Irritation. Methyl anthranilate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1973). Tested at 10% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1973) and this result was confirmed when the test was repeated (Epstein, 1974).

Sensitization. Maximization tests (Kligman, 1966) were carried out on groups of 24 and 26 volunteers. The material was tested at a 10% concentration in petrolatum and produced no sensitization reactions (Epstein, 1973 & 1974).

Metabolism. It is probable that this ester is hydrolysed and the anthranilate is excreted mostly as *o*-aminobenzoyl glucuronide (Charconnet-Harding, Dalgliesh & Neuberger, 1953).

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METHYL BENZOATE

Structure: $C_6H_5 \cdot OCO \cdot CH_3$.

Description and physical properties: EOA Spec. no. 193.

Occurrence: Found in oils of tuberose (flowers), ylang-ylang, clove, *Polianther tuberosa* L. (flowers) and *Narcissus jonquilla* L. (flowers) (*Fenaroli's Handbook of Flavor Ingredients*, 1971).

Preparation: By esterification of methy alcohol and benzoic acid.

Uses: In public use before the 1900s. Use in fragrances in the USA amounts to about 15,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·08
Maximum	0·10	0·01	0·03	0·40

Status

Methyl benzoate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) listed methyl benzoate giving an ADI of 5 mg/kg. Both the *Food Chemicals Codex* (1972) and Browning (1965) have monographs on methyl benzoate.

Biological data

Acute toxicity. The acute oral LD_{50} was reported as 3·43 g/kg in rats (Smyth, Carpenter, Weil & Pozzani, 1954), as 3·0, 3·5 and 4·1 g/kg in mice, rats and guinea-pigs, respectively (Kravets-Bekker & Ivanova, 1970) and as 1·35 and 3·33 g/kg in rats and mice, respectively (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964). Sublethal doses of methyl benzoate have been reported to increase the leucocyte, erythrocyte and reticulocyte counts and prothrombin time and, in a dose of 500 mg/kg, to reduce cholinesterase activity and ascorbic acid levels. Chronic administration of high doses resulted in damage to the central nervous system (Kravets-Bekker & Ivanova, 1970).

Enzyme induction. Oral doses of 0·1 LD_{50} of methyl benzoate given to rats had no effect on the hexobarbitone sleeping time or liver amidopyrine-*N*-demethylase activity but urinary ascorbic acid excretion was increased (Grübner, Klinger & Ankermann, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1970).

Percutaneous absorption. Methyl benzoate was slow to penetrate the skin of rats (Valette & Cavier, 1954).

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5-METHYL-3-BUTYLTETRAHYDROPYRAN-4-YL ACETATE

Structure: $H_2C \cdot CH(CH_3) \cdot CH(OCO \cdot CH_3) \cdot CH([CH_2]_3 \cdot CH_3) \cdot CH_2$ (O)

Description and physical properties: Colourless oily liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: Most methods are based upon the use of 2-octene and formaldehyde as starting materials.
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to approximately 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·12
Maximum	0·2	0·02	0·05	0·8

Analytical data: Gas chromatogram, RIFM no. 72-226; infra-red curve, RIFM no. 72-226.

Status

5-Methyl-3-butyltetrahydropyran-4-yl acetate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included 5-methyl-3-butyltetrahydropyran-4-yl acetate in the list of artificial flavouring substances that may be added temporarily to foodstuffs without hazard to public health.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 ml/kg (Levenstein, 1973).

Irritation. 5-Methyl-3-butyltetrahydropyran-4-yl acetate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was mildly irritating (Levenstein, 1973). Tested at 8% in petrolatum, it produced no irritation after a 48 hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1972).

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METHYL CHAVICOL

Synonyms: Estragole; *p*-allylanisole; chavicol methyl ether.
Structure: $CH_3 \cdot O \cdot C_6H_4 \cdot CH_2 \cdot CH{:}CH_2$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Isolated initially from the rind of *Persea gratissima* Gärtn. and subsequently from the oil of estragon. It has been found in large amounts (as much as 60–90%) in the oils of Russian anise, basil, fennel, turpentine, *Feronia elephatum* Corr., *Solidago odora*, *Agasnache rugosa* and *Orthodon methylchavicoliferum*, and has been obtained by steam distillation from the oil of *Fagara mantshurica* (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: Recovered from turpentine by distillation.
Uses: In public use since the 1900s. Use in fragrances in the USA amounts to approximately 4000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·08
Maximum	0·25	0·03	0·03	0·30

Analytical data: Gas chromatogram, RIFM no. 71-19; infra-red curve RIFM no. 71–19.

Status

Methyl chavicol was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included methyl chavicol at a level of 40 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health. The *Food Chemicals Codex* (1972) has a monograph on methyl chavicol.

Biological data

Acute toxicity. The acute oral LD_{50} values in mice and rats were reported as 1·25 and 1·82 g/kg, respectively (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964). Elsewhere, the acute oral LD_{50} value in rats was reported as 1·23 g/kg (1·08–1·38 g/kg) (Moreno, 1972). The acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1972). Rats given four daily oral doses of 605 mg/kg showed minor liver damage, consisting of discoloration, mottling and blunting of lobe edges (Taylor, Jenner & Jones, 1964).

Irritation. Methyl chavicol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1972). Tested at 3% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 3% in petrolatum and produced no sensitization reactions (Kligman, 1972).

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METHYL CINNAMATE

Synonym: Methyl 3-phenylpropenoate.
Structure: $CH_3 \cdot OCO \cdot CH{:}CH \cdot C_6H_5$.
Description and physical properties: EOA Spec. no. 59.
Occurrence: Reported to be found in oils from rhizomes of *Alpinia malaccensis*, from leaves of *Ocimum canum* Sims, from *Narcissus jonquilla* L., and from rhizomes of *Gastrochilus panduratum* Ridl. (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: By the esterification of cinnamic acid.
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to approximately 25,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·003	0·005	0·05
Maximum	0·1	0·01	0·03	0·2

Status

Methyl cinnamate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) listed methyl cinnamate, giving an ADI of 1·25 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on methyl cinnamate.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 2·61 g/kg (2·00–3·41 g/kg) (Weir, 1971). The acute dermal LD_{50} in rabbits exceeded 5 g/kg (Weir, 1971).

Irritation. Methyl cinnamate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Weir, 1971), and the ester produced no conjunctival irritation in the rabbit eye (Weir, 1971). Tested at 10% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1975). Thomssen (1947), however, reported it to be an irritant in high concentrations.

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material (RIFM sample no. E) was tested at a concentration of 2% in petrolatum and produced no sensitization reactions (Kligman, 1971). In a second maximization test on 25 volunteers, the material (RIFM no. 75-10-IFRA-6) was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1975).

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METHYLCINNAMIC ALCOHOL

Synonyms: α-Methylcinnamyl alcohol; 3-phenyl-2-methyl-propen-2-ol-1.
Structure: $C_6H_5 \cdot CH:C(CH_3) \cdot CH_2OH$.
Description and physical properties: EOA Spec. no. 203.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By selective hydrogenation of methylcinnamic aldehyde.
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to less than 5000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·05	0·005	0·03	0·3
Maximum	0·3	0·03	0·2	1·2

Status

Methylcinnamic alcohol is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974), or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 2·4 ml/kg (1·9–3·0 ml/kg) (Levenstein, 1974). The acute dermal LD_{50} in rabbits exceeded 5 g/kg (Levenstein, 1974).

Irritation. Methylcinnamic alcohol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was mildly irritating (Levenstein, 1974). Tested at 2% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 2% in petrolatum and produced no sensitization reactions (Kligman, 1974).

Metabolism. Cinnamic alcohol is mainly metabolized to benzoic acid, presumably via cinnamic acid, but substitution apparently prevents oxidation to benzoic acid, since 2-ethylcinnamic alcohol ($C_6H_5 \cdot CH:C(C_2H_5) \cdot CH_2OH$) is partly (30–33%) excreted as α-ethylcinnamic acid (Williams, 1959).

Micro-organisms. The vapour of methylcinnamic alcohol slightly inhibited the growth of *Phoma betae* but not of three other fungi, when tested *in vitro* against growing cultures (Maruzzella, Chiaramonte & Garofalo, 1961). The growth of *Escherichia coli* and *Staphylococcus aureus* (penicillin-sensitive) was inhibited by methylcinnamic alcohol at 1:500 dilution, while the growth of two other bacteria was not inhibited (Maruzzella & Bramnick, 1961).

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α-METHYLCINNAMIC ALDEHYDE

Synonyms: α-Methylcinnamaldehyde; α-methylcinnimal; 2-methyl-3-phenyl-2-propenal.
Structure: $C_6H_5 \cdot CH:C(CH_3) \cdot CHO$.
Description and physical properties: EOA Spec. no. 222.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By condensing benzaldehyde with propionic aldehyde.
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to approximately 5000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·001	0·001	0·005	0·04
Maximum	0·01	0·01	0·05	0·8

Analytical data: Gas chromatogram. RIFM no. 72–257; infra-red curve. RIFM no. 72–257.

Status

α-Methylcinnamic aldehyde was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) listed α-methylcinnamic aldehyde, giving an ADI of 1·25 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on α-methylcinnamic aldehyde.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 2·05 g/kg (1·83–2·27 g/kg) (Russell, 1973). The acute dermal LD_{50} in rabbits exceeded 5 g/kg (Russell, 1973).

Irritation. α-Methylcinnamic aldehyde applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Russell, 1973). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1973).

References

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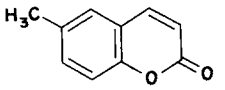
Russell, T. J. (1973). Report to RIFM, 6 March.

6-METHYLCOUMARIN

Synonyms: 6-Methyl-1,2-benzopyrone.
Structure:



Description and physical properties: *Givaudan Index* (1961).
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By condensation of *p*-cresol with maleic acid under heat in the presence of sulphuric acid.
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to less than 1000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·04
Maximum	0·1	0·01	0·03	0·4

Analytical data: Gas chromatogram, RIFM no. 72-196; infra-red curve, RIFM no. 72-196.

Status

6-Methylcoumarin was given GRAS status by FEMA (1965). The Council of Europe (1974) included 6-methylcoumarin at a level of 30 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported to be 1·68 g/kg (1·43–1·93 g/kg) (Moreno, 1973). The acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1973).

Subacute and long-term toxicity. In a 2-yr feeding study, five groups of rats, each containing 25 males and 25 females were given 6-methylcoumarin at levels of 500, 1000, 3500, 7500 and 15,000 ppm in the diet. No effects were seen at the 500, 1000, and 3500 ppm levels, but at 7500 ppm growth depression was observed in males and at 15,000 ppm growth depression in both males and females, microscopic liver changes and moderate atrophy were observed (Hagan, Hansen, Fitzhugh, Jenner, Jones, Taylor, Long, Nelson & Brouwer, 1967). In another feeding study involving groups of ten male and ten female rats, neither 1000 nor 10,000 ppm fed in the diet for 14 wk had any effects (Hagan *et al.* 1967).

A male dog fed 150 mg methylcoumarin/kg had to be killed after 39 days because of weakness, emaciation and dehydration, and showed moderate to severe hepatitis and slight to moderate muscle atrophy (Hagan *et al.* 1967). In a 2-yr feeding study involving one male and one female dog given 50 mg/kg/day, no effects were produced (Hagan *et al.* 1967).

Irritation. 6-Methylcoumarin applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was mildly irritating (Moreno, 1973). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 human volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1973).

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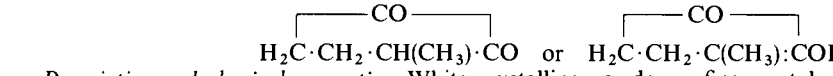
METHYLCYCLOPENTENOLONE

Synonyms: 2-Hydroxy-3-methyl-2-cyclopenten-1-one; 3-methylcyclopentane-1,2-dione; cyclotene.
Structure:



Description and physical properties: White crystalline powder or fine crystals.
Occurrence: Reported to be found during the dry distillation of wood and in the corresponding tar oil. It has also been identified in fenugreek (*Fenaroli's Handbook of Flavor Ingredients*, 1975).
Preparation: By ketonic hydrolysis of the corresponding dicarboxylic ester (Arctander, 1969).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to approximately 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·00125	0·00125	0·05
Maximum	0·025	0·00625	0·00625	0·25

Status

Methylcyclopentenolone was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The *Food Chemicals Codex* (1972) has a monograph on methylcyclopentenolone.

Biological data

Acute toxicity. The acute oral LD_{50} value in guinea-pigs was reported as 1·4 g/kg (Dow Chemical Company, 1953) and that in rats as > 1·85 g/kg, while the acute dermal LD_{50} value in guinea-pigs exceeded 2 g/kg (Moreno, 1976). Methylcyclopentenolone was lethal to mice and rats at ip doses of 0·5–1 g/kg (Shugaev, 1959), and at a concentration of 7×10^{-4} M was toxic to cultured human leucocytes (Withers, 1966).

Subacute toxicity. Groups of 15 male and female rats fed 1% methylcyclopentenolone for 6 months in the diet showed no adverse effects (Dow Chemical Company, 1953). Methylcyclopentenolone injected ip into mice and rats in daily doses of 100 mg/kg over a period of 20 days had no effect on the number or activity of leucocytes; such doses showed only a slight arresting effect on implanted carcinosarcomas and no arresting effect on the growth of Crocker sarcoma (Shugaev, 1959).

Irritation. Methylcyclopentenolone applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Moreno, 1976). Tested at 3% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1976).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 24 volunteers. The material was tested at a concentration of 3% in petrolatum and produced no sensitization reactions (Epstein, 1976).

Additional published data

Treatment of cultured human leucocytes with $3·5 \times 10^{-4}$ M-methylcyclopentenolone caused a significant increase in chromosomal aberrations (abnormal metaphases) but no chromosome breaks (Withers, 1966).

Methylcyclopentenolone, a component of the wood smoke used to smoke meat, did not react significantly with the ε-amino groups of the soluble protein, bovine serum albumin (Chen & Issenberg, 1972).

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METHYL DIPHENYL ETHER

Synonyms: *o*-Phenyl anisole; 2-methoxy biphenyl.
Structure: $C_6H_5 \cdot C_6H_4 \cdot OCH_3$.
Description and physical properties: EOA Spec. no. 285.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By methylation of *o*-phenyl phenol.
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to approximately 2000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·1
Maximum	0·2	0·02	0·05	0·2

Analytical data: Gas chromatogram, RIFM nos 70–42, 73–27; infra-red curve, RIFM nos 70–42, 73–27.

Status

Methyl diphenyl ether is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974), or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported 3·6 g/kg (3·17–4·03 g/kg) and the acute dermal LD_{50} in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. Methyl diphenyl ether applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was slightly irritating (Moreno, 1973). Tested at 2% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 2% in petrolatum and produced no sensitization reactions (Kligman, 1973).

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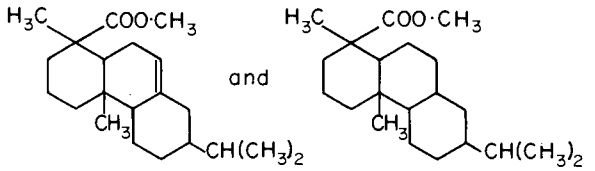
METHYL ESTER OF ROSIN (PARTIALLY HYDROGENATED)

Structure: A mixture of the methyl esters of hydrogenated rosin acids mainly:



Description and physical properties: *Food Chemicals Codex* (1972).
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By the esterification of rosin with methanol, followed by partial hydrogenation and purification by steam stripping (*Food Chemicals Codex*, 1972).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to about 200,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·2
Maximum	0·3	0·003	0·05	1·0

Analytical data: Infra-red curve, RIFM no. 72–259.

Status

Methyl ester of rosin (partially hydrogenated) has been approved by the FDA for food use (21 CFR 121.2592 & 121.1059). The *Food Chemicals Codex* (1972) has a monograph on methyl ester of rosin (partially hydrogenated).

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as >100 g/kg (Frawley, 1972).

Irritation. A patch test on 200 human subjects using the Schwartz prophetic patch technique produced no irritation reactions (Frawley, 1972). Methyl ester of rosin (partially hydrogenated) tested at 10% in petrolatum produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1973).

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METHYL ETHYL KETONE

Synonym: 2-Butanone. CAS Registry Number 78-93-3.
Structure: $CH_3 \cdot CO \cdot CH_2 \cdot CH_3$.
Description and physical properties: Merck Index (1976).
Occurrence: Has been reported to occur as an impurity among the products from the dry-distillation of wood and in the oil (extracted with ether) of black tea. It is also present in coffee, cheese, bread, some citrus oils and some other natural products including the grape and raspberry (*Fenaroli's Handbook of Flavor Ingredients*, 1975).
Preparation: By oxidation of *sec*-butanol (Arctander, 1969).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to approximately 50,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·08
Maximum	0·1	0·01	0·05	0·3

Analytical data: Gas chromatogram, RIFM no. 74-224; infra-red curve, RIFM no. 74-224.

Status

Methyl ethyl ketone (MEK) was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included MEK in the list of artificial flavouring substances that may be added temporarily to foodstuffs without hazard to public health. The *Food Chemicals Codex* (1972) has a monograph on this solvent and an extensive monograph was compiled earlier by Browning (1965).

Biological data

Acute toxicity. Acute oral LD_{50} values for MEK were found to be 3·4, 3·6, 3·1 and $<1·0$ mg/kg for older adult, young adult, 14-day-old and newborn rats, respectively, by Kimura, Ebert & Dodge (1971), who suggested that the maximum permissible limit for a single oral dose of MEK was 0·0005 ml/kg (1/1000 of the dose giving the first observable gross signs of drug action in young adult rats). Rowe & Wolf (1963) gave the acute oral toxic dose of MEK for rats as 3·3 g/kg, with development of lung irritation and narcosis at massive doses, and the acute dermal LD_{50} for rabbits as >8 ml/kg. The acute dermal LD_{50} value in rabbits reported by Moreno (1975) was >5 g/kg. In experimental animals, high concentrations cause narcosis, emphysema of the lungs and congestion of the liver and kidneys, while in liquid form the solvent is highly irritating to the eyes and has been reported to cause oedema of the cornea (Rowe & Wolf, 1963).

The acute ip LD_{50} of MEK for mice was found to be 616 mg/kg (National Institute for Occupational Safety and Health, 1975). When male guinea-pigs were given undiluted MEK in an ip dose of 750, 1500 or 2000 mg/kg, the top dose killed one out of four animals (DiVincenzo & Krasavage, 1974). After 24 hr, elevated levels of serum ornithine carbamoyltransferase (OCT) (indicative of liver damage) were demonstrated in animals given 2000 mg/kg, and lipid accumulation in the liver cells of those given 1500 or 2000 mg/kg. MEK was classified as of low hepatotoxicity, causing elevated serum OCT at doses above 500 mg/kg (DiVincenzo & Krasavage, 1974), a level incorrectly cited elsewhere (National Institute for Occupational Safety and Health, 1975) as the lethal dose for rats.

When administered iv to mice, MEK (0·15 ml of a 10% solution in a physiological medium) caused only temporary narcosis (De Castiglia, Cembal, Fraga de Suarez, Nicolini, Noto & Mitta, 1972).

A recent study was undertaken (Traiger, Bruckner & Cooke, 1975) to determine the effect of 2-butanol (2·2 ml/kg given orally) and MEK (1·87 ml/kg given orally) on the hepatic ultrastructure and microsomal drug-metabolizing activity in the rat. Rats were killed 16, 28 and 40 hr after dosing for the *in vitro* determination of the activities of microsomal acetanilide hydroxylase and aminopyrine *N*-demethylase. A 50–97% increase in acetanilide-hydroxylase activity was found at each of these times after treatment with either compound. Aminopyrine-*N*-demethylase activity was significantly increased in animals treated 40 hr earlier with MEK. Less pronounced increases in *N*-demethylase activity were noted in rats killed 16 or 28 hr after dosing with either agent. Electron microscopic examination of hepatocytes revealed a marginal increase in the amount of smooth endoplasmic reticulum 16 hr after administration of either 2-butanol or MEK and a marked proliferation of this membrane after 40 hr. These results would indicate that the potentiation of CCl_4 hepatotoxicity by 2-butanol or MEK may be related in part to their stimulatory effect on the drug-metabolizing system of the endoplasmic reticulum.

The 48-hr median tolerance level (lethal concentration) for MEK was found to be 5640 mg/litre for bluegill fish (Price, Waggy & Conway, 1974).

Inhalation. A 10% concentration (100,000 ppm) in air caused no deaths among guinea-pigs exposed for a few minutes. Exposure for 1 hr to a 1% concentration (10,000 ppm) had no serious effect, although irritation of the eyes and nose occurred soon after the start of the exposure and narcosis was observed in 4–5 hr (Patty, Schrenk & Yant, 1935). In animals subjected to lethal doses, marked congestion of internal organs and slight congestion of the brain were observed, the lungs showed emphysema and there was marked congestion in the liver and kidneys; animals that survived exposure to 100,000 ppm for 30 min or more developed corneal opacity, which improved and practically disappeared at the end of 8 days (Patty *et al.* 1935).

Narcosis was evident in guinea-pigs that inhaled 33,000 ppm for 48–90 min, while 10,000 ppm also caused narcosis, with eventual recovery after 240–280 min. Signs of vitamin deficiency were observed in guinea-pigs exposed repeatedly for 12 wk to atmospheric concentrations of 235 ppm MEK (La Belle & Brieger, 1955).

Rats survived inhalation of 2000 ppm MEK for 2 hr, but some deaths occurred after inhalation of 2000 pm for 4 hr or 4000 ppm for 2 hr. The most important effect of the inhalation was narcosis. The predicted effects of daily 8-hr inhalation included some irritation at 250 ppm, marked eye, nose or throat irritation at 500 ppm and definite narcosis (short of dizziness) at 250 ppm (Carpenter, Smyth & Pozzani, 1949; Smyth, 1956).

In rats exposed continuously for 7 days to vapours of methyl *n*-butyl ketone (MBK) at 225 ppm and MEK at 750 ppm separately or combined, hexobarbitone sleeping times were reduced by exposures which included MEK, but not by exposure to MBK alone. *In vitro* hepatic microsomal oxidative- and reductive-enzyme activities were enhanced two- or threefold by exposure to the MBK/MEK combination. This stimulation of enzyme activity may have an important influence on the metabolism of many foreign chemicals, and may help to explain the enhancement of MBK toxicity that occurs with combined MBK/MEK exposures (Hetland, Couri & Abdel-Rahman, 1976).

The threshold limit value for MEK has been set at 200 ppm in air (American Conference of Governmental Industrial Hygienists, 1973). In human studies, exposure to 90–270 ppm MEK vapour for 4 hr was associated with a shortening of time estimates in males and increased variation in females in time-estimation tests of 5, 10 and 30 sec (Nakaaki, 1974). Eye, nose and throat irritation was reported after exposure to 350 ppm for 3–5 min and it was estimated that 200 ppm would be satisfactory for an 8-hr working day (Nelson, Ege, Ross, Woodman & Silverman, 1943). Industrial exposures to MEK vapour have been reported to cause no permanent ill effects at 700 ppm, vomiting and nausea at 500 ppm (attributed to 2-nitropropane) and headaches and throat irritation at 300 ppm, while loss of consciousness resulted from a mixture of 398–561 ppm MEK and 330–496 ppm acetone (Rowe & Wolf, 1963).

Irritation. Methyl ethyl ketone applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1975). Tested at 20% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1975). Exposure of human forearm skin to MEK for 1 hr/day for 6 successive days resulted in damage to the horny layer, sometimes requiring complete regeneration (Malten, Spruit, Boemaars & de Keizer, 1968). It was earlier shown to cause defatting and partial dehydration of the stratum corneum of hydrated human forearm skin without producing irritation or inflammation (Munies, 1965; Wurster & Munies, 1965). While minor skin contacts encountered in industry did not cause irritation, dermatitis from excessive repeated prolonged skin contact by workers was not uncommon (Rowe & Wolf, 1963). Applied directly to skin affected by poison ivy and poison oak, MEK relieved symptoms and caused drying and whitening of the treated area (Crary, 1975).

Exposure of rabbit skin to MEK for 24 hr caused moderate skin irritation (Rowe & Wolf, 1963). A 50% solution did not aid penetration of Rhodamine B into guinea-pig skin (Meyer, 1965).

Methyl ethyl ketone has a greater capacity to cause oedema of the cornea than has acetone (Larson, Finnegan & Haag, 1956).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 24 volunteers. The material (RIFM no. 74-224) was tested at a concentration of 20% in petrolatum and produced no sensitization reactions (Epstein, 1975).

Metabolism. Ketones are not readily metabolized in the body and may be eliminated unchanged in the expired air and to some extent in the urine. The major metabolic change that ketones undergo is reduction to the corresponding secondary alcohol, which is usually eliminated as the glucuronide. This process has been demonstrated in rabbits, while in dogs, 30–33% of a dose of 0·3–0·5 g MEK/kg was eliminated in the expired air (Williams, 1959). A dose administered iv to mice was rapidly eliminated, primarily by pulmonary ventilation and the remainder as the glucuronic acid ester (De Castiglia *et al.* 1972). Because of its lower solubility in blood, MEK is excreted more rapidly than acetone through the lungs (Rowe & Wolf, 1963). When human subjects were exposed to 300 ppm MEK vapour for 2 hr, MEK was excreted in the expired air (23 ppm) and in the urine (Tada, Nakaaki & Fukabori, 1972). The contamination concentrations in the central nervous and respiratory systems, mucous membranes and kidneys of lunar-module crew members were tabulated for MEK and 300–400 other outgassing products of materials used in the crew compartment (Santoro & Holden, 1971).

Percutaneous absorption was studied by measuring MEK in the expired air of human subjects following application to normal hydrated and dehydrated forearm skin. The MEK was rapidly absorbed, as indicated by its prompt excretion in the expired air. In an 8-hr exposure, a constant level of absorption was reached in 2–5 hr, the absorption rate being increased by hydration of the stratum corneum. Similar elimination in the expired air was observed following ingestion by human subjects of 375 mg MEK in capsule form (Munies, 1965; Munies & Wurster, 1965; Wurster & Munies, 1965).

In cows fed various rations, MEK has been identified conclusively in the urine, milk and blood, the concentration being highest in the urine (Loney, Bassette & Ward, 1963). The rate of absorption of vapours of MEK through the shells of hens' eggs was reported by Kato, Wantanabe & Sato (1971).

An aerobic soil bacterium, Nocardia, was reported to catabolize MEK by an oxygenase to ethyl acetate, which was then hydrolysed by an acetylesterase to ethanol and acetic acid (Eubanks, 1973). Ilisescu (1971) considered MEK to be easily degradable in biological treatment plants for petrochemical wastes. In modified standard biochemical-oxygen-demand tests, it was found to be 76 and 32% biodegradable in 5 days in fresh water and sea water, respectively, and because of its rapid biodegradation, it is classified by EPA standards as a hazardous and polluting substance (Price *et al.* 1974).

Pharmacology. Anticonvulsant activity was demonstrated in rats given orally a dose of 80·5 mg MEK/kg, which significantly delayed the onset of isonicotinic acid hydrazide-induced convulsions and provided 60% protection against electroshock convulsions, but failed to protect against metrazole convulsions (Kohli, Kishor, Dua & Saxena, 1967). Golubev (1969) reported that 0·25 M-MEK caused contraction of the rabbit pupil, and MEK and other volatile substances isolated from human urine and injected iv into rabbits damaged cerebral and coronary arteries and caused increased capillary permeability, but did not alter the blood-sugar level (Mabuchi, 1969). In dogs, MEK caused vomiting, muscular debility and the formation of large quantities of urinary magnesium ammonium phosphate crystals (Verstraete, van der Stock & Mattheeuws, 1964).

Combined ip administration of MBK and MEK (1:3) to guinea-pigs increased the urinary excretion of the MBK metabolites 2-hexanol and 2,5-hexanedione (Couri, Abdel-Rahman & Hetland, 1976). If the neurotoxic action of MBK is mediated by a metabolite, stimulation of MBK metabolism by simultaneous exposure to MEK may help to explain the marked enhancement of neurotoxicity that is observed with combined MBK/MEK exposures (Hetland *et al.* 1976).

Neurotoxicity. Some workers exposed both to liquid MEK and to its vapours at 300–600 ppm complained of numbness of the fingers and arms (Smith & Mayers, 1944).

In a plastics factory where workers were not using protective gloves and masks and were exposed to tetrahydrofuran–polyester glue and to MEK, both by inhalation of the vapour and by contact with the hands during its use as a cleaning solvent, one worker developed a toxic polyneuritis involving paraesthesia of the fingers, loss of utility of the hand muscles and leucocytosis, which might have been due to MEK or to its combined use with tetrahydrofuran (Viader, Lechevalier & Morin, 1975).

It has been reported (Allen, Mendell, Billmaier, Fontaine & O'Neill, 1975) that in an industry producing plastics-coated and colour-printed fabrics, 86 of 1157 employees were diagnosed as having toxic distal polyneuropathy attributed to exposure to MBK which was present in a solvent mixture with MEK. In 194 employees described as suspected cases on the basis of electrodiagnostic studies, haematological studies showed results that were described as within normal limits. However, an unusual pattern was reported for erythrocyte- and plasma-cholinesterase values obtained for 96 employees with abnormal electrodiagnostic findings. Erythrocyte-acetylcholinesterase (AChE) activities were low (1·37 μmol AChE hydrolysed/mg protein/hr compared with values of 2·03 units obtained for volunteers and neurologically normal patients). Plasma-cholinesterase (butyrocholinesterase or BuChE) values were higher in the case of exposed workers (0·636 mmol BuChE/ml/hr) as compared with normal values (0·253 units). No relationship with the severity of the peripheral neuropathy was found. When a group of ten affected employees returned to work under conditions of reduced solvent exposure, values for erythrocyte AChE and serum BuChE did not differ significantly from values in ten unaffected workers. Average atmospheric levels of 36 ppm MBK and 516 ppm MEK were detected behind the printing machines. A possible synergistic effect with MEK, tetrahydrofuran, trichloroethylene or phthalate plasticizer could not be ruled out in this study. No cases of toxic neuropathy were detected in workers exposed to MEK in another plant where MBK had never been used. Experimental exposures to MEK (not fully described) caused elevated BuChE levels in mice, cats and chickens and depressed erythrocyte cholinesterase levels in mice and rats but not in chickens. Neuropathy has not been found in animals exposed to MEK alone, but combinations of MEK and MBK have shown a substantial synergistic effect in animals (Allen *et al.* 1975).

Rats exposed for 8 hr/day on 5 days/wk for 6 wk to vapours of MBK and MEK (200 and 2000 ppm) developed muscular weakness of the limbs, with some deaths (Duckett, Williams & Francis, 1974). Histological examination of the sciatic nerves of these rats and of rats exposed only to 200 ppm MBK showed axonal hypertrophy, beading and degeneration, associated with widespread perinodal and segmental breakdown of myelin, representing the early changes of neuropathy.

Teratogenicity. Methyl ethyl ketone (1000 or 3000 ppm) inhaled by pregnant rats for 7 hr/day on days 6–15 of gestation was shown to be embryotoxic, foetotoxic and potentially teratogenic (Schwetz, Leong & Gehring, 1974). The concentration of 3000 ppm caused some retardation of foetal development (delayed ossification of sternebrae) and increased gross, skeletal and soft-tissue anomalies, including acaudia, imperforate anus and brachygnathia. No significant maternal toxicity was observed.

Invertebrates. Methyl ethyl ketone does not release alarm behaviour in the honeybee *Apis mellifera* (Boch & Shearer, 1971) or in the ants *Iridomyrmex pruinosus* (Blum, Warter & Traynham, 1966) and *Pogonomyrmex badium* (Blum, Doolittle & Beroza, 1971). It was found to stimulate an increase in physiological age in ticks, *Ixodus persulcatus*, thus increasing their sensitivity to DDT for which MEK is commonly used as a solvent (Uspenskii & Repkina, 1974).

The 24-hr median tolerance level of MEK in the brine shrimp, *Artemia salina*, was found to be 1950 mg/litre (Price *et al.* 1974). It was reported to be an active hatching agent for cysts of the nematode *Heterodera schachtii*, causing maximum hatching (22%) at a concentration of 9 mM (Clarke & Shepherd, 1964).

Micro-organisms. In a study of the inhibitory action of 25 compounds associated with milk against *Escherichia coli*, *Salmonella typhimurium*, *Staphylococcus aureus*, *Streptococcus lactis* and *Leuconostoc citrovorum*, MEK exhibited some inhibitory action against *Str. lactis* and *L. citrovorum* and sometimes enhanced the growth of *S. typhimurium* (Kulshrestha & Marth, 1974). In other studies, MEK produced only moderate (65%) and temporary inhibition of *E. coli* proliferation at 0·001 M concentration (Együd, 1967; Hata, 1970), and caused little or no inhibition of growth in tests on nine species of bacteria (Kellner & Kober, 1955). It stimulated slightly the germination of uredospores of the wheat-stem rust organism *Puccinia graminis* (French, 1961), was used to inhibit excessive oxidation by the fungus *Fusarium caucasicum* in a patented microbiological oxidation process (Chinoin Gyogyszer es Vegyeszeti Termekek Gyara Rt, 1962), and in a concentration of 0·67 M, was toxic to yeast cells (Lindenberg & Gauchat, 1958). At a concentration of 50 mg/litre in water reservoirs, it inhibited the nitrification process somewhat but did not affect biochemical oxygen demand (Vertebnaya & Mozhaev, 1960).

Cells. At 100 ppm, MEK was moderately toxic *in vitro* to Ehrlich-Landschütz diploid ascites tumour cells (Holmberg & Malmfors, 1974), while at 5000 ppm it provided complete protection against the haemolysis of rat erythrocytes in hypotonic saline solutions (Holmberg, Jakobson & Malmfors, 1974).

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METHYL EUGENOL

Synonyms: Eugenyl methyl ether; 4-allylveratrole.
Structure: $CH_3O \cdot C_6H_3(OCH_3) \cdot CH_2 \cdot CH{:}CH_2$.
Description and physical properties: EOA Spec. no. 128.
Occurrence: Found as the main constituent in oils of *Dacrydium franklinii* Hook. (huon pine), *Melaleuca bracteata* F.v.M., *Asarum europaeum* L., *A. canadense* L., *Cinnamomun oliveri* Bail and a physiological variety of *Ocotea pretiosa* Benth. and as a minor constituent in oils of *Aetherosperma muscatum* Lab., betel, calamus, laurel, pimento, basil, ylang ylang, rose, hyacinth and many others (*Givaudan Index*, 1961).
Preparation: By methylation of eugenol.
Uses: In public use before the 1920s. Use in fragrances in the USA amounts to approximately 50.000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·3
Maximum	0·2	0·02	0·05	0·8

Analytical data: Gas chromatogram, RIFM nos 71–23, 72–33; infra-red curve, RIFM nos 71–23, 72–33.

Status

Methyl eugenol was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) listed methyl eugenol, giving an ADI of 5 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on methyl eugenol.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 1·56 g/kg (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964) and as 0·81 g/kg (0·58–1·13 g/kg) (Keating, 1972). The acute dermal LD_{50} in rabbits exceeded 5 g/kg (Keating, 1972).

Irritation. Methyl eugenol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was irritating (Keating, 1972). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1972).

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METHYL HEPTENONE

Synonym: 6-Methyl-5-hepten-2-one.
Structure: $CH_3 \cdot C(CH_3):CH \cdot [CH_2]_2 \cdot CO \cdot CH_3$.
Description and physical properties: EOA Spec. no. 262.
Occurrence: Originally reported in lemongrass. It has been reported to be found in the essential oils of palmarosa, lemon, citronella, vervain, geranium, *Ocimum canum*, *Artemisia scoparia*, *Urtria dioica* and others (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: From oil lemongrass or by chemical synthesis.
Uses: In public use before the 1920s. Use in fragrances in the USA amounts to approximately 2000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·04
Maximum	0·05	0·005	0·03	0·3

Analytical data: Gas chromatogram, RIFM no. 72–35; infra-red curve, RIFM no. 72–35.

Status

Methyl heptenone was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included methyl heptenone at a level of 1 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health. The *Food Chemicals Codex* (1972) has a monograph on methyl heptenone.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 3·5 g/kg (Bär & Griepentrog, 1967) and as 4·1 g/kg (3·33–5·04 g/kg) (Keating, 1972). The acute dermal LD_{50} exceeded 5 g/kg (Keating, 1972).

Irritation. Methyl heptenone applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was irritating (Keating, 1972). Tested at 3% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 3% in petrolatum and produced no sensitization reactions (Kligman, 1972).

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METHYL HEXYL KETONE

Synonyms: 2-Octanone; *n*-hexyl methyl ketone.
Structure: $CH_3 \cdot CO \cdot [CH_2]_5 \cdot CH_3$.
Description and physical properties: EOA Spec. no. 284.
Occurrence: Reported to be found in small quantities in the essential oil of *Ruta montana* L. and in a few varieties of banana and citrus fruits (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: By the oxidation of 2-octanol.
Uses: In public use since the 1940s. Use in fragrances in the USA amounts to less than 6000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·003	0·005	0·04
Maximum	0·1	0·01	0·02	0·4

Status

Methyl hexyl ketone was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included methyl hexyl ketone at a level of 2 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health.

Biological data

Acute toxicity. Both the acute oral LD_{50} in rats and the acute dermal LD_{50} in rabbits exceeded 5 g/kg (Moreno, 1973).

Inhalation. Symptoms of eye and nasal irritation developed immediately the guinea-pig was exposed to an essentially saturated atmosphere (1300 ppm) (Rowe & Wolf, 1963). This was followed by muscular weakness after exposure for approximately 10 hr and by coma after approximately 12 hr. An exposure of 1 hr was considered to be the maximum at this concentration causing no serious disturbance to guinea-pigs.

Irritation. Methyl hexyl ketone applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was slightly irritating (Moreno, 1973). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1973).

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p-METHYL HYDRATROPALDEHYDE

Synonyms: 2-(*p*-Tolyl)propionic aldehyde; 2-(*p*-methylphenyl)propionaldehyde.
Structure: $CH_3 \cdot C_6H_4 \cdot CH(CH_3) \cdot CHO$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Has apparently not been reported to occur in nature.
Preparation: From *p*-methylacetophenone via *p*-methylphenylmethylglycidic acid (Arctander, 1969).
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to approximately 7000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·12
Maximum	0·1	0·01	0·03	0·4

Analytical data: Gas chromatogram, RIFM no. 72-198; infra-red curve, RIFM no. 72-198.

Status

p-Methyl hydratropaldehyde was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164).

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 3·50 g/kg (2·40–4·60 g/kg) (Moreno, 1973). The acute dermal LD_{50} value in rabbits was reported as > 5 g/kg (Moreno, 1973).

Irritation. p-Methyl hydratropaldehyde tested at 4% in petrolatum produced no irritation after a 48-hr closed-patch test on three different panels of human subjects (Epstein, 1974; Kligman, 1972 & 1973).

Sensitization. A series of maximization tests (Kligman, 1966; Kligman & Epstein, 1975) were carried out on groups of 25 or 24 volunteers. One sample (RIFM no. 72-4-198), tested at a concentration of 4% in petrolatum, produced three sensitization reactions in the 25 test subjects (Kligman, 1972). Another sample (RIFM no. 81-4-37RG), tested at a concentration of 4% in petrolatum, produced no sensitization reactions in 25 test subjects (Kligman, 1973). A third sample [RIFM no. 74-4-156RG(3)], tested at a concentration of 4% in petrolatum, produced no sensitization reactions in 24 volunteers (Epstein, 1974). The retesting of *p*-methyl hydratropaldehyde with a second sample (which proved to be from the same lot as the original material) gave negative maximization results. Subsequent retesting of this material with a new sample and at a different facility came out completely clean. We can only interpret these results as indicative of some kind of contamination in the original sample.

