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Indoor Air Quality

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Preface

The International Conference on Indoor Air Quality, Tokyo, 1987 was held from November 4–6, 1987, at The New Otani Hotel in Tokyo, Japan, under the auspices of the Council for Environment and Health, whose president is Dr. Hitoshi Kasuga of Tokai University.

The 1980s have witnessed remarkable progress in numerous research programs on indoor air quality. It is noteworthy that the effects of environmental tobacco smoke (ETS) on nonsmokers and of nitrogen dioxide-induced indoor air pollution drew recognition as serious problems not only among epidemiologists, pathologists, and clinicians the world over, but from the general public as well.

There have been significant advances in the area of ETS alone. The separate findings of Takeshi Hirayama and Dimitrios Trichopoulos, released almost simultaneously in 1981, on the relationship between ETS and lung cancer drew immediate attention worldwide and triggered more than 10 follow-up studies. The controversy raised by this work still continues.

A number of international symposiums have been held on this topic, with those in Geneva (1983), Vienna (1984), and Essen (1986) commanding the greatest global attention. Yet, none have established a definite causal relationship between ETS and lung cancer.

A special report in 1986 by the U.S. Surgeon General, entitled "The Health Consequences of Involuntary Smoking", concluded that passive smoking is a cause of disease, including lung cancer, in healthy nonsmokers. This conclusion was reached through exhaustive study and despite many reservations, supporting the findings of Hirayama et al.

At about the same time, the Japanese Ministry of Public Health and Welfare published "Smoking and Health," its first such report, giving mild support to the view that smoking is harmful in stating:

> Although there is currently no worldwide support for the view of there being a significant risk of lung cancer from passive smoking, fear and concern have been expressed over its danger in many countries.

At the annual meetings of the World Health Organization and at the World Conference on Smoking and Health, discussions were based on the assumption of an established link between ETS and lung cancer. These conferences thus provide solid ground for antismoking campaigns.

Dr. Ernest Wynder, a keynote lecturer at the Tokyo conference, touched on one of the grounds for debate on the causal relationship between smoking and lung cancer. He pointed out that since this association is weak,

the conclusions drawn at these conferences are being highly influenced by biases involved in the measured amounts of ETS exposure, questionnaire responses, and subsequent classification of nonsmokers. This perhaps makes evaluation of what Dr. Wynder calls "critical association" extremely difficult.

As one of the planners and organizers of this conference, I believed it possible to objectively and scientifically evaluate this critical association by establishing a clear focus on an issue which has tended to become hopelessly obscured. I thus sought to establish an international forum for researchers to discuss ETS and pool available scientific data on indoor air quality produced over the past several years.

A total of 100 researchers, including younger people in the forefront of research, and leading scholars in their respective fields (60 from abroad and 40 from Japan) were invited to participate in the conference.

The conference opened with keynote lectures by Dr. Ernest L. Wynder, Dr. Barbara S. Hulka, Peter N. Lee, and Hitoshi Kasuga. These were followed by general presentations on ETS Measurement (Sessions 1 to 3), on the Biological Effects of ETS (Sessions 4 to 8), on the Epidemiology of Passive Smoking (Sessions 9 to 11), and on Indoor Air Pollution (Sessions 14 to 17).

Reports from the above presentations were summarized at three panel discussions: Epidemiology of Passive Smoking (Session 12), Reassessment of Passive Smoking as Lung Cancer Risk (Session 13), and ETS Measurement, Biological Effects of ETS, and Indoor Air Pollution (Session 18).

Session 13 proved to be a major highlight of the conference as exciting debate at this evening session extended into late hours.

Some 95% of all those invited attended the conference. Among those unable to come were Dr. Doll, who could not take the trip because of advanced age, and Mr. Garfinkel and Dr. Trichopoulos, who had other academic commitments and sent coresearchers on their behalf.

Special thanks go to Professor G. Lehnert, vice president of the conference, and Professor K. Maeda and Dr. Fukuma, who served as vice presidents and panelists.

I am also very much indebted to Messrs. Y. Yanagisawa and T. Namekata, from the United States, and Professors K. Maeda, K. Aoki, Y. Tsunetoshi, from Japan, who chaired the panel sessions.

Appreciation also is extended to Dr. Shimizu and Dr. Matsuki, who served as secretary general, for their efforts in organizing the conference.

In conclusion, heartfelt thanks go to all conference participants for their cooperation and excellent presentations. I wish them continued good health and success.

November 1989
Kanagawa, Japan

Hitoshi Kasuga

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The International Conference on Indoor Air Quality – Opening Address

H. Kasuga

Welcome to the International Conference on Indoor Air Quality, and welcome to Tokyo. It is indeed my great pleasure to be able to speak before this gathering of distinguished ladies and gentlemen.