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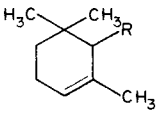
METHYL IONONE

Structure: A mixture of isomers, mainly:



in which R=CH:CH·CO·CH_2·CH_3 (α-methyl ionone) or CH:C(CH_3)·CO·CH_3 (α-isomethyl ionone; γ-type methyl ionone).

Description and physical properties: EOA Spec. no. 257.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By condensing citral and methyl ethyl ketone with subsequent cyclization of the pseudo-methyl ionone.
Uses: In public use since the 1900s. Use in fragrances in the USA amounts to approximately 250,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·015	0·4
Maximum	0·3	0·03	0·1	1·0

Analytical data: Gas chromatogram, RIFM nos 2833, 73–28; infra-red curve, RIFM nos 2833, 73–28.

Status

Methyl ionone was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) listed α-methyl ionone giving an ADI of 0·1 mg/kg, and included γ-type methyl ionone at a level of 5 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health.

Biological data

Acute toxicity. Both the acute oral LD_{50} in rats and the acute dermal LD_{50} in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. Methyl ionone applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1973). A patch test using methyl ionone at full strength for 24 hr produced no reactions in 16 subjects (Katz, 1946).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Greif, 1967).

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METHYL ISOEUGENOL

Synonyms: 1,2-Dimethoxy-4-propenylbenzene; 4-propenylveratrole.
Structure: $CH_3O \cdot C_6H_3(OCH_3) \cdot CH{:}CH \cdot CH_3$.
Description and physical properties: EOA Spec. no. 207.
Occurrence: Reported to be found in oils of *Cymbopogon javanensis* and *Asarum arifolium*, and in nearly 60 other essential oils (Gildemeister & Hoffman, 1966).
Preparation: By methylation of isoeugenol.
Uses: In public use before the 1920s. Use in fragrances in the USA amounts to approximately 3000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·3
Maximum	0·2	0·02	0·05	0·8

Analytical data: Gas chromatogram. RIFM no. 72–36; infra-red curve, RIFM no. 72–36.

Status

Methyl isoeugenol was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) listed methyl isoeugenol, giving an ADI of 5 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on methyl isoeugenol.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 1·5 g/kg (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964) and as 2·5 g/kg (2·03–3·08 g/kg) (Keating, 1972). The ip LD_{50} in mice was reported as 0·5 g/kg for the *cis*- isomer and as 0·35 g/kg for the *trans*- isomer (Caujolle & Meynier, 1960). The acute dermal LD_{50} in rabbits exceeded 5 g/kg (Keating, 1972).

Irritation. Methyl isoeugenol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was irritating (Keating, 1972). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1972).

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β-METHYL NAPHTHYL KETONE

Synonyms: β-Acetonaphthone; oranger crystals; methyl β-naphthyl ketone.
Structure: $C_{10}H_7 \cdot CO \cdot CH_3$.
Description and physical properties: EOA Spec. no. 82.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By Friedel-Crafts reaction of naphthalene and acetyl chloride (Bedoukian, 1967).
Uses: In public use before the 1920s. Use in fragrances in the USA amounts to approximately 50,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·003	0·005	0·1
Maximum	0·15	0·02	0·05	0·2

Analytical data: Gas chromatogram, RIFM no. 70–72; infra-red curve, RIFM no. 70–72.

Status

β-Methyl naphthyl ketone was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included β-methyl naphthyl ketone at a level of 5 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health. The *Food Chemicals Codex* (1972) has a monograph on β-methyl naphthyl ketone.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 599 mg/kg (Bär & Griepentrog, 1967).

Subacute toxicity. The no-effect level for β-methyl naphthyl ketone fed to rats for 12 wk was 34·2 mg/kg (Bär & Griepentrog, 1967).

Irritation. A patch test using β-methyl naphthyl ketone at full strength for 24 hr produced one irritation reaction in 24 human subjects (Katz, 1946).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 2% in petrolatum and produced no sensitization reactions (Kligman, 1971).

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METHYL NONYL KETONE

Synonyms: 2-Hendecanone; undecanone-2.
Structure: $CH_3 \cdot CO \cdot [CH_2]_8 \cdot CH_3$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Originally reported to be found in the essential oil of *Ruta graveolens* and subsequently identified in the essential oils of *Citrus limetta* Risso, *Fagara xanthoxyloides* Lamm and *Litsea odorifera* Val. (leaves), *Hottuynia cordata*, *Phellodendron anaurense* and *Schizandra migra* Maxim, and in coconut and palm oils; also identified as the main constituent of the essential oil of the physiological variety of *Boronia ledifolia* Gai, while a 92% content was reported in the essential oil of *Ruta chalepensis* (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: From decanoic acid and acetic acid.
Uses: In public use since the 1900s.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·002	0·005	0·04
Maximum	0·1	0·02	0·02	0·5

Analytical data: Gas chromatogram, RIFM no. 74–257; infra-red curve, RIFM no. 74–257.

Status

Methyl nonyl ketone was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included methyl nonyl ketone at a level of 3 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health.

Biological data

Acute toxicity. Both the acute oral LD_{50} in rats and the acute dermal LD_{50} in rabbits exceeded 5 g/kg (Levenstein, 1974). The acute oral LD_{50} for white mice was found to be 3·88 g/kg (Srepel & Akacić, 1962).

Irritation. Methyl nonyl ketone applied undiluted to the backs of hairless mice and swine (Urbach & Forbes, 1974) or to intact or abraded rabbit skin for 24 hr under occlusion (Levenstein, 1974) was not irritating. Tested at 5% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1974). It has been reported to cause skin irritation (Arctander, 1969), and the skin-irritating action of rue oil has been attributed to methyl nonyl ketone, which is the main constituent (Arctander, 1960).

Skin absorption. Methyl nonyl ketone aided only slightly in the penetration of Rhodamine B into the corium of guinea-pig skin (Meyer, 1965).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 5% in petrolatum and produced no sensitization reactions (Kligman, 1974).

Phototoxicity. No phototoxic effects were reported for undiluted methyl nonyl ketone on hairless mice and swine, although they have been reported for oil of rue which is 92% methyl nonyl ketone (Urbach & Forbes, 1974).

Metabolism. Ketones are not readily metabolized in the body; the lower ketones may be partially eliminated unchanged in the expired air and in the urine. The major metabolic change is reduction to the corresponding secondary alcohol, which is usually eliminated in combination with glucuronic acid (Williams, 1959). When 2 g methyl nonyl ketone dissolved in aqueous ethanol was fed into the rumen of a cow, a small amount (25 μg, 0·0013%) was detected unchanged in the milk (Honkanen, Karvonen & Virtanen, 1964).

Methyl nonyl ketone was utilized as a growth substrate by *Candida lipolytica* but not by seven other hydrocarbon-utilizing yeasts (Lowery, Foster & Jurtshuk, 1968). Its metabolic formation from lauric acid by the mould *Asperigillus niger* and its further reduction to methyl nonyl carbinol under anaerobic and aerobic conditions have been studied (Franke, Platzeck & Eichhorn, 1962).

Micro-organisms. Methyl nonyl ketone (0·001 M) produced only moderate and temporary inhibition of the growth of *Escherichia coli* (Együd, 1967). Growth of four bacteria was not inhibited by a 1:500 dilution (Maruzzella & Bramnick, 1961), but the compound slightly inhibited the growth of several wood-destroying fungi tested (Maruzzella, Scrandis, Scrandis & Grabon 1960) and in a subsequent study the vapour inhibited the growth of four fungi tested (Maruzzella, Chiaramonte

Anthelmintic activity. Lethal concentrations of methyl nonyl ketone (LC_{50} in g/100 ml) were found to be 0·090 for *Tubifex rivulorum* (worm), 0·061 for *Hirudo medicinalis* (leech) and 0·065 for *Ascaris suilla* (nematode). Concentrations of 100, 50 and 20 mg/100 ml were completely lethal to the nematode *Anguillula aceti* (vinegar eel) within 10, 15 and 20 min, respectively. The anthelmintic activity of rue oils was found to be proportional to their content of methyl nonyl ketone, their main constituent. Tests with innervated and denervated musculature of leeches indicated that these substances act on worms via the nervous system (Srepel & Akacić, 1962).

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METHYL NONYLENATE

Synonym: Methyl 2-nonenoate.
Structure: $CH_3 \cdot [CH_2]_5 \cdot CH{:}CH \cdot OCO \cdot CH_3$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By condensation of heptaldehyde with malonic acid followed by esterification of nonenylic acid with methanol (Bedoukian, 1967).
Uses: In public use since the 1940s. Use in fragrances in the USA amounts to approximately 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·04
Maximum	0·1	0·01	0·03	0·8

Analytical data: Gas chromatogram, RIFM no. 75–100; infra-red curve, RIFM no. 75–100.

Status

Methyl nonylenate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included methyl nonylenate in the list of artificial flavouring substances that may be added temporarily to foodstuffs without hazard to public health.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1975).

Irritation. Methyl nonylenate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1975). Tested at 20% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 20% in petrolatum and produced no sensitization reactions (Epstein, 1975).

Metabolism. 2-Nonenoic acid produced by the hydrolysis of methyl nonylenate will presumably pass through the normal pathways of fatty acid metabolism (Lehninger, 1970).

Insects. Methyl *trans*-2-nonenoate (0·3 µl/larva) exhibited low toxicity but marked melanogenic action on the larvae of the house fly, *Musca domestica*, and disturbed the normal sequence of pupation (Quraishi, 1972).

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METHYL OCTINE CARBONATE

Synonyms: Methyl 2-nonynoate; methyl octyne carbonate.
Structure: $CH_3 \cdot [CH_2]_5 \cdot C \equiv C \cdot COO \cdot CH_3$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Has apparently not been reported to occur in nature.
Preparation: From 2-octene via 1-octyne and octyne carboxylic acid (Bedoukian, 1967).
Uses: In public use before the 1920s. Use in fragrances in the USA amounts to approximately 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·002	0·0003	0·001	0·03
Maximum	0·03	0·004	0·01	0·2

Status

Methyl octine carbonate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included methyl octine carbonate at a level of 5 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 2·22 g/kg (1·79–2·65 g/kg) (Moreno, 1973) and the acute dermal LD_{50} in rabbits as less than 5 g/kg (Moreno, 1973).

Irritation. Methyl octine carbonate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Moreno, 1973). Tested at 2% in petrolatum, it produced no irritation after a 48-hr closed-patch test on two different panels of human subjects (Kligman, 1973 & 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material (RIFM no. 72–2–253) was tested at a concentration of 2% in petrolatum and produced no sensitization reactions (Kligman, 1973). In a maximization test (Kligman, 1966; Kligman & Epstein, 1975) on 25 new volunteers, the material (RIFM no. 75–2–IFRA–5) was tested at a concentration of 2% in petrolatum and again produced no sensitization reactions (Kligman, 1975).

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Moreno, O. M. (1973). Report to RIFM, 23 February.

METHYL OCTYL ACETALDEHYDE

Synonym: 2-Methyldecanal.
Structure: $CH_3 \cdot [CH_2]_7 \cdot CH(CH_3) \cdot CHO$.
Description and physical properties: A colourless liquid.
Occurrence: Has apparently not been reported to occcur in nature.
Preparation: From methyl octyl ketone and ethyl chloroacetate by the Daryens reaction.
Uses: Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·003	0·05
Maximum	0·1	0·01	0·01	0·5

Analytical data: Gas chromatogram, RIFM no. 74-225; infra-red curve, RIFM no. 74-225.

Status

Methyl octyl acetaldehyde is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974), or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1975).

Irritation. Methyl octyl acetaldehyde applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1975). Tested at 10% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1975).

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METHYL PHENYLACETATE

Synonym: Methyl α-toluate.
Structure: $C_6H_5 \cdot CH_2 \cdot OCO \cdot CH_3$.
Description and physical properties: EOA Spec. no. 39.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By methanolic esterification of the corresponding acid or nitrile with methanol.
Uses: In public use before the 1920s. Use in fragrances in the USA amounts to about 5000 lb/yr.

Concentration in final product (%):

	Soap	*Détergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·003	0·01	0·1
Maximum	0·2	0·02	0·05	0·8

Status

Methyl phenylacetate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). It was included by the Council of Europe (1970) in the list of temporarily admissible artificial flavouring substances, and is the subject of a *Food Chemicals Codex* (1972) monograph. The Joint FAO/WHO Expert Committee on Food Additives (1968) was unable to arrive at an ADI for methyl phenylacetate because of a lack of toxicological data.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 2·55 g/kg (1·67–3·43 g/kg) and the acute dermal LD_{50} in rabbits as 2·4 g/kg (0·15–4·7 g/kg) (Moreno, 1974).

Enzymic hydrolysis. Methyl phenylacetate was slowly hydrolysed by the proteases, α-chymotrypsin and subtilisin BPN′, and was the least reactive substrate towards these enzymes in a homologous series of phenyl alkanoate methyl esters examined (Pattabiraman & Lawson, 1972).

Irritation. Methyl phenylacetate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was very slightly irritating (Moreno, 1974). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1974).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1974).

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METHYLPHENYLCARBINYL ACETATE

Synonyms: Phenylmethylcarbinyl acetate; α-methylbenzyl acetate; styralyl acetate; styrolyl acetate.
Structure: $C_6H_5 \cdot CH(OCO \cdot CH_3) \cdot CH_3$.
Description and physical properties: EOA Spec. no. 46.
Occurrence: Reported to be found in gardenia oil (Gildemeister & Hoffman, 1966).
Preparation: By acetylation of methylphenylcarbinol (Bedoukian, 1967).
Uses: In public use since the early 1900s. Use in fragrances in the USA amounts to approximately 10,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·015	0·2
Maximum	0·30	0·03	0·1	0·7

Analytical data: Gas chromatogram, RIFM no. 2850; infra-red curve, RIFM no. 2850.

Status

Methylphenylcarbinyl acetate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The *Food Chemicals Codex* (1972) has a monograph on methylphenylcarbinyl acetate.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats exceeded 5 g/kg (Posner, 1971). The acute dermal LD_{50} value in rabbits exceeded 8 ml/kg (McGee, 1971).

Short-term toxicity. Groups of rats were given daily oral doses of 0 (control), 15, 50 or 150 mg methylphenylcarbinyl acetate/kg body weight for 13 wk. There were no effects on the rate of body-weight gain, although the food and water intakes were increased in the male rats given 150 mg/kg. The relative liver and kidney weights were increased in male rats given 50 or 150 mg/kg/day. There was an increased excretion of cells in the urine of male rats given 150 mg/kg for 6 wk. No histopathological changes were seen that could be related to treatment with methylphenylcarbinyl acetate. It was concluded that the no-untoward-effect level for methylphenylcarbinyl acetate when given to rats for 13 wk was 15 mg/kg (Gaunt, Mason, Hardy, Lansdown & Gangolli, 1974).

Irritation. Methylphenylcarbinyl acetate produced no irritation either in the rabbit eye in a primary eye irritation study (Posner, 1971) or on the skin of rabbits in a primary skin irritation study (Posner, 1971). Applied full strength to intact or abraded rabbit skin over a 14-day observation period, it produced little or no irritation (McGee, 1971).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1971).

Metabolism. Although no published data exist on the metabolism of methylphenylcarbinyl acetate, it is likely that hydrolysis to the carbinol and acetic acid is the initial step. Williams (1959) reports studies in which 50% of a dose of (±)-methylphenylcarbinol given to rabbits was excreted as the glucuronide in the urine within 24 hr. There was some evidence of oxidation and demethylation, as mandelic and hippuric acids were found in the urine. Previously, El Masry, Smith & Williams (1956) had reported that after the oral administration of methylphenylcarbinol to rabbits, 28% of the dose was oxidized to benzoic acid and excreted as hippuric acid, while 50% was recovered as a glucuronic acid conjugate.

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METHYLPHENYLCARBINYL PROPIONATE

Synonyms: α-Methylbenzyl propanoate; styralyl propionate; phenylmethylcarbinyl propionate; styrolyl propionate.

Structure: $C_6H_5 \cdot CH(OCO \cdot CH_2 \cdot CH_3) \cdot CH_3$.

Description and physical properties: A colourless liquid.

Occurrence: Has apparently not been reported to occur in nature.

Preparation: By direct esterification of methylphenylcarbinol with propionic acid, using azeotropic conditions (Arctander, 1969).

Uses: In public use since the 1920s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·015	0·2
Maximum	0·3	0·03	0·1	1·0

Analytical data: Gas chromatogram, RIFM no. 72-37; infra-red curve, RIFM no. 72-37.

Status

Methylphenylcarbinyl propionate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164).

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported to be 5·2 ml/kg (3·91–6·92 ml/kg) (Levenstein, 1973). The acute dermal LD_{50} value in rabbits was reported as >5 ml/kg (Levenstein, 1973).

Irritation. Methylphenylcarbinyl propionate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was mildly irritating (Levenstein, 1973). Tested at 10% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1973).

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MIMOSA ABSOLUTE

Description and physical properties: A viscous liquid, yellow-brownish in colour. The main constituents of mimosa absolute include anisaldehyde and hydrocarbons (Guenther, 1952).
Occurrence: Found in the flowers of *Acacia decurrens* var. *dealbata* (Fam. Leguminosae) (Guenther, 1952; Naves, 1974).
Preparation: From the concrete of mimosa (Guenther, 1952).
Uses: In public use before the 1920s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	rarely	0·003	0·08
Maximum	0·06	used	0·01	0·1

Analytical data: Gas chromatogram, RIFM no. 74–105; infra-red curve, RIFM no. 74–105.

Status

Mimosa was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1163). The Council of Europe (1974) included mimosa in the list of substances, spices and seasonings commonly added to foodstuffs in small quantities, the use of which is deemed admissible with the possible limitation of the active principle in the final product.

Biological data

Acute toxicity. Both the acute oral LD_{50} in mice and the acute dermal LD_{50} in guinea-pigs exceeded 5 g/kg (Moreno, 1974).

Irritation. Undiluted mimosa absolute applied to the backs of hairless mice and swine was not irritating (Urbach & Forbes, 1974). Applied full strength to intact or abraded guinea-pig skin for 24 hr under occlusion, it was slightly irritating (Moreno, 1974). Tested at 1% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 1% in petrolatum and produced no sensitization reactions (Kligman, 1974). Mimosa may produce dermatitis in hypersensitive individuals (Tulipan, 1938).

Phototoxicity. No phototoxic effects were reported for undiluted mimosa absolute on hairless mice and swine (Urbach & Forbes, 1974).

Micro-organisms. Mimosa composite and its vapour showed no *in vitro* antimicrobial activity against any of nine bacteria and seven fungi tested (Maruzzella, 1963).

Additional published data

In a study in ruminants on the nutritional value of leaves of several plants, including *A. decurrens*, the percentage digestibility of *A. mearnsi* in sheep and goats was reported without reference to any harmful effects (Nakahiro & Isshiki, 1961).

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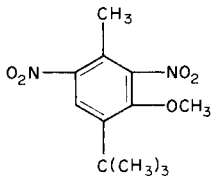
MUSK AMBRETTE

Synonym: 2,6-Dinitro-3-methoxy-4-*tert*-butyltoluene.
Structure:



Description and physical properties: EOA Spec. no. 25.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By nitration of the corresponding benzene derivative (Bedoukian, 1967).
Uses: In public use before the 1920s. Use in fragrances in the USA amounts to approximately 100,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·01	0·2
Maximum	0·2	0·02	0·07	2·0

Analytical data: Gas chromatogram, RIFM no. 71–52; infra-red curve, RIFM no. 71–52.

Status

The Council of Europe (1974) included musk ambrette at a level of 1 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health, and FEMA (1965) has given musk ambrette GRAS status.

Biological data

Acute toxicity. The acute oral LD_{50} in rats has been reported as 339 mg/kg (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964) and as 4·8 g/kg (4·3–5·3 g/kg) (Moreno, 1972a). The acute dermal LD_{50} in rabbits exceeded 2 g/kg (Moreno, 1972b).

Sub-acute toxicity. In a 12-wk feeding study in rats the no-effect level was 0·76 mg/kg (Bär & Griepentrog, 1967). In another feeding study, diets containing 500, 1500, 2500 or 4000 ppm were fed to male rats for 50 wk and to female rats for 20 wk (Davis, Taylor, Jones & Brouwer, 1967). All but the lowest dose level caused marked loss in weight, progressive weakness of the hind quarters, leading to complete loss of the use of the legs after 10–40 wk as a result of histologically confirmed muscular atrophy, and blood changes, including a decrease in erythrocyte count and clotting time and an icteric plasma (which was also observed at 500 ppm). The toxic effects observed in this study occurred at dietary levels 2500 times greater than those likely to be encountered in every-day human consumption.

Irritation. Musk ambrette applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1972b). Tested at 20% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 20% in petrolatum and produced no sensitization reactions (Kligman, 1972).

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Moreno, O. M. (1972a). Report to RIFM, 20 March.

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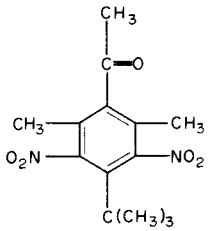
MUSK KETONE

Synonym: 3.5-Dinitro-2.6-dimethyl-4-*tert*-butylacetophenone.
Structure:



Description and physical properties: EOA Spec. no. 25.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: Nitration of the corresponding benzene derivative (Bedoukian, 1967).
Uses: In public use since the 1900s. Use in fragrances in the USA amounts to approximately 50,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·01	0·2
Maximum	0·15	0·015	0·05	0·5

Analytical data: Gas chromatogram, RIFM nos 71–91, 72–237; infra-red curve, RIFM nos 71–91, 72–237.

Status

The Council of Europe (1974) included musk ketone in the list of artificial flavouring substances that may be added temporarily to foodstuffs without hazard to public health.

Biological data

Acute toxicity. Both the acute oral LD_{50} in rats and the acute dermal LD_{50} in rabbits exceeded 10 g/kg (Fogleman, 1970).

Percutaneous toxicity. Musk ketone was tested for subacute dermal toxicity by repeated applications once daily, 5 days/wk for 3 wk, to the abraded and intact skin of albino rabbits (Rutter, 1971). The test material was dissolved in dimethyl phthalate and applied at levels of 175 and 750 mg/kg body weight. A control group received applications of dimethyl phthalate at a constant rate of 2 ml/kg body weight. Slight to moderate erythema followed by slight desquamation was noted in the skin of all groups. During wk 3, symptoms of disease began to appear in all groups and deaths, not considered to be compound-related, occurred before termination of the study. No consistent changes in clinical values or pathology attributable to the test procedure were observed apart from a variable decrease in bone-marrow haematogenic activity in three of the animals on the higher dose. The study was repeated because of the incidental disease.

In a third 21-day percutaneous toxicity test carried out at the same facility musk ketone (RIFM no. 71–91) was applied to the abraded and intact skin of rabbits daily (Powers 1971 & 1972). The test material was dissolved in dimethyl phthalate and was applied at levels of 175 and 750 mg/kg to groups of six rabbits. A control group received applications of 1·5 mg dimethyl phthalate/kg daily. There were no gross effects; behaviour, body weight and survival were comparable with the controls and cutaneous effects were minimal. Clinical chemistry studies, however, showed a terminal compound-related increase serum glutamic–pyruvic transaminase in five of the six rabbits on the high level and in one on the low level. This observation was supported by a general "nutmeg" appearance of the livers of the high-dose group on gross examination and by microscopic observation of hepatocyte vacuolization in five rabbits in this group and of necrosis in the sixth. Bone-marrow changes were inconclusive.

In a percutaneous toxicity test of 20 consecutive days duration the abraded skin of groups of 14 albino rabbits was treated either with dimethyl phthalate in a dose of 1 mg/kg/day or with musk ketone in dimethyl phthalate in daily doses of 10, 50 or 250 mg/kg (Calandra, 1972). There were six deaths in the high-dosage group. Animals in this group showed moderate to severe vacuolization of the hepatocytes typical of fatty change and serum glutamic–pyruvic transaminase activity was increased in the males. There were no other dose-related changes in behaviour, body weights,

haematology, clinical blood chemistry, urine analysis or histopathology of 35 organs (including thorough bone-marrow counts). It was concluded that the no-effect dose of this material was >50 mg/kg/day (Calandra, 1972).

Irritation. Musk ketone applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Fogleman, 1970).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 3·2% in petrolatum and produced no sensitization reactions (Greif, 1967). In another maximization test (Kligman, 1966; Kligman & Epstein, 1975) carried out on 25 volunteers, the material was tested at a concentration of 5% in petrolatum and again produced no sensitization reactions (Kligman, 1970).

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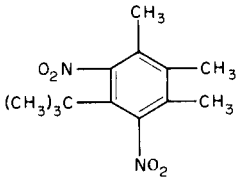
Powers, M. B. (1972). Report to RIFM, 21 February.

Rutter, H. A. (1971). Report to RIFM, 13 April.

MUSK TIBETENE

Synonym: 5-*tert*-Butyl-1,2,3-trimethyl-4,6-dinitrobenzene.
Structure:



Description and physical properties: *Givaudan Index* (1961).
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By nitration of the corresponding benzene derivative (Bedoukian, 1967).
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to approximately 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·01	0·1
Maximum	0·15	0·015	0·05	0·2

Analytical data: Gas chromatogram, RIFM no. 70–73; infra-red curve, RIFM no. 70–73.

Status

Musk tibetene is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974), or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as >6 g/kg and the acute dermal LD_{50} in rabbits as >5 g/kg (Weir, 1971).

Irritation. Musk tibetene applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Weir, 1971). In the rabbit eye, it produced slight conjunctival irritation, which disappeared within 72 hr (Weir, 1971).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 2% in petrolatum and produced no sensitization reactions (Kligman, 1971).

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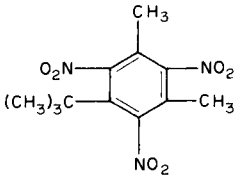
Kligman, A. M. (1971). Report to RIFM, 25 March.

Kligman, A. M. & Epstein, W. (1975). Updating the maximization test for identifying contact allergens. *Contact Dermatitis* **1**, 231.

Weir, R. J. (1971). Report to RIFM, 12 April.

MUSK XYLOL

Synonyms: 2,4,6-Trinitro-1,3-dimethyl-5-*tert*-butylbenzene; musk xylene.
Structure:



Description and physical properties: EOA Spec. no. 25.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By nitration of the corresponding benzene derivative (Bedoukian, 1967).
Uses: In public use since the 1900s. Use in fragrances in the USA amounts to approximately 150,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·01	0·2
Maximum	0·15	0·015	0·05	0·5

Analytical data: Gas chromatogram, RIFM no. 70–69; infra-red curve, RIFM no. 70–69.

Status

The Council of Europe (1974) included musk xylol in the list of artificial flavouring substances that may be added temporarily to foodstuffs without hazard to public health.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as >10 g/kg and the acute dermal LD_{50} in rabbits as >15 g/kg (Fogleman, 1970).

Irritation. Musk xylol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Fogleman, 1970). Tested at 5% in petrolatum, it produced a mild irritation after a 48-hr closed-patch test on human subjects (Kligman, 1970).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 5% in petrolatum and produced no sensitization reactions (Kligman, 1970).

References

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MYRCENE

Synonym: 3-Methylene-7-methyl-1,6-octadiene.
Structure: $CH_3 \cdot C(CH_3):CH \cdot [CH_2]_2 \cdot C(:CH_2) \cdot CH:CH_2$.
Description and physical properties: *Merck Index* (1968).
Occurrence: Reported to be found in bay oil, oil of hops, verbena oil, galbanum oil, Formosan and West Indian lemongrass oil etc. (Guenther, 1949).
Preparation: By pyrolysis of β-pinene.
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to approximately 2000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·2
Maximum	0·15	0·015	0·05	0·7

Analytical data: Gas chromatogram, RIFM no. 72-38; infra-red curve, RIFM no. 72-38.

Status

Myrcene was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included myrcene in the list of artificial flavouring substances that may be added temporarily to foodstuffs without hazard to public health.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1972).

Irritation. Myrcene applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1972). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1972).

Percutaneous absorption. Myrcene was well absorbed on to the skin of rats (Valette & Cavier, 1954).

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MYRCENOL

Synonym: 3-Methylene-7-methyl-1-octen-7-ol.
Structure: $CH_3 \cdot (OH)C(CH_3) \cdot [CH_2]_3 \cdot C(:CH_2) \cdot CH:CH_2$.
Description and physical properties: A colourless viscous liquid.
Occurrence: Found in the leaf oils of *Barosma venusta* and in the oil of hops (Gildemeister & Hoffman, 1960).
Preparation: Prepared by adding hydrogen chloride to myrcene followed by hydrolysis under mild conditions (Bedoukian, 1967).
Uses: In public use since the 1950s.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·2
Maximum	0·15	0·015	0·05	0·7

Analytical data: Gas chromatogram, RIFM no. 72-39; infra-red curve, RIFM no. 72-39.

Status

Myrcenol is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974) or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 5·3 g/kg (4·5–6·1 g/kg) (Moreno, 1972). The acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1972).

Irritation. Myrcenol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1972). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1972).

References

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Moreno, O. M. (1972). Report to RIFM, 1 & 5 May.

MYRCENYL ACETATE

Synonym: 3-Methylene-7-methyl-1-octen-7-yl acetate.
Structure: $CH_3 \cdot (CH_3)C(OCO \cdot CH_3) \cdot [CH_2]_3 \cdot C(:CH_2) \cdot CH:CH_2$.
Description and physical properties: A colourless liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By cold acetylation of myrcenol (Arctander, 1969).
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to approximately 10,000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·20
Maximum	0·20	0·02	0·05	0·70

Analytical data: Gas chromatogram, RIFM no. 72-40; infra-red curve, RIFM no. 72-40.

Status

Myrcenyl acetate is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974), or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 6·3 g/kg (5·3–7·3 g/kg) (Moreno, 1972). The acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1972).

Irritation. Myrcenyl acetate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1972). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1972).

References

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Council of Europe (1974). Natural Flavouring Substances, Their Sources, and Added Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. Strasbourg.

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Kligman, A. M. & Epstein, W. (1975). Updating the maximization test for identifying contact allergens. *Contact Dermatitis* **1**, 231.

Moreno, O. M. (1972). Report to RIFM, 5 & 31 May.

MYRRH OIL

Synonym: Oil of Heerabol-Myrrh.
Description and physical properties: EOA Spec. no. 141. The constituents of myrrh oil include *d*-pinene, dipentene and limonene (Gildemeister & Hoffman, 1959; Guenther, 1950).
Occurrence: Found in several species of gum-resin Commiphora (fam. Burseraceae), mainly *C. myrrha*, *C. abyssinica* and *C. schiniperi*.
Preparation: By steam distillation of the gum.
Uses: In public use before 1900. Use in fragrances in the USA amounts to less than 5000 lb/yr. Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·01	0·16
Maximum	0·10	0·01	0·03	0·80

Analytical data: Gas chromatogram, RIFM no. 72-202; infra-red curve, RIFM no. 72-202.

Status

Myrrh oil was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included myrrh oil in the list of substances, spices and seasonings deemed admissible for use, with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on myrrh oil.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 1·65 g/kg (1·40–1·90 g/kg) (Moreno, 1973).

Irritation. Myrrh oil applied undiluted to the backs of hairless mice and swine was not irritating (Urbach & Forbes, 1973). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1973).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 21 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Epstein, 1973).

Phototoxicity. No phototoxic effects were reported for undiluted myrrh oil on hairless mice and swine (Urbach & Forbes, 1973).

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Moreno, O. M. (1973). Report to RIFM, 21 September.

Urbach, F. & Forbes, P. D. (1973). Report to RIFM, 16 August.

β-NAPHTHYL ETHYL ETHER

Synonyms: Nerolin; 2-ethoxynaphthalene.
Structure: $C_{10}H_7 \cdot O \cdot CH_2 \cdot CH_3$.
Description and physical properties: EOA Spec. no. 80.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By the ethylation of β-naphthol (Bedoukian, 1967).
Uses: In public use before the 1900s. Use in fragrances in the USA amounts to approximately 10,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·2
Maximum	0·1	0·01	0·04	0·2

Analytical data: Gas chromatogram, RIFM no. 71–54; infra-red curve, RIFM no. 71–54.

Status

β-Naphthyl ethyl ether was given GRAS status by FEMA (1965), and the Council of Europe (1974) included it (as nerolin) in the list of artificial flavouring substances that may be added temporarily to foodstuffs without hazard to public health.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 3·11 g/kg (1·94–5·50 g/kg) and the acute dermal LD_{50} in rabbits exceeded 5 g/kg (Weir, 1971).

Irritation. β-Naphthyl ethyl ether applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Weir, 1971). Tested at 2% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 2% in petrolatum and produced no sensitization reactions (Kligman, 1972). It was also tested in 2% concentration by the repeated insult patch-test procedure (Shelanski & Shelanski, 1953), using fifteen 24-hr exposures in 50 human subjects, and no sensitization reactions occurred (Shelanski, 1971).

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Kligman, A. M. (1972). Report to RIFM, 18 February.

Kligman, A. M. & Epstein, W. (1975). Updating the maximization test for identifying contact allergens. *Contact Dermatitis* **1.** 231.

Shelanski, M. V. (1971). Report to RIFM, 30 August.

Shelanski, H. A. & Shelanski, M. V. (1953). Modified repeated insult patch test. *Proc. scient. Sect. Toilet Goods Ass.* **19.** 46.

Weir, R. J. (1971). Report to RIFM, 25 August.

β-NAPHTHYL METHYL ETHER

Synonyms: Yara-yara; 2-methoxynaphthalene; naphthyl β-methyl ether.
Structure: $C_{10}H_7 \cdot OCH_3$.
Description and physical properties: EOA Spec. no. 118.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By the methylation of β-naphthol in the presence of alkali (Bedoukian, 1967).
Uses: In public use since the 1900s. Use in fragrances in the USA amounts to approximately 5000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·005	0·2
Maximum	0·15	0·015	0·04	0·4

Analytical data: Gas chromatogram, RIFM no. 74–109; infra-red curve, RIFM no. 74–109.

Status

β-Naphthyl methyl ether is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974), or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} in rats and the acute dermal LD_{50} in rabbits exceeded 5 g/kg (Levenstein, 1974).

Irritation. β-Naphthyl methyl ether applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Levenstein, 1974). A patch test using β-naphthyl methyl ether full strength for 24 hr produced one irritation reaction in 20 human subjects (Katz, 1946).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 26 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Epstein, 1974).

References

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Kligman, A. M. & Epstein, W. (1975). Updating the maximization test for identifying contact allergens. *Contact Dermatitis* **1.** 231.

Levenstein, I. (1974). Report to RIFM, 14 March.

NEROL

Synonym: 2-*cis*-3,7-Dimethyl-2,6-octadien-1-ol.
Structure: $CH_3 \cdot (CH_3)C{:}CH \cdot [CH_2]_2 \cdot C(CH_3){:}CH \cdot CH_2OH$.
Description and physical properties: *Merck Index* (1968).
Occurrence: Reported to be found in neroli oil (with geraniol) and in the essential oils of lemon grass, Ceylon citronella, ylang-ylang, champaca, cajenne bois-de-rose and bergamot, also in lemon, sweet orange and petitgrain bergamot, and in clary sage, lavandin, lavender, Mexican linaloe, myrrh, jasmine and Paraguay petitgrain. Has been reported also among the volatile constituents of currant aroma. *Helichrysum angustifolium* contains up to 30–50% nerol (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: By careful fractional distillation of crude nerol obtained from myrcene (Bedoukian, 1967).
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to approximately 20,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·015	0·2
Maximum	0·20	0·020	0·050	0·8

Analytical data: Gas chromatogram, RIFM no. 71–53; infra-red curve, RIFM no. 71-53.

Status

Nerol was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included nerol in the list of artificial flavouring substances that may be added temporarily to foodstuffs without hazard to public health. The *Food Chemicals Codex* (1972) has a monograph on nerol.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 4·5 g/kg (3·4–5·6 g/kg) (Moreno, 1972). The acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1972).

Nerol was found to have an acute intramuscular LD_{50} value in mice of 3 g/kg (Northover & Verghese, 1962). The vasodilator action of nerol has been studied by Northover & Verghese (1962) in dogs, rabbits and mice. Nerol has been claimed to be useful as a sedative and spasmolytic in doses of 0·01–1 g (Laboratoires Meram, 1966). The effects of nerol on local capillary permeability were studied in rabbits by intracutaneous injection of various concentrations dissolved in isopropyl myristate and measurement of the resulting extravasal leakage of Evans blue injected iv (Suzuki & Arai, 1966). Antineoplastic and antiviral properties of nerol against chick lymphoma and avian leukosis in chicks were described by Baranger (1971). The cytotoxic activity of nerol against Chang, HeLa and KB cells was studied by Nachev, Zolotovich, Silyanovska & Stojcev (1967).

Irritation. Nerol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1972). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1972).

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Baranger, P. (1971). Antineoplastic and antiviral terpene and alicyclic alcohols for veterinary administration. French Patent 2,062,871, appln date 19 September 1969.

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Suzuki, M. & Arai, H. (1966). The relation between the chemical structure of alcohols and their increasing effect on capillary permeability in skin. *Nippon Yakurigaku Zasshi* **62,** 241.

NEROLIDOL

Synonym: 3,7,11-Trimethyl-1,6,10-dodecatrien-3-ol.
Structure: $CH_3 \cdot C(CH_3):CH \cdot [CH_2]_2 \cdot C(CH_3):CH \cdot [CH_2]_2 \cdot (CH_3)C(OH) \cdot CH:CH_2$.
Description and physical properties: EOA Spec. no. 190.
Occurrence: Reported to be found in cabreuva oil, oil of neroli, balsam Peru, ylang ylang and many others (Gildemeister & Hoffman, 1959).
Preparation: By isolation from a suitable essential oil or by chemical synthesis.
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to approximately 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·2
Maximum	0·1	0·01	0·05	0·4

Analytical data: Gas chromatogram, RIFM no. 72–203; infra-red curve, RIFM no. 72–203.

Status

Nerolidol was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included nerolidol at a level of 6 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health. The *Food Chemicals Codex* (1972) has a monograph on nerolidol.

Biological data

Acute toxicity. Both the acute oral LD_{50} in rats and the acute dermal LD_{50} in rabbits exceeded 5 g/kg (Russell, 1973).

Irritation. Nerolidol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Russell, 1973). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1973).

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Russell, T. J. (1973). Report to RIFM, 6 March.

NEROLI OIL, TUNISIAN

Synonym: Neroli bigarade oil, Tunisian.
Description and physical properties: A pale yellow to amber liquid. The main constituents of neroli oil include dipentene, pinene, camphene, *l*-linalool and *l*-linalyl acetate (Poucher, 1974). Appell (1968) identified the constituents as linalool (30%), linalyl acetate (7–15%), pinene, camphene, dipentene, aldehyde C-10, indole and methyl anthranilate (0·5–1·2%) and farnesol. The composition of Italian neroli oil, primarily alcohols, esters and terpenes, has been reported in detail by Muller (1965). Other reports have described the compositions of Egyptian neroli oil from *Citrus aurantium* (Balbaa, Hifnawy & Karawya, 1972) and neroli oil from *C. bigaradia* in France (Corbier & Teisseire, 1974).
Occurrence: Found in the blossoms of *C. aurantium* L. (Fam. Rutaceae) (Guenther, 1949).
Preparation: By distillation of the blossoms of *C. aurantium* (Poucher, 1974).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 1000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams. lotions*	*Perfume*
Usual	0·005	0·0005	0·003	0·1
Maximum	0·06	0·006	0·02	0·4

Analytical data: Gas chromatogram, RIFM no. 74–226.

Status

Neroli was given GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1974) included it in the list of substances, spices and seasonings deemed admissible for use with a possible limitation of the active principle in the final product.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as $4{\cdot}55 \pm 0{\cdot}105$ g/kg and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (McGee, 1974).

Irritation. Undiluted neroli oil tunisian was not irritating when applied to the backs of hairless mice and swine (Urbach & Forbes, 1974) or to intact or abraded rabbit skin for 24 hr under occlusion (McGee, 1974). Tested at 4% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1975). Following at least 20 dermal patch tests with no dermatitis development, neroli oil (bigarade petale) was reported to be devoid of irritating properties (Peterson & Hall, 1946).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1975).

Phototoxicity. No phototoxic effects were reported for undiluted neroli oil, Tunisian on hairless mice and swine (Urbach & Forbes, 1974).

Micro-organisms. Neroli bigarade oil was 5·5 times more effective as a bactericidal agent than phenol (Führer, 1972). Neroli oil inhibited the growth of two of four Gram-positive and two of four Gram-negative organisms (Rao & Nigam, 1970) and in another study showed *in vitro* antibacterial activity against all five bacteria studied, the activity being decreased by combination with turpentine and oil of geranium, Algerian (Maruzzella & Henry, 1958). The vapour of neroli bigarade petale oil NF showed strong *in vitro* antibacterial activity against one of five bacteria studied (Maruzzella & Sicurella, 1960). Moderate *in vitro* antifungal activity was shown by neroli oil against 13 of 15 fungi studied (Maruzzella & Liguori, 1958), and by oil of neroli bigarade petale NF on 11 of 12 phytopathogenic fungi (Maruzzella & Balter, 1959). A 1:50 dilution of neroli oil exhibited antifungal activity against all of a group of eight phytopathogenic fungi (Rao & Joseph, 1971). Neroli bigarade oil (10 mg as a 2% solution in olive oil injected im weekly) had a weak therapeutic effect on experimental tuberculosis of the guinea-pig when combined with sub-effective doses of dihydrostreptomycin, but 100 μg neroli oil/ml had no antibacterial effect on tubercle bacilli *in vitro* (Kato & Gözsy, 1958).

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McGee, G. (1974). Report to RIFM, 17 October.
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Peterson, H. R. & Hall, A. (1946). Dermal irritating properties of perfume materials. *Drug Cosmet. Ind.* **58** (January), 113.
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Urbach, F. & Forbes, P. D. (1974). Report to RIFM, 6 December.

NERYL ACETATE

Synonym: 2-*cis*-3,7-Dimethyl-2,6-octadien-1-yl acetate.
Structure: $CH_3 \cdot (CH_3)C{:}CH \cdot [CH_2]_2 \cdot C(CH_3){:}CH \cdot CH_2 \cdot OCO \cdot CH_3$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Reported to be found in Hungarian lemon petitgrain oil, sweet orange leaf oil, Helichrysum oil, Hinoki oil, Neroli oil and many other essential oils (Gildemeister & Hoffman, 1966).
Preparation: As a co-product in the manufacture of geranyl acetate from myrcene by hydrogenation and esterification. Separated by fractionation.
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to approximately 2000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·2
Maximum	0·15	0·015	0·03	0·6

Analytical data: Gas chromatogram, RIFM no. 71-56; infra-red curve, RIFM no. 71-56.

Status

Neryl acetate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included neryl acetate in the list of artificial flavouring substances that may be added temporarily to foodstuffs without hazard to public health.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Levenstein, 1972).

Irritation. Neryl acetate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Levenstein, 1972). Tested at 10% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1972).

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Levenstein, I. (1972). Report to RIFM, 9 February & 7 April.

NERYL FORMATE

Synonym: 2-*cis*-3,7-Dimethyl-2,6-octadien-1-yl formate.
Structure: $CH_3 \cdot (CH_3)C{:}CH \cdot [CH_2]_2 \cdot C(CH_3){:}CH \cdot CH_2 \cdot OCO \cdot H$.
Description and physical properties: A colourless liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By cold formylation of nerol (Arctander, 1969).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to approximately 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·2
Maximum	0.15	0·015	0·03	0·6

Analytical data: Gas chromatogram, RIFM no. 75-IFRA-17; infra-red curve, RIFM no. 75-IFRA-17.

Status

Neryl formate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included neryl formate in the list of artificial flavouring substances that may be added temporarily to foodstuffs without hazard to public health.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1975).

Irritation. Neryl formate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1975). Tested at 6% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 6% in petrolatum and produced no sensitization reactions (Kligman, 1975).

References

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Kligman, A. M. & Epstein, W. (1975). Updating the maximization test for identifying contact allergens. *Contact Dermatitis* **1**, 231.

Moreno, O. M. (1975). Report to RIFM, 25 June.

NERYL ISOVALERATE

Synonyms: 3,7-Dimethyl-2-*cis*-6-octadien-1-yl isovalerate; neryl isovalerianate; neryl β-methyl butyrate.

Structure: $CH_3 \cdot C(CH_3):CH \cdot [CH_2]_2 \cdot C(CH_3):CH \cdot CH_2 \cdot OCO \cdot CH_2 \cdot CH(CH_3) \cdot CH_3$.

Description and physical properties: Colourless or pale straw-coloured liquid.

Occurrence: Has apparently not been reported to occur in nature.

Preparation: By an exchange reaction between methyl isovalerate and nerol in the presence of a sodium methylate catalyst.

Uses: In public use since the 1940s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·05
Maximum	0·15	0·015	0·05	0·6

Analytical data: Gas chromatogram. RIFM no. 75–107; infra-red curve, RIFM no. 75–107.

Status

Neryl isovalerate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included neryl isovalerate at a level of 5 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1976).

Irritation. Neryl isovalerate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1976). Tested at 6% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 6% in petrolatum and produced no sensitization reactions (Kligman, 1975).

References

Council of Europe (1974). Natural Flavouring Substances, Their Sources, and Added Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List 1. no. 508. p. 231. Strasbourg.

Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. No. 2778. *Fd Technol., Champaign* **19**(2), part 2, 155.

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Moreno, O. M. (1976). Report to RIFM. 5 January.

NERYL PROPIONATE

Synonym: 2-*cis*-3,7-Dimethyl-2,6-octadien-1-yl propionate.
Structure: $CH_3 \cdot (CH_3)C{:}CH \cdot [CH_2]_2 \cdot C(CH_3){:}CH \cdot CH_2 \cdot OCO \cdot CH_2 \cdot CH_3$.
Description and physical properties: A clear colourless liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By azeotropic esterification of nerol with propionic acid (Arctander, 1969).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to approximately 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·2
Maximum	0·15	0·015	0·03	0·6

Analytical data: Gas chromatogram, RIFM nos 75-IFRA-15, 75-108; infra-red curve, RIFM nos 75-IFRA-15, 75-108.

Status

Neryl propionate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included neryl propionate at a level of 20 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1975).

Irritation. Neryl propionate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was mildly irritating (Moreno, 1975). Tested at 6% in petrolatum, the material (RIFM no. 75-IFRA-15) produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material (RIFM no. 75-IFRA-15) was tested at a concentration of 6% in petrolatum and produced no sensitization reactions (Kligman, 1975).

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Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. No. 2777. *Fd Technol., Champaign* **19** (2), part 2, 155.

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Kligman, A. M. (1975). Report to RIFM, 16 June.

Kligman, A. M. & Epstein, W. (1975). Updating the maximization test for identifying contact allergens. *Contact Dermatitis* **1**, 231.

Moreno, O. M. (1975). Report to RIFM, 25 June.

γ-NONALACTONE

Synonyms: 4-Hydroxynonanoic acid γ-lactone; aldehyde C-18 (so-called).
Structure: $CH_3 \cdot [CH_2]_4 \cdot CH \cdot CH_2 \cdot CH_2$ (with CH bonded to O and CH_2 bonded to CO, forming a lactone ring)
Description and physical properties: EOA Spec. no. 92.
Occurrence: Reported to be found in nature in peaches and apricots (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: By the acid lactonization of nonylenic acid.
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to approximately 7000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·0005	0·002	0·04
Maximum	0·1	0·01	0·04	1·0

Analytical data: Infra-red curve, RIFM no. 72–41.

Status

γ-Nonalactone was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) listed γ-nonalactone, giving an ADI of 1·25 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on γ-nonalactone and the Joint FAO/WHO Expert Committee on Food Additives (1967) has published a monograph and specifications, giving it an unconditional ADI of 0–1·25 mg/kg.

Biological data

Acute toxicity. The acute oral LD_{50}s in rats and guinea pigs were reported as 9·78 and 3·44 g/kg, respectively (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964). The acute oral LD_{50} in rats was reported as 6·6 g/kg (5·8–7·4 g/kg) (Moreno, 1972a). The acute dermal LD_{50} in rabbits exceeded 5 g/kg (Moreno, 1972b).

Subacute and long-term toxicity. A 90-day feeding study on 15 male and 15 female rats fed 0 or 67·5 mg/kg body weight/day showed no adverse effect (Oser, Carson & Oser, 1965). In a 2-wk study, 61·4 mg/kg fed to rats in the diet produced no effects (Bär & Griepentrog, 1967). In another study, 0·1–0·5% fed to groups of 20 male and female rats in the diet for 2 yr produced no effects (Bär & Griepentrog, 1967).

Irritation. γ-Nonalactone applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was slightly irritating (Moreno, 1972b). Tested at 10% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1972).

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Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. No. 2781. *Fd Technol., Champaign* **19** (2), part 2, 155.

Food Chemicals Codex (1972). 2nd ed. Prepared by the Committee on Specifications, Food Chemicals Codex, of the Committee on Food Protection. p. 553. National Academy of Sciences–National Research Council Publ. 1406, Washington, D.C.

Jenner, P. M., Hagan, E. C., Taylor, Jean M., Cook, E. L. & Fitzhugh, O. G. (1964). Food flavourings and compounds of related structure. I. Acute oral toxicity. *Fd Cosmet. Toxicol.* **2**, 327.

Joint FAO/WHO Expert Committee on Food Additives (1967). Toxicological Evaluation of Some Flavouring Substances and Non-nutritive Sweetening Agents. *F.A.O. Nutr. Mtg Rep. Ser. no.* 44A, Geneva, p. 67; WHO/Food Add./68.33.

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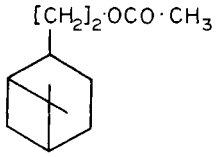
Moreno, O. M. (1972a). Report to RIFM, 5 May.
Moreno, O. M. (1972b). Report to RIFM, 1 May.
Oser, B. L., Carson, S. & Oser, M. (1965). Toxicological tests on flavouring matters. *Fd Cosmet. Toxicol.* **3**, 563.

NOPYL ACETATE

Synonyms: Lignyl acetate; 6-6-dimethylbicyclo-(3,1,1)-2-heptene-2-ethyl acetate.
Structure:



Description and physical properties: A colourless liquid with a sweet wood like odour of moderate tenacity (Arctander, 1969).
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By acetylation of nopol (Bedoukian, 1967).
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to about 200,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·015	0·3
Maximum	0·25	0·025	0·1	1·0

Analytical data: Gas chromatogram, RIFM no. 71–57; infra-red curve, RIFM no. 71–57.

Status

Nopyl acetate is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1970), nor in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 3·0 ml/kg (2·4–3·6 ml/kg) (Moreno, 1972a). The acute dermal LD_{50} value in rabbits was reported as >2 g/kg (Moreno, 1972b).

Irritation. Nopyl acetate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was slightly irritating (Moreno, 1972b). Tested at 10% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1972).

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Bedoukian, P. Z. (1967). *Perfumery and Flavoring Synthetics*. 2nd ed., p. 377. Elsevier Publishing Co., New York.

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Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. *Fd Technol., Champaign* **19**(2), part 2, 155.

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Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.

Kligman, A. M. (1972). Report to RIFM, 27 March.

Moreno, O. M. (1972a). Report to RIFM, 14 March.

Moreno, O. M. (1972b). Report to RIFM, 19 February.

NUTMEG OIL, EAST INDIAN

Synonym: Myristica oil.

Description and physical properties: *Food Chemicals Codex* (1972). The major components of nutmeg oil, including α- and β-pinene, camphene, myristicin, dipentene and sabinene, have been identified by gas chromatography–mass spectrometry (Matthews, Pickering & Robinson, 1974; Sammy & Nawar, 1968). The myristicin fraction of nutmeg has been shown to include *cis* and *trans* isomers of isomyristicin, methylisoeugenol and elemicin (Shulgin, 1963).

Occurrence: Found in the fruit of *Myristica fragrans* Houtt. (Fam. Myristicaceae) (Gildemeister & Hoffman, 1956; Guenther, 1952).

Preparation: By steam distillation of the dried nutmeg (Guenther, 1952).

Uses: In public use before 1900. Use in fragrances in the USA amounts to approximately 10,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·05
Maximum	0·1	0·01	0·02	0·3

Analytical data: Gas chromatogram, RIFM nos. 71-58, 71-59; infra-red curve, RIFM nos. 71-58, 71-59.

Status

Nutmeg was given GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1974) included nutmeg in the list of substances, spices and seasonings deemed admissible for use, with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on nutmeg oil, which has also been included in extensive studies in the GRAS review programme (National Technical Information Service (NTIS) publications PB221-222 & PB221-807).

Biological data

Acute toxicity. The acute oral LD_{50} value of nutmeg oil in rats has been reported as 2620 mg/kg (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964) and as 2600 ± 220 mg/kg (NTIS, 1972a). The acute oral LD_{50} value of East Indian nutmeg in rats was reported as 500 ± 140 mg/kg (Truitt, Callaway, Braude & Krantz, 1961). The acute oral LD_{50} values of nutmeg oil in mice and hamsters were reported as 5620 ± 520 mg/kg and 6000 ± 230, respectively (NTIS, 1972a). The acute dermal LD_{50} value in rabbits exceeded 10 ml/kg (Owen, 1971), while 10 ml/kg injected ip into cats was fatal (Ahmad & Thompson, 1975). The latter authors failed to produce local mydriatic action when they dropped nutmeg oil on the cornea of a cat or injected 1 ml subconjunctivally.

In animals, lethal doses produce fatty degeneration of the liver and central nervous system paralysis (Weil, 1965), the liver changes being attributable to the myristicin component (Christomanos, 1927). Large doses of nutmeg produce vasomotor instability, tachycardia, hypothermia, absence of saliva flow, constricted pupils and emotional lability, due largely but not entirely to the myristicin content (Truitt *et al.* 1961), and have also been reported to induce narcosis, delirium and death, in man as well as animals, following ingestion (Dale, 1909; *Merck Index*, 1968).

Several cases of nutmeg poisoning in man have been reported (Green, 1959; Hamond, 1906; Hinman, 1901; Painter, Shanor & Winek, 1971; Payne, 1963). A group of male prisoners in a New Jersey state prison attempted to achieve a state of euphoria by eating large quantities of nutmeg. Two of the men developed toxic psychoses as a result, suffering from disorientation, confusion and auditory and visual hallucinations, but they recovered within 6 months (Weiss, 1960). Two instances of attempted nutmeg intoxication have been reported in Sweden, where a 17-yr-old girl consumed 25 g and a 22-yr-old woman 15 g of powdered nutmeg (Akesson & Walinder, 1965). They both described dreamlike feelings with impaired visual perception and reported experiencing music intensely. The girl slept continuously for 40 hr and woke up in a euphoric state. No abnormal need of sleep or euphoric reaction was reported by the older woman. The duration of nutmeg intoxication is dose-dependent. In the case of the girl, symptoms lasted for 10 days, but usually they disappear after 2–3 days.

Irritation. Nutmeg oil, EI, applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Owen, 1971). Tested at 2% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1971).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 2% in petrolatum and produced no sensitization reactions (Kligman, 1971).

Metabolism. Nutmeg demonstrates a mild degree of monoamine oxidase (MAO)-inhibiting activity *in vitro* and *in vivo* (Truitt, 1967; Truitt & Ebersberger, 1962). In a test based on interference with tryptamine metabolism, nutmeg was shown to possess a weak enzyme-inhibitory action, but inhibition by myristicin was approximately one third as powerful as that of iproniazid, a well known antidepressant of this class (Truitt & Ebersberger, 1962). When oral doses of 0·2 or 1·0 g/kg nutmeg powder (as an acacia suspension) were given to mice and rats, the onset of the inhibiting action was first noted 17–24 hr after feeding as a lowering of the convulsive threshold in mice following iv injection of tryptamine. In rats, after the tryptamine injection, the MAO inhibition took the form of an increase in concentration of 5-hydroxytryptamine in the brain (Truitt, Duritz & Ebersberger, 1963).

Pharmacology. The principal pharmacologically active component of nutmeg, myristicin, caused ataxia and disorientation in monkeys and enhanced morphine-induced rage in cats (Truitt *et al.* 1961). Doses of 400 mg on alternate days produced in normal volunteers some evidence of slight euphoria, but none resembling the symptoms of excitation seen in acute nutmeg poisoning (Truitt *et al.* 1961).

Teratology. The administration of up to 560 mg nutmeg oil/kg body weight to pregnant mice for 10 consecutive days, of up to 260 mg/kg to pregnant rats for 10 consecutive days and of up to 600 mg/kg to pregnant hamsters for 5 consecutive days had no clearly discernible effect on nidation or on maternal or foetal survival (NTIS, 1972b). The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls.

Additional published data

Prolonged storage of nutmeg resulted in changes in the volatile composition, as determined by gas chromatography. The variation in composition of the nutmeg constituents appears to be mainly a function of their volatilization (Sanford & Heinz, 1971).

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OAKMOSS CONCRETE

Description and physical properties: A green to brownish-green semi-solid or viscous liquid. The chief volatile constituents are α- and β-thujone (Guenther, 1952). The non-volatile constituents are primarily high molecular weight complex organic acids. A review of the phenolic and monoterpene compounds of oakmoss has been published (Gavin & Tabacchi, 1975). *Evernia prunastri* (oakmoss) contains evernic acid which is not present in treemoss (*E. furfuracea* and *Usnea barbata*) (Arctander, 1960). Most Evernia species, including *E. prunastri*, were found to contain some usnic acid (Culberson, 1963; Savich, Litvinov & Moiseeva, 1960). *Evernia prunastri* was found to contain polysaccharides, including glucans (Takeda, Funatsu, Shibata & Fukuoka, 1972).

Occurrence: Found in the lichen, *E. prunastri* (L.) Ach. (Fam. Usneaceae), which occurs on the trunks of oak trees (Guenther, 1952; Naves, 1974).

Preparation: By solvent extraction of *E. prunastri*; the solvent is evaporated and removed, usually under vacuum, and the resultant product is normally dispersed in benzyl benzoate or a similar diluent to facilitate handling. Commercially available oakmoss preparations are frequently compounded products (Châtelain, 1953).

Uses: In public use since the 1900s. Use in fragrances in the USA amounts to approximately 75,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·005	0·1
Maximum	0·1	0·01	0·03	0·5

Analytical data: Infra-red curve, RIFM no. 72–73.

Status

Oakmoss is approved by the FDA for food use (21 CFR 121.1163) provided the finished food is thujone-free. The Council of Europe (1974) included oakmoss in the list of substances, spices and seasonings deemed admissible for use, with a possible limitation of the active principle in the final product.

Biological data

Acute toxicity. The actual oral LD_{50} in rats was reported as 2·9 (2·6–3·2 g/kg), while the acute dermal LD_{50} in rabbits exceeded 5 g/kg (Moreno, 1972).

Irritation. Oakmoss concrete applied undiluted to the backs of hairless mice and swine (Urbach & Forbes, 1972) or to intact or abraded rabbit skin for 24 hr under occlusion (Moreno, 1972) was not irritating. Tested at 10% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1973).

Phototoxicity. No phototoxic effects were reported for undiluted oakmoss concrete on hairless mice and swine (Urbach & Forbes, 1972).

Additional published data

While there is an abundant literature on the subject of oakmoss most if not all of it deals with compounded products (Châtelain, 1953).

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OCIMENOL

Synonym: 2,6-*Dimethyl*-5,7-*octadien*-2-*ol*.
Structure: $CH_3 \cdot (CH_3)COH \cdot [CH_2]_2 \cdot CH{:}C(CH_3) \cdot CH{:}CH_2$.
Description and physical properties: A colourless oily liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: From ocimene by hydration (Arctander, 1969).
Uses: In public use since the 1960s.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·2
Maximum	0·15	0·015	0·05	0·7

Analytical data: Gas chromatogram. RIFM no. 74–229; infra-red curve, RIFM no. 74–229.

Status

Ocimenol is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974) or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported to be 1·7 g/kg and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Wohl, 1974).

Irritation. Ocimenol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Wohl, 1974). Tested at 4% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1974).

Metabolism. Tertiary aliphatic alcohols, which are much more stable biologically than are primary or secondary alcohols, are usually highly conjugated with glucuronic acid and excreted in the urine both unchanged and as the glucuronides. The tertiary carbinol group resists oxidation, but oxidation of alkyl substituents may occur (Williams, 1959).

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OCIMENYL ACETATE

Synonyms: *cis*-Ocimenyl acetate; 2,6-dimethyl-5.7-octadien-2-yl acetate.
Structure: $CH_3 \cdot (CH_3)C(OCO \cdot CH_3) \cdot [CH_2]_2 \cdot CH:C(CH_3) \cdot CH:CH_2$.
Description and physical properties: A colourless liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By acetylation of ocimenol (Arctander, 1969).
Uses: In public use since the 1960s. Use in fragrances in the USA amounts to approximately 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·2
Maximum	0·15	0·015	0·05	0·7

Analytical data: Gas chromatogram, RIFM no. 74–230; infra-red curve, RIFM no. 74–230.

Status

Ocimenyl acetate is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974) or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Wohl, 1974).

Irritation. Ocimenyl acetate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Wohl, 1974). Tested at 4% in petrolatum it produced no irritation after a 48-hr closed-patch test on two different panels of human subjects (Kligman, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced two sensitization reactions in the 25 subjects (Kligman, 1974; see preface note no. 1). Repetition of the maximization test on 50 volunteers using the same sample at a concentration of 4% in petrolatum produced no sensitization reactions (Kligman, 1974).

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γ-OCTALACTONE

Synonyms: Octanolide-1,4; γ-*n*-butyl-γ-butyrolactone.
Structure: $CH_3 \cdot [CH_2]_3 \cdot CH \cdot CH_2 \cdot CH_2 \cdot CO$ (O)

Description and physical properties: *Givaudan Index* (1961).
Occurrence: Reported to be found in apricots and peaches (*Fenaroli's Handbook of Flavor Ingredients*. 1975).
Preparation: By isomerization and lactonization of 2-octenoic acid made from *n*-hexaldehyde and malonic acid.
Uses: In public use since the 1950s.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·0005	0·003	0·05
Maximum	0·15	0·015	0·05	1·2

Analytical data: Gas chromatogram, RIFM no. 74-231; infra-red curve, RIFM no. 74-231.

Status

γ-Octalactone was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included γ-octalactone at a level of 10 ppm in the list of artificial flavouring substances that may be added temporarily to foodstuffs without hazard to public health.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 4·4 g/kg (Bär & Griepentrog. 1967), while Moreno (1974) reported both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits as >5 g/kg.

Subacute toxicity. Female Swiss–Webster mice given inguinal sc injections of 12·0 mg γ-octalactone three times/wk for 4 wk (total 144 mg in 1·2 ml tricaprylin) did not show excessive weight losses or gains during an observation period of 18–24 months. Out of 16 mice, 15 were alive at 9 months, 13 at 12 months, 12 at 15 months and eight at 18 months. One sc sarcoma appeared at 12 months (Swern, Wieder, McDonough, Meranze & Shimkin, 1970).

Irritation. γ-Octalactone applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1974). Tested at 12% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 24 volunteers. The material was tested at a concentration of 12% in petrolatum and produced no sensitization reactions (Epstein, 1974).

Metabolism. γ-Octalactone is hydrolysed by an enzyme present in rat liver, rat plasma and human plasma (Fishbein & Bessman, 1966). The γ-lactone of 4-hydroxyoctanoic acid was tentatively identified in butterfat samples in quantities of 0·25–0·5 ppm (Kinsella, Patton & Dimick, 1967).

Carcinogenicity. γ-Octalactone was considered to be devoid of significant carcinogenic activity for the subcutaneous tissues of mice, since inguinal sc injection of 12 mg three times/wk for 4 wk into 16 female Swiss–Webster mice produced only one subcutaneous sarcoma at 12 months and no other types of tumour (Swern *et al.* 1970).

Micro-organisms. The vapour of γ-octalactone inhibited the growth of two out of four fungi tested by Maruzzella, Chiaramonte & Garofalo (1961), but the growth of four bacteria was not inhibited by γ-octalactone in 1:500 dilution (Maruzzella & Bramnick, 1961).

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OCTYL ISOBUTYRATE

Structure: $CH_3 \cdot [CH_2]_7 \cdot OCO \cdot CH(CH_3)_2$.
Description and physical properties: A colourless liquid.
Occurrence: Reported to be found among the volatile components of hops (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: By azeotropic esterification of *n*-octanol with isobutyric acid (Arctander, 1969).
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·0005	0·0025	0·03
Maximum	0·05	0·0005	0·02	0·2

Status

Octyl isobutyrate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included octyl isobutyrate at a level of 5 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health.

Biological data

Acute toxicity. Both the acute oral LD_{50} in rats and the acute dermal LD_{50} in rabbits exceeded 5 g/kg (Levenstein, 1974).

Irritation. Octyl isobutyrate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Levenstein, 1974). Tested at 2% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 26 volunteers. The material was tested at a concentration of 2% in petrolatum and produced no sensitization reactions (Epstein, 1974).

Metabolism. Isobutyrates are hydrolysed to materials that are either normally in the diet or readily converted to such materials (Fassett, 1963a). Isobutyric acid occurs normally in the metabolism of valine, being converted to a propionyl group and entering into the glycogenic process (Fassett, 1963b). *n*-Octanol is largely oxidized *in vivo*; about 10% is excreted conjugated with glucuronic acid in rabbits. Isomeric octanols may be more highly conjugated; they may also be oxidized to the ketone or may be excreted unchanged (Williams, 1959).

Micro-organisms. Octyl isobutyrate in a dilution of 1:500 had no inhibitory effect *in vitro* on growing cultures of four bacteria (Maruzzella & Bramnick, 1961). The vapour of octyl isobutyrate had no inhibitory effect on growing cultures of four fungi (Maruzzella, Chiaramonte & Garofalo, 1961).

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ORANGE OIL EXPRESSED

Description and physical properties: *Food Chemicals Codex* (1972). The main constituent of orange oil is limonene (Gildemeister & Hoffman, 1959; Guenther, 1949).
Occurrence: Found in the peel of the fruit *Citrus sinensis* (Linn.) Osbeck (Fam. Rutaceae) (Gildemeister & Hoffman, 1959; Guenther, 1949).
Preparation: By expression of the peel of the ripe fruit (Arctander, 1960).
Uses: In public use since the 1800s. Use in fragrances in the USA amounts to about 200,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·05	0·005	0·03	0·5
Maximum	0·4	0·04	0·1	0·80

Analytical data: Gas chromatogram, RIFM nos 71-63, 72-43 and 73-30; infra-red curve, RIFM nos 71-63, 72-43 and 73-30.

Status

Orange oil was granted GRAS status by FEMA (1965) and is approved by the FDA as GRAS for food use. The Council of Europe (1970) included orange oil in the list of substances, spices and seasonings whose use is deemed admissible, with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) and the *United States Pharmacopeia* (1965) both have monographs on orange oil.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. Orange oil undiluted applied to the backs of hairless mice was not irritating (Urbach & Forbes, 1972). Applied full strength to intact or abraded rabbit skin for 24 hr under occlusion it was moderately irritating (Moreno, 1973). Orange oil tested at 8% in petrolatum produced no irritation after a 48-hr closed-patch test in 21 human subjects (Epstein, 1973), and a patch test using orange oil full strength for 24 hr produced no reactions in 25 subjects (Katz, 1946).

Sensitization. A maximization test (Kligman, 1966) was carried out on 21 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Epstein, 1973).

Phototoxicity. No phototoxic effects were reported for orange oil (Urbach & Forbes, 1972).

Additional published data

Orange oil has been reported to promote tumour formation on the skins of mice treated with the primary carcinogen, 7,12-dimethylbenz[*a*]anthracene (Roe & Field, 1965). While orange oil and various terpenes have been described as co-carcinogens (Pierce, 1959; Roe, 1959), it appears that a terpene, namely *d*-limonene, also exerts anticarcinogenic or chemoprophylactic effects against the carcinogenic effects of sc injected benzo[*r,s,t*]pentaphene (Homburger, Treger & Boger, 1971).

Antibacterial properties have been reported for orange oil (Dabbah, Edwards & Moats, 1970).

The presence and identity of terpenes, paraffin waxes and α,β-dialkyl acroleins in orange oil have been reported (Kesterson, Hendrickson & Braddock, 1971).

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BITTER ORANGE OIL

Description and physical properties: EOA Spec. no. 155. The main constituent of bitter orange oil is *d*-limonene (Guenther, 1949).
Occurrence: Found in the fresh peel of the fruit *Citrus aurantium* Linne (Fam. Rutaceae).
Preparation: By the expression of the fresh peel of the fruit, *Citrus aurantium* Linne, by various methods, without the use of heat.
Uses: In public use since the 1900s. Use in fragrances in the USA amounts to less than 20,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	—	0·02	0·25
Maximum	0·14	0·005	0·10	1·0

Analytical data: Gas chromatogram, RIFM nos 71-94 and 72-60; infra-red curve, RIFM no. 72-60.

Status

Bitter orange oil was granted GRAS status by FEMA (1965) and is approved by the FDA as GRAS for food use. The Council of Europe (1970) included bitter orange oil in the list of substances, spices and seasonings whose use is deemed admissible, with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on bitter orange oil.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as >5 g/kg (Owen, 1971a). The acute dermal LD_{50} value in rabbits was reported as >10 g/kg (Owen, 1971b).

Irritation. Undiluted bitter orange oil applied to the backs of hairless mice was very mildly irritating (Urbach & Forbes, 1972). Bitter orange oil applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Owen, 1971b). Tested at 10% in petrolatum, it produced no irritation after a 48-hr closed-patch test in 25 human subjects (Kligman, 1971).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1971).

Phototoxicity. Distinct phototoxic effects have been reported for bitter orange oil (Urbach & Forbes, 1972).

Additional published data

Cutaneous irritation due to oil of bitter orange has been reported (Schwartz, Tulipan & Peck, 1947). A case of dermatitis has been reported in a girl employed to peel bitter orange; the condition was characterized by small vesicular eruptions on the fingers, hands, forearms and face (Murray, 1921). Sensitization of the skin of some individuals to light following the use of cologne waters containing oil of bitter orange has been reported (Szanto, 1928).

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ORIGANUM OIL

Description and physical properties: EOA Spec. no. 142. The main constituent of origanum oil is carvacrol (Guenther, 1949).

Occurrence: Found in the herb *Thymus capitatus* Hoffmgg. et Link and various other species of Origanum (Fam. Labiatae).

Preparation: By steam distillation of the flowering herb.

Uses: In public use before the 1900s. Use in fragrances in the USA amounts to less than 6000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·08
Maximum	0·05	0·005	0·03	0·2

Analytical data: Gas chromatogram, RIFM no. 72–206; infra-red curve, RIFM no. 72–206.

Status

Origanum oil was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1163). The Council of Europe (1970) included origanum oil (*Thymus capitatus*) in the list of flavouring substances temporarily admitted for use with a possible limitation on the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on origanum oil.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 1·85 g/kg (1·5–2·2 g/kg) (Moreno, 1973). The acute dermal LD_{50} in rabbits was reported as between 0·32 and 0·64 g/kg (Moreno, 1973).

Irritation. Undiluted origanum oil applied to the backs of hairless mice was severely irritating (Urbach & Forbes, 1973). Applied full strength to intact or abraded rabbit skin for 24 hr under occlusion, it was moderately irritating (Moreno, 1973). Tested at 2% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 2% in petrolatum and produced no sensitization reactions (Kligman, 1973).

Phototoxicity. No phototoxic effects were reported for origanum oil (Urbach & Forbes, 1973).

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ORRIS ABSOLUTE

Description and physical properties: A yellow to brownish liquid. Orris absolute consists chiefly of isomeric irones (Guenther, 1952).

Occurrence: Found in the rhizomes of *Iris pallida*. Lam. (Fam. Iridaceae) (Guenther, 1952; Naves, 1974).

Preparation: By alcoholic extraction of the concrete (*Fenaroli's Handbook of Flavor Ingredients*, 1971).

Uses: In public use since the 1920s. Use in fragrances in the USA amounts to approximately 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·0005	0·001	0·04
Maximum	0·02	0·002	0·02	0·2

Analytical data: Gas chromatogram, RIFM no. 71–64; infra-red curve, RIFM no. 71–64.

Status

Orris concrete was given GRAS status by FEMA (1965) and orris root is approved by the FDA for food use (21 CFR 121.1163). The Council of Europe (1974) included orris in the list of substances, spices and seasonings deemed admissible for use with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on orris root.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 9·4 g/kg (8·5–10·3 g/kg) (Moreno, 1972).

Irritation. Undiluted orris absolute applied to the backs of hairless mice and swine was not irritating (Urbach & Forbes, 1972). A patch test using orris at full strength for 24 hr produced no irritation reactions in 20 subjects (Katz, 1946). Orris absolute tested at 3% in petrolatum produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972). It produced no primary irritation in a repeated insult patch test on 43 human subjects (Majors, 1972).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 3% in petrolatum and produced no sensitization reactions (Kligman, 1972). Orris absolute (2%) was also tested by the repeated insult patch test procedure (Draize, 1959), using eleven 24-hr exposures on 43 human subjects, without producing sensitization reactions (Majors, 1972).

Phototoxicity. No phototoxic effects were reported for undiluted orris absolute on hairless mice and swine (Urbach & Forbes, 1972).

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PALMAROSA OIL

Description and physical properties: EOA Spec. no. 29. The main constituent of palmarosa oil is geraniol (Guenther, 1950).
Occurrence: Found in the grass of *Cymbopogon martini* Stapf. var Motia (Fam. Graminae).
Preparation: By steam distillation of the partially dried grass *Cymbopogon martini* Stapf. var. Motia.
Uses: In public use before the 1900s. Use in fragrances in the USA amounts to about 30,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·3
Maximum	0·2	0·02	0·1	0·8

Analytical data: Gas chromatogram, RIFM no. 72–207; infra-red curve, RIFM no. 72–207.

Status

Palmarosa oil was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The *Food Chemicals Codex* (1972) has a monograph on palmarosa oil.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. Palmarosa oil applied full strength to intact or abraded rabbit skin for 24 hr under occlusion produced a moderate irritation (Moreno, 1973), but applied undiluted to the backs of hairless mice, it was not irritating (Urbach & Forbes, 1973). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 26 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Epstein, 1973).

Phototoxicity. No phototoxic effects were reported for palmarosa oil (Urbach & Forbes, 1973).

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PARSLEY SEED OIL

Description and physical properties: EOA Spec. no. 139. The main constituents of parsley seed oil include apiole, α-pinene and myristicin (Guenther, 1950).
Occurrence: Found in the seed of the herb *Petroselinum sativum* Hoffm. (*Apium petroselinum* L., *Carum petroselinum* Benth et Hook) of the family Umbelliferae.
Preparation: By careful steam distillation of the ripe seed.
Uses: In public use before the 1900s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·0005	0·003	0·04
Maximum	0·05	0·005	0·02	0·2

Status

Parsley oil was given GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1974) included parsley oil in the list of substances, spices and seasonings deemed admissible for use with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on parsley seed oil.

Biological data

Acute toxicity. The acute oral LD_{50} in mice was reported as 1·52 g/kg (1·28–1·76 g/kg) (Moreno, 1974). The acute oral LD_{50} of parsley seed oil in rats was found to be 3·96 g/kg body weight, corresponding to 277 g/70-kg man, with liver and kidney damage (von Skramlik, 1959). An extract of parsley seed given to mice in a single dose of 0·01 ml/g body weight caused anuria, drowsiness, dyspnoea, and hyperaemia of the viscera, with death after 24–60 hr (Amerio, DeBenedictis, Leondeff, Mastrangelo & Coratelli, 1968). The acute dermal LD_{50} in guinea-pigs was reported as >5 g/kg (Moreno, 1974).

No toxic effects were observed in dogs receiving sc doses of parsley (*P. hortense*) as large as 60 g/kg body weight (Sharaf, Abdou & Saddik, 1969). Parsley plants (*P. hortense*) were found to be toxic to chickens, with an intramuscular LD_{50} of 17·8 g/kg body weight with diarrhoea, convulsions, paralysis and death (Sharaf *et al.* 1969).

Irritation. Parsley seed oil applied undiluted to the backs of hairless mice and swine was not irritating (Urbach & Forbes, 1974). Applied full strength to the backs of guinea-pigs and to intact or abraded rabbit skin for 24 hr under occlusion, it was slightly irritating (Moreno, 1974). Tested at a concentration of 2% in petrolatum, it was mildly irritating after a 48-hr closed-patch test in human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 26 volunteers. The material was tested at a concentration of 2% in petrolatum and produced no sensitization reactions (Epstein, 1974).

Phototoxicity. No phototoxic effects were reported for undiluted parsley seed oil on hairless mice and swine (Urbach & Forbes, 1974).

Micro-organisms. Parsley seed oil showed no antibacterial activity against six bacteria studied by Maruzzella & Sicurella (1960). An extract of parsley seed (*P. hortense*) strongly inhibited the growth of nine bacteria and one fungus (Kresanek & Vittek, 1962). *P. sativum* oil inhibited growth of *Bacillus subtilis* and *Staphylococcus aureus* at dilutions of 1:80 and 1:100, respectively (Dovgich, 1971). Parsley oil showed only slight *in vitro* antifungal activity against seven of 15 fungi studied by Maruzzella & Liguori (1958). The bactericidal properties of parsley oil against three organisms were studied by Abdullin (1962).

Percutaneous absorption. In studies of percutaneous absorption through the intact shaved abdominal skin of the mouse, absorption of parsley oil was relatively slow (Meyer & Meyer, 1959). In an evaluation of skin penetrating agents, parsley oil did not aid deep penetration of Rhodamine B into guinea-pig skin (Meyer, 1965).

Pharmacology. In pharmacological studies of Egyptian *P. hortense* (*P. sativum*), plant extracts stimulated spontaneous activity of rat uterus and intestine *in vitro* and lowered blood pressure and respiratory movements in anaesthetized dogs. Growth of rats was stimulated and uterine weight was increased by parsley in the diet. The results suggested therapeutic uses of *P. hortense* as a laxative, hypotensive, ecbolic and emmenagogue, and promoter of growth (Sharaf *et al.* 1969).

Additional published data

The tonic effect of parsley on the uterine musculature, formerly attributed to apiole, was observed also with aqueous extracts of parsley leaves and roots, from which apiole had been removed (Tsonev, Rainova & Penova, 1967).

An aqueous extract of parsley contained an antithiamine-active substance which was unaffected by cooking or by contact with synthetic gastric juice (Kuendig & Somogyi, 1963).

Essential oils from parsley, given with food to pregnant women, increased diuresis and blood plasma protein and calcium (Kryzhanovskaya, 1970).

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PENNYROYAL OIL EURAFRICAN

Description and physical properties: EOA Spec. no. 72. The chief constituent of pennyroyal oil eurafrican is *d*-pulegone (Guenther, 1949).

Occurrence: Found in the plant *Mentha pulegium* L. (Fam. Labiatae).

Preparation: By steam distillation of the fresh or partly dried plant *Mentha pulegium* L.

Uses: In public use before the 1850s. Use in fragrances in the USA amounts to less than 11,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·12
Maximum	0·1	0·01	0·03	0·6

Analytical data: Gas chromatogram, RIFM no. 72–208; infra-red curve, RIFM no. 72–208.