Among the numerous environmental problems facing modern man today, indoor air quality has become a serious social issue of vital concern.

This conference has been organized in recognition of the need to address this issue from an international perspective, by assembling researchers renowned worldwide in the relevant fields as well as younger members of the scientific community engaged in promising new research endeavors. It is hoped that the participants will engage in truly fruitful academic interchange that offers a comprehensive presentation of both the present and future of research on indoor air quality.

As a member of the Organizing Committee, it also gives me great pleasure to inform you that, aside from two or three who could not attend due to illness, virtually all of those invited to this conference are here today – a remarkable feat in itself.

We are faced with a veritable mountain of problems deserving of efforts toward their quick resolution. To name a few from the topic of ETS, we have, for example, the measurement of ETS exposure levels, classification of involuntary smokers, and ETS health effects and their markers. Unless these issues are subjected to thorough clarification, we could see a trend of emphasis on smoking restrictions, with the debut of unwise legislation as farcical as the prohibition laws of years gone by.

The introduction of tobacco into Japan took place some four centuries ago in 1590, exactly one hundred years after the explorer Columbus imported the plant into Europe. The use of tobacco in this country, nevertheless, has since developed into a "culture" all its own.

Consequently, we too have our own popular cigarette-related sayings or slogans. One, recently used in a commercial, goes something like this in English: "I feel fine today, too! And this cigarette tastes great!" At the opposite extreme, also, we are informed by Professor Hirayama that: "Cigarettes are like canned poison."

It is our responsibility as scientists to calmly bring forth greater objective understanding of tobacco and human health to fill in the wide void between the two extremes portrayed by the above catchphrases. This is, I believe, the true goal this Conference should strive to realize. If not the case, then there is no sense in the WHO (World Health Organization) slogan – "Smoking or health? The choice is yours!"

Finally, my colleagues and I hope that all of you will gain new insight through this Conference, and meet old friends as you make new ones.

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Keynote Lectures

Environmental Tobacco Smoke and Lung Cancer: A Critical Assessment*

E. L. Wynder and G. C. Kabat

Summary

The possibility that exposure to environmental tobacco smoke (ETS) may increase the lung cancer risk of nonsmokers has become a cause of public concern. It is unknown whether the levels of carcinogens in the diluted sidestream smoke of tobacco products that reach the nonsmoker's lung are sufficient to induce cancer. Available epidemiologic studies suggest a slight increase in the relative risk of lung cancer in nonsmokers due to exposure to ETS created by a smoking spouse. However, not all studies have found a significant association. The epidemiologic studies are examined in the light of the criteria of judgment of causality, including strength of association, consistency, temporality, methodological issues, and biological plausibility. Suggestions for further research, including studies in high-exposure populations and greater attention to histology, are proposed.

Introduction

Epidemiologists, chemists, biologists, physiologists, physicians, and public health officials have given much attention to the association of environmental tobacco smoke (ETS) exposure and the development of lung cancer in nonsmokers. A biological basis for such an association clearly exists because smoke constituents demonstrated to be carcinogenic in laboratory animals are inhaled and retained by the nonsmoker. Metabolites of tobacco-specific smoke constituents have been identified in the saliva, blood, and urine of nonsmokers after exposure to ETS (Greenberg et al. 1984; Hoffmann et al. 1984; National Academy of Sciences 1986; USDHHS 1987; Sepkovic et al. 1988). Several epidemiological studies have found a positive association between ETS exposure – usually defined as being due to a smoking spouse – and lung cancer (Hirayama 1981; Trichopoulos et al. 1981; Correa et al. 1983; Sandler et al. 1985; Garfinkel et al. 1985; Akiba et al. 1986; Dalager et al. 1986; Pershagen et al. 1987). Other studies have found no significant association (Garfinkel 1981; Chan and Fung 1982; Koo et al. 1983; Kabat and Wynder 1984; Wu et al. 1985; Lee et al. 1986). No consistent association has been reported for lung cancer and exposure to ETS in childhood, which might be expected to exert a greater effect, especially when followed by exposure throughout adulthood. Of course, recall of ETS exposure in childhood is more difficult than recall of such exposure in adulthood.

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The epidemiological study of weak associations is burdened with problems that may yield artifactual positive findings or may show negative findings where a real association exists. The association of ETS and lung cancer risk, even if weak, would still be of concern as a public health problem in that most people are at one time or another exposed to smoke from burning tobacco products and the exhaled pollutants of tobacco smokers. A weak association in epidemiology requires careful examination and an understanding of the variables in question and all of the factors influencing the association (Wynder 1987).

In this overview we critically examine the published studies on ETS exposure and lung cancer to determine whether the evidence presented to date permits a sound conclusion as to causation.

General Exposure to ETS

At the outset we need to emphasize that an association between ETS and lung cancer must be deemed possible. A recent survey of self-reported exposure in a hospitalized population revealed that 66% of men and 60% of women had ETS exposure in childhood; 32% of the men and 61% of the women reported ETS exposure in the home in adulthood; and 60% of the men and 62% of the women who worked outside the home reported ETS exposure at work (Kabat and Wynder, unpublished data, 1987).

Critical Assessment

The first Surgeon-General's Report on Smoking and Health, published in 1964 (USPHS 1964), clearly delineated the criteria of judgment for causality. These criteria included: the magnitude of the association, consistency, temporality, and biological plausibility. Since these criteria were considered necessary to prove causation for a strong association, namely, active smoking and lung cancer, they should be equally required to determine the causality of weak associations (Wynder 1987). Let us examine the epidemiological evidence linking ETS with lung cancer in respect to these criteria.

Strength of the Association

An association is generally considered weak if the odds ratio is under 3.0 and particularly when it is under 2.0, as is the case in the relationship of ETS and lung cancer (Table 1). If the observed relative risk is small, it is important to determine whether the effect could be due to biased selection of subjects, confounding, biased reporting, or anomalies of particular subgroups.

Consistency

If an association is real, internal consistency should be apparent within and between different studies. The majority, but not all of the studies of ETS and lung cancer have shown a positive association for ETS-exposure due to a smoking spouse (Table 1). In most of the studies, the confidence interval includes 1.0. While the prospective study by Hirayama (1981a) among Japanese women showed a significant association with the husband's smoking (largely adenocarcinomas), the prospective study among American

Table 1. Summary of results of studies relating lung cancer risk in married women to their husbands' smoking habits

	Relative risk	95% Confidence interval
Prospective studies		
Hirayama (1981)	1.63	1.25–2.11
Garfinkel (1981)	1.18	0.90–1.54
Case-control studies		
Trichopoulos et al. (1981)	2.1	1.18–3.78
Chan & Fung (1982)	0.75	0.44–1.30
Correa et al. (1983)	2.03	0.83–5.03
Koo et al. (1983)	1.54	0.90–2.64
Kabat & Wynder (1984)	0.79	0.26–2.43
Wu et al. (1985)	1.2	0.6 –2.5
Garfinkel et al. (1985)	1.12	0.74–1.69
Lee et al. (1985)	1.03	0.41–2.47
Akiba et al. (1986)	1.48	0.88–2.50
Pershagen et al. (1987)	1.28	0.75–2.16

Table 2. Distribution of lung cancer by histologic groups in smokers and never-smokers. (From Kabat and Wynder 1984)

	Smokers		Never-smokers	
	Males (N = 1882) [%]	Females (N = 652) [%]	Males (N = 37) [%]	Females (N = 97) [%]
Kreyberg I	63	52	35	21
Kreyberg II	32	43	54	74
Mixed and undifferentiated/anaplastic	5	5	11	5

women by Garfinkel (1981) did not. It has been suggested that Japanese and American women are exposed to different levels of ETS due to different conditions in the two countries. Such differences could account for this disparity (Hirayama 1981b).

Within those studies presenting specific histologic analysis, differences exist in respect to the type of lung cancer involved. In active smokers, tobacco smoke exposure has a causative effect predominantly on squamous and small cell types of lung cancer (Kreyberg I), with a lesser, though still significant causative effect on the glandular type (Kreyberg II) (Wynder and Stellman 1977). Among nonsmokers, however, the glandular type of lung cancer predominates among both men and women (Kabat and Wynder 1984) (Table 2). The effect of ETS would thus be expected to be primarily responsible for the higher rate of adenocarcinomas among nonsmokers. The studies by Dalager et al. (1986) and Pershagen et al. (1987), however, suggest that the effect of ETS exposure is limited to induction of squamous cell lung cancer (Table 3). If this were, in fact, the case, then only the squamous or small cell type of lung cancer in nonsmokers

Table 3. Histology-specific odds ratios for spouse smoking from two studies

Study	Histologic type	N	Odds ratio	95% C.I.
Dalager et al. (1986)	Adenocarcinoma	16	1.02*	0.33- 3.16
	Squamous & Small Cell Ca.	14	2.88*	0.91- 9.10
	Other	18	1.31*	0.48- 3.57
Pershagen et al. (1987)	Squamous or Small Cell Ca.	20	3.3	1.1 -11.4
	Other	47	0.8	0.4 - 1.5

would be affected by ETS. Clearly, it is important that investigations of the effect of ETS exposure on lung cancer development in nonsmokers take histology into account, so as to determine whether an effect of ETS is limited to certain histological types.