Status

Pennyroyal oil was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1163). The Council of Europe (1970) included pennyroyal oil (*Mentha pulegium*) in the list of flavouring substances temporarily admitted for use with a possible limitation on the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on pennyroyal oil.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 0·4 g/kg (0·22–0·58 g/kg) (Moreno, 1973). The acute dermal LD_{50} value in rabbits was reported as 4·2 g/kg (1·9–6·5 g/kg) (Moreno, 1973).

Irritation. Pennyroyal oil eurafrican applied full strength for 24 hr under occlusion on intact or abraded rabbit skin was not irritating (Moreno, 1973), but applied undiluted to the backs of hairless mice it was moderately irritating (Urbach & Forbes, 1973). Tested at 6% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 6% in petrolatum and produced no sensitization reactions (Kligman, 1973).

Phototoxicity. No phototoxic effects were reported for undiluted pennyroyal oil eurafrican (Urback & Forbes, 1973).

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PERU BALSAM

Description and physical properties: A dark-brown viscous liquid (Naves, 1974).
Occurrence: Peru balsam is the exudation from the trunk of *Myroxylon pereirae* (Royle) Klotzsche (Fam. Leguminosae) (Guenther, 1952).
Preparation: By collection of the exudation from the trunk of *Myroxylon pereirae* (Arctander, 1960).
Uses: In public use before 1860. Use in fragrances in the USA amounts to less than 20,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·20
Maximum	0·15	0·015	0·04	0·80

Analytical data: Infra-red curve, RIFM no. 71–67.

Status

Peru balsam was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) included Peru balsam in the list of substances, spices and seasonings deemed admissible for use, with a possible limitation of the active principle in the final product.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as >5 g/kg (Lynch, 1971a). The acute dermal LD_{50} value in rabbits was reported as >10 g/kg (Lynch, 1971b).

Irritation. Peru balsam applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Lynch, 1971b). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1971). Again tested at 8%, it produced no irritation after a 24-hr closed-patch test in 50 human subjects (Shelanski, 1971).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced sensitization reactions in seven of those tested (Kligman, 1971). Peru balsam (8%) was also tested by the repeated insult patch test procedure (Shelanski & Shelanski, 1953), using 15 24-hr exposures in 50 human subjects, without producing sensitization reactions (Shelanski, 1971).

Hjorth (1961), in a monumental treatise on eczematous reactions to balsams with special reference to balsam of Peru, reported the incidence of positive reactions to patch tests with Peru balsam. Analysis of patch tests at six Scandinavian clinics (represented on the Scandinavian committee for standardization of routine patch testing) showed that the incidences of reactions to the substances differed from one clinic to another and according to sex, and that of 5558 patients tested, 6·9% produced a reaction to Peru balsam (Magnusson, Blohm, Fregert, Hjorth, Høvding, Pirilä & Skog, 1968). In a further series of 4000 patients patch-tested in five European clinics, 1000 were engaged in domestic work only, including 281 women with contact dermatitis of the hands. Half of the 281 women gave a positive patch test, the commonest allergen being balsam (27%) (Calnan, Bandmann, Cronin, Fregert, Hjorth, Magnusson, Malten, Meneghini, Pirilä & Wilkinson, 1970).

A collaborative study of contact dermatitis in five departments of dermatology has yielded a detailed analysis of the first 4000 patients. A diagnosis of dermatitis of occupational origin was reached in 28% of 1618 men and 13% of the 2382 women. Peru balsam was equally involved in both occupational and non-occupational groups and may be considered a consumer hazard as well as an occupational one (Malten, Fregert, Bandmann,

Cross allergies between balsam of Peru and poplar resins were reported in a beekeeper, the positive reaction probably being due to an agent commonly found in poplar resins and in various balsams (Rothenborg, 1967). Allergic reactions to balsam of Peru in feminine hygiene sprays have been reported (Fisher, 1973). Peru balsam is among the most common contact allergens, accounting for 7·9% reactions among 340 patients tested (Baer, Ramsey & Biondi, 1973). Cross reactions between balsam of Peru and resorcinol monobenzoate have been reported (Jordan, 1973). Other citations of dermatitis include reports by Cummer (1927), Harry (1948), Jadassohn (1932), Schwartz, Tulipan & Birmingham (1957) and Wood & Osol (1943).

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PERU BALSAM OIL

Description and physical properties: EOA Spec. no. 65. Both benzyl benzoate and benzyl cinnamate are prominent constituents of Peru balsam oil (Gildemeister & Hoffman, 1959; Guenther, 1952).

Occurrence: Found in the balsam of *Myroxylon pereirae* (Royle) Klotzsch (Fam. Leguminosae).

Preparation: By extraction with volatile solvents or distillation from balsam of Peru.

Uses: In public use since the 1920s. Use in fragrances in the USA amounts to less than 14,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·10
Maximum	0·10	0·01	0·03	0·80

Analytical data: Gas chromatogram, RIFM nos 72–1 & 72–5; infra-red curve, RIFM nos 72–1, 72–2 & 72–5.

Status

Peru balsam oil was granted GRAS status by FEMA (1965) and is the subject of a *Food Chemicals Codex* (1972) monograph.

Biological data

Acute toxicity. The acute oral LD_{50}s in rats were reported as 3·5 ml/kg (3·0–3·8 ml/kg) for RIFM no. 72–1 (Moreno, 1972b) and as 2·36 ml/kg (2·05–2·71 ml/kg) for RIFM no. 72–2 (Levenstein, 1972). The acute dermal LD_{50}s in rabbits were reported as >2 g/kg for RIFM no. 72–1 (Moreno, 1972a) and as >5 g/kg for RIFM no. 72–2 (Levenstein, 1972).

Irritation. Peru balsam oil applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was slightly irritating (Moreno, 1972a; RIFM no. 72–1). Applied full strength to intact or abraded rabbit skin for 24 hr under occlusion, it was not irritating (Levenstein, 1972; RIFM no. 72–2). Two different samples of Peru balsam oil (RIFM nos 72–1 & 72–2) applied undiluted to the backs of hairless mice produced no irritating effects (Urbach & Forbes, 1972). Five different samples (RIFM nos 72–1, 72–2, 72–3, 72–4 & 72–5) tested at a concentration of 8% in petrolatum produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. Maximization tests (Kligman, 1966) carried out on 25 volunteers at a concentration of 8% in petrolatum using five different samples of Peru balsam oils (RIFM nos 72–1, 72–2, 72–3, 72–4 & 72–5) produced no reactions (Kligman, 1972).

Phototoxicity. No phototoxic effects were reported for two samples of Peru balsam oil (RIFM nos 72–1 & 72–2) (Urbach & Forbes, 1972).

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PHENOXYACETALDEHYDE

Synonym: Cortex aldehyde.
Structure: $C_6H_5 \cdot O \cdot CH_2 \cdot CHO$.
Description and physical properties: Colourless viscous liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: From phenol in weak aqueous alkali with monochloroacetaldehyde dimethyl acetal to yield the acetal which is then hydrolysed.
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to approximately 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·0005	0·002	0·04
Maximum	0·06	0·006	0·02	0·4

Analytical data: Gas chromatogram, RIFM no. 74-176; infra-red curve, RIFM no. 74-176.

Status

Phenoxyacetaldehyde is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974) or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1975).

Irritation. Phenoxyacetaldehyde applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was markedly irritating (Moreno, 1975). Tested at 4% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1975).

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PHENOXYETHYL ISOBUTYRATE

Synonym: 2-Phenoxyethyl isobutyrate.
Structure: $C_6H_5 \cdot O \cdot [CH_2]_2 \cdot OCO \cdot CH(CH_3)_2$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By azeotropic esterification of 2-phenoxyethanol with isobutyric acid (Arctander, 1969).
Uses: In public use since the 1940s. Use in fragrances in the USA amounts to less than 4000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·0005	0·003	0·08
Maximum	0·05	0·05	0·02	0·4

Status

Phenoxyethyl isobutyrate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). Phenoxyethyl isobutyrate is included in the Council of Europe (1970) list of temporarily admissible artificial flavouring substances, and is the subject of a *Food Chemicals Codex* (1972) monograph.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. Phenoxyethyl isobutyrate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Moreno, 1973). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1973).

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PHENOXYETHYL PROPIONATE

Synonym: Ethyleneglycol monophenyl ether propionate.
Structure: $C_6H_5 \cdot O \cdot [CH_2]_2 \cdot OCO \cdot CH_2 \cdot CH_3$.
Description and physical properties: A colourless oily liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: From ethyleneglycol monophenyl ether and propionic anhydride (Arctander. 1969).
Uses: In public use since the 1960s. Use in fragrances in the USA amounts to less than 4000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·015	0·25
Maximum	0·3	0·03	0·15	1·0

Analytical data: Gas chromatogram. RIFM no. 72-235; infra-red curve. RIFM no. 72-235.

Status

Phenoxyethyl propionate is not included in the listings of the FDA. FEMA (1965) or the Council of Europe (1974) or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 4·4 ml/kg (4·07–4·75 ml/kg) and the acute dermal LD_{50} in rabbits was reported as >5 ml/kg (Levenstein. 1973).

Irritation. Phenoxyethyl propionate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Levenstein. 1973). Tested at 10% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman. 1973).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman. 1973).

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PHENYLACETALDEHYDE DIMETHYL ACETAL

Synonym: α-Tolyl aldehyde dimethyl acetal.
Structure: $C_6H_5 \cdot CH_2 \cdot CH(OCH_3)_2$.
Description and physical properties: EOA Spec. no. 134.
Occurrence: Has been found to occur in cocoa (Centraal Instituut Voor Voedingsonderzolk, 1973).
Preparation: By the reaction of the parent aldehyde with methanol or with orthoformic ester in the presence of acid (Bedoukian, 1967).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to approximately 6000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·003	0·1
Maximum	0·1	0·01	0·02	0·2

Analytical data: Gas chromatogram, RIFM no. 70–77; infra-red curve, RIFM no. 70–77.

Status

Phenylacetaldehyde dimethyl acetal was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included phenylacetaldehyde dimethyl acetal at a level of 1 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health. The *Food Chemicals Codex* (1972) has a monograph on phenylacetaldehyde dimethyl acetal.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 3·5 ml/kg (2·6–4·7 ml/kg) (Shelanski, 1971). The acute dermal LD_{50} in rabbits exceeded 2 ml/kg (Shelanski, 1971).

Irritation. Phenylacetaldehyde dimethyl acetal tested at 2% in petrolatum produced no irritation after a 48-hr closed-patch test on two different panels of human subjects (Kligman, 1971).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 2% in petrolatum and produced sensitization reactions in seven of those tested (Kligman, 1971; see Preface Note no. 1). In a second maximization test on 25 new volunteers, the material was retested at a concentration of 2% in petrolatum and produced no sensitization reactions (Kligman, 1971).

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PHENYLACETALDEHYDE ETHYLENEGLYCOL ACETAL

Synonym: 2-Benzyldioxolan.

Structure: $C_6H_5 \cdot CH_2 \cdot CH \cdot OCH_2 \cdot CH_2O$

Description and physical properties: *Givaudan Index* (1961).

Occurrence: Has apparently not been reported to occur in nature.

Preparation: By condensation of phenylacetaldehyde and ethylene glycol (Arctander, 1969).

Uses: In public use since the 1950s.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·2
Maximum	0·15	0·015	0·05	1·0

Status

Phenylacetaldehyde ethyleneglycol acetal is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974) or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 2·2 ml/kg and the acute dermal LD_{50} value in rabbits as 2·6 ml/kg (Levenstein, 1975).

Irritation. Phenylacetaldehyde ethyleneglycol acetal applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Levenstein, 1975). Tested at 6% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 6% in petrolatum and produced no sensitization reactions (Kligman, 1975).

Metabolism. Phenylacetaldehyde ethyleneglycol acetal is presumably capable of being hydrolysed to form phenylacetaldehyde and ethylene glycol (Fassett, 1963).

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Levenstein, I. (1975). Report to RIFM, 10 June.

PHENYLACETALDEHYDE GLYCERYL ACETAL

Synonyms: 5-Hydroxymethyl-2-benzyl-1,3-dioxolan; 5-hydroxy-2-benzyl-1,3-dioxan; 2-benzyl-4-hydroxymethyl-1,3-dioxolane.

Structure: $C_6H_5 \cdot CH_2 \cdot CH(O \cdot CH_2) \cdot CH \cdot CH_2OH$ and $C_6H_5 \cdot CH_2 \cdot CH(O \cdot CH_2) \cdot CHOH \cdot CH_2$.

Description and physical properties: A colourless viscous liquid.

Occurrence: Has apparently not been reported to occur in nature.

Preparation: From phenylacetaldehyde and glycerol by condensation (Arctander, 1969).

Uses: In public use since the 1930s. Use in fragrances in the USA amounts to approximately 6000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·2
Maximum	0·15	0·015	0·05	1·0

Analytical data: Gas chromatogram. RIFM no. 72-6; infra-red curve, RIFM no. 72-6.

Status

Phenylacetaldehyde glyceryl acetal was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included phenylacetaldehyde glyceryl acetal at a level of 20 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 1·72 ml/kg (1·57–1·87 ml/kg) and the acute dermal LD_{50} value in rabbits exceeded 2 g/kg (Moreno, 1972). The ip LD_{50} for mice was found to be 2·7 ± 0·23 mmol/kg (523·8 ± 44·62 mg/kg) and the mean paralysing dose (ED_{50}) for ip administration to mice was found to be 0·77 ± 0·07 mmol/kg (Berger, 1951).

Irritation. Phenylacetaldehyde glyceryl acetal applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1972). Tested at 3% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 3% in petrolatum and produced no sensitization reactions (Kligman, 1972).

Micro-organisms. Phenylacetaldehyde glyceryl acetal was found by a zone-inhibition technique to be an effective antibacterial agent against Gram-positive *Staphylococcus aureus* and six Gram-negative bacteria, including *Pseudomonas aeruginosa* (Felton & Kapp, 1970).

Metabolism. Acetals hydrolyse readily in the presence of acids to generate the corresponding aldehydes and alcohols (Fassett, 1963).

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PHENYLACETIC ACID

Synonym: α-Toluic acid.
Structure: $C_6H_5 \cdot CH_2 \cdot COOH$.
Description and physical properties: EOA Spec. no. 19.
Occurrence: Reported to be found among the constituents of a few essential oils, notably of tobacco, *Rosa centifolia*, Bulgarian rose, orange flowers absolute, neroli and *Mentha arvensis* of Japanese origin; also reported to be present among the volatile constituents of cocoa (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: By the hydrolysis of benzyl cyanide with dilute sulphuric acid or by any other suitable means.
Uses: In public use before the 1920s. Use in fragrances in the USA amounts to approximately 7000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·1
Maximum	0·1	0·01	0·03	0·2

Analytical data: Gas chromatogram, RIFM no. 72–63; infra-red curve, RIFM no. 72–63.

Status

Phenylacetic acid was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included phenyl acetic acid at a level of 25 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health. The *Food Chemicals Codex* (1972) has a monograph on phenylacetic acid.

Biological data

Acute toxicity. Both the acute oral LD_{50} in rats and the acute dermal LD_{50} in rabbits exceeded 5 g/kg (Keating, 1972).

Irritation. Phenylacetic acid tested at 2% in petrolatum produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 2% in petrolatum and produced no sensitization reactions (Kligman, 1972).

Metabolism. Phenylacetic acid is conjugated in man and the chimpanzee, but probably in no other species, with glutamine. In most other animals, except the hen, it behaves like benzoic acid, forming glycine and glucuronic acid conjugates. In the hen, it conjugates with ornithine, forming phenacetornithuric acid. Phenacetylglutamine and its addition compound with urea were isolated from human urine after the administration of phenylacetic acid (Williams, 1959).

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PHENYLETHYL ACETATE

Synonym: β-Phenethyl acetate.
Structure: $C_6H_5 \cdot [CH_2]_2 \cdot OCO \cdot CH_3$.
Description and physical properties: EOA Spec. no. 60.
Occurrence: Reported to be found in a dozen natural products (Gildemeister & Hoffman, 1966).
Preparation: By the acetylation of phenylethyl alcohol.
Uses: In public use since the 1900s. Use in fragrances in the USA amounts to about 50,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·005	0·01	0·3
Maximum	0·20	0·025	0·05	1·0

Analytical data: Gas chromatogram, RIFM nos 70–28, 73–33; infra-red curve, RIFM nos 70–28, 73–33.

Status

Phenylethyl acetate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). It was included by the Council of Europe (1970) in the list of admissible artificial flavouring substances at a level of 5 ppm and is the subject of a *Food Chemicals Codex* (1972) monograph.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as >5 g/kg (Moreno, 1973) and the acute dermal LD_{50} in rabbits as 6·21 g/kg (3·89–9·90 g/kg) (Fogleman, 1970).

Enzymic hydrolysis. Phenylethyl acetate was not hydrolysed by a partially-purified human plasma arylesterase (Augustinsson & Ekedahl, 1962).

Irritation. Phenylethyl acetate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was slightly irritating (Fogleman, 1970). A patch test using undiluted phenylethyl acetate for 24 hr produced no irritation reactions in 20 subjects (Katz, 1946).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1970).

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Kligman, A. M. (1970). Report to RIFM, 1 June.

Moreno, O. M. (1973). Report to RIFM, 14 May.

PHENYLETHYL ALCOHOL

Synonyms: Phenethyl alcohol; β-phenylethyl alcohol.
Structure: $C_6H_5 \cdot [CH_2]_2 \cdot OH$.
Description and physical properties: EOA Spec. no. 20.
Occurrence: Reported to be found (as the free alcohol or esterified) in several natural products, including rose concrete, rose absolute (60% or more) and rose distillation waters, and the essential oils of neroli, ylang-ylang, narcissus, hyacinth, lily, tea leaves, *Michelia champaca*, *Pandamus odoratissimus*, Congo and Reunion geranium, tobacco and others. It has been identified also in wines (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: By one of several syntheses using benzene and ethylene oxide or ethylene chlorhydrin as the starting materials (Bedoukian, 1967).
Uses: In public use since the 1900s. Use in fragrances in the USA amounts to approximately 1,000,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·02	0·4
Maximum	0·5	0·05	0·2	2·0

Analytical data: Gas chromatogram, RIFM no. 70-17; infra-red curve, RIFM no. 70-17.

Status

Phenylethyl alcohol was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included it at a level of 20 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health. The *Food Chemicals Codex* (1972) and the *National Formulary* (1970) have monographs on phenylethyl alcohol.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 1·79 g/kg (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964). The oral LD_{50}s in mice and guinea-pigs have been reported as 0·8–1·5 g/kg and 0·4–0·8 g/kg, respectively (Treon, 1963), the ip LD_{50}s in mice and guinea-pigs as 0·2–0·4 g/kg and 0·4–0·8 g/kg, respectively and the dermal LD_{50} in guinea-pigs as 5–10 ml/kg (Treon, 1963).

Irritation. Phenylethyl alcohol was reported to be slightly irritating to the skin of guinea-pigs (Treon, 1963). A patch test using phenylethyl alcohol full strength for 24 hr produced no irritation reactions in 20 human subjects (Katz, 1946).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Greif, 1967).

Metabolism. Phenylethyl alcohol is oxidized almost entirely to the corresponding acid (Williams, 1959).

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PHENYLETHYL ANTHRANILATE

Synonyms: β-Phenethyl-*o*-aminobenzoate; phenethyl anthranilate.
Structure: $C_6H_5 \cdot [CH_2]_2 \cdot OCO \cdot C_6H_4 \cdot NH_2$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Has apparently not been reported to occur in nature.
Preparation: From phenylethyl alcohol and methyl anthranilate (Arctander. 1969).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 1000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams. lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·2
Maximum	0·2	0·02	0·1	1·0

Analytical data: Gas chromatogram. RIFM no. 75-115; infra-red curve. RIFM no. 75-115.

Status

Phenylethyl anthranilate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included phenylethyl anthranilate at a level of 6 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno. 1975).

Irritation. Phenylethyl anthranilate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno. 1975). Tested at 10% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman. 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1975). When applied full strength for 48 hr in the standard occluded aluminium patch test used by the North American Contact Dermatitis Research Group (NACDRG), phenylethyl anthranilate did not produce any irritation or sensitization in a 62-yr-old subject with a perfume dermatitis (Larsen, 1975).

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PHENYLETHYL BENZOATE

Synonym: Phenethyl benzoate.
Structure: $C_6H_5 \cdot [CH_2]_2 \cdot OCO \cdot C_6H_5$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Reported to occur in the essential oil from flowers of rose and orange (*Fenaroli's Handbook of Flavor Ingredients*. 1971).
Preparation: Fom phenylethyl alcohol and methyl benzoate or by azeotropic esterification of phenylethyl alcohol with benzoic acid (Arctander, 1969).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·2
Maximum	0·2	0·02	0·05	0·8

Status

Phenylethyl benzoate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included it at a level of 1 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported to be 5 g/kg and the acute dermal LD_{50} in rabbits exceeded 5 g/kg (Wohl, 1974).

Irritation. Phenylethyl benzoate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion (Wohl, 1974) or to the backs of hairless mice and swine (Urbach & Forbes, 1974) was not irritating. Tested at 8% in petrolatum, it produced no irritation after a 48 hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 22 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Epstein, 1974).

Phototoxicity. No phototoxic effects were reported for undiluted phenylethyl benzoate on hairless mice and swine (Urbach & Forbes, 1974).

Metabolism. The metabolism of benzoic acid has been extensively studied in more than 20 species, including man (Williams, 1959). Depending on species and other factors, such as availability of glycine, benzoic acid may be excreted in the urine as hippuric acid, benzoyl glucuronide or other compounds (see, for example, Bridges, French, Smith & Williams, 1970; Irjala, 1972; Kato, 1972; Martin, 1966; Runyan, 1971; Strahl & Barr, 1971; Wan & Riegelman, 1972). The major route of biotransformation of benzoic acid in man is conjugation with glycine to form hippuric acid, the rate-limiting factor in this reaction being the availability of glycine (Amsel & Levy, 1969). In man at a dose of 1 mg/kg, benzoic acid is excreted entirely as hippuric acid (Bridges *et al.* 1970). Phenylethyl alcohol is oxidized almost entirely to phenylacetic acid (Williams, 1959). In rabbits, a small amount of benzoic acid is also formed; the phenylacetic acid is excreted mainly as phenaceturic acid (Smith, Smithies & Williams, 1954).

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PHENYLETHYL FORMATE

Synonym: Phenethyl formate.
Structure: $C_6H_5 \cdot [CH_2]_2 \cdot OCOH$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Reported to be found in several natural products (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: By cold formylation of phenylethyl alcohol (Arctander, 1969).
Uses: In public use since the early 1900s. Use in fragrances in the USA amounts to about 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·2
Maximum	0·1	0·01	0·03	0·6

Analytical data: Gas chromatogram, RIFM no. 72–210; infra-red curve, RIFM no. 72–210.

Status

Phenylethyl formate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) listed phenylethyl formate, giving an ADI of 5 mg/kg.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported to be 3·22 ml/kg (2·82–3·67 ml/kg) (Levenstein, 1973a). The acute dermal LD_{50} value was reported as >5 ml/kg in the rabbit (Levenstein, 1973b).

Irritation. Phenylethyl formate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Levenstein, 1973b). Tested at 6% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 6% in petrolatum and produced no sensitization reactions (Kligman, 1972).

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PHENYLETHYL ISOVALERATE

Synonym: Phenethyl isovalerate.
Structure: $C_6H_5 \cdot [CH_2]_2 \cdot OCO \cdot CH_2 \cdot CH(CH_3)_2$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By azeotropic esterification of phenylethyl alcohol with isovaleric acid (Arctander, 1969).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to about 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·003	0·04
Maximum	0·1	0·01	0·03	0·2

Analytical data: Gas chromatogram, RIFM no. 74–112; infra-red curve, RIFM no. 74–112.

Status

Phenylethyl isovalerate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). It was included by the Council of Europe (1970) in the list of admissible artificial flavouring substances at a level of 5 ppm (except for chewing gum), and is the subject of a *Food Chemicals Codex* (1972) monograph.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Levenstein, 1974).

Irritation. Phenylethyl isovalerate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Levenstein, 1974).

Sensitization. A maximization test (Kligman, 1966) was carried out on 26 volunteers. The material was tested at a concentration of 2% in petrolatum and produced no sensitization reactions (Epstein, 1974).

References

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Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.

Levenstein, I. (1974). Report to RIFM, 18 March.

PHENYLETHYL METHYLETHYLCARBINYL ACETATE

Synonyms: Methylethyl phenylethyl carbinyl acetate; 1-phenyl-3-methyl-3-pentanyl acetate.
Structure: $C_6H_5 \cdot [CH_2]_2 \cdot (CH_3 \cdot CH_2)C(CH_3) \cdot OCO \cdot CH_3$.
Description and physical properties: A colourless liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By azeotropic esterification of the carbinol with acetic acid (Arctander, 1969).
Uses: In public use since the 1950s.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·015	0·25
Maximum	0·2	0·02	0·05	1·0

Analytical data: Gas chromatogram, **RIFM** no. 75-144; infra-red curve, **RIFM** no. 75-144.

Status

Phenylethyl methylethylcarbinyl acetate is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974) or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1976).

Irritation. Phenylethyl methylethylcarbinyl acetate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1976). Tested at 10% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1976).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 27 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Epstein, 1976).

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Epstein, W. L. (1976). Report to RIFM, 26 January.

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Moreno, O. M. (1976). Report to RIFM, 5 January.

PHENYLETHYL PHENYLACETATE

Synonyms: Phenethyl phenylacetate; phenethyl α-toluate.
Structure: $C_6H_5 \cdot [CH_2]_2 \cdot OCO \cdot CH_2 \cdot C_6H_5$.
Description and physical properties: EOA Spec. no. 279.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By esterification of phenylethyl alcohol with phenylacetic acid or by any other suitable means.
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to approximately 10,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·2
Maximum	0·15	0·015	0·05	0·8

Status

Phenylethyl phenylacetate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included it at a level of 10 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health. The *Food Chemicals Codex* (1972) has a monograph on phenylethyl phenylacetate.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 15·3 g/kg (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964).

Subacute toxicity. In feeding studies, 1000, 2500 and 10,000 ppm fed to rats in the diet for 17 wk produced no macroscopic effect (Hagan, Hansen, Fitzhugh, Jenner, Jones, Taylor, Long, Nelson & Brouwer, 1967).

Irritation. Phenylethyl phenylacetate tested at 2% in petrolatum produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1971). It was not a primary irritant when tested at 2% in a repeated insult patch-test procedure (Blau & Kanof, 1971).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 2% in petrolatum and produced no sensitization reactions (Kligman, 1971). Phenylethyl phenylacetate (2%) was also tested by the repeated insult patch test procedure (Draize, 1959), using eleven 24-hr exposures on 40 human subjects, and produced no sensitization reactions (Majors, 1971). A 2% concentration again produced no sensitization reactions in another repeated insult patch test involving eleven 48-hr exposures on 105 human subjects (Blau & Kanof, 1971).

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Food Chemicals Codex (1972). 2nd ed. Prepared by the Committee on Specifications, Food Chemicals Codex, of the Committee on Food Protection. p. 602. National Academy of Sciences–National Research Council Publ. 1406, Washington, D.C.

Hagan, E. C., Hansen, W. H., Fitzhugh, O. G., Jenner, P. M., Jones, W. I., Taylor, Jean M., Long, Eleanor L., Nelson, A. A. & Brouwer, J. B. (1967). Food flavourings and compounds of related structure. II. Subacute and chronic toxicity. *Fd Cosmet. Toxicol.* **5**, 141.

Jenner, P. M., Hagan, E. C., Taylor, Jean M., Cook, E. L. & Fitzhugh, O. G. (1964). Food flavourings and compounds of related structure. I. Acute oral toxicity. *Fd Cosmet. Toxicol.* **2**, 327.

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Kligman, A. M. (1971). Report to RIFM, 20 April.

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Majors, P. A. (1971). Report to RIFM, 13 April.

PHENYLETHYL PROPIONATE

Synonym: Phenethyl propionate.

Structure: $C_6H_5 \cdot [CH_2]_2 \cdot OCO \cdot CH_2 \cdot CH_3$.

Description and physical properties: *Givaudan Index* (1961).

Occurrence: Has apparently not been reported to occur in nature.

Preparation: By azeotropic esterification of phenylethyl alcohol with propionic acid (Arctander, 1969).

Uses: In public use before the 1920s. Use in fragrances in the USA amounts to about 5000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·2
Maximum	0·2	0·02	0·03	0·8

Analytical data: Gas chromatogram, RIFM no. 72–211; infra-red curve, RIFM no. 72–211.

Status

Phenylethyl propionate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included phenylethyl propionate in the list of admissible artificial flavouring substances, with a technological limit.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 4·0 g/kg (2·63–5·37 g/kg) (Moreno, 1973). The acute dermal LD_{50} value in rabbits was reported as >5 g/kg (Moreno, 1973).

Irritation. Phenylethyl propionate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Moreno, 1973). Tested at 8% concentration in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1973).

References

Arctander, S. (1969). *Perfume and Flavor Chemicals* (*Aroma Chemicals*). Vol. 2, no. 2549. S. Arctander, Montclair, New Jersey.

Council of Europe (1970). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List A(1), Series 1, no. 420, p. 71. Strasbourg.

Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. No. 2867. *Fd Technol., Champaign* **19**(2), part 2, 155.

Givaudan Index (1961). *Specifications of Synthetics and Isolates for Perfumery*. 2nd ed., p. 303. Givaudan-Delawanna, Inc., New York.

Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.

Kligman, A. M. (1973). Report to RIFM, 25 May.

Moreno, O. M. (1973). Report to RIFM, 1 February.

PHENYLETHYL TIGLATE

Synonyms: Phenethyl tiglate; phenylethyl-α-methylbutenoate.
Structure: $C_6H_5 \cdot [CH_2]_2 \cdot OCO \cdot C(CH_3):CH \cdot CH_3$.
Description and physical properties: A colourless, slightly viscous liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By direct esterification of phenylethyl alcohol with tiglic acid.
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·2
Maximum	0·15	0·015	0·05	0·6

Analytical data: Gas chromatogram, RIFM no. 74–160; infra-red curve, RIFM no. 74–160.

Status

Phenylethyl tiglate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included it in the list of artificial flavouring substances that may be added temporarily to foodstuffs without hazard to public health.

Biological data

Acute toxicity. Both the acute oral LD_{50} in rats and the acute dermal LD_{50} in rabbits exceeded 5 g/kg (Levenstein, 1974).

Irritation. Phenylethyl tiglate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was mildly irritating (Levenstein, 1974). Tested at 6% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 26 volunteers. The material was tested at a concentration of 6% in petrolatum and produced no sensitization reactions (Epstein, 1974).

References

Council of Europe (1974). Natural Flavouring Substances, Their Sources, and Added Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List 2, no. 2186, p. 321. Strasbourg.

Epstein, W. L. (1974). Report to RIFM, 19 August.

Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. No. 2870. *Fd Technol., Champaign* **19** (2), part 2, 155.

Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.

Kligman, A. M. & Epstein, W. (1975). Updating the maximization test for identifying contact allergens. *Contact Dermatitis* **1**, 231.

Levenstein, I. (1974). Report to RIFM, 18 July.

PHENYLPROPYL ACETATE

Synonyms: 3-Phenyl-1-propyl acetate; hydrocinnamyl acetate.
Structure: $C_6H_5 \cdot [CH_2]_3 \cdot OCO \cdot CH_3$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Reported to be found among the constituents of the essential oils of narcissus and *Heracleum candicans* and probably in cinnamon (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: By azeotropic esterification of phenylpropyl alcohol with acetic acid (Arctander, 1969).
Uses: In public use before the 1920s. Use in fragrances in the USA amounts to about 10,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·2
Maximum	0·2	0·02	0·05	0·8

Analytical data: Gas chromatogram, RIFM no. 72–215; infra-red curve, RIFM no. 72–215.

Status

Phenylpropyl acetate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included phenylpropyl acetate in the list of admissible artificial flavouring substances at a level of 6 ppm. It is the subject of a *Food Chemicals Codex* (1972) monograph.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 4·70 g/kg (3·84–5·56 g/kg) (Moreno, 1973). The acute dermal LD_{50} in rabbits was reported as > 5 g/kg (Moreno, 1973).

Irritation. Phenylpropyl acetate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Moreno, 1973). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1973).

References

Arctander, S. (1969). *Perfume and Flavor Chemicals (Aroma Chemicals)*. Vol. 2, p. 2588. S. Arctander, Montclair, New Jersey.

Council of Europe (1970). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List A(1), Series 1, no. 223, p. 60. Strasbourg.

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Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. No. 2890. *Fd Technol., Champaign* **19**(2), part 2, 155.

Food Chemicals Codex (1972). 2nd ed. Prepared by the Committee on Specifications, Food Chemicals Codex, of the Committee on Food Protection. p. 615. National Academy of Sciences–National Research Council Publ. 1406, Washington, D.C.

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Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.

Kligman, A. M. (1973). Report to RIFM, 21 May.

Moreno, O. M. (1973). Report to RIFM, 1 February.

PHENYLPROPYL ALDEHYDE

Synonyms: Hydrocinnamaldehyde; 3-phenylpropionaldehyde.
Structure: $C_6H_5 \cdot [CH_2]_2 \cdot CHO$.
Description and physical properties: EOA Spec. no. 290.
Occurrence: Found in cinnamon oil.
Preparation: By hydrogenation of cinnamic aldehyde.
Uses: In public use before the 1920s. Use in fragrances in the USA amounts to about 10,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·003	0·1
Maximum	0·2	0·02	0·02	0·8

Analytical data: Gas chromatogram, RIFM no. 72–258; infra-red curve, RIFM no. 72–258.

Status

Phenylpropyl aldehyde was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included phenylpropyl aldehyde in the list of admissible artificial flavouring substances, and it is the subject of a *Food Chemicals Codex* (1972) monograph.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Russell, 1973).

Irritation. Phenylpropyl aldehyde applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Russell, 1973). A patch test using full-strength phenylpropyl aldehyde for 24 hr produced one irritation reaction in 13 subjects (Katz, 1946). Tested at 8% in petrolatum, the material produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1973).

References

Council of Europe (1970). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List A(1), Series 2, no. 15, p. 94. Strasbourg.

Flavoring Extract Manufacturers' Association (1965). Survey of flavoring ingredient usage levels. No. 2887. *Fd Technol., Champaign* **19**(2), part 2, 155.

Food Chemicals Codex (1972). 2nd ed. Prepared by the Committee on Specifications, Food Chemicals Codex, of the Committee on Food Protection. p. 613. National Academy of Sciences–National Research Council Publ. 1406, Washington, D.C.

Katz, A. (1946). *Spice Mill* **69** (July), 46.

Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.

Kligman, A. M. (1973). Report to RIFM, 27 July.

Russell, T. J. (1973). Report to RIFM, 6 March.

PHENYLPROPYL CINNAMATE

Synonyms: 3-Phenylpropyl cinnamate; hydrocinnamyl cinnamate.
Structure: $C_6H_5 \cdot [CH_2]_3 \cdot OCO \cdot CH{:}CH \cdot C_6H_5$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Found in Oriental styrax, American styrax, Peru balsam from Honduras and Sumatra benzoin (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: From phenylpropyl alcohol and methyl cinnamate by transesterification (Arctander, 1969).
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to about 3000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·1
Maximum	0·1	0·01	0·03	0·4

Analytical data: Gas chromatogram, RIFM no. 72–46; infra-red curve, RIFM no. 72–46.

Status

Phenylpropyl cinnamate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included phenylpropyl cinnamate in the list of admissible artificial flavouring substances at a level of 5 ppm.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Keating, 1972).

Irritation. Phenylpropyl cinnamate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Keating, 1972). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1972).

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PHENYLPROPYL FORMATE

Synonyms: 3-Phenyl-1-propyl formate; hydrocinnamyl formate.
Structure: $C_6H_5 \cdot [CH_2]_3 \cdot OCOH$.
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By cold formylation of phenylpropyl alcohol (Arctander. 1969).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to approximately 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·2
Maximum	0·2	0·02	0·05	0·8

Analytical data: Gas chromatogram. RIFM no. 75-117; infra-red curve. RIFM no. 75-117.

Status

Phenylpropyl formate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) listed phenylpropyl formate giving an ADI of 5 mg/kg.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 4·09 ml/kg and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Levenstein, 1975).

Irritation. Phenylpropyl formate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was mildly irritating (Levenstein, 1975). Tested at 8% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 24 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Epstein, 1975).

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PHENYL SALICYLATE

Synonyms: Salol; phenyl-*o*-hydroxybenzoate.
Structure: $HO \cdot C_6H_4 \cdot OCO \cdot C_6H_5$.
Description and physical properties: *Merck Index* (1968).
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By the action of phosphorus oxychloride on a mixture of phenol and salicylic acid (*Merck Index*, 1968).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to approximately 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·1
Maximum	0·1	0·01	0·03	0·6

Status

The Council of Europe (1974) included phenyl salicylate in the list of artificial flavouring substances not fully evaluated.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 3 g/kg and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Levenstein, 1975). The probable LD in man is 50–500 mg/kg. The toxic effects of phenyl salicylate are similar to those of phenol but do not include a corrosive action on the alimentary canal (Dittmer, 1959).

Subacute toxicity. Preliminary clinical observations have indicated that workers employed in the production of phenyl salicylate may excrete unusually high amounts of phenol in the urine. In a 51-day toxicity study conducted by Kociba, Kalnins, Wade, Garfield & Fishbeck (1976), beagle dogs were given by capsule daily doses of phenyl salicylate large enough to result in urinary excretion of high concentrations of phenol. Doses of 500 or 250 mg/kg/day were not tolerated by the dogs, which showed decreased appetite, body weight and activity; the urine and faeces were darkened, there were transient increases in the percentage of non-segmented neutrophilic leucocytes in peripheral blood and activities of serum glutamic–pyruvic and glutamic–oxalacetic transaminases were increased. Following adjustment of the dose level to 125 mg/kg/day, values for all affected parameters returned to within normal limits. Repeated subsequent examination of haematological, urinary, clinical, chemical and morphological parameters revealed no changes associated with repeated ingestion of 125 mg phenyl salicylate/kg/day, in spite of the fact that this level of treatment caused urinary phenols to be increased to as much as 6144 ppm (control <5 ppm). There appeared to be marked variation from day to day in the degree to which urinary phenols were raised.

In one human subject who had ingested 1 oz Pepto-Bismol® hourly for eight doses, the urinary phenol level peaked at 260 ppm during the 8-hr period following ingestion, but returned to 5.5 ppm within 48 hr of the treatment (Fishbeck, Langner & Kociba, 1975). Ingestion of phenyl salicylate by the same subject in the same time sequence and in the amount contained in the Pepto-Bismol dose (90 mg/hr for 8 hr) resulted in a maximum total urinary phenol level of 472 ppm during the second 8-hr period after ingestion. No unchanged phenyl salicylate was found in the urine. These findings on urinary phenol levels conflict with the NIOSH proposed benzene standard, which implies that only benzene exposure can raise urinary phenol levels above 75 ppm (Fishbeck *et al.* 1975).

Chronic toxicity. A 23-yr-old white male, who during the course of his work continually exposed part of his skin and clothing to an alcohol solution of phenyl salicylate, was found to have elevated urinary phenol levels (150–1371 ppm). After he had been away from his job for 48 hr, the level dropped to 6 ppm and with a correction in his work practices the level regressed to normal. A complete health evaluation revealed no significant physical abnormalities (Fishbeck *et al* 1975).

Irritation. Phenyl salicylate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Levenstein, 1975). Tested at 6% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1975). Phenyl salicylate caused slight local irritation when applied to the ear, eye and abdomen of rabbits (Kociba *et al.* 1976).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 6% in petrolatum and produced

no sensitization reactions (Kligman, 1975). In a doctoral thesis presented in dental surgery (Bloch, 1975), several references were made to lipstick dermatitis in which one of the materials producing positive patch-test reactions was phenyl salicylate, which in mouthwashes had earlier been reported to cause reactions in the mouth and lips (Bonnevie, 1939). In a group of 31 aspirin-sensitive patients with chronic urticaria, 26·3% were found to be sensitive to oral doses of 500 or 1000 mg phenyl salicylate (Doeglas, 1975).

Metabolism. According to Baas (1890) from 44 to 96% of a dose (5–8 g) of phenyl salicylate is hydrolysed in man and none of it is found in the faeces. An increase in the ethereal sulphates of the urine after its ingestion is due, no doubt, to the phenol liberated (Williams, 1959). Phenyl salicylate is hydrolysed in the gut primarily to phenol and salicylic acid, which are rapidly absorbed and excreted (Fassett, 1963), but it was not hydrolysed by a partially purified preparation of acetylaryl-esterase from human plasma (Augustinsson & Ekedahl, 1962). Intestinal absorption and excretion of orally administered phenyl salicylate were studied in rabbits and dogs by analysis of blood and urine samples; oral administration of glucosamine hydrochloride increased the blood concentration of phenyl salicylate but had little effect on urinary excretion (Tanaka, Kojima & Matsubara, 1961).

Medicinal use. Phenyl salicylate has been used as an analgesic, antipyretic, 'antirheumatic', intestinal antiseptic, enteric coating for tablets and 10% ointment for sunburn prevention (*Merck Index*, 1968; *United States Dispensatory*, 1967), and as an active ingredient (0·3%) in a mouthwash (Gritz, Hofmann & Vlazak, 1976). It is present in Pepto-Bismol, a common over-the-counter medication, in amounts (90 mg/oz) sufficient to raise urinary phenol levels above 75 ppm (Fishbeck *et al.* 1975). It has been administered at dosage levels of 2–15 g to horses and 0·25–1·0 g to dogs, but its use is contra-indicated in cats (*Merck Index*, 1968).

Skin absorption. Percutaneous absorption of phenyl salicylate was studied in male white rats by immersing the tails in a perfusion chamber containing a phenyl salicylate-buffer solution. The total amount of phenyl salicylate absorbed was 2·18–2·90 $\mu g/mm^2/hr$ at several pH levels (Siddiqi & Ritschel, 1972).

Haematology. A decrease in erythrocyte osmotic resistance and in erythrocyte swelling during storage for 21 days at 4–6°C was prevented by addition of 1% phenyl salicylate to the blood (Katsadze & Shulutko, 1973). Phenyl salicylate (0·001 M) was found to increase the deformability of dense red-blood-cell packs (Jacobs, 1965). The binding constant of phenyl salicylate to the high-affinity bilirubin-binding site of human serum albumin was found to be $2·9 \times 10^4 M^{-1}$ (Brodersen, 1974).

Enzymology. Inhibition of the activity of proteases by phenyl salicylate was studied by Umarova & Mednik (1972), and the ester was reported to exhibit weak (5%) inhibition against apricot phenolase (Soler-Martinez, Sabater-Garcia & Lozano, 1965).

Pharmacology. Phenyl salicylate was found to have slight analgesic activity against pain stimuli in mice (Kameyama, 1961), but ip administration of 500 mg/kg showed no analgesic action against an electric shock applied to the tails of mice (McKenzie & Beechey, 1962). *In vitro* studies on cartilage and rat-liver mitochondria have shown that phenyl salicylates are more active than salicylates in uncoupling oxidative phosphorylation (Bostrom, Berntsen & Whitehouse, 1964).

Micro-organisms. Phenyl salicylate showed marked tuberculostatic action in dilutions up to 1:250,000 (Jeney & Zsolnai, 1956). The LD_{50} of phenyl salicylate for the fungus *Stemphylium sarcinaeforme* was reported to be $>1000 \mu g/cm^2$; germination of the spores was not inhibited by 10,000 ppm. The LD_{50} for spores of *Monilinia fructicola was* $50 \mu g/cm^2$. Germination of spores of the fungus *Sclerotinia fructicola* was inhibited by 1000 ppm (Dittmer, 1959). Phenyl salicylate showed fungistatic action at 1:10,000 dilution in a liquid medium against *Achorion quincheanum*, *Trichophyton gypseum* and *Epidermophyton Kaufman-Wolff* and at 1:5000 dilution against *Trichothecium roseum* (Zsolnai, 1960). Combination of phenyl salicylate with fungicidal hydroxyphenylpyrazolones, anilides of salicylic acid or esters of *p*-hydroxybenzoic acid increased the fungicidal activity and decreased the toxicity to warm-blooded animals (Neumann, 1958). Phenyl salicylate applied at 0·50% (w/w) did not prevent mould growth for 11 wk in alfalfa hay containing 40% moisture (Schenk & Kennedy, 1955).

Teratogenicity. Phenyl salicylate administered orally to four groups of adult female primiparous rats in doses of 400 mg/kg on days 7–9 of gestation or 300 mg/kg on days 7–12 produced high rates of resorption and maceration in the foetuses. Development malformations were related to dosage and duration of administration (Baba, Nagahama, Akiyama & Miki, 1966).

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PIMENTA LEAF OIL

Synonym: Oil pimento leaf.
Description and physical properties: EOA Spec. no. 73. The main constituent of pimenta leaf oil is eugenol (*Fenaroli's Handbook of Flavor Ingredients*, 1971; Guenther, 1950).
Occurrence: Found in the leaves of the shrub *Pimenta officinalis* Lindl. (Fam. Myrtaceae).
Preparation: By steam distillation of the leaves of *Pimenta officinalis* Lindl.
Uses: In public use before the 1900s. Use in fragrances in the USA amounts to less than 5000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·2
Maximum	0·3	0·03	0·05	1·2

Analytical data: Gas chromatogram, RIFM no. 72–216; infra-red curve, RIFM no. 72–216.

Status

Pimenta leaf oil was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The *Food Chemicals Codex* (1972) has a monograph on pimenta leaf oil.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 3·6 ml/kg (2·9–4·5 ml/kg) (Shelanski, 1972). The acute dermal LD_{50} value in rabbits was reported as 2·82 ml/kg (1·97–4·06 ml/kg) (Shelanski, 1972).

Irritation. Undiluted pimenta leaf oil applied to the backs of hairless mice was not irritating (Urbach & Forbes, 1972), but applied full strength to intact or abraded rabbit skin for 24 hr under occlusion, the oil was severely irritating (Shelanski, 1972). Tested at 12% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 12% in petrolatum and produced no sensitization reactions (Kligman, 1972).

Phototoxicity. No phototoxic effects were reported for pimenta leaf oil (Urbach & Forbes, 1972).

Percutaneous absorption. Pimenta leaf oil was not absorbed within 2 hr by the intact shaved abdominal skin of the mouse (Meyer & Meyer, 1959).

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PINACOL

Synonyms: 2,3-Dimethyl-2,3-butanediol; tetramethylethylene glycol.
Structure: $CH_3 \cdot (HO)C(CH_3) \cdot (CH_3)C(OH) \cdot CH_3$.
Description and physical properties: *Merck Index* (1968).
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By the bimolecular reduction of acetone.
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to approximately 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·002	0·1
Maximum	0·1	0·015	0·03	0·8

Analytical data: Gas chromatogram, RIFM no. 75-118; infra-red curve, RIFM no. 75-118.

Status

Pinacol is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974) or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1975). The acute oral LD_{50} of pinacol for male albino mice was found to be 28·6 mmol/kg (Wenzel & Koff, 1956). Pinacol showed anticonvulsant activity for electroshock seizures and Metrazol® convulsions; the PD_{50} values (a measure of the protective dose) determined 15 min after oral administration of pinacol to mice were found to be 16·4 and 3·44 mmol/kg for electroshock and Metrazol convulsions, respectively (Wenzel & Koff, 1956).

Irritation. Pinacol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1975). Tested at 8% in petrolatum it produced no irritation after a 48-hr closed-patch test on two different panels of human subjects (Epstein, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 22 volunteers. The material was tested at a concentration of 8% in petrolatum and produced one sensitization reaction in the 22 subjects (Epstein, 1975; Spillover effect from Costus, see preface note no. 2). Repetition of the maximization test (Kligman, 1966; Kligman & Epstein, 1975) on 24 volunteers, using the material again at a concentration of 8% in petrolatum, produced no sensitization reactions (Epstein, 1975).

Metabolism. Pinacol forms a glucuronide in the rabbit (Williams, 1959), and was found highly conjugated with glucuronic acid in the urine of chinchilla rabbits following oral administration of 1·0–1·5 g pinacol/kg body weight (Gessner, Parke & Williams, 1960). Pinacol was not utilized to any significant extent by endocrine tissues from human placenta, rat ovary, rat testis or rat adrenal gland (Ferguson, Baillie, Calman & Hart, 1966).

Micro-organisms. Pinacol was found to be an ineffective acceptor for the β-glucosidase of the fungus *Stachybotrys atra* (Jermyn, 1966).

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PINUS PUMILIO OIL

Synonyms: Dwarf pine needle oil; *Pinus mugo* Turra var. *pumilio*; Latschenkieferöl.
Description and physical properties: *Merck Index* (1968). The principal constituents of Pinus pumilio oil were listed by Guenther (1952) as *l*-α-pinene, β-pinene, *l*-limonene, dipentene, borneol and bornyl acetate, by Jori, Bianchetti & Prestini (1969) as pinene, phellandrene, dipentene, sylvestrene and 5% bornyl acetate, and in the *Merck Index* (1968) as *l*-pinene, *l*-phellandrene, sylvestrene, dipentene, cadinene and 5–7% bornyl acetate. The monoterpene hydrocarbon fraction, representing 70·4% of pinus pumilio oil, was reported by Ikeda, Stanley, Vannier & Spitler (1962) to contain *d*-limonene (42·1%), α-pinene (18·4), Δ^3-carene (11·5), β-pinene (8·1), β-phellandrene (8·0), camphene (4·3), myrcene (3·6) and smaller amounts of α- and γ-terpinene, *p*-cymene, terpinolene and α-phellandrene.
Occurrence: Found in the branches and adherent leaves of *P. mugo* Turra var. *pumilio* (Fam. Pinaceae) (Guenther, 1952).
Preparation: By steam distillation of the branches and leaves of *P. mugo* Turra var. *pumilio* (Guenther, 1952).
Uses: In public use before the 1900s. Use in fragrances in the USA amounts to less than 1000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·05	0·005	0·02	0·2
Maximum	0·6	0·06	0·2	1·2

Analytical data: Gas chromatogram, RIFM no. 75-120; infra-red curve. RIFM no. 75-120.

Status

Pinus pumilio was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1163). The Council of Europe (1974) included it in the list of substances, spices and seasonings deemed admissible for use with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) and the National Formulary (1975) have monographs on pinus pumilio.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Levenstein, 1975). The acute oral LD_{50} to rats was reported elsewhere to be 10·64 g/kg body weight (von Skramlik, 1959).

Irritation. Undiluted Pinus pumilio oil was not irritating when applied to the backs of hairless mice and swine (Urbach & Forbes, 1975) or to intact or abraded rabbit skin for 24 hr under occlusion (Levenstein, 1975). It was reported to be irritating to human skin (Harry, 1948) and at 12% in petrolatum produced irritant responses in three out of 22 human subjects (Epstein, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 22 volunteers. The material was tested at a concentration of 12% in petrolatum and produced no sensitization reactions (Epstein, 1975). In patch tests on 21 patients with essential-oil dermatoses, positive reactions to full strength or diluted oils, including Pinus pumilio oil, were attributed by Woeber & Krombach (1969) to the presence of Δ^3-carene, phellandrene and eugenol, the first two of which are major components of Pinus pumilio oil (Ikeda *et al.* 1962; Martinek, 1969).

Phototoxicity. No phototoxic effects were reported for undiluted Pinus pumilio oil on hairless mice and swine (Urbach & Forbes, 1975).

Metabolism. Following immersion of young pigs and one human subject for 30 min in baths containing 150 ml of a pine-oil mixture (Fichtennadel-Latschenkieferöl, Kneipp) in 450 litres of water, α- and β-pinene and limonene (components of Latschenkieferöl) were detected in the exhaled air within 20 min, reaching maximum levels 50–75 min after the start of the bath and remaining detectable after 1 day (Römmelt, Zuber, Dirnagl, & Drexel, 1974).

Micro-organisms. An oil-water mixture of Pinus pumilio oil suppressed the growth of *Staphylococcus aureus* in approximately 3–4 hr (Schürmann & Spitzner, 1960), but the oil did not exhibit antibacterial activity against *S. albus* (Niccolini, Pasotti & Caliari, 1964). It showed weak *in vitro* antibacterial activity against each of five bacteria studied; combination with eucalyptus oil and cinnamon oil increased the *in vitro* antibacterial activity but combination with other essential oils decreased its activity (Maruzzella & Henry, 1958). The oil exhibited slight *in vitro* fungistatic activity against one of 15 fungi studied (Maruzzella & Liguori, 1958).

Pharmacology. In man. Pinus pumilio oil increased bronchial secretions (Thomas, 1958). A dose of 500 mg/kg was reported to have no effect *in vivo* on the metabolism and pharmacological activity of pentobarbitone (25 mg/kg) in rats or *in vitro* on the metabolism of amidopyrene, *p*-nitroanisole and aniline by rat liver (Jori *et al.* 1969). Intravenous injection of the oil dissolved in sorbitol monostearate–water caused no toxic effects in warm-blooded animals and large doses caused no changes in blood pressure, but it showed digitalis-like action of the isolated toad heart (Primavori, 1960).

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PINUS SYLVESTRIS OIL

Synonyms: Oil of Scots pine; Kiefernadelöl.

Description and physical properties: EOA Spec. no. 133. According to Guenther (1952), the principal constituents of Pinus sylvestris oil include α- and β-pinene, limonene, borneol, bornyl acetate and Δ^3-carene. Nilov. Chirkina, Akimov & Lishtvanova (1970) describe the oil as being composed primarily (50–97%) of the terpene hydrocarbons α-pinene, camphene, β-pinene, Δ^3-carene, limonene, γ-terpene, *p*-cymene and terpinolene, while the *Merck Index* (1968) lists dipentene, pinene, sylvestrene, cadinene and 3–3·5% bornyl acetate. Studies have been reported on the composition of Bulgarian (Obnyatov, Vlahov & Tsankova, 1964), Crimean (Lishtvanova & Akimov, 1971) and Turkish (Okay, 1963–64) Pinus sylvestris oil, and a detailed study of Kiefernadelöl (Pinus silvestris) was reported by Juvonen (1970). The monoterpene hydrocarbon fraction representing 68·9% of Pinus sylvestris oil was reported by Ikeda, Stanley, Vannier, & Spitler (1962) to contain α-pinene (65·8%), Δ^3-carene (11·1), β-pinene (9·5), *d*-limonene (4·1), myrcene (3·6), camphene (2·9), β-phellandrene (1·2) and smaller amounts of terpinolene, ocimene, sabinene and γ-terpinene.

Occurrence: Found in the leaves (needles) of *Pinus sylvestris* L. (Fam. Pinaceae).

Preparation: By steam-distillation of the leaves (needles) of *P. sylvestris* L.

Uses: In public use before the 1900s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·05	0·005	0·02	0·2
Maximum	0·3	0·03	0·2	1·2

Analytical data: Gas chromatogram, RIFM no. 75-121; infra-red curve, RIFM no. 75-121.

Status

Pinus sylvestris was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1163). The Council of Europe (1974) included it in the list of currently used flavouring substances for which the toxicological and technological data are deemed insufficient; their use is temporarily admitted, possibly with a limitation on the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on Pinus sylvestris.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Levenstein, 1975). The acute oral LD_{50} for rats was determined by von Skramlik (1959) as 6·88 g/kg body weight, calculated to correspond to approximately 482 g/70 kg body weight in man.

Irritation. Undiluted Pinus sylvestris oil was not irritating when applied to the backs of hairless mice and swine (Urbach & Forbes, 1975) or to intact or abraded rabbit skin for 24 hr under occlusion (Levenstein, 1975). Tested at 12% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 23 volunteers. The material was tested at a concentration of 12% in petrolatum and produced no sensitization reactions (Epstein, 1975). In patch tests on 21 patients with essential oil dermatoses, positive reactions to full strength or diluted oils including Pinus sylvestris oil, were attributed by Woeber & Krombach (1969) to the presence of Δ^3-carene, phellandrene and eugenol, only the first of which is a major component of Pinus sylvestris oil (Ikeda *et al.* 1962).

Phototoxicity. No phototoxic effects were reported for undiluted Pinus sylvestris oil on hairless mice and swine (Urbach & Forbes, 1975).

Insects. Susceptibility of *P. sylvestris* trees to attack by the bark beetle *Blastophagus piniperda* was found to be related to the combined repellent (α-pinene and Δ^3-carene) and attractant properties of phloem fractions and their component compounds (Oksanen, Perttunen & Kangas, 1970).

Micro-organisms. Pinus sylvestris oil (10 mg as a 2% solution in olive oil), injected im once weekly had a therapeutic effect on experimental tuberculosis in the guinea-pig when combined with sub-effective doses of dihydrostreptomycin. *In vitro*, the oil had no antibacterial action in a concentration of 100 μg/ml on tubercle bacilli (Kato & Gözsy, 1958), but in another *in vitro* study it showed

antibacterial activity against four of five bacteria studied; several combinations of essential oils with Pinus sylvestris oil all resulted in decreased activity (Maruzzella & Henry, 1958). The oil exhibited moderate *in vitro* antifungal activity against all of 15 fungi studied by Maruzzella & Liguori (1958), and weakly inhibited two of 12 phytopathogenic fungi (Maruzzella & Balter, 1959).

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PIPERONYL ACETATE

Synonyms: Heliotropyl acetate; 3,4-methylene dioxybenzylacetate.
Structure: $O \cdot CH_2 \cdot O \cdot C_6H_3 \cdot CH_2 \cdot OCO \cdot CH_3$.
Description and physical properties: A colourless oily liquid with a floral-like odour (Arctander, 1969).
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By esterification of heliotropyl alcohol with acetic acid under azeotropic conditions (Arctander, 1969).
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·01	0·2
Maximum	0·1	0·01	0·05	0·8

Analytical data: Gas chromatogram, RIFM no. 72–158; infra-red curve, RIFM no. 72–158.

Status

Piperonyl acetate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included piperonyl acetate in the list of temporarily admissible artificial flavouring substances.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 2·1 g/kg (1·81–2·39 g/kg) (Moreno, 1973). The acute dermal LD_{50} value in rabbits was reported as >5 g/kg (Moreno, 1973).

Irritation. Piperonyl acetate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was slightly irritating (Moreno, 1973). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1973).

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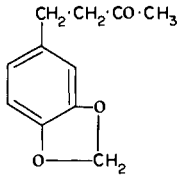
PIPERONYL ACETONE

Synonyms: Heliotropyl acetone; 3,4-methylenedioxybenzyl acetone; 4-(3,4-methylenedioxyphenyl)-2-butanone.

Structure:



Description and physical properties: Colourless crystals.

Occurrence: Has apparently not been reported to occur in nature.

Preparation: By condensation of heliotropine with acetone, followed by hydrogenation in the presence of a palladium catalyst (Arctander, 1969).

Uses: In public use since the 1940s. Use in fragrances in the USA amounts to less than 1000 lb/yr. Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·05	0·005	0·05	0·2
Maximum	0·10	0·01	0·10	0·4

Analytical data: Gas chromatogram, RIFM no. 74-190; infra-red curve, RIFM no. 74-190.

Status

Piperonyl acetone was given GRAS status by FEMA (1965) and the Council of Europe (1974) included piperonyl acetone at a level of 45 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 4·0 g/kg and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Wohl, 1974).

Irritation. Piperonyl acetone applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Wohl, 1974). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 22 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Epstein, 1974).

Metabolism. The oxygen–aromatic carbon link of aromatic ethers is generally biologically stable, and possible metabolites include the *p*-hydroxy derivative of the ether, the phenol or the *p*-hydroxyphenol (Williams, 1959). Ketones are not readily metabolized in the body. As a derivative of 2-butanone, piperonyl acetone might be expected to be partially reduced to the secondary alcohol and excreted as the glucuronide (Williams, 1959), since Saneyoshi (1911) isolated the glucuronide of 2-butanol from the urine of rabbits receiving methyl ethyl ketone.

Insects. Piperonyl acetone was found to be inferior to 4-(*p*-acetoxyphenyl)-2-butanone (cue-lure) as an attractant for the male melon fly, *Dacus cucurbitae* (Alexander, Beroza, Oda, Steiner, Miyashita & Mitchell, 1962).

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RHODINYL ACETATE

Structure: Mixture of acetates of geraniol and *l*-citronellol.
Description and physical properties: EOA Spec. no. 205.
Occurrence: Found in geranium oil.
Preparation: By acetylation of rhodinol ex geranium.
Uses: In public use before the 1920s. Use in fragrances in the USA amounts to less than 2000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·2
Maximum	0·1	0·01	0·03	1·2

Analytical data: Gas chromatogram, RIFM no. 72–217; infra-red curve, RIFM no. 72–217.

Status

Rhodinyl acetate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). Rhodinyl acetate was listed by the Council of Europe (1970), with an ADI of 0·25 mg/kg, and is the subject of a *Food Chemicals Codex* (1972) monograph.

Biological data

Acute toxicity. The acute oral LD_{50} was reported to be >5 ml/kg in the rat (Levenstein, 1973a). The acute dermal LD_{50} was reported to be >5 ml/kg in the rabbit (Levenstein, 1973b).

Irritation. Rhodinyl acetate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was mildly irritating (Levenstein, 1973b). Tested at 12% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at 12% concentration in petrolatum and produced no sensitization reactions (Kligman, 1972).

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Levenstein, I. (1973b). Report to RIFM, 15 February.

RHODINYL BUTYRATE

Structure: $CH_3 \cdot C(CH_3):CH \cdot [CH_2]_2 \cdot CH(CH_3) \cdot [CH_2]_2 \cdot OCO \cdot [CH_2]_2 \cdot CH_3$.
Description and physical properties: *Givaudan Index* (1961). Consists of a mixture of the butyrates of 1-citronellol and geraniol, principally 3,7-dimethyl-6-octen-1-yl butyrate.
Occurrence: Reported to be found in geranium essential oil (*Fenaroli's Handbook of Flavor Ingredients*, 1975).
Preparation: By the esterification of rhodinol with butyric anhydride or by isolation from geranium oil (*Givaudan Index*, 1961).
Uses: In public use before the 1920s. Use in fragrances in the USA amounts to approximately 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·1
Maximum	0·1	0·01	0·03	0·5

Analytical data: Gas chromatogram, RIFM no. 75-IFRA-16; infra-red curve, RIFM no. 75-IFRA-16.

Status

Rhodinyl butyrate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) listed rhodinyl butyrate giving it an ADI of 0·25 mg/kg.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1975).

Irritation. Rhodinyl butyrate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was mildly irritating (Moreno, 1975). Tested at 12% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 12% in petrolatum and produced no sensitization reactions (Kligman, 1975).

Metabolism. Open-chain olefinic terpene esters are presumably hydrolysed to the alcohol and the acid (Fassett, 1963). In the rabbit, the open-chain terpenes undergo ω-oxidation (Williams, 1959).

Micro-organisms. Rhodinyl butyrate and citronellyl butyrate in concentrations of 100 μg/ml showed no antibacterial effect *in vitro* on tubercle bacilli, but moderately enhanced the effectiveness of small daily doses of dihydrostreptomycin when given im in weekly 10-mg doses to guinea-pigs infected with tuberculosis (Kato & Gözsy, 1958).

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RHODINYL FORMATE

Structure: $CH_3 \cdot C(CH_3):CH \cdot [CH_2]_2 \cdot CH(CH_3) \cdot [CH_2]_2 \cdot OCOH$.

Description and physical properties: *Givaudan Index* (1961). Consists of a mixture of the formates of l-citronellol and geraniol, principally 3,7-dimethyl-6-octen-1-yl formate.

Occurrence: Has apparently not been reported to occur in nature.

Preparation: By cold formylation of rhodinol from geranium (Arctander, 1969).

Uses: In public use before the 1920s. Use in fragrances in the USA amounts to less than 2000 lb/yr. Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·12
Maximum	0·1	0·01	0·03	0·4

Analytical data: Gas chromatogram, RIFM no. 74-149; infra-red curve, RIFM no. 74-149.

Status

Rhodinyl formate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) listed rhodinyl formate giving it an ADI of 0·25 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on rhodinyl formate.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1974).

Irritation. Rhodinyl formate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Moreno, 1974). Tested at 4% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 20 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Epstein, 1974).

Skin. Rhodinyl formate applied to rat skin as a 2% ethanolic solution induced a slight accumulation of iv-administered Indian ink and trypan blue (Gözsy & Kato, 1958).

Metabolism. Open-chain olefinic terpene esters are presumably hydrolysed to the alcohol and the acid (Fassett, 1963). In the rabbit, the open-chain terpenes undergo ω-oxidation (Williams, 1959).

Micro-organisms. Rhodinyl formate in concentrations of 100 μg/ml showed no antibacterial effect *in vitro* on tubercle baccili and did not enhance the effectiveness of small daily doses of dihydrostreptomycin when given im in weekly 10-mg doses to guinea-pigs infected with tuberculosis (Kato & Gözsy, 1958).

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RHODINYL ISOBUTYRATE

Structure: $CH_3 \cdot C(CH_3):CH \cdot [CH_2]_2 \cdot CH(CH_3) \cdot [CH_2]_2 \cdot OCO \cdot CH(CH_3) \cdot CH_3$.
Description and physical properties: A colourless oily liquid. Consists of a mixture of the isobutyrates of 1-citronellol and geraniol, principally 3,7-dimethyl-6-octen-1-yl isobutyrate.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: From rhodinol and isobutyric anhydride (Arctander, 1969).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to approximately 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·12
Maximum	0·1	0·01	0·03	0·4

Analytical data: Gas chromatogram, RIFM no. 75-126; infra-red curve, RIFM no. 75-126.

Status

Rhodinyl isobutyrate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included rhodinyl isobutyrate at a level of 5 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1975).

Irritation. Rhodinyl isobutyrate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Moreno, 1975). Tested at 4% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1975).

Metabolism. Open-chain olefinic terpene esters are presumably hydrolysed to the alcohol and the acid (Fassett, 1963). In the rabbit, the open-chain terpenes undergo ω-oxidation (Williams, 1959).

Insects. The 3,7-dimethyl-6-octenyl ester of isobutyric acid was not effective as an insect attractant for the eye gnats *Conioscinella flavescens* and *Siphonella neglecta* (Rogoff, Davis, McGovern, Ilcken & Kreasky, 1973).

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ROSE ABSOLUTE FRENCH

Synonym: Rose de Mai Absolute.
Description and physical properties: A yellowish to light-brown viscous liquid. The main volatile constituents of rose absolute French include phenylethyl alcohol, geraniol and citronellol (Guenther, 1952).
Occurrence: Found in the flowers of *Rosa centifolia* L. (Fam. Rosaceae) (Guenther, 1952; Naves, 1974).
Preparation: By extraction with volatile solvents, which are subsequently removed, usually under vacuum, followed by redisolution in alcohol, chilling, filtration and removal of the alcohol.
Uses: In public use before the 1920s. Use in fragrances in the USA amounts to approximately 4000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·0005	0·003	0·1
Maximum	0·03	0·003	0·02	0·2

Analytical data: Gas chromatogram, RIFM nos. 72–220, NAK-5R; infra-red curve, RIFM nos. 72–220, NAK-5R.

Status

Rose absolute was given GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1974) included rose in the list of substances, spices and seasonings deemed admissible for use, with a possible limitation of the active principle in the final product.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as >5 g/kg and the acute dermal LD_{50} in rabbits, determined on an inadequate sample, as >0·8 g/kg (Moreno, 1973).

Irritation. Rose absolute French applied undiluted to the backs of hairless mice and swine was not irritating (Urbach & Forbes, 1973). Applied full strength to intact or abraded rabbit skin for 24 hr under occlusion, it was moderately irritating (Moreno, 1973). Three different samples of rose absolute French tested at 2% in petrolatum produced no irritation after 48-hr closed-patch tests on human subjects (Epstein, 1975; Kligman, 1973 & 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material (RIFM no. 72-2-220) was tested at a concentration of 2% in petrolatum and produced one sensitization reaction in the 25 subjects (Kligman, 1973). This same subject reacted to another material tested at the same time (see Preface Note no. 2). The maximization test was repeated on two additional samples (RIFM nos. 74-2-118 & NAK-2-5R) and produced no sensitization reactions (Epstein, 1975; Kligman, 1974).

Phototoxicity. No phototoxic effects were reported for undiluted rose absolute French on hairless mice and swine (Urbach & Forbes, 1973).

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ROSE OIL BULGARIAN

Synonym: Otto of rose, Bulgarian; oil of rose Bulgarian.

Description and physical properties: *Food Chemicals Codex* (1972). The main constituents of rose oil Bulgarian are *l*-citronellol and geraniol (Gildemeister & Hoffman, 1959; Guenther, 1952; Naves, 1974).

Occurrence: Found in the flowers from the plant *Rosa damascena* Mill. var. alba (Fam. Rosaceae) (Guenther, 1952).

Preparation: By steam distillation from the flowers of *Rosa damascena* Mill. var. alba (Gildemeister & Hoffman, 1959; Naves, 1974).

Uses: In public use since the early 1800s. Use in fragrances in the USA amounts to about 2000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·003	—	0·002	0·005
Maximum	0·03	—	0·01	0·2

Analytical data: Gas chromatogram, RIFM no. 72–221; infra-red curve, RIFM no. 72–221.

Status

Rose oil was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) included rose oil in the list of substances, spices and seasonings deemed admissible for use with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) and the *National Formulary* (1970) both have a monograph on rose oil.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as >5 g/kg (Moreno, 1973). The acute dermal LD_{50} in rabbits was reported as 2·5 g/kg (Moreno, 1973).

Irritation. Rose oil Bulgarian applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was slightly irritating (Moreno, 1973), but applied undiluted to the backs of hairless mice, it was not irritating (Urbach & Forbes, 1973). Tested at 2% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 2% in petrolatum and produced no sensitization reactions (Kligman, 1973).

Phototoxicity. No phototoxic effects were reported for rose oil Bulgarian (Urbach & Forbes, 1973).

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ROSE OIL MOROCCAN

Synonym: Otto of rose, Moroccan; oil of rose Moroccan.

Description and physical properties: *Food Chemicals Codex* (1972). The main constituents of rose oil Moroccan are *l*-citronellol and geraniol (Gildemeister & Hoffman, 1959; Guenther, 1952; Naves, 1974).

Occurrence: Found in the flowers of *Rosa centifolia* L. (Fam. Rosaceae) (Guenther, 1952).

Preparation: By steam distillation of the flowers of *Rosa centifolia* L. (Gildemeister & Hoffman, 1959; Naves, 1974).

Uses: In public use since the 1940s. Use in fragrances in the USA amounts to less than 2000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·003	—	0·002	0·05
Maximum	0·03	—	0·01	0·2

Analytical data: Gas chromatogram, RIFM no. 72–219; infra-red curve, RIFM no. 72–219.

Status

Rose oil was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) included rose oil Moroccan (*Rosa centifolia*) in the list of substances, spices and seasonings deemed admissible for use with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) and the *National Formulary* (1970) both have a monograph on rose oil.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as >5 g/kg (Moreno, 1973). The acute dermal LD_{50} in rabbits was reported as $>2{\cdot}5$ g/kg (Moreno, 1973).

Irritation. Rose oil Moroccan applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1973), but applied undiluted to the backs of hairless mice, it was not irritating (Urbach & Forbes, 1973). Tested at 2% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 24 volunteers. The material was tested at a concentration of 2% in petrolatum and produced no sensitization reactions (Epstein, 1973).

Phototoxicity. No phototoxic effects were reported for rose oil Moroccan (Urbach & Forbes, 1973).

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OIL ROSE TURKISH

Synonyms: Otto Rose Turkish; attar rose Turkish.
Description and physical properties: *Food Chemicals Codex* (1972). The main constituents of oil rose Turkish include citronellol and geraniol (Guenther, 1952).
Occurrence: Found in the flowers of *Rosa damascena* Mill (Fam. Rosaceae) (Guenther, 1952; Naves, 1974).
Preparation: By steam distillation of the flowers of *Rosa damascena* Mill (Guenther, 1952).
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to less than 2000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·003	0·0003	0·0015	0·05
Maximum	0·03	0·003	0·01	0·2

Analytical data: Gas chromatogram, RIFM no. 73–63; infra-red curve, RIFM no. 73–63.

Status

Rose oil was given GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1974) included it in the list of substances, spices, and seasonings deemed admissible for use, with a possible limitation of the active principle in the final product. Both the *Food Chemicals Codex* (1972) and the *National Formulary* (1970) have a monograph on rose oil.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as >5 g/kg and the acute dermal LD_{50} in rabbits as >2·5 g/kg (Moreno, 1973).

Irritation. Oil rose Turkish applied undiluted to the backs of hairless mice and swine was not irritating (Urbach & Forbes, 1973). Applied full strength to intact or abraded rabbit skin for 24 hr under occlusion, it was moderately irritating (Moreno, 1973). Tested at 2% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 2% in petrolatum and produced no sensitization reactions (Kligman, 1974).

Phototoxicity. No phototoxic effects were reported for undiluted oil rose Turkish on hairless mice and swine (Urbach & Forbes, 1973).

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ROSEMARY OIL

Description and physical properties: EOA Spec. no. 287. The main constituents of rosemary oil are α-pinene, camphene and cineole (*Fenaroli's Handbook of Flavor Ingredients*, 1971; Gildemeister & Hoffman, 1961; Guenther, 1949).

Occurrence: Found in the flowering tops of *Rosmarinus officinalis* L. (Fam. Labiatae).

Preparation: By steam distillation of the fresh flowering tops of *Rosmarinus officinalis* L.

Uses: In public use before the 1860s. Use in fragrances in the USA amounts to about 50,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·015	0·2
Maximum	0·3	0·03	0·1	1·0

Analytical data: Gas chromatogram, RIFM no. 71–74; infra-red curve, RIFM no. 71–74.

Status

Rosemary oil was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) included rosemary oil in the list of substances, spices and seasonings deemed admissible for use, with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on rosemary oil.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as approximately 5 ml/kg (Lynch, 1971). The acute dermal LD_{50} in rabbits was reported as >10 ml/kg (Lynch, 1971).

Irritation. Rosemary oil applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Lynch, 1971). Tested at 10% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1971).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1971).

Antimicrobial activity. Ten essential oils, including rosemary, were studied for their activity against certain gram-negative and gram-positive organisms, using the agar cup plate method. The most susceptible organisms were found to be *Staphylococcus aureus*, *S. albus*, *Vibrio cholerae*, *Escherichia coli* and Corynebacteria (Narasimha & Nigam, 1970).

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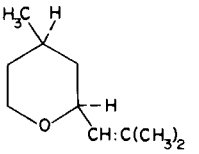
ROSE OXIDE LEVO

Synonym: 2-(2′-Methyl-1′-propenyl)-4-methyltetrahydropyran.
Structure:



Description and physical properties: A colourless mobile liquid.
Occurrence: Reported as occurring naturally in the oils of rose Bulgarian and of geranium, reunion (*Fenaroli's Handbook of Flavor Ingredients*, 1975).
Preparation: By autoxidation of citronellol followed by reduction and finally acid-catalysed cyclization.
Uses: In public use since the 1960s. Use in fragrances in the USA amounts to less than 5000 lb/yr. Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0.005	0·0005	0·003	0·04
Maximum	0·05	0·005	0·02	0·2

Analytical data: Gas chromatogram, RIFM no. 73-222; infra-red curve, RIFM no. 73-222.

Status

Rose oxide was given GRAS status by FEMA (1970).

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 4·3 g/kg (3·7–4·9 g/kg) and the acute dermal LD_{50} value in rabbits as >5 g/kg (Moreno, 1973).

Irritation. Rose oxide levo applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1973). Tested at 2% in petrolatum, it produced no irritation after a 48-hr closed-patch test on two different panels of human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 2% in petrolatum and produced three false sensitization reactions in the 25 subjects (Kligman, 1973: spillover effect from costus oil—see preface note no. 2). Repetition of the maximization test on the same material, again in a concentration of 2% in petrolatum, produced no sensitization reactions in a further 25 volunteers (Kligman, 1973).

Insects. Rose oxide acted as an attractant in a bait mixture for control of the boll weevil, *Anthonomus grandis* (McKibben, Hedin, McLaughlin & Davich, 1971).

Cells. Rose oxide (1–100 μg/ml) showed no cytotoxic effects on HeLa cell cultures (Zolotovitch, Silkjanowska, Stojcev & Nachev, 1969).

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RUE OIL

Description and physical properties: EOA Spec. no. 90. The main constituent of rue oil is methyl nonyl ketone (Guenther, 1949).
Occurrence: Found in the plants *Ruta montana* L., *R. gravolens* L. and *R. bracteosa* L. (Fam: Rutaceae).
Preparation: By steam distillation from the fresh blossoming plants.
Uses: In public use before the 1900s. Use in fragrances in the USA amounts to less than 1000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·003	0·04
Maximum	0·05	0·005	0·01	0·15

Analytical data: Gas chromatogram, RIFM no. 74-114; infra-red curve, RIFM no. 74-114.

Status

Rue oil was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1974) included rue oil in the list of flavouring substances temporarily admitted for use, possibly with a limitation on the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on rue oil.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1974). The acute oral LD_{50} (g/kg) of volatile oils of Ruta species to white mice was 2·54 for leaves and 3·73 for fruit of *R. graveolens*, 3·99 for leaves of *R. bracteosa* and 2·07 for leaves of *R. divaricata* (Srepel, 1964; Srepel & Akacic, 1962).

In guinea-pigs and rabbits, large oral doses of commercial rue oil produced dyspnoea, diarrhoea, torpor, sometimes haematemesis and loss of weight. The most important lesions were granular fatty hepatitis and parenchymatous nephritis (Patoir, Patoir & Bédrine, 1938).

Anthelmintic activity. The anthelmintic activity *in vitro* was proportional to the concentration in the oil of methyl nonyl ketone, the major constituent. LC_{50} (g/100 ml) values of *R. graveolens*, *R. bracteosa* and *R. divaricata* were 0·094–0·155 for *Tubiflex rivulorum* (worm), 0·076–0·128 for *Hirudo medicinalis* (leech) and 0·063–0·120 for *Ascaris suilla* (nematode). The LT_{100} value for *Anguillula aceti* (nematode) ranged from 10 min at 200 mg/100 ml to 45 min at 20 mg/100 ml (Srepel, 1962).

Irritation. Undiluted rue oil applied to the backs of hairless mice was not irritating (Urbach & Forbes, 1974). Applied full strength to intact or abraded rabbit skin for 24 hr under occlusion, it was slightly irritating (Moreno, 1974). When tested at 1% in petrolatum on human subjects by a 48-hr occluded-patch test, rue oil was not irritating (Kligman, 1974). Rue oil may harm the mucous membranes and irritate the skin (Arctander, 1960), producing erythema and vesication after frequent dermal contact (*Merck Index*, 1968).

Human toxicity. Taken internally, rue oil may produce haemorrhages (Arctander, 1960). Ingestion of large quantities of rue oil causes epigastric pain, nausea, vomiting, confusion, convulsions, and death; abortion may also result (*Merck Index*, 1968).

Sensitization. A maximization test (Kligman, 1966, modified) was carried out on volunteers, using 1% rue oil in petrolatum. No sensitization reactions were produced (Kligman, 1974).