Since smoking is more prevalent in lower income groups, at least among men, lung cancer in nonsmoking women in these groups should have a higher incidence. Thus, the influence of the level of education on smoking habits in the examined population needs to be considered as a possible confounder. Few studies to date have done this.

Methodological Issues

A particular concern in weak associations is reporting bias, that is, potentially differential reporting of exposures between cases and controls. In terms of ETS, does the lung cancer patient report exposure to tobacco smoke, be it at work, at home, at social functions, in childhood or adulthood, differently than the control? The case is likely to have a different attitude toward this question than does the control, a handicap not applicable to prospective studies. It needs to be determined whether the case's attitude towards questions on ETS exposure leads to under- or overreporting. Cases are likely to underreport their own smoking (Lee 1987), and they may tend to overreport their exposure to ETS and other potential hazards that could account for their illness. In studies that use proxy reports, different relatives may respond differently. Garfinkel et al. (1985) provides some insight into this phenomenon by showing that if the response came from the patient, the odds ratio was 1.0, if from the husband it was 0.92, and if from the daughter or son, 3.19 (Table 4). More work is needed on the validity of ETS-exposure information obtained from different relatives before we can evaluate which of these relative risks is closer to the truth.

In general, possible reporting bias represents a serious problem in case-control studies because it can produce a systematic artefact. It is particularly worrisome in that it cannot be effectively measured.

We also need to consider misclassification that can occur in both retrospective and prospective studies. Lee has proposed (Lee et al. 1986; Lee 1987) that the reported ETS effect on lung cancer risk can be explained by a misclassification of smokers as nonsmokers. According to these studies, a substantial percentage of respondents misrepresent their smoking habits. Using a 10.0% misclassification rate of ex-smokers as self-reported neversmokers coupled with the concordance of spouses' smoking habits,

Table 4. Data from Garfinkel et al. (1985) by type of respondent

	Husband's smoking habits at home		
	N of cases	OR	95% C.I.
Self	16	1.00	0.55– 1.74
Husband	34	0.92	0.63– 1.34
Daughter/son	48	3.19	0.91–11.19
Other	36	0.77	0.57– 1.03

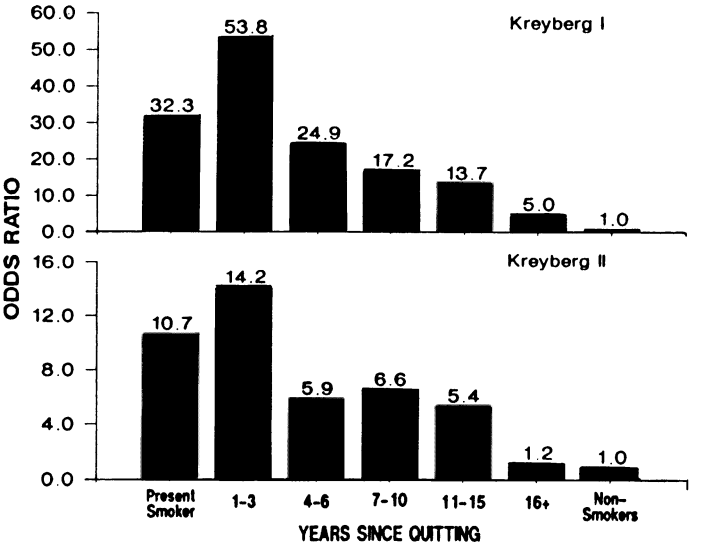

Fig. 1. Odds ratio of male ex-smokers for Kreyberg I (N = 687) and Kreyberg II (N = 301) lung cancer by years since quitting (controls = 6534). Source: American Health Foundation data

Lee calculated that an apparent increase in lung cancer risk can be obtained among nonsmokers married to smokers that approximates the increased risk observed in a number of epidemiologic studies (Lee 1987). At the extreme, Garfinkel et al. (1985) showed that 40% of lung cancer cases classified as "nonsmokers" in the hospital chart were in fact smokers as determined by interview. Although such a high rate of misclassification does not occur when cases are interviewed personally, to some extent denial is likely to occur even then, particularly among ex-smokers who had stopped smoking ten or more years ago. The risk of lung cancer among long-term ex-smokers, and even among ex-smokers who quit more than 16 years earlier, does remain elevated above the rate among those who never smoked (Fig. 1). Denial of past smoking may also not be uncommon in populations where smoking is or was socially unacceptable, as is the case among older Japanese women.

Table 5. Percent of lung cancer cases who never smoked by histologic group (A.H.F. data)

	Males				Females			
	KI*		KII**		KI*		KII**	
	[%]	N	[%]	N	[%]	N	[%]	N
1969–1973	1.2	488	5.6	142	10.7	103	23.7	76
1974–1976	1.6	887	3.0	305	16.4	263	25.3	146
1977–1980	2.1	628	4.6	390	5.6	231	22.0	245
1981–1985	1.4	725	5.6	463	6.8	311	16.6	284

* Kreyberg I
** Kreyberg II

Another problem for epidemiologists involves subgroup analysis (Stallones 1987). Investigators are likely to examine numerous subgroups, and then prefer to present those subgroups that best fit the hypothesis. This tendency represents an inherent problem in epidemiology. The investigator should at a minimum give an idea of how many subgroups were originally examined and how many subgroups were discarded.

Temporality

One of the factors that led to the conclusion that active smoking causes lung cancer was that the increase in cigarette consumption preceded the increase in lung cancer rates, first in men and later in women. Enstrom (1979) has reported an increase in the lung cancer rate in nonsmokers over recent years, suggesting that factors in addition to personal cigarette smoking influence lung cancer mortality rates. The groups examined, however, are not strictly comparable, and misclassification of smokers as nonsmokers in the national surveys needs to be considered. Our data from a long-term, hospital-based case-control study do not indicate an increase in the percentage of male nonsmokers with lung cancer in either of the two main histologic groupings (Kreyberg I and II) over the last 30 years (Table 5).

In fact, the percentage of nonsmokers with lung cancer among women has declined, which may be a consequence of the diminishing pool of women who have never smoked.

Biological Plausibility

Several studies have demonstrated that most tumorigenic agents are present in undiluted sidestream smoke in higher concentrations than in mainstream smoke (Hoffmann et al. 1983; National Academy of Sciences 1986; Hoffmann and Wynder 1986) (Table 6). Biochemical studies indicate that nonsmokers exposed to ETS have levels of nicotine or cotinine in the blood or urine that are about 1/100th the level seen in active smokers (Table 7) (Jarvis et al. 1984; National Academy of Sciences 1986). Some of the nicotine measured in the blood and urine represents nicotine that is absorbed by the saliva of nonsmokers and does not reach the lung directly (Jarczyk et al. 1987). It is important to

Table 6. Distribution of compounds in undiluted cigarette mainstream smoke (MS) and sidestream smoke (SS)

Nonfilter cigarettes

	MS	SS/MS
(A) Vapor phase		
Carbon monoxide	10 – 23 mg	2.5– 4.7
Carbon dioxide	20 – 40 mg	8 – 11
Benzene	20 – 50 µg	10
Formaldehyde	5 – 100 µg	0.1–≃50
Acrolein	50 – 100 µg	8 – 15
Acetone	100 – 250 µg	2 – 5
Hydrogen cyanide	400 – 500 µg	0.1– 0.25
Hydrazine	24 – 43 ng	3.0
Ammonia	50 – 170 µg	40 – 170
Methylamine	11.5 – 28.7 µg	4.2– 6.4
Nitrogen oxides	50 – 600 µg	4 – 10
N-nitrosodimethylamine	10 – 180 ng	20 – 100
N-nitrosopyrrolidine	2 – 110 ng	6 – 30
(B) Particulate phase		
Particulate matter	15 – 40 mg	1.3– 1.9
Nicotine	1 – 2.5 mg	2.6– 3.3
Phenol	60 – 140 µg	1.6– 3.0
Catechol	100 – 350 µg	0.6– 0.9
Hydroquinone	110 – 300 µg	0.7– 0.9
Aniline	360 ng	30
2-Toluidine	30 – 160 ng	19
2-Naphthylamine	4.3 – 27 ng	30
4-Aminobiphenyl	2.4 – 4.6 ng	31
Benz(a)anthracene	40 – 70 ng	2 – 4
Benzo(a)pyrene	10 – 40 ng	2.5– 3.5
N'-Nitrosonornicotine	120 –3,700 ng	0.5– 3
NNK	120 – 950 ng	1 – 4
Cadmium	100 ng	7.2
Nickel	20 –3,000 ng	13 – 30
Polonium-210	0.03– 1.0 pCi	?