Phototoxicity. Distinct phototoxic effects were reported for two samples of undiluted rue oil (Urbach & Forbes, 1974a). Various concentrations of rue oil in methanol were also tested for phototoxicity in mice, positive results being obtained with concentrations of 100, 50, 25, 12·5, 6·25 and 3·125%, borderline (positive and negative) results with 1·56% and negative results with 0·78% (Urbach & Forbes, 1974b). Rue oil has been included in a list of plants reported to cause phototoxicity (Pathak, Daniels & Fitzpatrick, 1962).

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SAFROLE

Synonym: 1,2-Methylenedioxy-4-allylbenzene.
Structure: $CH_2{:}CH \cdot CH_2 \cdot C_6H_4 \cdot O \cdot CH_2 \cdot O$.

Description and physical properties: EOA Spec. no. 18.
Occurrence: Found naturally as a constituent of over 70 essential oils. It is the principal constituent of oils of sassafras, *Ocotea cymbarum* and *Cinnamomum micranthum* and is present in appreciable quantities in brown camphor oil. Its presence has also been observed in small quantities in the oils of ylang ylang, cinnamon leaf, star anise, *Asarum arifolium*, nutmeg and massoy bark (Gildemeister & Hoffman, 1966).
Preparation: By distillation and/or freezing of such oils as *Cinnamomum micranthum*, *Octea cymbarum* and oil of sassafras.
Uses: In public use since the 1890s. Use in fragrances in the USA amounts to about 50,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·01	0·2
Maximum	0·20	0·025	0·05	0·8

Analytical data: Gas chromatogram, RIFM no. 72–47; infra-red curve, RIFM no. 72–47.

Status

The FDA does not permit safrole to be used in foods (21 CFR 121.106).

Biological data

Acute toxicity. The acute oral LD_{50} was reported as 1·95 g/kg in rats and as 2·35 g/kg in mice (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964). The acute dermal LD_{50} value in rabbits was reported as >5 g/kg (Moreno, 1972). Four daily oral doses of 650 mg safrole/kg given to rats produced macroscopic liver lesions, characterized by discoloration, enlargement and fatty infiltration (Taylor, Jenner & Jones, 1964). Oral doses of 750 mg safrole/kg/day given as a 25% solution in corn oil to rats for 19 days killed 9/10 animals, while 500 mg/kg/day killed only 1/10 in 46 days and 250 mg/kg/day killed none in 34 days (Hagan, Jenner, Jones, Fitzhugh, Long, Brouwer & Webb, 1965).

Chronic toxicity. Hepatomas developed in 46/67 mice given safrole orally at 464 mg/kg/day during the period from 7 to 28 days after birth followed by 1112 ppm in the diet for 78 wk (Innes, Ulland, Valerio, Petrucelli, Fishbein, Hart, Pallotta, Bates, Falk, Gart, Klein, Mitchell & Peters, 1969).

Five groups of rats, each containing 25 males and 25 females, were fed dietary levels of 0, 100, 500, 1000 and 5000 ppm safrole for 2 yr (Long, Nelson, Fitzhugh & Hansen, 1963). Liver damage was minimal at the lowest test levels, benign (adenomas) but not malignant tumours developed in 8/46 rats on 1000 ppm, while at 5000 ppm malignant and benign liver tumours were seen in 14/47 and 5/47 rats respectively.

In another 2-yr feeding study in rats involving groups of ten males and ten females on 1000, 2500 and 10,000 ppm and of 25 males and 25 females on 5000 ppm, slight to moderate liver damage occurred at the two lowest levels, but no liver tumours were seen, while both malignant and benign liver tumours appeared at the two higher levels (Hagan *et al.* 1965).

In a feeding study in dogs, groups of two males and two females fed 5 or 20 mg safrole/kg/day for 6 yr showed liver enlargement, fatty change, minimal focal necrosis, mild post-necrotic cirrhosis, bile-duct and Kupffer-cell proliferation, hepatic-cell atrophy and leucocytic infiltration; similar liver changes were seen with higher doses of 40 and 80 mg/kg/day given over much shorter periods of 91–116 and 26–39 days, respectively (Long *et al.* 1963).

In an sc study in infant mice given four injections totalling 0·66 or 6·6 mg during the first 3 wk of life, hepatomas developed at 1 yr in 6/12 animals on the lower dose and in 18/31 mice on the higher dose (Epstein, Fujii, Andrea & Mantel, 1970).

In a dermal study in mice, the incidence of skin papillomas in female mice given twice-weekly topical applications of 1·8 moles safrole for 7 wk, followed by twice-weekly applications of phorbol-12,13-didecanoate, was no greater than that in mice given the tumour promoter alone (Borchert, Miller, Miller & Shires, 1973a).

The carcinogenicity of safrole has been compared with that of its known metabolite, 1′-hydroxysafrole, and its possible metabolite, 1′-acetoxysafrole. Rats fed 0·55% 1′-hydroxysafrole in the diet for up to 10 months and killed up to 8 months later showed a higher liver-carcinoma incidence than did safrole-treated rats. Stomach papillomas were seen with the two safrole derivatives but not with safrole. The liver-tumour incidence was also higher in infant male mice given four sc doses of the two safrole derivatives, as compared with those given safrole. Moreover, sarcomas developed at the site of repeated sc injections in rats in the case of the two safrole derivatives but not in response to safrole (Borchert *et al.* 1973a).

Irritation. Safrole applied at full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1972). Applied undiluted to the backs of hairless mice, it was not irritating (Urbach & Forbes, 1973). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test in human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1972).

Phototoxicity. No phototoxic effects were reported for safrole (Urbach & Forbes, 1973).

Metabolism. Rats and guinea-pigs, dosed orally or ip with safrole, excreted in the urine 3-*N*,*N*-dimethylamino-1-(3′,4′-methylenedioxyphenyl)-1-propanone (Oswald, Fishbein, Corbett & Walker, 1971). In addition, the rats excreted in the urine a major metabolite, 3-piperidyl-1-(3′,4′-methylenedioxyphenyl)-1-propanone, and traces of 3-pyrrolidinyl-1-(3′,4′-methylenedioxyphenyl)-1-propanone. All three aminoketones decomposed to form 1-(3′,4′-methylenedioxyphenyl)-3-propen-1-one. Two metabolites formed by the epoxide-diol pathway and excreted in the urine of rats and guinea-pigs dosed with safrole were identified as 1,2-methylenedioxy-4-(2′,3′-dihydroxypropyl)benzene and 1,2-dihydroxy-4-(2′,3′-dihydroxypropyl)benzene (Horning, Bell, Carman & Stillwell, 1974).

Evidence obtained from chemical-reaction studies indicates that, on oxidation, safrole gives rise initially to an allyl alcohol and another unidentified conjugated alcohol, which are further oxidized to the vinyl ketone and piperonyl acrolein respectively. Condensation of the vinyl ketone with an amine would then lead to the formation of tertiary aminomethyl-enedioxypropiophenones (Mannich bases) (McKinney, Oswald, Fishbein & Walker, 1972). The alcohol reported above as unidentified was later identified as 1′-hydroxysafrole and was found in the urine of rats, hamsters, guinea-pigs and mice dosed orally or ip with safrole (Borchert, Wislocki, Miller & Miller, 1973b). 1′-Hydroxysafrole, excreted in the urine as the glucuronide conjugate, accounted for up to 33% of the safrole dose in mice but only up to 10% of the dose in the other three species. Unlike 1′-hydroxysafrole, its acetoxy ester proved to be an active alkylating agent.

As indicated earlier (Borchert *et al.* 1973a), 1′-hydroxysafrole is more hepatocarcinogenic than safrole, suggesting the former to be a proximate carcinogenic metabolite, but if 1′-acetoxysafrole is shown to be an important metabolite of safrole it may prove to be the ultimate carcinogenic metabolite.

Enzyme induction. Various studies have shown contrasting effects of safrole on microsomal-enzyme activity. Thus depression of microsomal-enzyme activity was evidenced by the prolongation of the hexobarbitone sleeping time and zoxazolamine paralysis time in mice 5 hr after ip dosage with safrole (Fujii, Jaffe, Bishop, Arnold, Mackintosh & Epstein, 1970), by the prolongation of the pentobarbitone sleeping time in mice (Seto & Keup, 1969) and by the synergistic inhibition of biphenyl 4-hydroxylase by a mixture of safrole and piperonyl butoxide in mice 1 hr after ip dosage (Friedman, Arnold, Bishop & Epstein, 1971).

In contrast, microsomal-enzyme induction has been demonstrated by several workers. Parenteral dosage of safrole to rats resulted in increased activities of biphenyl 2- and 4-hydroxylases as well as in increases in the activities of nitroreductase and glucuronyl transferase, in the content of cytochrome *P*-450 and in the size of the liver (Parke & Rahman, 1970). Rats fed on a 0·25% safrole diet exhibited increased benzopyrene-hydroxylase activity not only in the liver but also in the lungs, kidneys and gut, maximum activity being attained at 14 days (Lake & Parke, 1972). Rats given safrole orally at 150 mg/kg/day for 1 wk showed increases in the activities of ethylmorphine *N*-demethylase, biphenyl 4-hydroxylase, aniline *p*-hydroxylase and NADPH-cytochrome *c* reductase, in cytochrome *P*-450 and cytochrome b_5 contents, in microsomal protein and in liver weight. However after dosage for 8 wk, when liver cell necrosis appeared, values were depressed and by 16 wk, enzyme activities fell significantly, although the cytochrome *P*-450 and b_5 contents retained their increased values, suggesting an interaction between safrole and the microsomal haemoprotein. It would appear that the enzyme-inductive effect of safrole is a transient phenomenon and that the onset of liver damage coincides with the fall in enzyme activity (Gray, Parke, Grasso & Crampton, 1972).

Positive results were also obtained by Lotlikar & Wasserman (1972) who, after pretreating rats ip with safrole, observed both an enhanced urinary excretion of the *N*-, 3- and 5-hydroxy metabolites of subsequently-administered 2-acetamidofluorene and an enhanced ring- and *N*-hydroxylation of 2-acetamidofluorene by rat-liver microsomes *in vitro*. The lack of effect of safrole on enzyme induction was evidenced by its inability to affect either 2-acetamidofluorene hydroxylation in hamsters (Lotlikar & Wasserman, 1972) or the excretion of its urinary metabolite 1′-hydroxysafrole in rats pretreated with safrole (pretreatment with phenobarbitone or 3-methylcholanthrene increased tenfold the urinary excretion of 1′-hydroxysafrole) (Borchert *et al.* 1973b).

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SAGE OIL DALMATIAN

Description and physical properties: EOA Spec. no. 44. The main constituent of sage oil Dalmatian is thujone (Guenther, 1949).
Occurrence: Found in the leaves of *Salvia officinalis* L. (Fam. Labiatae).
Preparation: By steam distillation of the partially dried leaves of *Salvia officinalis* L. (Gildemeister & Hoffman, 1961).
Uses: In public use before the 1900s. Use in fragrances in the USA amounts to less than 20,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·2
Maximum	0·2	0·02	0·05	0·8

Analytical data: Gas chromatogram, RIFM no. 72–50; infra-red curve, RIFM no. 72–50.

Status

Sage oil Dalmatian was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) included sage oil Dalmatian in the list of substances, spices and seasonings deemed admissible for use, with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on sage oil Dalmatian.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 2·6 g/kg (1·9–3·3 g/kg) (Moreno, 1972a). The acute dermal LD_{50} value in rabbits was reported as > 5 g/kg (Moreno, 1972b).

Irritation. Sage oil Dalmatian applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1972b). A patch test using full strength sage oil Dalmatian for 24 hr produced one irritation reaction in 20 subjects (Katz, 1946). Tested at 8% in petrolatum, the oil produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1972).

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SAGE OIL. SPANISH

Description and physical properties: EOA Spec. no. 71. The principal constituents of Spanish sage oil include cineole, linalool, linalyl acetate, linalyl isovalerate and *d*-camphor (Guenther, 1949). Spanish sage oil from *Salvia lavandulaefolia* was found to contain mono- and sesquiterpenoids, including 34% camphor, 29% cineole, 6–7% each of α- and β-pinene and camphene, and 1–3% each of limonene, terpinyl acetate and linalool, borneol, isoborneol and their acetates (Brieskorn & Dalferth, 1964). Specimens of Spanish sage oil from seven provinces were characterized by De Gavina Mugica, Torner Ochoa, Isabel-Fernandez-Vega, Munoz Lopez De Bustamante, Garcia Martin & Garcia Vallejo (1969). Major components were found to be 11–32% camphor, 18–29% cineole or 21–41% limonene, 4–20% α-pinene, 18–19% β-pinene, and 5–14% camphene. Forty terpenoids were identified in the essential oil of *S. lavandulaefolia*, including 22 of the 35 previously reported constituents plus 18 constituents previously unreported (Lawrence, Hogg & Terhune, 1970).
Occurrence: Found in the plant *S. lavandulaefolia* Vahl (or *S. hispanorum* Lag., Fam. Labiatae) (Guenther, 1949).
Preparation: By distillation of *S. lavandulaefolia* Vahl (Gildemeister & Hoffman, 1961).
Uses: In public use before the 1900s. Use in fragrances in the USA amounts to about 4000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·015	0·2
Maximum	0·2	0·02	0·1	0·8

Analytical data: Gas chromatogram, RIFM no. 72-223; infra-red curve, RIFM no. 72-223.

Status

Spanish sage oil was given GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1974) included Spanish sage in the list of currently used flavouring substances for which the toxicological and technological data are deemed insufficient; their use is temporarily admitted, possibly with a limitation on the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on sage oil, Spanish.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Wohl, 1974).

Irritation. Undiluted Spanish sage oil was not irritating when applied to the backs of hairless mice and swine (Urbach & Forbes, 1973) or to intact or abraded rabbit skin for 24 hr under occlusion (Wohl, 1974). Tested at 8% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1973).

Phototoxicity. No phototoxic effects were reported for undiluted Spanish sage oil on hairless mice and swine (Urbach & Forbes, 1973).

Micro-organisms. Spanish sage oil showed moderate *in vitro* antifungal activity against all of 15 pathogenic and non-pathogenic fungi studied in tests using the filter-paper-disc method (Maruzzella & Liguori, 1958), but inhibited the *in vitro* growth of only one of ten pathogenic and non-pathogenic Gram-positive and Gram-negative bacteria (Maruzzella & Lichtenstein, 1956). Grecian sage oil showed comparable activity.

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SANDALWOOD OIL, EAST INDIAN

Description and physical properties: EOA Spec. no. 103. The main constituent of sandalwood oil, East Indian (EI), is α-santalol (Gildemeister & Hoffman, 1956; Guenther, 1952).
Occurrence: Found in the roots and wood of *Santalum album* L. (Fam. Santalaceae) (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: By steam distillation of the ground dried wood of *Santalum album* L.
Uses: In public use since the early 1800s. Use in fragrances in the USA amounts to approximately 48,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·3
Maximum	0·3	0·03	0·05	1·0

Analytical data: Gas chromatogram, RIFM no. 71–75; infra-red curve, RIFM no. 71–75.

Status

Sandalwood oil was granted GRAS status by FEMA (1965). The Council of Europe (1970) included sandalwood in the list of substances, spices and seasonings deemed admissible for use with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on sandalwood oil.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 5·58 g/kg (Bär & Griepentrog, 1967). The acute dermal LD_{50} value in rabbits was reported as >5 g/kg (Shelanski, 1971).

Irritation. Undiluted sandalwood oil EI applied to the backs of hairless mice was slightly irritating (Urbach & Forbes, 1972), and applied full strength to intact or abraded rabbit skin for 24 hr under occlusion it was irritating (Shelanski, 1971). A patch test using sandalwood oil full strength for 24 hr produced no reactions in 18 subjects (Katz, 1946). Tested at 10% in petrolatum, the oil produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1971).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1971).

Phototoxicity. No phototoxic effects were reported for sandalwood oil EI (Urbach & Forbes, 1972).

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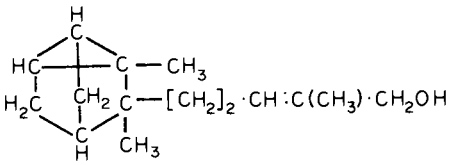
α-SANTALOL

Synonym: *d*-α-Santalol.
Structure:



Description and physical properties: EOA Spec. no. 234.
Occurrence: Found among the constituents of various sandalwood species, notably *Santalum album* L., *Santalum spicatum* and *Santalum autrocaledonicum* (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: From sandalwood oil by distillation.
Uses: In public use before the 1900s. Use in fragrances in the USA amounts to less than 4000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	—	0·01	0·3
Maximum	0·3	—	0·05	2·0

Analytical data: Gas chromatogram, RIFM no. 72–51; infra-red curve, RIFM no. 72–51.

Status

Santalol was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1970) included santalol in the list of admissible artificial flavouring substances at a level of 2 ppm. The *Food Chemicals Codex* (1972) has a monograph on santalol.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 3·8 g/kg (3·06–4·71 g/kg) (Keating, 1972). The acute dermal LD_{50} value in rabbits was reported as >5 g/kg (Keating, 1972).

Irritation. α-Santalol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was irritating (Keating, 1972). Tested at 20% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 20% in petrolatum and produced no sensitization reactions (Kligman, 1972).

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SANTALYL ACETATE

Structure: $C_{15}H_{23} \cdot OCO \cdot CH_3$ (for the structure of α-santalol, $C_{15}H_{23} \cdot OH$, see monograph thereon).

Description and physical properties: *Givaudan Index* (1961).

Occurrence: Has apparently not been reported to occur in nature.

Preparation: By acetylation of santalol (Arctander, 1969).

Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	—	0·01	0·3
Maximum	0·3	—	0·05	2·0

Analytical data: Gas chromatogram, RIFM no. 72–52; infra-red curve, RIFM no. 72–52.

Status

Santalyl acetate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). It was included by the Council of Europe (1970) in the list of admissible artificial flavouring substances at a level of 2 ppm, and is the subject of a *Food Chemicals Codex* (1972) monograph.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Keating, 1972).

Irritation. Santalyl acetate tested at 20% in petrolatum produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 20% in petrolatum and produced no sensitization reactions (Kligman, 1972).

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SAVORY OIL (SUMMER VARIETY)

Description and physical properties: EOA Spec. no. 197. The chief constituents of savory oil include *p*-cymene and carvacrol (Guenther, 1949). Egyptian savory oil from *Satureia hortensis* was found to contain 77% terpene hydrocarbons such as β-phellandrene, β-pinene and camphene, and oxygenated hydrocarbons such as borneol, eucalyptol and camphor (Karawya, Balbaa & Hifnawy, 1970). The composition of the steam-distilled oils of *S. montana* and *S. hortensis* was studied by Thieme & Nguyen Thi Tam (1972).

Occurrence: In a flowering herb *S. hortensis* L. (Fam. Labiatae) (Gildemeister & Hoffman, 1961; Guenther, 1949).

Preparation: By steam-distillation of the flowering herb.

Uses: In public use since the 1900s. Use in fragrances in the USA amounts to approximately 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·1
Maximum	0·1	0·01	0·03	0·6

Status

Savory oil (summer variety) was given GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1974) included savory (summer variety) in the list of substances, spices and seasonings deemed admissible for use with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on savory oil (summer variety).

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 1·37 g/kg (0·79–1·95 g/kg) and the acute dermal LD_{50} value as 0·34 g/kg (0·25–0·43 g/kg) in rabbits and as >2·5 g/kg in guinea-pigs (Moreno, 1975).

Irritation. Undiluted savory oil (summer variety) applied to the backs of hairless mice caused excoriation and the death of 50% of the group in 48 hr. In a concentration of 10% in methanol it produced oedema, while 1% in methanol was non-irritating (Urbach & Forbes, 1975). Savory oil (summer variety) applied full strength to intact or abraded rabbit or guinea-pig skin for 24 hr under occlusion was strongly irritating (Moreno, 1975). Tested at 6% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 6% in petrolatum and produced no sensitization reactions (Kligman, 1975).

Phototoxicity. No phototoxic effects were reported for undiluted savory oil on hairless mice and swine (Urbach & Forbes, 1975).

Pharmacology. The essential oil of *S. hortensis*, in concentrations of 50–100 μg/ml, produced spasmolytic effects, considered to be chiefly myotropic, on isolated smooth muscles from rabbits, guinea-pigs and cats (Shipochliev, 1968a). General depression without ataxia was observed in mice receiving ip injections of 50 mg/kg as a 5% emulsion, with or without preliminary treatment with 150 mg iproniazid phosphate/kg given ip 24 hr earlier. The effect on the central nervous system did not resemble that of reserpine (Shipochliev, 1968b).

Micro-organisms. The essential oil from fresh plants of *S. hortensis* showed weak bactericidal activity against *Bacillus subtilis* and *Staphylococcus aureus* in a 1:320 dilution and against *Escherichia coli* in a 1:40 dilution, and inhibited the growth of the fungi *Penicillium chrysogenum*, *Aspergillus oryzae* and *Alternaria tenuis* (Dovgich, 1971). The vapour of savory select oil was found to exert strong *in vitro* activity against five Gram-positive and Gram-negative bacteria (Maruzzella & Sicurella, 1960), and the oil itself showed weak to strong *in vitro* activity against 13 of 15 pathogenic and non-pathogenic fungi in tests using the filter-paper-disc method (Maruzzella & Liguori, 1958).

Savory oil showed bactericidal activity, both on direct contact and at a distance, against *Vibrio cholerae* and *V. paracholerae* (Petrovski, 1971).

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Urbach, F. & Forbes, P. D. (1975). Report to RIFM, 18 June.

SCHINUS MOLLE OIL

Description and physical properties: A pale green to olive green liquid. The main constituents of schinus molle oil include α-pinene, phellandrene and carvacrol (Guenther, 1952). The essential oil from green or ripe fruits of the California pepper tree, *Schinus molle*, was found to contain α-pinene, camphene, β-pinene, sabinene, myrcene, α-phellandrene, α-terpinene, limonene, γ-terpinene, *p*-cymene, terpinolene, methyl octanoate, bourbonene, α-*trans*-bergamontene, β-caryophyllene, α-terpineol, germacrene D and δ-cadinene (Bernhard & Wrolstad, 1963; Jennings & Bernhard, 1975). Other components of the essential oil include *o*-ethylphenol, and a newly isolated product, β-spathulene (Terhune, Hogg & Lawrence, 1974).

Occurrence: Found in the berries (fruit) of *Schinus molle* L. (Fam. Anacardiaceae) (Gildemeister & Hoffman, 1959; Guenther, 1952).

Preparation: By steam distillation of the fruits of *S. molle* L. (*Fenaroli's Handbook of Flavor Ingredients*, 1975).

Uses: In public use before the 1920s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·1
Maximum	0·1	0·01	0·03	0·4

Analytical data: Gas chromatogram, RIFM no. 74-241; infra-red curve, RIFM no. 74-241.

Status

Schinus molle was given GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1974) included schinus molle in the list of substances, spices and seasonings deemed admissible for use with a possible limitation of the active principle in the final product.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1974).

Irritation. Undiluted schinus molle oil was not irritating when applied to the backs of hairless mice and swine (Urbach & Forbes, 1974), but was moderately irritating when applied to intact or abraded rabbit skin for 24 hr under occlusion (Moreno, 1974). Tested at 4% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1974).

Phototoxicity. No phototoxic effects were reported for undiluted schinus molle oil on hairless mice and swine (Urbach & Forbes, 1974).

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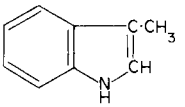
SKATOLE

Synonyms: 3-Methylindole; β-methylindole.
Structure:



Description and physical properties: *Givaudan Index* (1961).
Occurrence: Reported to be found in faeces, civet, different species of Nectandra, and in the woods of *Celtis reticulosa* and *C. Durandii*, Engl. (Urticaceae) (*Fenaroli's Handbook of Flavor Ingredients*, 1975; Poucher, 1974).
Preparation: Prepared synthetically from the phenylhydrazone of propionaldehyde or by cyclization of *o*-toluidides (Bedoukian, 1967).
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to approximately 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·003	0·0003	0·0015	0·02
Maximum	0·03	0·003	0·01	0·1

Analytical data: Gas chromatogram, RIFM no. 74-150; infra-red curve, RIFM no. 74-150.

Status

Skatole was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included skatole at a level of 1 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 3·45 ± 0·372 g/kg and the acute dermal LD_{50} value in rabbits as <5 g/kg (McGee, 1974). The ip LD_{50} of skatole in mice was determined as 175 mg/kg, the toxic effects being seen as macroscopic and microscopic lesions in the liver, spleen, kidneys and lungs (Kader, Zaki & Moustafa, 1961), and subsequently as >2 mmol/kg (Shinoda, Ohta, Hino & Akaboshi, 1974). A dose of 4 mmol skatole/kg injected sc was toxic to mice (Mirsky, Diengott & Perisutti, 1957).

In frogs, the minimum lethal dose of skatole administered sc or into the abdominal lymph sac was 1 g/kg (*Merck Index*, 1968); a paralytic action on the central nervous system resulted in a complete abolition of spontaneous reflex and respiratory movements (Yanai, 1935).

An oral dose of 0·3 g skatole/kg given to goats produced diffuse pulmonary oedema which resulted in death, and oral or iv administration to cows caused pulmonary lesions. Death from pulmonary oedema and emphysema resulted in 3/3, 0/2 and 1/3 cows given 0·2 (oral), 0.1 (oral) and 0.06 g/kg (iv in propylene glycol), respectively. Skatole is a product of ruminal tryptophan fermentation and may be the causative agent in tryptophan-induced pulmonary disease in cattle (Carlson, Dickinson, Yokoyama & Bradley, 1975; Carlson, Yokoyama & Dickinson, 1972; Yokoyama & Carlson, 1974). Mice treated orally with 100 mg skatole/kg showed no signs of pulmonary disease. Oral ingestion of 200 mg/kg by mice also failed to induce pulmonary emphysema, but pulmonary congestion did occur, as shown by a reduction in the phospholipid content of the lung and increases in haemoglobin content (Watanabe & Aviado, 1974).

Subacute toxicity. When mice were given skatole (10 mg/kg body weight) ip for 15 consecutive days, macroscropic and microscopic lesions of the liver, spleen, kidney and lungs were present but showed marked regeneration after the dose was stopped (Kader *et al.* 1961). Rabbits, injected in the knee joint with a single dose of skatole (0·26 mmol in 1 ml aqueous 50% propylene glycol) developed acute arthritis and an acute inflammation originating in the synovial tissue, while rabbits injected in the knee joint with 0·04–0·26 mmol skatole once weekly for 6 wk developed chronic arthritis, the severity increasing with increasing dosages (Nakoneczna, Forbes & Rogers, 1969; Rogers, Forbes & Nakoneczna, 1969).

Irritation. Skatole applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (McGee, 1974). Tested at 2% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 20 volunteers. The material was tested at a concentration of 2% in petrolatum and produced no sensitization reactions (Epstein, 1974).

Metabolism. 3-Methylindole (skatole) has been reported by several authors to be excreted as an ethereal sulphate by dogs, rats and man; distillation of the urine results in the formation of indole, which might well be derived by decarboxylation of indolyl-3-carboxylic acid, an expected oxidation product of skatole (Williams, 1959). Oral administration of skatole to rats resulted in the urinary excretion of a mixture of sulphate esters of hydroxyskatoles (Dalgliesh, Kelly & Horning, 1958; Horning, Sweeley, Dalgliesh & Kelly, 1959). The faeces of rats fed a chow diet were found to contain typtophan metabolites, including up to 0·78 μg skatole/g wet faeces (Anderson, 1975). Metabolites of skatole were detected in the urine of a human subject fed skatole (Sano & Miyanoki, 1955). In man, skatole has been shown to undergo hydroxylation mainly at position 6. In rats and man, 6-hydroxyskatole is excreted chiefly as the sulphate (Horning *et al.* 1959), but it may also be excreted as the glucuronide (Sohler, 1966). The metabolites of skatole excreted in the urine of man and 16 species of domestic and wild mammals were also studied by Decker & Gerdemann (1959). After administration of skatole to cattle in a dose of 0·1–0·2 g skatole/kg intraruminally or 0·06 g/kg by jugular infusion, the mean plasma concentration of skatole became maximal at 3 and 9 hr, respectively (Carlson *et al.* 1975).

Skatole is produced in the gastro-intestinal tract (small intestine and rumen) by the bacterial degradation of dietary tryptophan residues, the absorbed skatole being metabolized by hydroxylation, chiefly in position 6 (Horning & Dalgliesh, 1958; Horning *et al.* 1959; Parke, 1968; Yokoyama & Carlson, 1974). On the basis of studies of microsomal 6-hydroxylation in the liver tissues of man, rabbit, rat, mouse, frog, hamster and guinea-pig, which produce little or no 6-hydroxyskatole, it was suggested that the hydroxylation of skatole occurs chiefly in the gut rather than in the liver (Jaccarini & Jepson, 1968).

Frydman, Tomaro & Frydman (1971) isolated from wheat germ and rat liver a new enzyme, a pyrrolooxygenase. This oxidizes skatole efficiently to 2-formimidoacetophenone, which is subsequently hydrolysed by a formylase to 2-aminoacetophenone, and this in turn is transformed to 2-amino-3-hydroxyacetophenone, a known metabolic product present as its sulphate in human urine.

Skatole and its metabolic intermediates may be related to human pathological conditions, including malabsorption syndromes and certain anaemias (Horning & Dalgliesh, 1958) and hepatic coma (Lascelles & Taylor, 1968; Walshe, De Carli & Davidson, 1958). 6-Hydroxyskatole, the major metabolite of skatole in man, may be a psychotropic substance; it is excreted as the sulphate in elevated amounts in the urine of some schizophrenic patients (Reio, 1964; Sprince, 1969).

Insects. Skatole (0·001–0·1% in the diet) adversely affected larval growth and development and the subsequent reproductive capacity of the bollworm, *Heliothis zea* (Guerra, 1970). It is an attractant for the palm weevil *Rhynchophorus palmarum* (Hagley, 1965) and for Hippelates eye gnats (Hwang, Mulla & Axelrod, 1976).

Micro-organisms. Skatole has been shown to induce pleomorphism in *Escherichia coli* and *Proteus vulgaris* (Cavallo & D'Onofrio, 1955–56), to cause, at levels of 0·2–0·4 mg/ml, total inhibition of lateral growth by *Sclerotinia trifoliorum*, the clover rot fungus (Koivistoinen, Risser & Pohjakallio, 1959), to effect in 100 ppm concentration $\geqslant 75\%$ inhibition against the rubber-tree mouldy-rot fungus mycelium (Coles, Martin & Byrde, 1956), and to be toxic to rumen ciliate protozoa and to Tetrahymena, and bacteriostatic against Gram-negative enteric bacteria (Yokoyama & Carlson, 1974). It can also delay the spread of tuberculosis in guinea-pigs (Whitehead & Whitesitt, 1974). Injected im for 15 consecutive days to infected guinea-pigs weighing 200–300 g, 5 mg skatole/day exhibited tuberculostatic activity against *Mycobacterium tuberculosis hominis* (Kader *et al.* 1961). Sub-inhibitory concentrations of skatole had some synergistic effect on the activity of antibiotics against *Staphylococcus aureus* 209 but not against *Sarcina lutea* (Scherr & Bechtle, 1959).

Plants. Skatole acts as a plant hormone, showing auxinic effects in *Lens culinaris* roots (Collet & Pilet, 1965; Pilet, 1966; Pilet, Bonhote & Baillod, 1959) and affecting seed germination and growth of *Stellaria media* (Seiler-Kelbitsch, 1967) and *Hyptis suaveolens* (Bhargava & Sinha, 1967) as well as the growth of plant tissues *in vitro* (Bouriquet, 1963).

Haematology. Cows infused iv with skatole developed some haemolysis and haematuria (Carlson *et al.* 1972). The binding of skatole with modified bovine plasma albumin at the primary site was studied by Pande & McMenamy (1974). Skatole induced structural perturbations in bovine erythrocyte membranes, as measured by EPR spectroscopy, and a direct physical interaction of skatole with erythrocyte membranes was shown to result in structural changes of the erythrocyte ghosts (Bray, Sandberg & Carlson, 1975). Bray & Carlson (1974) demonstrated a sigmoidal relationship between the percentage haemolysis of bovine erythrocytes and duration of incubation with skatole, with 75% of the haemoglobin being released during the second 2 hr of incubation. At a sub-haemolytic concentration (500 μg/ml) skatole produced no significant effect on passive and active $^{22}Na^{+}$ transport in resealed bovine erythrocyte ghosts. After incubation for 1 hr, 100–500 μg/ml significantly increased the total and Mg^{2+}-dependent ATPase activities in the membranes of bovine erythrocytes (Bray & Carlson, 1974).

Cell biology. The uptake of glycine into Ehrlich ascites carcinoma cells, mouse melanoma, lymphoma and spleen cells was inhibited by 2–4 mM-skatole under anaerobic conditions (95% N_2, 5% CO_2) in the presence of 10 mM-glucose in a 1-hr incubation at 37°C (Johnstone & Quastel, 1961). Skatole (1 mg/3 ml reaction mixture) inhibited by 68% the destruction of the azo dye, 4-dimethylaminoazobenzene, by rat-liver homogenates (Clayton, 1958).

Enzymology. The strength of the inhibitory effect of skatole (I_{50} 3·4 mM) on the enzyme hydroxyindole-*o*-methyltransferase was attributed to the presence of the 3-alkyl group (Ho, McIsaac & Tansey, 1969). Concentrations of skatole between 0·025 and 0·1 M showed some (about 4–18%) inhibition of insulinase activity in rat-liver extracts containing insulin (Mirsky *et al.* 1957).

Physiology. The effect of skatole on lipid monolayers from bovine olfactory epithelium was determined in a study of the mechanism of olfactory reception (Koyama & Kurihara, 1972). Skatole was used to investigate the external chemoreceptors of fishes (Bardach, Fujiya & Holl, 1967).

Reptiles. Skatole attracts blind snakes, *Leptotyphlops dulcis*, and repels certain ophiophagous and insectivorous snakes (Watkins, Gehlbach & Kroll, 1969).

Inhalation. Male rats, mice and rhesus monkeys were continuously exposed for 90 days to the mixed vapours of indole (10·5 ppm), skatole (3·5 ppm), H_2S (20 ppm) and methyl mercaptan (50 ppm), the concentrations being the industrial threshold limit values (Sandage, 1961). Although there was no evidence of impairment of haematopoietic function, a low-grade haemolytic process appeared in all animals. Blood of rats and monkeys showed sulphaemoglobin formation to a certain degree, but ten times as much was present in the mice. Liver pathology was observed in 60% of the mice (possibly partly because of the particular strain used) and 75% of the mice showed lung pathology. Weight loss was significant only in the mice. Stress tests on rats showed a significant decrease in endurance. Death rates from toxic effects were lower than those predicted by reputable toxicological theory; eight of the ten monkeys used in this test died from obscure causes, whereas no rat deaths were attributable to the chemical environment. The number of mouse deaths in the exposed group was twice that in the control group.

There is a possible link between human pulmonary emphysema and various indole derivatives, including skatole, present in cigarette smoke (Carlson *et al.* 1972; Schmeltz, Stedman, Chamberlain & Stills, 1965).

Pharmacology. Skatole (10·0 mg dissolved in 2 ml sesame oil administered by gastric intubation) failed to prevent apoplexy in the adrenals of rats when administered 24 hr before injection of 5 mg of 7,12-dimethylbenz[*a*]anthracene (Huggins & Fukunishi, 1964).

In rat costal cartilage, skatole inhibited $^{35}SO_4^{2-}$-incorporation into chondroitin sulphate and ^{14}C-labelled proline incorporation into protein (Liberti & Rogers, 1970). In concentrations of 5–10 mM, it inhibited oxygen uptake in slices of rat liver and rat-brain cortex (Lascelles & Taylor, 1968; Walshe *et al.* 1958). Skatole has also shown depressant (catatonic-like) activity on the swimming behaviour of guppies and the exploratory behaviour of rats (Sprince, 1969). When injected ip, 1 mmol/kg did not have any radioprotective effect in mice, the survival effect (ratio of mean survival time in a treated group to that of the control in 30 days after irradiation) being 0·97 or 0·70 when skatole was administered 30 or 5 min, respectively, before X-irradiation with 800 R (Shinoda *et al.* 1974).

Skatole (1·0 mM) caused >50% inhibition of the anaphylactic release of histamine from chopped, sensitized guinea-pig lung by chymotrypsin substrates and inhibitors (Austen & Brocklehurst, 1961). It had a non-specific excitatory action on the heart of the marine mollusc *Venus mercenaria* (Greenberg, 1960) and in a 194 μM concentration produced half-maximal positive inotropic activity in isolated left guinea-pig atria (Zetler, 1974).

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STYRALLYL ALCOHOL

Synonyms: α-Methylbenzyl alcohol; methylphenyl carbinol.
Structure: $C_6H_5 \cdot CH(OH) \cdot CH_3$.
Description and physical properties: EOA Spec. no. 47.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By hydrogenation or reduction of acetophenone; or from methyl magnesium chloride plus benzaldehyde by a Grignard-type reaction (Bedoukian, 1967).
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to about 10,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·015	0·2
Maximum	0·2	0·02	0·07	0·8

Analytical data: Gas chromatogram, RIFM no. 72–225; infra-red curve, RIFM no. 72–225.

Status

Styrallyl alcohol was granted GRAS status by FEMA (1965), is approved by the FDA for food use (21 CFR 121.1164) and was included by the Council of Europe (1970) in the list of temporarily admissible artificial flavouring substances. The *Food Chemicals Codex* (1972) has a monograph on styrallyl alcohol.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 400 mg/kg (Smyth & Carpenter, 1944). The acute dermal LD_{50} value in rabbits exceeded 2·5 g/kg (Moreno, 1973).

Irritation. Styrallyl alcohol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1973). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1973).

Metabolism. Styrallyl alcohol is converted in rabbits into hippuric acid and methylphenylcarbinyl glucuronide, both optical forms of the carbinol behaving similarly. A small proportion (1–2%) is excreted as mandelic acid (Williams, 1959).

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TANSY OIL

Description and physical properties: EOA Spec. no. 117. The principal constituents of tansy oil are thujone, camphor and borneol (Guenther, 1952; Poucher, 1974). The composition of tansy oil from the leaves and flowers of *Tanacetum vulgare* varies widely, apparently depending on botanical strain and geographical location, but the average content of thujones (α- or *l*-thujone and β- or *d*-isothujone) is approximately 50%.

Occurrence: Found in the plant *T. vulgare* L. (Fam. Compositae).

Preparation: By steam distillation of the whole *T. vulgare* plant (Gildemeister & Hoffman, 1961).

Uses: In public use before the 1900s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·015	0·12
Maximum	0·1	0·01	0·03	0·4

Analytical data: Gas chromatogram, RIFM no. 74-117; infra-red curve, RIFM no. 74-117.

Status

The Council of Europe (1974) included tansy oil in the list of currently used flavouring substances for which the toxicological and technological data are deemed insufficient; their use is temporarily admitted possibly with a limitation on the active principle in the final product. Because of its thujone content, use of tansy (*T. vulgare*) as a flavouring substance is limited in the USA to alcoholic beverages, which in their finished form must be thujone-free (21 CFR 121.1163).

Biological data

Toxicity. The acute oral LD_{50} value in rats was reported as 1·15 g/kg (0·58–1·72 g/kg) and the acute dermal LD_{50} value in rabbits as >5 g/kg (Moreno, 1974). In mice, the LD_{50} of essential oils, including tansy oil, was 3–5 mg; no conjunctivitis was produced by a 1% emulsion of tansy oil given as eye drops daily for 1 wk (Rotmistrov, Gendenshtein & Matveenko, 1957).

When tested on dogs with intestinal helminths, β-thujone, oleum tanaceti and an ether extract of the oil were found to have toxic doses of 0·25, 0·30 and 0·35 g/kg respectively; the ratio of toxic dose to therapeutic dose was 2·5:1, but when administered in increasing amounts, doses twice as large could be tolerated (Ionescu, Anitescu, Lungu & Stoican, 1958).