note that nicotine occurs in ETS primarily as a vapor phase constituent rather than in the particulate matter of the aerosol as is the case in mainstream cigarette smoke (Eudy et al. 1987). Measurement of nicotine or its metabolites will, therefore, not reflect the proportional uptake of particulate matter from ETS. In the light of our present knowledge of dose-response in carcinogenesis and because the carcinogenic activity of tobacco smoke as measured in animal systems is relatively low, the question needs to be raised whether the carcinogenic potential of inhaled ETS suffices to induce lung cancer. Hoffmann and Hecht (1985) have proposed nicotine-derived nitrosamines in ETS as organ-specific carcinogens for the lung. It is possible that these chemicals reach the lungs in sufficient dose to induce neoplastic changes. These carcinogens may also be formed endogenously from inhaled or ingested nicotine and appropriate nitrosating agents (Hoffmann and Hecht 1985). Tumor promoters are less likely to play a role in ETS

Table 7. Approximate relations of nicotine as a parameter between non-smokers, passive smokers and active smokers[a]. (From Jarvis et al. 1984)

Nicotine/cotinine	Non-smokers without ETS exposure No. = 46		Non-smokers with ETS exposure No. = 54		Active smokers No. = 94
	Mean value	% of active smokers value	Mean value	% of active smokers value	Mean value
Nicotine (ng/ml)					
in plasma	1.0	7	0.8	5.5	14.8
in saliva	3.8	0.6	5.5	0.8	673
in urine	3.9	0.2	12.1*	0.7	1,750
Cotinine (ng/ml)					275
in plasma	0.8	0.3	2.0*	0.7	275
in saliva	0.7	0.2	2.5**	0.8	310
in urine	1.6	0.1	7.7**	0.6	1,390

[a] Differences between non-smokers exposed to ETS compared with non-smokers without exposure

* $p < 0.01$

** $p < 0.001$

carcinogenesis than in active smoking because of their much lower concentration. In general, tumor promoters are effective only when applied repeatedly in relatively large amounts.

In considering the existing data on ETS exposure and lung cancer, it is noteworthy that Auerbach et al. (1961) showed only minor histological changes in the bronchial epithelium of nonsmokers and found that the ciliated columnar epithelium that covers their bronchi were largely intact. Deposition of carcinogenic smoke particulates can take place only upon inhibition of the protective functioning of the lung clearance system. Squamous cell lung cancer can arise only from ciliated columnar cells that have undergone squamous metaplasia.

An active smoker with each puff from a cigarette inhales a volume of 35–50 ml of a concentrated aerosol containing 3–5 billion particles per ml that adversely affect the protective cilia and mucous defense system of the bronchi (Ferin et al. 1965). The passive smoker is at no time exposed with such force to such a highly polluted inhalant. Furthermore, ETS particles are more likely to be deposited in the upper respiratory tract and not predominantly in the bronchi as is the case in active smoking. Thus, our respiratory defense system may be able to deal more readily with the relatively lighter deposition of particles and exposure to volatiles in ETS, as the observation by Auerbach et al. (1961) would suggest.

Future Studies

Future epidemiological studies on the association of ETS with lung cancer should attempt to avoid the pitfalls discussed above. The definitive evidence that a factor causes

human cancer requires support from descriptive, metabolic, and molecular epidemiology.

Beyond extension of prospective studies, such as those now in progress by Garfinkel and Stellman at the American Cancer Society, we suggest:

1) Continuing ongoing case-control studies with special reference to histologic type and careful consideration of methodological issues.
2) Estimating the relative importance of ETS exposure in different settings – in the home, in the workplace, in social situations, and during transportation.
3) Further studying lung cancer rates among pipe and cigar smokers, and, if feasible, among nonsmokers exposed to ETS from these products.
4) Studying lung cancer incidence in groups occupationally exposed to high levels of ETS at their worksite such as waiters, bartenders, train conductors, airplane personnel, and office workers.
5) Studying bronchial epithelium in autopsy material of established never-smokers whose exposure to ETS is known.
6) Determining the incidence of lung cancer by histological type in confirmed never-smokers.
7) Comparing the presence of adducts of tobacco-specific carcinogens with DNA in smokers, passive smokers, and "never-smokers" (Hoffmann and Hecht 1985; Hecht et al. 1987).

In summary, verification of the possible association of ETS and lung cancer represents an important challenge to epidemiologists, laboratory scientists, and public health authorities. The public is entitled to inhale the cleanest possible air regardless of whether ETS is proven to be cancer-inducing. Additional efforts on the part of epidemiologists are required to firmly establish the nature and significance of the reported associations between passive smoking and lung cancer.

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Measuring Exposure and Assessing Health Effects of Environmental Tobacco Smoke

B. S. Hulka

Summary

The predominant source of environmental tobacco smoke (ETS) is sidestream smoke (SS) emitted from the smoldering end of cigarettes. While SS is known to contain toxic and carcinogenic compounds, SS is diluted and its physicochemical characteristics are altered in the formation of ETS. Exposure to ETS can be assessed by questionnaires, air monitoring, mathematical modeling of ambient concentrations, or biological markers. Nicotine and its metabolic product, cotinine, are useful biological markers of integrated dose over the past several hours or days, respectively. Detectable concentrations of cotinine can be found in the urine of ETS exposed nonsmokers and in the urine of infants exposed to smoking parents.

Health effects of ETS can be classified as acute irritant effects, pulmonary, and nonpulmonary effects in children, and lung cancer, other cancers and cardiovascular alterations in adults. Acute irritant effects include noxious odor and reactions of the eyes, nose, and throat.

The most consistent findings on adverse health effects of ETS are on the respiratory tracts of young children. There is a 20% to 80% increase in respiratory symptoms – coughing, sneezing and sputum production – among young children of smoking parents as compared to those of nonsmoking parents. Bronchitis and pneumonia are diagnosed nearly twice as often during the first year of life among children of smoking parents compared to children of nonsmoking parents. There is a dose-response relationship between risk of respiratory problems and number of smokers in the home and/or number of cigarettes smoked.

The most significant nonpulmonary effect of ETS on children is the risk of reduction in birthweight. Nonsmoking pregnant women with smoking spouses produce newborns of slightly lower average birthweight than similar women with nonsmoking spouses.

Compilation of numerous studies from many countries indicates that the risk of lung cancer to nonsmoking spouses of smokers is about 30% greater than the risk for nonsmoking spouses of nonsmokers. The size of the relative risk estimates vary by author and country but the 95% confidence intervals around all the point estimates include a relative risk (RR) of 1.3. A positive association between number of cigarettes smoked per day and the RR has been reported. Studies of cancers, other than lung, have been few and methodologically problematic.

With respect to cardiovascular effects, ETS exposure in healthy adults and children has not been shown to increase pulse rate or blood pressure under resting conditions or during exercise. ETS exposure to persons with preexisting cardiovascular disease has produced inconsistent results. Recent reports from population-based studies indicate

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that chronic exposure to ETS increases the risk of morbidity and mortality from cardiovascular diseases in nonsmoking persons.

Introduction

Characterization of ETS

Environmental tobacco smoke (ETS) is that complex mixture of chemical compounds which are found in the ambient air as the result of smoking combustible tobacco products. The major source of ETS is sidestream smoke (SS) which is emitted from the burning end of a cigarette in-between puffs. The remainder of ETS consists of exhaled mainstream smoke (MS), smoke which escapes from the burning end of the cigarette during puff-drawing, and gases which diffuse through the cigarette paper during smoking. Each of the mixtures – MS, SS and ETS – is an aerosol consisting of a particulate and a vapor phase.

However, the composition of MS, SS and ETS differ considerably as the result of

1) changes in the concentrations of individual constituents,
2) the phase (particulate or vapor) in which the constituents are present, and
3) various secondary reactions that chemically and physically alter, or "age", the smoke.

More than 3,800 chemical compounds have been identified in MS cigarette smoke, many of which are toxic and/or carcinogenic. Undiluted SS smoke contains even higher concentrations of some toxic compounds; these include ammonia, volatile amines, nicotine decomposition products and aromatic amines. However, concentrations of these SS emissions are significantly diluted in the indoor space where ETS exposure takes place.

ETS contains both vapor and particulate phases. The hydropohobic vapor phase constituents of ETS are likely to enter the lung of the exposed individual, while the hydrophilic vapor phase constituents are likely to be absorbed in the upper respiratory tract. Much of the particulate phase is comprised of small particles, $<2.5\,\mu m$ referred to as respirable suspended particles (RSP). These can be inhaled deeply into the lung. To the extent that radioactive decay products in tobacco itself and/or short-lived radon daughters present in ambient air are adsorbed on the RSP, the carcinogenic potential of ETS is enhanced.

ETS Exposure Assessment

Exposure to ETS can be assessed by questionnaire, air monitoring, mathematical modeling of ambient constituents or biological markers. At present there is no ideal indicator of cumulative, long-term exposure to ETS.

Replies to *qestionnaires* can be used as a basis for classifying individuals into broad categories of ETS exposure, recognizing the potential for misclassification of exposure through

1) errors in reporting current smoking habits,
2) reporting an exsmoker as a nonsmoker and
3) neglecting exposure to ETS in the full range of microenvironments experienced in daily life.

Quantification of integrated exposure over many years is not likely to be fully reliable or accurate, although this is the information which would be most useful in accessing longterm health effects. In many studies of health effects, the proxy measure of ETS exposure is smoking status of spouse or parents. The individual may be his or her own informant, or serve as a surrogate informant for the spouse. Smoking histories obtained from closely related surrogates have been found to be reasonably accurate.