Solvent extracts of tansy leaves, flowers and stems increased bile flow in dogs with a permanent fistula of the gall bladder, the extract with 70° alcohol being most effective (Saratikov, Solov'eva & Gorel'nikova, 1963). These authors suggested that the choleretic activity of tansy extracts might be attributable to caffeic acid, a known bile stimulant reported by Ignat'eva (1960) to be present in tansy. A strong choleretic effect without toxic effects was observed when patients with liver and gall-bladder disease received half a teaspoon of alcoholic tansy extract three times daily for 7–30 days (Saratikov *et al.* 1963).

Oral doses of 0·7 ml tansy extract/kg/day for 10 days had no effect on the haemoglobin, erythrocytes, leucocytes or reticulocytes of rabbits and iv injection of 0·3–0·6 ml/kg) did not affect respiration or arterial blood pressure in anaesthetized cats (Saratikov *et al.* 1963). At concentrations of 1:500–1:50, tansy extracts decreased the tonus of isolated rabbit intestine (Saratikov *et al.* 1963). An extract of *T. vulgare* was found to stimulate intestinal secretion in dogs, acting immediately in healthy dogs but only after 12 hr in dogs infested with ascarides (Karamysheva, 1959).

The effect of an alcoholic extract of *T. vulgare* on liver metabolism was studied in rabbits with CCl_4-induced hepatitis, the effect being more pronounced in these than in intact animals. Daily intragastric doses of 0·3–0·5 ml diluted extract/kg for 10 days decreased serum lipids and inhibited further development of hypercholesterolaemia. Twice-daily doses for 10 days inhibited recovery of the blood-sugar level, caused a stable increase in albumins and decreased γ-globulins (Kazantseva, 1966). Aqueous and ethanolic extracts of *T. vulgare* showed some *in vitro* and *in vivo* antitumour activity and inhibited germination of seeds of *Lepidum sativum* (Konopa, Jereczek, Matuszkiewicz & Nazarewicz, 1967).

Tansy oil, like other essential oils containing large amounts of thujone, is a poison which causes convulsions and epileptic-like attacks (Tucakov, 1960). Signs of Tanacetum poisoning, due to thujone, include vomiting, gastro-enteritis, flushing, cramps, loss of consciousness, rapid breathing, irregular heartbeat, rigid pupils, uterine bleeding and hepatitis. Death results from circulatory and respiratory arrest and degenerative organ changes. Most fatalities result from ingestion of tansy oil, but fatal cases of poisoning with infusions and powders have also been reported (Jaspersen-Schib, 1969).

Irritation. Undiluted tansy oil was not irritating when applied to the backs of hairless mice and swine (Urbach & Forbes, 1974), but was slightly irritating when applied to intact or abraded rabbit skin for 24 hr under occlusion (Moreno, 1974). Tested at 4% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1974).

Phototoxicity. No phototoxic effects were reported for undiluted tansy oil on hairless mice and swine (Urbach & Forbes, 1974).

Skin. In studies on the intact shaved abdominal skin of mice, percutaneous absorption of tansy oil was rapid (38 min) (Meyer & Meyer, 1959). In an evaluation of skin-penetrating agents, oleum tanaceti aided slightly in the deep penetration of Rhodamine B into the corium and subcutis of guinea-pig skin (Meyer, 1965).

A severe case of eczematous dermatitis caused by *T. vulgare* plants, including a similar reaction to ingestion of an extract intended for desensitization, was reported by Greenhouse & Sulzberger (1933). One of six dermatitis patients who had been exposed to wood products or vegetation, showed a positive patch test to tansy oleoresin (Tan & Mitchell, 1968). Oleoresin from tansy also caused dermatitis in closed-patch tests in three out of six patients with suspected plant sensitivity (Bergh, 1975).

The possible role of sesquiterpene lactones in allergic eczematous contact dermatitis has been studied by Mitchell and co-workers (Mitchell & Dupuis, 1971). Two patients allergic to Compositae species showed no primary irritant reaction to an acetone extract of *Chrysanthemum tanacetum* (*T. vulgare*) or to the lactone parthenolide derived from *C. tanacetum*, but showed moderately strong patch test reactions (allergic contact dermatitis) to the tansy extract and strong reactions to parthenolide (Mitchell, Geissman, Dupuis & Towers, 1971).

Helminths. In dogs with intestinal helminths, *T. vulgare* preparations (β-thujone and tansy oil and its ether extracts) were 70–100% effective against adult ascarides (roundworms) but only 30–42% effective against Ancylostoma (hookworm), Trichuris (whipworms) and immature ascarides (Ionescu *et al.* 1958). In *in vitro* tests, *T. vulgare* extract acted as a strong convulsant, killing helminths in 24–72 hr (Karamysheva, 1959).

Micro-organisms. Tansy oil exhibited *in vitro* antifungal activity against all of 15 pathogenic and non-pathogenic fungi (Maruzzella & Liguori, 1958) and against 11 of 12 phytopathogenic fungi (Maruzzella & Balter, 1959) tested by the filter-paper-disc method, but was inactive against three wood-destroying fungi (Maruzzella, Scrandis, Scrandis & Grabon, 1960). The vapour of tansy oil strongly inhibited *in vitro* growth of *Mycobacterium avium*, but was inactive against three other bacteria (Maruzzella & Sicurella, 1960). *T. vulgare* plant material inhibited only slightly the development of *Bacillus larvae* (Haragsimova, 1963). Tansy oil was toxic to Infusoria at 500 ppm (Rotvistrov *et al.* 1957).

Medicinal and veterinary use. The essential oil of Tanacetum is a vermifuge (because of its thujone content), emmenagogue and abortifacient (Tucakov, 1960). Preparations (powders, tinctures and infusions) from Tanacetum leaves or flowers are folk medicines, used chiefly as anthelmintics and abortives and in the treatment of diarrhoea. Because of the wide variation in thujone content in various strains of *T. vulgare*, one ordinary dose of Tanacetum preparations may contain toxic amounts of thujone (1–167 mg for the samples tested, mostly as *d*-isothujone), and the dispensing of Tanacetum drugs should therefore be severely regulated (Jaspersen-Schib, 1969). Aqueous infusions and alcoholic extracts of tansy have been shown clinically to be effective bile stimulants in diseases of the liver and gall bladder. Treatment with half a teaspoon of alcoholic extract of tansy three times daily for 7–30 days produced a strong choleretic effect in patients with liver and gall-bladder disease. The treatment also alleviated pain and increased appetite and digestion. The extract was well tolerated and non-toxic, as confirmed by special studies on the functional state of the liver (Saratikov *et al.* 1963).

Addition of an aqueous extract of tansy to a remedy prepared from juniper berries, fenugreek seed, cinnamon, aqueous extract of sedum, St. John's wort flower, extract of bitter orange rind and hydrated ferric oxide was claimed to enhance the therapeutic action of the composition on fibromas (Soliman, 1973).

When administered to dogs with intestinal helminths, β-thujone, tansy oil and an ether extract of the oil were found to exert a therapeutic effect at doses of 0·10, 0·12 and 0·15 g/kg, respectively. The anthelmintic efficiencies against mature ascarides were 85–100 80–95 and 70–80%, respectively, and the ratio of toxic to therapeutic dose was 2·5:1. *T. vulgare* preparations should be administered with castor oil (Ionescu *et al.* 1958).

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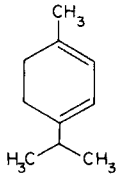
α-TERPINENE

Synonyms: 1-Methyl-4-isopropylcyclohexadiene-1,3; *p*-menthadiene-1,3.
Structure:



Description and physical properties: *Merck Index* (1968).
Occurrence: Reported to be found in cardamom essential oil; also found in orange, coriander, wormseed, *Eucalyptus australiana* and in approximately 20 additional essential oils (*Fenaroli's Handbook of Flavor Ingredients*, 1975).
Preparation: From acid isomerization of terpinolene.
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to less than 1000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·015	0·15
Maximum	0·2	0·02	0·20	0·50

Analytical data: Gas chromatogram, RIFM no. 72-227; infra-red curve, RIFM no. 72-227.

Status

α-Terpinene is approved by the FDA for food use (21 CFR 121.1164).

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 1·68 g/kg (1·46–1·90 g/kg) (Moreno, 1973). Because of its action as a liver poison and methaemoglobin former, α-terpinene should be used very sparingly, or not at all, in foods (Bär & Griepentrog, 1967).

Irritation. α-Terpinene tested at 5% in petrolatum produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 5% in petrolatum and produced no sensitization reactions (Kligman, 1973).

Pharmacology. Combinations of terpenes, such as terpinene, with nonionic surfactants and stabilizers have been patented for use as gallstone solvents. Artificial or human cholesterol calculi placed in terpinene with or without human bile at 37°C were dissolved within 1–2 hr (Hisamitsu Pharmaceutical Co., Inc., 1973).

Micro-organisms. α-Terpinene inhibited the growth of nine bacteria, and may be partially responsible for the antibacterial effect of some essential oils used for room disinfection (Kellner & Kober, 1955 & 1956). It inhibited the growth of the fungal root pathogens *Phytophthora cinnamomi* and *Fomes annosus* (Krupa & Nylund, 1972).

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Krupa, S. & Nylund, J.-E. (1972). Studies on ectomycorrhizae of pine. III. Growth inhibition of two root pathogenic fungi by volatile organic constituents of ectomycorrhizal root systems of Pinus sylvestris L. *Eur. J. Forest Pathol.* **2** (2), 88.
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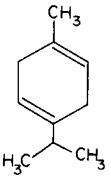
γ-TERPINENE

Synonyms: 1-Methyl-4-isopropylcyclohexadiene-1,4; *p*-menthadiene-1,4.
Structure:



Description and physical properties: *Merck Index* (1968).
Occurrence: Found in oils of coriander, lemon, cumin, *Ocimum viride*, ajowan, thyme, *Eucalyptus dives*, *Crithmum maritimum* (oil of samphire or seafennel) and *Mosla japonica* (Guenther, 1949).
Preparation: From *p*-cymene with sodium and alcohol in liquid ammonia, or by any other suitable means.
Uses: In public use since the 1950s. Use in fragrances in the USA amounts to less than 1000 lb/yr. Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·015	0·15
Maximum	0·2	0·02	0·02	0·50

Analytical data: Gas chromatogram, RIFM no. 72-228; infra-red curve, RIFM no. 72-228.

Status

γ-Terpinene is approved by the FDA for food use (21 CFR 121.1164).

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 3·65 g/kg (2·71–4·59 g/kg) and the acute dermal LD_{50} in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. γ-Terpinene applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1973). Tested at 5% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 5% in petrolatum and produced no sensitization reactions (Kligman, 1973). In skin tests of 20 persons allergic to turpentine, γ-terpinene produced only one positive reaction (Michailov, Berowa and Zuzulowa, 1970). Woeber & Krombach (1969) reported that it was not a sensitizer for human skin.

Pharmacology. Combinations of terpenes, such as terpinene, with nonionic surfactants and stabilizers have been patented for use as gallstone solvents. Artificial or human cholesterol calculi placed in terpinene with or without human bile at 37°C were dissolved within 1–2 hr (Hisamitsu Pharmaceutical Co., Inc., 1973).

Micro-organisms. γ-Terpinene inhibited the growth of the fungal root pathogens *Phytophthora cinnamomi* and *Fomes annosus* (Krupa & Nylund, 1972).

References

Guenther, E. (1949). *The Essential Oils.* Vol. II, p. 40. D. Van Nostrand, Inc., Princeton, New Jersey.

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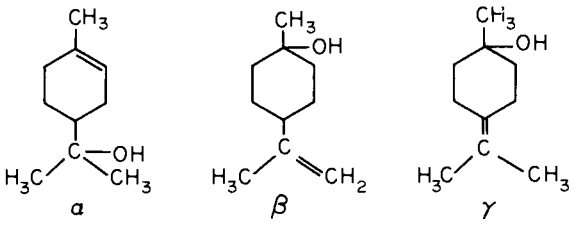
TERPINEOL

Synonym: Mixture of *p*-menthenols.
Structure: May be a mixture of α, β and γ isomers.



Description and physical properties: EOA Spec. no. 8.
Occurrence: Reported to be found in more than 200 derivatives from leaves, herbs and flowers (*Fenaroli's Handbook of Flavor Ingredients*, 1971; Gildemeister & Hoffman, 1962).
Preparation: From terpin hydrate by the splitting off of the elements of water by chemical means (Bedoukian, 1967).
Uses: In public use since the 1890s. Use in fragrances in the USA amounts to about 1 million lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·05	0·005	0·02	0·4
Maximum	0·60	0·1	0·2	3·0

Analytical data: Gas chromatogram, RIFM no. 70–18; infra-red curve, RIFM no. 70–18.

Status

Terpineol was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). It was listed by the Council of Europe (1970) with an ADI of 1 mg/kg, and is the subject of a *Food Chemicals Codex* (1972) monograph.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 4·3 g/kg (2·9–5·7 g/kg) (Moreno, 1971). The acute dermal LD_{50} in rabbits was reported as >3 g/kg (Moreno, 1971).

Irritation. Terpineol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1971).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 12% in petrolatum and produced no sensitization reactions (Greif, 1967).

Percutaneous absorption. Terpineol was rapidly absorbed through the intact shaved abdominal skin of the mouse (Meyer & Meyer, 1959).

Antimicrobial activity. Terpineol has been reported to have antimicrobial properties (Dabbah, Edwards & Moats, 1970).

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TERPINOLENE

Synonyms: *p*-Mentha-1,4(8)-diene; *p*-mentha-2,4(8)-diene.
Structure: $CH_3 \cdot C(CH_3):C_6H_7 \cdot CH_3$.
Description and physical properties: Colourless or pale straw-coloured liquid.
Occurrence: Reported to be found as a minor constituent of a few essential oils, notably *Manilla elemi*, a few pine and fir varieties, *Nectandra elaiophora*, *Dacrydium colensoi* and a few others (*Fenaroli's Handbook of Flavor Ingredients*, 1975).
Preparation: By alcoholic sulphuric acid treatment of pinene (Arctander, 1969).
Uses: In public use since the 1930s. Use in fragrances in the USA exceeds 50,000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·12
Maximum	0·4	0·04	0·1	0·5

Analytical data: Gas chromatogram, RIFM no. 75-132; infra-red curve, RIFM no. 75-132.

Status

Terpinolene was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included it in the list of artificial flavouring substances that may be added temporarily to foodstuffs without hazard to public health.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 4·39 ml/kg (Levenstein, 1975) and similarly that in mice and rats was reported to be 4·4 ml/kg (Hisamitsu Pharmaceutical Co., Inc., 1973). The acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Levenstein, 1975).

Irritation. Terpinolene applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Levenstein, 1975). Tested at 20% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1975).

Skin. Applied to rat skin, it did not induce storage of iv administered Indian ink (Gözsy & Kato, 1958).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 24 volunteers. The material was tested at a concentration of 20% in petrolatum and produced no sensitization reactions (Epstein, 1975). Terpinolene was found not to be a sensitizer for human skin (Woeber & Krombach, 1969).

Pharmacology. Combinations of terpenes, such as terpinolene, with nonionic surfactants and stabilizers have been patented for use as gallstone solvents. Human cholesterol calculi heated in mixtures containing terpinolene and human bile were dissolved within 1–2 hr (Hisamitsu Pharmaceutical Co., Inc., 1973).

Insects. Terpinolene was found to be the major component of the cephalic secretion of the Australian termite *Amitermes herbertensis*, and was presumed to be a pheromone (Moore, 1968). It attracted the bark beetle *Dendroctonus ponderosae* when used with *trans*-verbenol (Billings, Gara & Hrutfiord, 1976).

Micro-organisms. Terpinolene inhibited the microbial activity of sheep rumen and slightly stimulated that of deer rumen (Oh, Sakai, Jones & Longhurst, 1967). It did not show antimicrobial activity against *Staphylococcus aureus* (Stepanov & Komarova, 1972). The antibacterial activity of the terpene fraction of Enteromorpha seaweed was attributed, at least partially, to volatile components, which included terpinolene (Katayama, 1956–57).

Terpinolene showed no antibacterial activity *in vitro* against tubercle bacilli when tested at 100 μg/ml, and no therapeutic activity against tuberculosis in guinea-pigs receiving daily sub-effective doses of dihydrostreptomycin, when given im in weekly 10-mg doses (Kato & Gözsy, 1958). The vapour inhibited the growth of two mycorrhizal fungi (Melin & Krupa, 1971), two fungal root pathogens (Krupa & Nylund, 1972), three wood-inhabiting fungi (De Groot, 1972) and the root fungus *Fomitopsis annosa* (Fedorov, Staichenko & Manukov, 1973). In a 1:10,000 dilution, terpinolene stimulated to a moderate degree the germination of uredospores of the wheat stem rust organism *Puccinia graminis* (French, 1961).

A preparation containing 50–80% terpinolene, when sprayed into the atmosphere and onto surfaces, inactivated foot and mouth virus of cattle within 10 min at room temperature and retained its antiviral activity for long periods of time (Bellet, 1965).

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Woeber, K. & Krombach, M. (1969). Zur Frage der Sensibilisierung durch ätherische Öle (Vorläufige Mitteilung). *Berufsdermatosen* **17.** 320.

TERPINYL ACETATE

Synonym: Mixture of *p*-menthenyl acetates.

Structure: May be a mixture of α, β and γ isomers of $C_{10}H_{17} \cdot OCO \cdot CH_3$ (for the structure of the corresponding isomers of terpineol, $C_{10}H_{17} \cdot OH$, see monograph thereon).

Description and physical properties: EOA Spec. no. 9.

Occurrence: Reported in over 40 essential oils, including cypress, Malabar cardamom, cajeput, niaouli, Siberian pine needles, pine, *Melaleuca trichostachya*, *Melaleuca pauciflora* and others; also identified in the essential oils of bitter orange (*Fenaroli's Handbook of Flavor Ingredients*, 1971; Gildemeister & Hoffman, 1966).

Preparation: By acetylation of α-terpineol or mixed isomeric terpineols (Bedoukian, 1967).

Uses: In public use before the 1920s. Use in fragrances in the USA amounts to approximately 1 million lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·04	0·004	0·015	0·5
Maximum	0·3	0·03	0·1	0·5

Analytical data: Gas chromatogram, RIFM no. UC–70; infra-red curve, RIFM no. UC–70.

Status

Terpinyl acetate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). It was listed by the Council of Europe (1970), with an ADI of 1 mg/kg, and is the subject of a *Food Chemicals Codex* (1972) monograph.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 5·075 g/kg (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964).

Chronic toxicity. In feeding studies, up to 10,000 ppm fed to rats in the diet for 20 wk produced no macroscopic effect (Hagan, Hansen, Fitzhugh, Jenner, Jones, Taylor, Long, Nelson & Brouwer, 1967).

Irritation. Terpinyl acetate tested at 5% in petrolatum produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1971).

Sensitization. A maximization test (Kligman, 1966) was carried out on 26 volunteers. The material was tested at a concentration of 5% in petrolatum and produced no sensitization reactions (Kligman, 1971).

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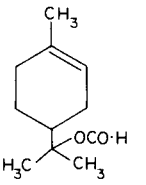
Kligman, A. M. (1971). Report to RIFM, 20 April.

TERPINYL FORMATE

Synonym: *p*-Menth-1-en-8-yl formate.
Structure:



(usually a mixture of isomers)

Description and physical properties: A colourless liquid.
Occurrence: Probably occurs in Ceylon cardamom oil (*Fenaroli's Handbook of Flavor Ingredients*, 1975).
Preparation: By cold formylation of terpineol, using formic-acetic anhydride (Arctander, 1969).
Uses: In public use before the 1920s. Use in fragrances in the USA amounts to approximately 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·2
Maximum	0·2	0·02	0·06	1·0

Analytical data: Gas chromatogram, RIFM no. 75-133; infra-red curve, RIFM no. 75-133.

Status

Terpinyl formate was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) listed terpinyl formate giving an ADI of 1 mg/kg.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1976).

Irritation. Terpinyl formate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1976). Tested at 2% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 21 volunteers. The material was tested at a concentration of 2% in petrolatum and produced no sensitizativon reactions (Epstein, 1975).

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Kligman, A. M. & Epstein, W. (1975). Updating the maximization test for identifying contact allergens. *Contact Dermatitis* **1**, 231.

Moreno, O. M. (1976). Report to RIFM, 5 January.

TERPINYL PROPIONATE

Synonym: *p*-Menthanyl propionate (mixed isomers).

Structure: $C_{10}H_{17} \cdot OCO \cdot CH_2 \cdot CH_3$ (for the structure of the α, β and γ isomers of terpineol, $C_{10}H_{17} \cdot OH$, see monograph thereon).

Description and physical properties: EOA Spec. no. 233.

Occurrence: Reported to be found in citrus fruits and celery (*Fenaroli's Handbook of Flavor Ingredients*, 1971).

Preparation: By esterification of terpineols.

Uses: In public use before the 1920s. Use in fragrances in the USA amounts to about 10,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·01	0·2
Maximum	0·2	0·02	0·05	0·4

Analytical data: Gas chromatogram, RIFM no. 71–78; infra-red curve, RIFM no. 71–78.

Status

Terpinyl propionate was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). It was included by the Council of Europe (1970) in the list of admissible artificial flavouring substances at a level of 10 ppm. The *Food Chemicals Codex* (1972) has a monograph on terpinyl propionate.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. Terpinyl propionate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was slightly irritating (Moreno, 1973). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 27 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Epstein, 1973).

References

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Food Chemicals Codex (1972). 2nd ed. Prepared by the Committee on Specifications, Food Chemicals Codex, of the Committee on Food Protection. p. 814. National Academy of Sciences–National Research Council Publ. 1406, Washington, D.C.

Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.

Moreno, O. M. (1973). Report to RIFM, 12 November.

TETRAHYDROMUGUOL

Synonym: Tetrahydro allo-ocimenol.
Structure: A mixture of 2,6-dimethyl-2-octanol, 3,7-dimethyl-3-octanol and dihydro-α-terpineol.
Description and physical properties: A colourless liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: From allo-ocimene, via allo-ocimenol followed by hydrogenation (Arctander, 1969).
Uses: Use in fragrances in the USA amounts to approximately 35,000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·015	0·2
Maximum	0·2	0·02	0·05	0·4

Analytical data: Gas chromatogram, RIFM no. 74-245; infra-red curve, RIFM no. 74-245.

Status

Tetrahydromuguol is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974) or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Wohl, 1974).

Irritation. Tetrahydromuguol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Wohl, 1974). Tested at 4% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 24 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Epstein, 1974).

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Council of Europe (1974). Natural Flavouring Substances, Their Sources, and Added Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. Strasbourg.

Epstein, W. L. (1974). Report to RIFM, 27 August.

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Kligman, A. M. & Epstein, W. (1975). Updating the maximization test for identifying contact allergens. *Contact Dermatitis* **1**, 231.

Wohl, A. J. (1974). Report to RIFM, 19 August.

TETRAHYDROMUGYL ACETATE

Structure: A mixture of 2,6-dimethyl-2-octanyl acetate, 3,7-dimethyl-3-octanyl acetate and dihydro-α-terpinyl acetate.
Description and physical properties: A colourless oily liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By acetylation of tetrahydromuguol (Arctander, 1969).
Uses: Use in fragrances in the USA amounts to less than 1000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·015	0·3
Maximum	0·2	0·02	0·06	0·4

Analytical data: Gas chromatogram, RIFM no. 74-246; infra-red curve, RIFM no. 74-246.

Status

Tetrahydromugyl acetate is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974) or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Wohl, 1974).

Irritation. Tetrahydromugyl acetate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Wohl, 1974). Tested at 4% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 22 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Epstein, 1974).

References

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Wohl, A. J. (1974). Report to RIFM, 19 August.

THYME OIL, RED

Synonym: Spanish thyme oil.

Description and physical properties: *Food Chemicals Codex* (1972). The main constituents of thyme oil are thymol and carvacrol (*Fenaroli's Handbook of Flavor Ingredients*, 1971; Gildemeister & Hoffman, 1961; Guenther, 1949).

Occurrence: Found in the plants *Thymus vulgaris* L. and *Thymus zygis* L. (Fam. Labiatae) (Guenther, 1949).

Preparation: By water and steam distillation of the partially dried plants *Thymus vulgaris* L. and *Thymus zygis* L. (Gildemeister & Hoffman, 1961).

Uses: In public use since the early 1800s. Use in fragrances in the USA amounts to less than 7000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·0005	0·002	0·05
Maximum	0·1	0·01	0·02	0·8

Analytical data: Gas chromatogram, RIFM no. 72–229; infra-red curve, RIFM no. 72–229.

Status

Thyme oil red was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) included thyme oil, red in the list of substances, spices and seasonings deemed admissible for use, with a possible limitation of the active principle in the final product. The *Food Chemicals Codex* (1972) has a monograph on thyme oil.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 4·70 g/kg (3·75–5·67 g/kg) (Moreno, 1973). The acute dermal LD_{50} value in rabbits was reported as >5 g/kg (Moreno, 1973).

Irritation. Undiluted thyme oil, red applied to the backs of hairless mice was severely irritating (Urbach & Forbes, 1973). Applied full strength to intact or abraded rabbit skin for 24 hr under occlusion, it was again severely irritating (Moreno, 1973). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1973).

Phototoxicity. No phototoxic effects were reported for thyme oil, red (Urbach & Forbes, 1973).

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BALSAM TOLU

Description and physical properties: *Merck Index* (1968). Balsam tolu contains approximately 80% resin, together with benzoic and cinnamic acids, benzyl benzoate, benzyl cinnamate, vanillin and a small amount of volatile oil (Poucher, 1974). It contains 12–15% free cinnamic and benzoic acids, about 40% benzyl and other esters of these acids, including 5–13% cinnamein, and 1·5–3% volatile oil (*Merck Index*, 1968; Wahlberg, Hjelte, Karlsson & Enzell, 1971). A commercial sample of balsam tolu was found by gas-liquid chromatography to contain 7·8% benzoic acid, 11·0% cinnamic acid, 11·4% benzyl benzoate and a trace of benzyl cinnamate. Measurable amounts of benzyl cinnamate occur in museum samples (Harkiss & Linley, 1973a,b).

The hexane-soluble part (32%) of an ethanolic solution of commercial balsam tolu, accounting for most of the aroma, was separated into three fractions containing the strong acids cinnamic acid and benzoic acid (12%), a complex mixture of weak acids (2·4%), including eugenol and vanillin, benzyl ferulate or isoferulate and triterpene acids, and a neutral fraction (17%). The neutral fraction was separated into a hydrocarbon fraction (1·6%) containing a number of unsaturated sesquiterpenes and other hydrocarbons, a minor fraction (0·06%) of polar hydrocarbons, and a major fraction (15·4%) of oxygenated compounds including benzaldehyde, cinnamaldehyde, and related alcohols and esters (Wahlberg *et al.* 1971).

Occurrence: In the tree of *Myroxylon balsamum*, also known as *M. toluiferum* L. Harms (Fam. Leguminosae) (Guenther, 1952).

Preparation: By the tapping of the tree, *M. balsamum* L. Harms (Guenther, 1952).

Uses: In public use before the 1800s. Use in fragrances in the USA amounts to approximately 20,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·1
Maximum	0·1	0·01	0·03	0·2

Analytical data: Infra-red curve, RIFM no. 71-81.

Status

Balsam tolu was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1163). The Council of Europe (1974) included balsam tolu in the list of substances, spices and seasonings deemed admissible for use with a possible limitation of the active principle in the final product. The *United States Pharmacopeia* (1965) has a monograph on balsam tolu.

Biological data

Acute toxicity. Both the acute oral LD_{50} in rats and the acute dermal LD_{50} in rabbits exceeded 5 g/kg (Hart, 1971).

Inhalation. Steam inhalation of Friar's balsam, a long-used drug mixture which includes tolu balsam, had no effect upon the volume, specific gravity, total solids or insoluble mucus of respiratory-tract fluid produced by rabbits until the doses inhaled were more than 1000 times the therapeutic dose recommended for croup. These large doses were toxic and produced an acute inflammation of the tracheal mucosa, an increase in the output of respiratory-tract fluid due to the large amount of inhaled alcohol, and an increase in the specific gravity of the fluid due to the large amounts of benzoin, storax, tolu balsam (which was also tested separately as a 4% tincture) and aloe (Boyd & Sheppard, 1966).

Irritation. Balsam tolu applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was mildly irritating (Hart, 1971). Tested at 2% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1971).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 2% in petrolatum and produced no sensitization reactions (Kligman, 1971). Balsam tolu applied full strength for 48 hr in the standard occluded aluminium-patch test used by the North American Contact Dermatitis Research Group (NACDRG) did not produce any irritation or sensitization in a 62-yr-old subject with a perfume dermatitis (Larsen, 1975). The standard aluminium-patch test was designed by the International Contact Dermatitis Research Group to standardize testing for contact dermatitis worldwide and is described extensively by Malten, Nater & van Ketel (1976).

In patch tests of preparations of brittle balsam tolu carried out on 67 patients allergic to Peru balsam (Hjorth, 1961), positive reactions were obtained in 21% with 5% powdered balsam tolu in vaseline (34 tests), in 100% with Vernix tolutanum Ph.D (three tests), in 50% with 10% balsam

tolu in alcohol (ten tests) and in 73% with 1% balsam tolu in alcohol (27 tests). Sensitivity to balsam tolu was frequent among patients sensitive to Peru balsam, which also contains coniferyl alcohol esters of benzoic and cinnamic acids. Positive reactions were frequent with alcoholic solutions, but rare with powdered balsam in vaseline. Sensitivity to balsam tolu was always accompanied by sensitivity to coniferyl benzoate and also to benzoin or Peru balsam (Hjorth, 1961).

Metabolism. The absorption and excretion of balsams such as balsam tolu has been reviewed by LeNouene (1966). Benzoic and cinnamic acids, which are major components of balsam tolu, are excreted in the urine, chiefly as hippuric acid.

Micro-organisms. In tests using the filter-paper-disc method, tolu balsam oil inhibited the *in vitro* growth of nine out of ten pathogenic and non-pathogenic Gram-positive and Gram-negative bacteria (Maruzzella & Lichtenstein, 1956) and all of 15 pathogenic and nonpathogenic fungi (Maruzzella & Liguori, 1958).

Medical and veterinary use. Balsam tolu has been used as a weak expectorant for man (0·6–2 g orally or by inhalation) and for dogs (2–8 ml). Friar's balsam, a mixture that includes balsam tolu, is used as an expectorant and also externally as a skin protective; for animals it has been used orally for chronic bronchitis and externally as a wound antiseptic and styptic (*Merck Index*, 1968).

Percutaneous absorption. Tolu balsam oil was not absorbed through the intact skin of mice (Meyer & Meyer, 1959) or guinea-pigs (Meyer, 1965).

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TOLUALDEHYDE

Synonyms: Tolyl aldehyde, o.m.p.; methylbenzaldehyde.
Structure: $CH_3 \cdot C_6H_4 \cdot CHO$ (a mixture of *o*-, *m*- and *p*-methylbenzaldehydes).
Description and physical properties: *Givaudan Index* (1961).
Occurrence: Reported to be found in roasted nuts (*Fenaroli's Handbook of Flavor Ingredients*, 1975).
Preparation: By oxidation of *o*-, *m*- or *p*-xylene (*Fenaroli's Handbook of Flavor Ingredients*, 1975).
Uses: In public use since the 1940s. Use in fragrances in the USA amounts to approximately 3000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·08
Maximum	0·75	0·075	0·25	0·4

Analytical data: Gas chromatogram, RIFM no. 73-37; infra-red curve, RIFM no. 73-37.

Status

Tolualdehyde was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included it at a level of 55 ppm (except for chewing gum) in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 2·25 g/kg (1·93–2·57 g/kg) and the acute dermal LD_{50} value exceeded 2·5 g/kg (Moreno, 1973).

Subacute toxicity. In a 12-wk feeding study in rats the no-effect-level was reported to be 36·1 mg/kg (Bär & Griepentrog, 1967). Administration of tolualdehyde to rats in the daily diet for 90 days at levels providing intakes of 36 and 43 mg/kg/day in males and females, respectively (at least 100 times the maximum estimated human dietary level) produced no adverse effects on growth, food consumption, haematology, blood chemistry, liver and kidney weights or the gross and microscopic appearance of major organs (Oser, Carson & Oser, 1965).

Daily oral administration of mixed *m*- and *p*-tolualdehyde in doses of 50, 250 or 500 mg/kg body weight to rats for up to 13 wk produced no adverse effects on body-weight gain, food and water consumption, haematology, serum analyses, renal concentration tests, urinary cell excretion or histopathology of numerous organs (Brantom, Gaunt, Grasso, Lansdown & Gangolli, 1972). The only effect attributed to tolualdehyde was a decrease in relative pituitary weight, without any associated histopathological abnormality, in female rats receiving 500 mg/kg/day for 6 or 13 wk. The no-untoward-effect level was considered to be 250 mg/kg/day, an amount 1250 times greater than the maximum likely intake in man.

Irritation. Tolualdehyde applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1973). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Kligman, 1973).

Metabolism. Aromatic aldehydes are oxidized *in vivo* almost entirely to the corresponding acid. Thus, in rabbits, *p*-tolualdehyde is converted to *p*-toluic acid which has been detected in the urine as the ester glucuronide (Williams, 1959). *p*-Tolualdehyde was oxidized to *p*-toluic acid by resting cells of *Pseudomonas aeruginosa* (Omori & Yamada, 1970). Perillaldehyde dehydrogenase, isolated from a soil pseudomonad, catalysed the oxidation of *m*- and *p*-tolualdehyde but not of *o*-tolualdehyde (Ballal, Bhattacharyya & Rangachari, 1967). The reduction of *p*-tolualdehyde by NADH was catalysed by horse-liver alcohol dehydrogenase (Blomquist, 1966) and by yeast alcohol dehydrogenase at pH 8·5-9·5 (Klinman, 1975). A non-specific NADPH-linked aldehyde reductase isolated from various areas of bovine brain also catalysed the reduction of *p*-tolualdehyde (Tabakoff & Erwin, 1970).

Micro-organisms. Tolualdehyde in a 1:500 dilution did not inhibit the *in vitro* growth of four Gram-positive and Gram-negative bacteria (Maruzzella and Bramnick, 1961). The bactericidal ac-

tivity of *o*- and *p*-tolualdehyde and other substituted benzaldehydes probably involves condensation of the formyl group with amino groups in the bacterial cell wall (Burton, Clarke & Gray, 1964).

Enzymes. Bovine liver glutamic dehydrogenase was inactivated by 1·25 mM-*p*-tolualdehyde (Anderson, Anderson & Churchich, 1966).

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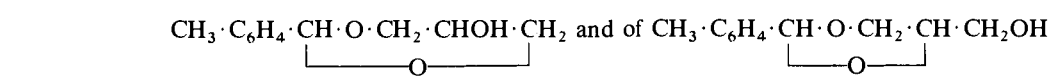
TOLUALDEHYDE GLYCERYL ACETAL*

Synonyms: Mixed *o*-, *m*- and *p*-isomers of 2-(methylphenyl)-1,3-dioxan-5-ol; tolylaldehyde glyceryl acetal.

Structure: Mixed isomers of



Description and physical properties: A colourless slightly viscous liquid.

Occurrence: Has apparently not been reported to occur in nature.

Preparation: From tolualdehydes and glycerol in the presence of phosphoric acid, using azeotropic distillation for water removal (Arctander, 1969).

Uses: Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·001	0·1
Maximum	0·075	0·0075	0·25	1·25

Analytical data: Gas chromatogram, RIFM no. 72-58; infra-red curve, RIFM no. 72-58.

Status

Tolualdehyde glyceryl acetal was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) included tolualdehyde glyceryl acetal at a level of 15 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 3·4 g/kg (3·0–3·8 g/kg) and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1972).

Irritation. Applied full strength to intact or abraded rabbit skin for 24 hr under occlusion, tolualdehyde glyceryl acetal was moderately irritating (Moreno, 1972). Tested at 10% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1972).

Metabolism. Acetals hydrolyse readily in the presence of acids to generate the corresponding aldehydes and alcohols (Fassett, 1963).

Micro-organisms. p-Tolualdehyde glyceryl acetal was found by a zone-inhibition technique to be an effective antibacterial agent against Gram-positive *Staphylococcus aureus* and six Gram-negative bacteria, including *Pseudomonas aeruginosa* (Felton & Kapp, 1970).

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*See monograph on tolualdehyde.

TONKA ABSOLUTE

Description and physical properties: A semi-solid or crystalline mass of pale amber or pale brownish-yellow colour with a coumarinic-herbaceous odour. Its main constituent is coumarin (*Fenaroli's Handbook of Flavor Ingredients*, 1971; Naves, 1974).
Occurrence: Found in the seeds of the fruit of the tree *Dipteryx odorata* (Naves, 1974).
Preparation: By alcoholic extraction of the concrete (Naves, 1974).
Uses: In public use since the 1930s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·0005	0·003	0·08
Maximum	0·05	0·005	0·02	0·8

Analytical data: Gas chromatogram, RIFM no. 72–245.

Status

The FDA does not permit tonka absolute to be used in foods (21 CFR 121.106). The Council of Europe (1970) included tonka absolute in the list of flavouring substances temporarily admitted for use, possibly with a limitation on the active principle (coumarin) in the final product.

Biological data

Acute toxicity. The acute oral LD_{50} value in rats was reported as 1·38 g/kg (1·04–1·72 g/kg) (Moreno, 1973). The acute dermal LD_{50} in rabbits was reported as 1·26 g/kg (0·36–2·16 g/kg) (Moreno, 1973).

Irritation. Tonka absolute was slightly irritating when applied undiluted to the backs of hairless mice (Urbach & Forbes, 1972), or to intact or abraded rabbit skin for 24 hr under occlusion (Moreno, 1973). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 27 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Epstein, 1973).

Phototoxicity. No phototoxic effects were reported for Tonka absolute (Urbach & Forbes, 1972).

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TREEMOSS CONCRETE

Description and physical properties: A greyish-black to brownish semi-solid or viscous liquid. The principal constituents of treemoss are lichen acids, some of which are atranorin, furfuracinic acid and chloroatranorin (Guenther, 1952).

Occurrence: In the lichens, *Evernia furfuracea* (L.) Mann and *Usnea barbata* (L.) Wigg (Fam: Usneaceae), found on the bark of fir and pine trees (Guenther, 1952). The lichens include a large number of species, many of which have been studied with regard to their composition and properties (Kjellman, 1957). By selective extraction, several classes of lichen substances can be separated, accounting for 1–8% of the dry weight of lichens and including fatty acids, lactones, triterpenoids, polyhydric alcohols and aromatic substances such as depsides, depsidones, quinones and derivatives of pulvic acid, xanthone, dibenzofuran, and diketopiperazine (Mitchell & Armitage, 1965). One of the most important and widely distributed of the lichen acids is usnic acid, a dibenzofuran first isolated from *Usnea barbata*, which occurs in considerable quantities in a wide variety of species (Savich, Litvinov & Moiseeva, 1960). Lichen polysaccharides are isolated chiefly from the aqueous extracts (Shibata, Nishikawa, Tanaka, Fukuoka & Nakanishi, 1968c).

Preparation: By extraction of the moss, twigs and needles with volatile solvents and their subsequent removal, usually under vacuum.

Uses: In public use since the 1930s. Use in fragrances in the USA amounts to about 35,000 lb/yr. Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·005	0·1
Maximum	0·1	0·01	0·03	0·5

Status

Treemoss concrete is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974), or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 4·33 ml/kg (4·01–4·68 ml/kg), and the acute dermal LD_{50} in rabbits exceeded 5 g/kg (Levenstein, 1974). Lichen substances appear to be non-toxic to reindeer and other animals that consume large amounts of lichens in their normal diet (Söderberg, 1953).

Irritation. Undiluted treemoss concrete applied to the backs of hairless mice and swine was not irritating (Urbach & Forbes, 1974). Applied full strength to intact or abraded rabbit skin for 24 hr under occlusion, it was mildly irritating (Levenstein, 1974). Tested at 10% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1974). "Cedar-poisoning" in forest workers is probably a contact dermatitis caused by exposure to usnic acid or other lichen chemicals (Mitchell & Armitage, 1965). Two cases were reported by Mitchell (1965), and eight of 21 forest workers tested by Tan & Mitchell (1968) showed positive patch tests to these substances, while none was sensitive to cedar oleoresins.

Phototoxicity. No phototoxic effects were reported for undiluted treemoss concrete on hairless mice and swine (Urbach & Forbes, 1974).

Liver. Lichen polysaccharides injected ip into mice produced no observable signs of toxicity, except for a temporary widespread multifocal mesenchymal-cell accumulation in the liver, an effect probably not related to antitumour activity (Tokuzen, Nakahara, Fukuoka, Shibata & Nishikawa, 1970).

Tumours. Products obtained from aqueous extracts of Usnea, Evernia or other lichens, containing mainly polysaccharides but also sometimes usnic acid or *N*-containing compounds, showed marked antitumour effects in cancer patients (Adachi, 1973) and in mice with Sarcoma-180 or Ehrlich tumours (Fujikawa, Hirayama, Watanabe, Nakazawa & Kuroda, 1973; Nishikawa, Tanaka, Shibata & Fukuoka, 1970; Shibata, Nishikawa & Fukuoka, 1971; Shibata, Nishikawa, Takeda & Tanaka, 1968a; Shibata, Nishikawa, Takeda, Tanaka, Fukuoka & Nakanishi, 1968b; Shibata *et al.* 1968c; Takeda, Funatsu, Shibata & Fukuoka, 1972).

Micro-organisms. In a study of 201 lichen components and their decomposition products and derivatives, Fujikawa, Hitosa, Yagi, Nakazawa & Omatsu (1957) found that some compounds possessed antibacterial activity against *Sarcina lutea*, but none were effective as antifungal agents against

Candida albicans. Extracts of Usnea (four species) and Evernia (three species, including *E. furfuracea* and *E. prunastri*) possessed high antibacterial activity against *Staphylococcus aureus* (Litvinov & Rassadina, 1958).

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TRICHLORMETHYLPHENYLCARBINYL ACETATE

Synonym: Rose crystals.
Structure: $C_6H_5 \cdot CH(CCl_3) \cdot OCO \cdot CH_3$.
Description and physical properties: EOA Spec. no. 107.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By the reaction of benzene and chloral, in the presence of a catalyst, followed by acetylation.
Uses: In public use since the 1920s. Use in fragrances in the USA amounts to approximately 40,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·0005	0·003	0·05
Maximum	0·1	0·01	0·02	0·4

Analytical data: Gas chromatogram, RIFM no. 71–84; infra-red curve, RIFM no. 71–84.

Status

Trichlormethylphenylcarbinyl acetate is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974), or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 6·8 g/kg and the acute dermal LD_{50} in rabbits as $>2·0$ g/kg (Calandra, 1971a).

Subacute toxicity. In a subacute dermal toxicity test carried out on the intact and abraded skin of rabbits, 300 mg of the test material at a concentration of 50% in dimethyl phthalate was applied daily for 20 applications (Calandra, 1971b). Except for a mild skin irritation, no changes attributable to the compound were elicited, the parameters examined being haemological values, urine analyses, blood chemistry, weight gains and pathology of liver, kidney and bone marrow.

Irritation. Trichlormethylphenylcarbinyl acetate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was very slightly irritating (Calandra, 1971a). Tested at 1% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1971).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 1% in petrolatum and produced no sensitization reactions (Kligman, 1971).

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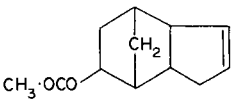
Kligman, A. M. & Epstein, W. (1975). Updating the maximization test for identifying contact allergens. *Contact Dermatitis* **1**, 231.

TRICYCLODECEN-4-YL 8-ACETATE

Synonym: Dihydro-nordicyclopentadienyl acetate.
Structure:



Description and physical properties: A colourless viscous liquid.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By hydration and acetylization of dicyclopentadiene.
Uses: Use in fragrances in the USA amounts to less than 50,000 lb/yr.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·03	0·003	0·01	0·15
Maximum	0·3	0·03	0·1	0·8

Analytical data: Gas chromatogram, RIFM no. 74-253; infra-red curve, RIFM no. 74-253.

Status

Tricyclodecen-4-yl 8-acetate is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1974) or in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1974).

Irritation. Applied full strength to intact or abraded rabbit skin for 24 hr under occlusion, tricyclodecen-4-yl 8-acetate was moderately irritating (Moreno, 1974). Tested at 8% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 21 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Epstein, 1974).

References

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Kligman, A. M. & Epstein, W. (1975). Updating the maximization test for identifying contact allergens. *Contact Dermatitis* **1.** 231.

Moreno, O. M. (1974). Report to RIFM, 26 August.

3,5,5-TRIMETHYLCYCLOHEXANOL

Synonyms: Trimethylcyclohexanol: 1-methyl-3,3-dimethylcyclohexanol-5; homomenthol.
Structure: $CH_3 \cdot C_6H_8(CH_3)_2 \cdot OH$.
Description and physical properties: A translucent, colourless, fused mass or crystals with a powerful menthol-like odour (Arctander, 1969).
Occurrence: Has apparently not been reported to occur in nature.
Preparation: By complete hydrogenation of isophorone (Arctander, 1969).
Uses: In public use since the 1940s. Use in fragrances in the USA amounts to less than 2000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·04
Maximum	0·1	0·01	0·03	0·4

Analytical data: Gas chromatogram, RIFM no. 72–230; infra-red curve, RIFM no. 72–230.

Status

3,5,5-Trimethylcyclohexanol is not included in the listings of the FDA, FEMA (1965) or the Council of Europe (1970) nor in the *Food Chemicals Codex* (1972).

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 3·25 g/kg (Smyth, Carpenter & Weil, 1949). The acute dermal LD_{50} in rabbits was reported as >5 g/kg (Moreno, 1973).

Irritation. 3,5,5-Trimethylcyclohexanol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1973). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 26 volunteers. The material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Epstein, 1973).

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Council of Europe (1970). Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. Strasbourg.

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Moreno, O. M. (1973). Report to RIFM, 6 July.

Smyth, H. F., Jr., Carpenter, C. P. & Weil, C. S. (1949). Range-finding toxicity data. List III. *J. ind. Hyg. Toxicol.* **31**, 60.

3,5,5-TRIMETHYLHEXYL ACETATE

Synonym: Isononyl acetate.

Structure: $CH_3 \cdot C(CH_3)_2 \cdot CH_2 \cdot CH(CH_3) \cdot [CH_2]_2 \cdot OCO \cdot CH_3$.

Description and physical properties: A colourless liquid with a fruit-like odour of moderate tenacity (Arctander, 1969).

Occurrence: Has apparently not been reported to occur in nature.

Preparation: From trimethylhexanol by acetylation (Arctander, 1969).

Uses: In public use since the 1960s. Use in fragrances in the USA amounts to about 15,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·2
Maximum	0·1	0·01	0·05	0·4

Analytical data: Gas chromatogram, RIFM nos 72–231 & 73–62; infra-red curve, RIFM nos 72–231 & 73–62.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 4·25 g/kg (3·54–4·96 g/kg) (Moreno, 1973). The acute dermal LD_{50} in rabbits was reported as >5 g/kg (Moreno, 1973).

Irritation. 3,5,5-Trimethylhexyl acetate applied undiluted to intact or abraded rabbit skin for 24 hr under occlusion was not irritating (Moreno, 1973). Tested at 4% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1973). Retested at 4% in petrolatum, it again produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material was tested at a concentration of 4% in petrolatum and produced one sensitization reaction among the 25 subjects tested (Kligman, 1973) (RIFM no. 72–4–231). In a second maximization test (Kligman, 1966), carried out on 24 volunteers, the material was tested at a concentration of 4% in petrolatum and produced no sensitization reactions (Epstein, 1973) (RIFM no. 73–4–62). An additional maximization test was carried out on 26 volunteers, using a concentration of 4% in petrolatum, and did not produce any sensitization reactions (Epstein, 1974).

References

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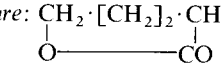
Kligman, A. M. (1966). The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. *J. invest. Derm.* **47**, 393.

Kligman, A. M. (1973). Report to RIFM, 10 July.

Moreno, O. M. (1973). Report to RIFM, 23 February.

δ-UNDECALACTONE

Synonyms: Undecanolide-1,5; 5-hydroxyundecanoic acid lactone.
Structure: $CH_2 \cdot [CH_2]_2 \cdot CH \cdot [CH_2]_5 \cdot CH_3$.



Description and physical properties: A colourless viscous liquid.
Occurrence: Reported to occur in coconut flavour (*Fenaroli's Handbook of Flavor Ingredients*, 1975).
Preparation: From heptaldehyde and acetaldehyde via 3-nonenal by Michael's addition of acetaldehyde to 2-hexylglutaraldehyde. An internal Canizzaro reaction yields the cyclized lactone (Arctander, 1969).
Uses: Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·001	0·0001	0·0005	0·03
Maximum	0·03	0·003	0·01	0·2

Analytical data: Gas chromatogram, RIFM no. 75-27; infra-red curve, RIFM no. 75-27.

Status

δ-Undecalactone was given GRAS status by FEMA (1972), and the Council of Europe (1974) included it at a level of 2 ppm in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1975).

Irritation. δ-Undecalactone applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1975). Tested at 2% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 2% in petrolatum and produced no sensitization reactions (Kligman, 1975).

References

Arctander, S. (1969). *Perfume and Flavor Chemicals (Aroma Chemicals)*. Vol. 2, no. 3025. S. Arctander, Montclair, New Jersey.

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Fenaroli's Handbook of Flavor Ingredients (1975). Edited by T. E. Furia and N. Bellanca. 2nd Ed. Vol. II, p. 550. Cleveland, Ohio.

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Kligman, A. M. (1975). Report to RIFM, 16 June.

Kligman, A. M. & Epstein, W. (1975). Updating the maximization test for identifying contact allergens. *Contact Dermatitis* **1**, 231.

Moreno, O. M. (1975). Report to RIFM, 25 June.

γ-UNDECALACTONE

Synonyms: Aldehyde C-14; peach aldehyde.

Structure: $CH_3 \cdot [CH_2]_6 \cdot \underset{\displaystyle O}{\underset{|}{CH}} \cdot CH_2 \cdot \underset{\displaystyle CO}{\underset{|}{CH_2}}$.

Description and physical properties: EOA Spec. no. 79.

Occurrence: Reported to be found in apricots, peaches, milk products, meat and passion fruits (Centraal Instituut Voor Voldingsonderzolk, 1973).

Preparation: By the action of diluted sulphuric acid on undecylenic acid (Bedoukian, 1967).

Uses: In public use since the 1920s. Use in fragrances in the USA amounts to approximately 15,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·005	0·0005	0·003	0·05
Maximum	0·05	0·005	0·02	0·2

Status

γ-Undecalactone was given GRAS status by FEMA (1965), is approved by the FDA for food use (21 CFR 121.1164) and is listed by the Council of Europe (1974) with an ADI of 1·25 mg/kg. The *Food Chemicals Codex* (1972) has a monograph on γ-undecalactone and the Joint FAO/WHO Expert Committee on Food Additives (1967) has published a monograph and specifications, giving an unconditional ADI of 0–1·25 mg/kg.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 18·5 g/kg (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964). Fatty infiltration of liver parenchymal cells occurred in rats fed 13–115 mg γ-undecalactone for 5–9 days (Shillinger, 1950).

Subacute and long-term toxicity. In a 12-wk feeding study in rats, the no-effect level was 14·1 mg/kg (Bär & Griepentrog, 1967). Groups of 20 male and 20 female rats were fed diets containing 0·1 or 0·5% γ-undecalactone for 2 yr without any specific adverse effects (Bär & Griepentrog, 1967).

Irritation. γ-Undecalactone tested at 2% in petrolatum produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1971).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 25 volunteers. The material was tested at a concentration of 2% in petrolatum and produced no sensitization reactions (Kligman, 1971).

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Bär, F. u. Griepentrog, F. (1967). Die Situation in der gesundheitlichen Beurteilung der Aromatisierungsmittel für Lebensmittel. *Medizin Ernähr.* **8**, 244.

Bedoukian, P. Z. (1967). *Perfumery and Flavoring Synthetics.* 2nd ed., p. 226. Elsevier Publishing Co., New York.

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Council of Europe (1974). Natural Flavouring Substances, Their Sources, and Added Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field. List 1, no. 178, p. 161. Strasbourg.

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Food Chemicals Codex (1972). 2nd ed. Prepared by the Committee on Specifications, Food Chemicals Codex, of the Committee on Food Protection. p. 844. National Academy of Sciences–National Research Council Publ. 1406, Washington, D.C.

Jenner, P. M., Hagan, E. C., Taylor, Jean M., Cook, E. L. & Fitzhugh, O. G. (1964). Food flavourings and compounds of related structure. I. Acute oral toxicity. *Fd Cosmet. Toxicol.* **2**, 327.

Joint FAO/WHO Expert Committee on Food Additives (1967). Toxicological Evaluation of Some Flavouring Substances and Non-nutritive Sweetening Agents. *F.A.O. Nutr. Mtg Rep. Ser. no.* 44A, Geneva, p. 76; WHO/Food Add./68.33.

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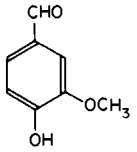
Kligman, A. M. & Epstein, W. (1975). Updating the maximization test for identifying contact allergens. *Contact Dermatitis* **1**, 231.

Shillinger, J. I. (1950). Action of some synthetic substance on animal organism. *Gig. Sanit.* **3**, 37.

VANILLIN

Synonyms: 4-Hydroxy-3-methoxybenzaldehyde; methyl protocatechuic aldehyde; protocatechualdehyde-3-methylether. CAS Registry No. 121-33-5.
Structure:



Description and physical properties: Merck Index (1976).
Occurrence: Vanillin occurs widely in nature. It has been reported in the essential oil of Java citronella (*Cymbopogon nardus Rendl.*), in benzoin, Peru balsam and clove-bud oil and, chiefly, in vanilla pods (*Vanilla planifolia, V. tahitensis* and *V. pompona*). Vanillin is also present in the plants as glucose and vanillin, and another source of vanillin is the waste (liquor) of the wood-pulp industry (*Fenaroli's Handbook of Flavor Ingredients*, 1975).
Preparation: Made synthetically from eugenol or guaiacol. Most vanillin used in fragrances is from the waste (lignin) of the wood pulp industry (Bedoukian, 1967).
Uses: In public use since the 1900s. Use in fragrances in the USA amounts to approximately 250,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·2
Maximum	0·1	0·01	0·03	0·8

Analytical data: Gas chromatogram, RIFM no. 70-10; infra-red curve, RIFM no. 70-10.

Status

Vanillin was given GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1974) listed vanillin, giving it an ADI of 10 mg/kg. Both the *Food Chemicals Codex* (1972) and the *United States Pharmacopeia* (1975) have monographs on vanillin and the Joint FAO/WHO Expert Committee on Food Additives (1967) has published a monograph and specifications for vanillin, giving an unconditional ADI of 0–10 mg/kg.

Biological data

Acute toxicity. The minimum lethal dose of vanillin for rabbits was 3·0 g/kg following oral administration as a 5% solution in milk; toxic signs included increased rate of respiration followed by muscular weakness, lachrymation, dyspnoea, collapse and death in coma, without convulsions (Deichmann & Kitzmiller, 1940). The acute oral LD_{50} of vanillin (administered as a 20% solution in propylene glycol) was found to be 1·58 g/kg for rats, with coma, and 1·40 g/kg for guinea-pigs, with depression (Jenner, Hagan, Taylor, Cook & Fitzhugh, 1964; Taylor, Jenner & Jones, 1964), and elsewhere the oral LD_{50} for rats was reported as 2·0 g/kg (Hake & Rowe, 1963) and as approximately 2·8 g/kg (Hodge & Downs, 1961).

The lethal dose administered by slow iv infusion to dogs was found to be 1·32 g/kg (Caujolle, Meynier & Moscarella, 1953), and the acute ip LD_{50} values reported were 0·78 g/kg for mice and 1·19 g/kg for guinea-pigs (Caujolle & Meynier, 1954), 1·16 g/kg for rats (Caujolle, Meynier & Farthouat, 1956) and 475 mg/kg for mice (National Institute for Occupational Safety and Health, 1975). Four daily oral doses of 530 mg vanillin/kg given to rats produced no deaths and no macroscopic liver lesions (Taylor *et al.* 1964).

In rats the lethal sc dose was reported as 1·8 g/kg (Deichmann & Kitzmiller, 1940) and the sc LD_{50} as 1·5 g/kg (Binet, 1896), but the sc LD_{50} for vanillin administered as a 4% solution in milk was 2·6 g/kg (Deichmann & Kitzmiller, 1940).

Subacute and chronic toxicity. Intragastric administration of 300 mg vanillin/kg to rats twice weekly for 14 wk produced no adverse effects (Deichmann & Kitzmiller, 1940). Groups of 16 rats were fed diets containing vanillin at levels to provide 20 mg/kg body weight/day for 18 wk without any adverse effects, but 64 mg/kg/day for 10 wk caused growth depression and damage to the myocardium, liver, kidney, lung, spleen and stomach (Deichmann & Kitzmiller, 1940). When ten male and ten female rats were fed diets containing 0·3, 1·0 or 5·0% vanillin for 13 wk, there were growth depression and enlargement of liver, kidney and spleen at the highest level, mild changes at 1·0%

and none at 0·3% (Deichmann & Kitzmiller, 1940). In another study (Hake & Rowe, 1963), matched groups of ten male and ten female rats, 4–6 wk old, were maintained for 91 days on diets containing up to 50,000 ppm vanillin, equivalent to about 2500 mg/kg/day. Records of appearance, behaviour, growth, mortality, terminal body and organ weights, terminal haematological examinations and histological studies, revealed no adverse effects when the diet contained 3000 ppm vanillin, equivalent to as much as 150 mg/kg/day, mild adverse effects followed ingestion of the 10,000-ppm diet and at 50,000 ppm growth was depressed and the liver, kidneys and spleen were enlarged.

Fed to rats at dietary levels of 10,000 ppm for 16 wk, 1000 ppm for 27–28 wk, 20,000 or 50,000 ppm for 1 yr, or 5000, 10,000 or 20,000 ppm for 2 yr, vanillin had no effect on growth or haematology and produced no macroscopic or microscopic changes in the tissues (Hagan, Hansen, Fitzhugh, Jenner, Jones, Taylor, Long, Nelson & Brouwer, 1967).

Rats fed for 5 wk on a diet containing a mixture of the maximum permissible amounts of 15 compounds, including vanillin (0·5 g/kg of diet), dyes and insecticides, showed symptoms of intoxication, including decreases in adrenal vitamin C and in liver protein (Sporn & Schöbesch, 1963).

Vanillin injected ip into strain A mice in total doses of 3·6–18·0 g/kg over a period of 24 wk produced no excess of lung tumours and was not considered to be carcinogenic (Stoner, Shimkin, Kniazeff, Weisburger, Weisburger & Gori, 1973).

Irritation. In closed-patch tests on human skin, vanillin caused no primary irritation when tested at concentrations of 20% on 29 normal subjects, of 2% on 30 normal subjects and of 0·4% in 35 subjects with dermatoses (Fujii, Furukawa & Suzuki, 1972).

Sensitization. Maximization tests (Kligman, 1966; Kligman & Epstein, 1975) were carried out on groups of 25 volunteers. The material was tested at concentrations of 2% (Greif, 1967) and 5% (Kligman, 1970) in petrolatum and produced no sensitization reactions.

Vanillin applied undiluted for 48 hr in the standard occluded aluminium-patch test used by the North American Contact Dermatitis Research Group (NACDRG) did not produce any irritation or sensitization in a 62-yr-old subject with a perfume dermatitis (Larsen, 1975). The standard aluminium patch test, designed by the International Contact Dermatitis Research Group to standardize testing for contact dermatitis worldwide, is described extensively by Malten, Nater & van Ketel (1976).

Positive reactions to vanillin were reported in eight out of 142 patients who were already sensitized to balsam of Peru (Mitchell, 1975). In studies of sensitization to balsam of Peru and its components (Hjorth, 1961), vanillin (pure or 10% in vaseline) produced positive patch-test reactions in 21 out of 164 patients sensitive to the balsam. Vanillin was considered to be a secondary allergen, since sensitivity was found only in patients sensitive to vanilla, isoeugenol and coniferyl benzoate. Cross-sensitization to other substituted benzaldehydes was particularly uncommon. Vanillin was found not to be responsible for most cases of sensitivity to natural vanilla.

Vanillin, which appears on the published list of 400 Canadian food additives and is used in artificial flavourings, is known to cause reactions in people previously sensitized to balsam of Peru, benzoin, rosin, benzoic acid, orange peel, cinnamon and clove (Mitchell, 1971).

Metabolism. Early observers noted conversion of vanillin to vanillic acid which was excreted mainly as the free acid, a conjugated ethereal sulphate or glucurovanillic acid (Preusse, 1880). In man, vanillin is broken down by the liver to vanillic acid which is excreted in the urine. Human liver homogenates readily convert vanillin to vanillic acid *in vitro* (Dirscherl & Brisse, 1966). Endogenous vanillic acid production and excretion in man from body catecholamines amounts to <0·5 mg/day, compared with the normal contribution from dietary sources of about 9 mg/day (Dirscherl & Wirtzfeldt, 1964).

In rats, also, vanillin is broken down by the9liver to vanillic acid which is excreted in the urine (Dirscherl & Brisse, 1966). A study of urinary and biliary metabolism of vanillin in rats indicated that oxidative metabolism predominated (65–70%) but that reduction also occurred, with excretion of 19% of the dose as benzyl alcohol derivatives (Strand & Scheline, 1975). When vanillin was fed to rats in doses of 100 mg/kg, most metabolites were excreted in the urine within 24 hr, chiefly as glucuronide and/or sulphate conjugates, although the acids formed were also excreted free and as their glycine conjugates. In 48 hr, 94% of the dose was accounted for, 7% as vanillin, 19% as vanillyl alcohol, 47% as vanillic acid, 10% as vanilloylglycine, 8% as catechol, 2% as 4-methylcatechol, 0·5% as guiacol and 0·6% as 4-methylguaiacol. By investigation of biliary metabolites, prevention of biliary excretion, suppression of intestinal bacteria and inhibition of intestinal β-glucuronidase, it was found that glucuronides of vanillin and its alcohol and acid derivatives are excreted in the bile and that the conjugates are metabolized by the intestinal bacteria to toluene derivatives and decarboxylated products (Strand & Scheline, 1975). Vanillin was found to be reduced to 4-methylcatechol, catechol and 4-methylguaiacol and oxidized to vanillic acid and protocatechuic acid by the intestinal microflora in incubated rat caecal extracts (Scheline, 1972).

When 2-g doses of vanillin were fed to rabbits, products excreted in the urine included 14% conjugated as glucurovanillin and 69% oxidized to vanillic acid, of which two thirds was the free acid and one third was conjugated as the ethereal sulphate and glucuronide (Sammons & Williams, 1941). Glucuronide and sulphate conjugates of vanillin were also identified in cows' milk (Brewington, Parks & Schwartz, 1973).

Metabolism by micro-organisms. Bacteria (21 strains) were able to utilize vanillin, which was oxidized on incubation with chernozem soil to vanillic acid, protocatechuic acid and ring-cleavage products (Kunc, 1971). Vanillin occurring in soil was decomposed by soil micro-organisms, with maximum activity occurring during October to December (Gnittke, Kunze & Steubing, 1971). Vanillin was found to be oxidized by the soil fungus *Actinomyces aureus* to vanillic acid, which was subsequently demethylated and hydroxylated to produce protocatechuic acid, and this was further degraded to succinic acid (Tsai, Chu, Yang & Tsao, 1965). Vanillin was utilized by micro-organisms of both dry mud and sandy sediments of a eutrophic lake (Strzelcyzyk, Donderski & Lewosz, 1972), and vanillin-resistant rhizobia from legume root nodules can utilize vanillin as the sole carbon source (Gupta, Aggarwal & Makkar, 1974). Vanillin was demethoxylated to *p*-hydroxybenzoic acid, alcohol and aldehyde by Saccharomyces yeast in aerobic culture; vanillic acid and vanillyl alcohol were also found but no vanillin remained (Kyowa Fermentation Industry Co. Ltd., 1972).

Insects. Vanillin stimulated feeding behaviour in *Scolytus multistriatus* (the elm bark beetle), with maximum response at a concentration of 0·01 M (Meyer & Norris, 1974), acted as an insect attractant in a patented insecticide composition (Koppers Co., Inc. 1965), and in concentrations of 0·01–0·02 μmol/litre air produced 90% repulsion of the mosquito *Aedes Aegypti* (Burton, 1969).

Invertebrates. Vanillin, which is probably present in the egg-water substance secreted by eggs of *Psammechinus miliaris* (the sea urchin), produced an increase in the fertilization rate but not in sperm respiration (Lybing & Hagström, 1957). The ascaricidal time of vanillin for ascarids of pigs was found to be 3–4 days (Miyama, 1958).

Micro-organisms. Vanillin was reported as having bactericidal activity 5·4 times that of phenol (Führer, 1972). In dilutions of 1:2000 or more it showed antibacterial activity against five bacteria (Katayama & Nagai, 1960), and in a 1:10,000 dilution it exhibited tuberculostatic action against *Mycobacterium tuberculosis* (Jeney & Zsolnai, 1956). Kellner & Kober (1955) reported that vanillin showed low to moderate activity against nine species of bacteria, but Mashimo, Serisawa & Kuroda (1953) found little or no inhibitory activity against four species of bacteria and according to Fiedler & Kaben (1966), vanillin showed no antifungal or antibacterial action against six bacteria and fungi. Rhizobia isolated from legume-root nodules varied in their sensitivity to vanillin (Gupta *et al.* 1974).

Vanillin, a fungitoxic aldehyde found in leaf wound sap, prevented germination of fungal uredospores and teliospores at concentrations of 25–150 μg/ml (Bell, 1970) and, like other lignin destruction products, was found to have fungicidal properties (Telysheva, Sergeeva & Gavare, 1968). At 1 mg/ml it suppressed the growth of *Botrytis cinerea* mould (Ivanova, Davydova & Rubin, 1965), while 1% vanillin stimulated growth of *Coniophora olivacea* but was found to be moderately toxic to *Lenzites trabea* (Rudman, 1963). On the other hand, Zsolnai (1960) reported that vanillin showed no fungicidal activity against seven fungi.

Plants. Vanillin is active as a plant-growth substance, exerting both inhibiting and stimulating effects. These have been studied in Chlorella (Dedonder & Van Sumere, 1971; Dushkova, 1971 & 1973), cereal and leguminous plants (Georgiev & Ivanova, 1972a, b), rice (Uotani, Umezu, Meguro, Tuzimura & Takahashi, 1972), corn (Langdale & Giddens, 1967), Scots pine (Michniewicz & Galoch, 1974), barley (Minchenkova, 1971; Pursakova & Chizhova, 1973; Terent'ev, Tsareva, Semenova & Oskerko, 1974), cotton (Palesiko, Shubert & Ovcharov, 1966), and various crop plants (Helfrich, 1962; Pashkar, Smirnov & Zakharova, 1969). Vanillin was found to be active in retarding the ageing of detached leaves (Karanov, 1969 & 1973; Knypl & Mazurczyk, 1971 & 1972), was toxic to carrot tissue (Goris, 1964) and protected onion cells and barley seedlings against ultraviolet irradiation (Dubrov, 1968).

Pharmacology. Lethal or sublethal doses of vanillin administered orally to anaesthetized rabbits produced sudden depression of the blood pressure and stimulated respiration (Deichmann & Kitzmiller, 1940). Similar results were obtained in dogs (Caujolle *et al.* 1953).

Vanillin produced only a small increase in bile output when administered iv to rats (Rohrbach & Robineau, 1958), and induced some choleretic activity when injected ip into rats in doses of 10–250 mg/kg (Pham-Huu-Chanh, Bettoli-Moulas & Maciotta-Lapoujade, 1968). Injected sc in doses of 1 mg/day for 4 days into immature female rats, it caused a decrease in the ovarian- and an increase in the uterine-weight response to exogenous gonadotropic hormone (Kar, Mundle & Roy, 1960). Vanillin had no effect on the nervous system of fish (Bohinc & Wesley-Hadzija, 1956). In dietary concentrations of 0·05 and 0·1% it had a cariostatic effect in hamsters without impairing growth (Stralfors, 1967).

Vanillin administered as an aerosol had no effect on normally-functioning isolated perfused guinea-pig lungs and did not prevent spontaneous pneumoconstriction (Pham-Huu-Chanh, 1963 & 1964). It did not act as a cross-linking (tanning) agent for corium and aorta, since in 0·15 M solution it did not increase the observed *in vitro* hydrothermal shrinkage temperatures of goat skin and human, bovine and canine aortae (Milch, 1965). It decreased slightly the deformability of dense red cell packs (Jacobs, 1965), and in 1–2 mM concentration produced 50–100% inhibition of collagen-induced platelet aggregation in human blood (Jobin & Tremblay, 1969).

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VERATRALDEHYDE

Synonyms: *p*-Veratric aldehyde; 3.4-dimethoxybenzaldehyde.
Structure: $CH_3O \cdot C_6H_3(OCH_3) \cdot CHO$.
Description and physical properties: White crystals.
Occurrence: Reported to be found among the constituents of the essential oils of *Cymbopogon javanensis* and *Erynagium poterium* (*Fenaroli's Handbook of Flavor Ingredients*, 1971).
Preparation: By methylation of vanillin with dimethyl sulphate in mild aqueous alkali (Arctander, 1969).
Uses: In public use since the 1950s.
Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·01	0·001	0·005	0·08
Maximum	0·1	0·01	0·03	1·5

Analytical data: Gas chromatogram, RIFM no. 74–252; infra-red curve, RIFM no. 74–252.

Status

Veratraldehyde was given GRAS status by FEMA (1965) and is approved by the FDA for food use (21 CFR 121.1164). The Council of Europe (1974) listed veratraldehyde, giving an ADI of 10 mg/kg.

Biological data

Acute toxicity. The acute oral LD_{50} in rats was reported as 2·0 g/kg (1·84–2·16 g/kg) and the acute dermal LD_{50} in rabbits as >5 g/kg (Moreno, 1974).

Irritation. Veratraldehyde applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1974). Tested at 15% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1974).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 20 volunteers. The material was tested at a concentration of 15% in petrolatum and produced no sensitization reactions (Epstein, 1974).

Metabolism. Veratraldehyde is metabolized in the rabbit to the corresponding ester glucuronide (Williams, 1959).

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VETIVER ACETATE

Synonyms: Vetivert acetate; vetiveryl acetate.
Structure: $C_{15}H_{24} \cdot OCO \cdot CH_3$.
Description and physical properties: EOA Spec. no. 152.
Occurrence: Has apparently not been reported to occur in nature.
Preparation: (a) By acetylation of vetiver oil and subsequent isolation of the ester (71–90, 72–74). (b) By acetylation of the alcohol, vetiverol, isolated from vetiver oil (72–236).
Uses: In public use since the late 1920s. Use in fragrances in the USA amounts to less than 75,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·02	0·002	0·4
Maximum	0·2	0·02	0·1	2·0

Analytical data: Gas chromatogram, RIFM nos 71–90, 72–74 & 72–236; infra-red curve, RIFM nos 71–90, 72–74 & 72–236.

Status

The Council of Europe (1970) included vetiver acetate (vetiveryl acetate) in the list of artificial flavouring substances not admissible at present.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1972a).

Irritation. Undiluted vetiver acetate applied to hairless mice was not irritating (Urbach & Forbes, 1972). Vetiver acetate applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating (Moreno, 1972b). Two different samples of vetiver acetate tested at 20% in petrolatum and one sample tested at 8% in petrolatum produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1972a, b & 1973).

Sensitization. A maximization test (Kligman, 1966) was carried out on 25 volunteers. The material (RIFM no. 71–20–90) was tested at a concentration of 20% in petrolatum and produced sensitization reactions in three of the 25 (Kligman, 1972a). The maximization test was repeated using the same sample (RIFM no. 71–20–90) at a concentration of 20% on a separate panel of subjects and produced sensitization reactions in two out of 25 (Kligman, 1972a). A maximization test (Kligman, 1966) was carried out on 25 volunteers using a sample of better quality (i.e. one with a lower acid value). The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1973) (RIFM no. 72–8–74). Vetiver acetate was then specially prepared from the alcohol and tested in a maximization test (Kligman, 1966) carried out on 25 volunteers. The material (RIFM no. 72–20–236) was tested at a concentration of 20% in petrolatum and produced no sensitization reactions (Kligman, 1972b).

Phototoxicity. No phototoxic effects were reported for vetiver acetate (Urbach & Forbes, 1972).

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VETIVER OIL

Description and physical properties: EOA Spec. no. 24. The main constituents of vetiver oil are vetiverol and vetiverone (*Fenaroli's Handbook of Flavor Ingredients*, 1971; Guenther, 1950).

Occurrence: Found in the root of *Vetiveria zizanoides* Stapf (Fam. Graminae) (Gildemeister & Hoffman, 1956; Naves, 1974).

Preparation: By steam distillation of partially dried roots of *Vetiveria zizanoides* Stapf (Gildemeister & Hoffman, 1956; Naves, 1974).

Uses: In public use before the 1860s. Use in fragrances in the USA amounts to approximately 75,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·3
Maximum	0·2	0·02	0·05	0·8

Analytical data: Gas chromatogram, RIFM no. 73–39; infra-red curve, RIFM no. 73–39.

Status

Vetiver oil is approved by the FDA for food use (21 CFR 121.1163). The Council of Europe (1970) included vetiver oil in the list of flavouring substances temporarily admitted for use, possibly with a limitation on the active principle in the final product.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. Undiluted vetiver oil applied to the backs of hairless mice was not irritating (Urbach & Forbes, 1973). Applied full strength to intact or abraded rabbit skin for 24 hr under occlusion, the oil was moderately irritating (Moreno, 1973). Tested at 8% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1971).

Sensitization. A maximization test (Kligman, 1966) was carried out on 26 volunteers. The material was tested at a concentration of 8% in petrolatum and produced no sensitization reactions (Kligman, 1971).

Phototoxicity. No phototoxic effects were reported for vetiver oil (Urbach & Forbes, 1973).

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Urbach, F. & Forbes, P. D. (1973). Report to RIFM, 26 July.

VIOLET LEAF ABSOLUTE

Description and physical properties. A viscous dark green liquid. The main constituent of violet leaf absolute is 2-*trans*-6-*cis*-nonadien-1-al (Guenther, 1952; Naves, 1974). Violet leaves contain the aldehyde 2,6-nonadien-1-al (Bunina-Krivorukova & Petrov, 1963), which is present at levels of 30–50% in violet leaf absolute along with trace amounts of eugenol (Appell, 1968). Leaves of *Viola odorata* from Kashmir were reported to contain a triterpene ketone, probably friedelin (0·016%), β-sitosterol (0·033%), and a straight-chain alcohol (Ladwa & Dutta, 1969). Residues of pesticides applied to violet leaves were not detected in violet leaf absolute, but residues were detected by odour and by chromatography in the concrete prepared from leaves treated with oxydemeton-methyl. It was pointed out that non-odorous and non-persistent pesticides should be used on plants to be used in perfumes (Peyron, 1972). Decoctions prepared from leaves and roots of *V. odorata* contain alkaloids similar to emetine (Kroutil & Kroutilova, 1968).

Occurrence: Found in the leaves of the plant *V. odorata* L. (Fam. Violaceae) (Guenther, 1952).

Preparation: By treatment of the concrete with alcohol, and filtration to remove insoluble matter (Guenther, 1952).

Uses: In public use before the 1930s. Use in fragrances in the USA amounts to less than 1000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·003	0·0003	0·0015	0·04
Maximum	0·03	0·003	0·01	0·2

Status

Violet leaf was given GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1974) included violet leaf in the list of substances, spices and seasonings deemed admissible for use with a possible limitation of the active principle in the final product.

Biological data

Irritation. Undiluted violet leaf absolute applied to the backs of hairless mice and swine was not irritating (Urbach & Forbes, 1975). Tested at 2% in petrolatum it produced no irritation after a 48-hr closed-patch test on human subjects (Epstein, 1975).

Sensitization. A maximization test (Kligman, 1966; Kligman & Epstein, 1975) was carried out on 22 volunteers. The material was tested at a concentration of 2% in petrolatum and produced no sensitization reactions (Epstein, 1975).

Phototoxicity. No phototoxic effects were reported for undiluted violet leaf absolute on hairless mice and swine (Urbach & Forbes, 1975).

Pharmacology. A simple extract from violet herbage administered as a decoction (10 ml/kg body weight) orally or sc to rats following experimentally induced inflammation showed a favourable anti-inflammatory effect in acute and subacute (8–10-day) experiments (Kroutil & Kroutilova, 1968).

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YLANG YLANG OIL

Description and physical properties: EOA Spec. no. 200.

Occurrence: Found in the flowers of *Cananga odorata* Hook f. et Thomson forma genuina (Fam. Anonaceae).

Preparation: By steam distillation of the flowers of *Cananga odorata* Hook f. et Thomson forma genuina (Gildemeister & Hoffman, 1956; Naves, 1974).

Uses: In public use since the 1880s. Use in fragrances in the USA amounts to approximately 76,000 lb/yr.

Concentration in final product (%):

	Soap	*Detergent*	*Creams, lotions*	*Perfume*
Usual	0·02	0·002	0·01	0·3
Maximum	0·3	0·03	0·1	1·0

Status

Ylang ylang was granted GRAS status by FEMA (1965) and is approved by the FDA for food use (GRAS). The Council of Europe (1970) included ylang ylang in the list of flavouring substances temporarily admitted for use, possibly with a limitation on the active principle in the final product.

Biological data

Acute toxicity. Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value in rabbits exceeded 5 g/kg (Moreno, 1973).

Irritation. Undiluted ylang ylang oil applied to the backs of hairless mice was not irritating (Urbach & Forbes, 1973). Applied full strength to intact or abraded rabbit skin for 24 hr under occlusion, it was slightly irritating (Moreno, 1973). Two different samples (RIFM nos OYYF & Y–10–YR) tested at 10% in petrolatum produced no irritation after a 48-hr closed-patch test on human subjects (Kligman, 1971 & 1972).

Sensitization. Maximization tests (Kligman, 1966) on two different samples (RIFM nos OYYF & Y–10–YR) were carried out on 25 volunteers. The materials were tested at a concentration of 10% in petrolatum and produced no sensitization reactions (Kligman, 1971 & 1972). A repeated-insult patch test (Draize, 1959), carried out on 40 subjects using a 10% concentration of ylang ylang, sensitized 5% of the subjects (Majors, 1971a) (RIFM no. OYYF). A rechallenge patch test using 36 of the original 40 subjects was carried out using the same sample of ylang ylang (RIFM no. OYYF) and produced no sensitization reactions (Majors, 1971b). A repeated-insult patch test using a 10% concentration of ylang ylang was carried out on 105 subjects and produced no sensitization reactions (Kanof, 1971) (RIFM no. OYYF). Another repeated-insult patch test (Draize, 1959) using a 10% concentration of ylang ylang was carried out on 43 subjects and similarly produced no sensitization reactions (Majors, 1972) (RIFM no. Y–10–YR).

Phototoxicity. No phototoxic effects were reported for ylang ylang oil (Urbach & Forbes, 1973).

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