The use of *air monitoring* by personal or indoor space monitors is handicapped by the lack of definition of the physicochemical properties of ETS and the inadequate identification of the individual constituents associated with the particular health effects under study. Surrogate constituents have been used as indicators of current ETS exposure in both personal and indoor space monitoring. Foremost among these are RSP and nicotine. An ideal marker of exposure to ETS should be

1) unique to tobacco smoke,
2) present in sufficient quantity in tobacco smoke to be measurable at low concentrations,
3) present in a fairly constant ratio to other tobacco smoke constituents which may be the actual culprits with respect to adverse health effects.

Nicotine appears to meet at least the first two criteria, whereas ETS is the primary, but not exclusive, source of RSP in indoor air.

It should also be noted that ETS levels are the result of complex interactions of several factors including room size, temperature, humidity, air exchange rates, number of persons occupying the space and number of cigarettes smoked.

Biological markers that have been most useful for assessing recent exposures to ETS are nicotine and its metabolite, cotinine. They are derived almost exclusively from tobacco products, of which tobacco smoke is the most important direct source. They can be identified and quantified in blood, urine, saliva and cervical mucous. The mean concentration of cotinine in urine of nonsmokers exposed to ETS is one percent or less than the mean values observed in active smokers. Urinary cotinine concentrations in infants and children have been reported o increase directly with the number of smokers in the home.

The main deficiency with these proxies for ETS exposure is their relatively short half lives in body fluids. For nicotine it is a matter of hours, and for cotinine more nearly a day. (The duration is dependent on the particular body fluid being studied.) Recently, an adduct of hemoglobin (4-aminobiphenyl hemoglobin) with a half life of four months has been reported in active smokers [1], but its utility as a biological marker of ETS exposure has yet to be determined.

Health Effects of ETS

Acute Irritant Effects

Almost all nonsmokers are familiar with the irritant effects of ETS. They tend to be of two types: Unpleasant odor is most commonly experienced by nonsmokers entering an area with active smoking or an area which has been permeated previously with tobacco smoke. Eye, nose and throat irritation are frequent complaints of nonsmokers occupying a space also used by active smokers. Headaches, nausea and dizziness may be a part of this reaction. There are hypersensitive individuals who have enhanced reactivity to ETS. That such persons exist is certain; the areas of uncertainty involve identifying which

smoke constituents are responsible for the effects and the inherited or acquired susceptibility factors which account for the hypersusceptibility.

It is known that vapor phase ETS constituents are responsible for the odor and irritant effects. This information in itself poses problems since ventilation and filtration systems are engineered primarily to remove particulates, which provide little relief from the irritant constituents in the vapor phase. The ventilation rate required to alleviate just the olfactory insult experienced by nonsmokers entering a smoking area is at least 5 fold greater than that required on entry to a nonsmoking area.

Health Effects in Children

Pulmonary Effects: Respiratory symptoms such as wheezing, coughing and sputum production are more common in children of smoking parents than in children of nonsmokers. Data from the largest studies place the increased risk at 20% to 80%, depending on the particular symptom being assessed and the number of smokers in the household. Bronchitis, pneumonia and other lower respiratory tract illnesses occur up to twice as often during the first year of life in children of smoking parents than in children of nonsmokers. This observation is also reflected in the increased rate of hospitalizations for respiratory infections among infants of smoking parents. For both respiratory symptoms and medically diagnosed respiratory infections, there is a dose-response relationship between number of smokers in the home and/or number of cigarettes smoked. The relationships are stronger for maternal than for paternal smoking. These associations persist after allowing for possible confounding factors such as occupational history, socioeconomic status, respiratory illness in the parents and birthweight of the child.

These points are illustrated in Table 1 and Fig. 1. The table shows the positive association between rates of hospital admission for respiratory illnesses during the first year of life and number of cigarettes smoked daily by the mother. Figure 1 illustrates a similar point relating the risk of three different indicators of respiratory illness to number of cigarettes smoked per day by the mother.

The mechanism of the increased risk of respiratory illness in young children of smoking parents may operate either through a direct effect of ETS on the respiratory tract or through a greater opportunity for cross infection in homes of smokers.

Table 1. Hospital admission rates in the first year of life for bronchitis and pneumonia per 100 infants by maternal smoking and number of cigarettes smoked daily. (From [4])

Nonsmokers		Smokers			Total
Never smoked	Former smokers	Cigarettes per day			
		1–10	11–20	21+	
(8,900)*	(786)	(747)	(179)	(60)	(10,672)
9.6	7.8	10.8	16.2	31.7	9.8

Note: Differences among three categories of smoker $p < 0.001$

* Number of infants in parentheses

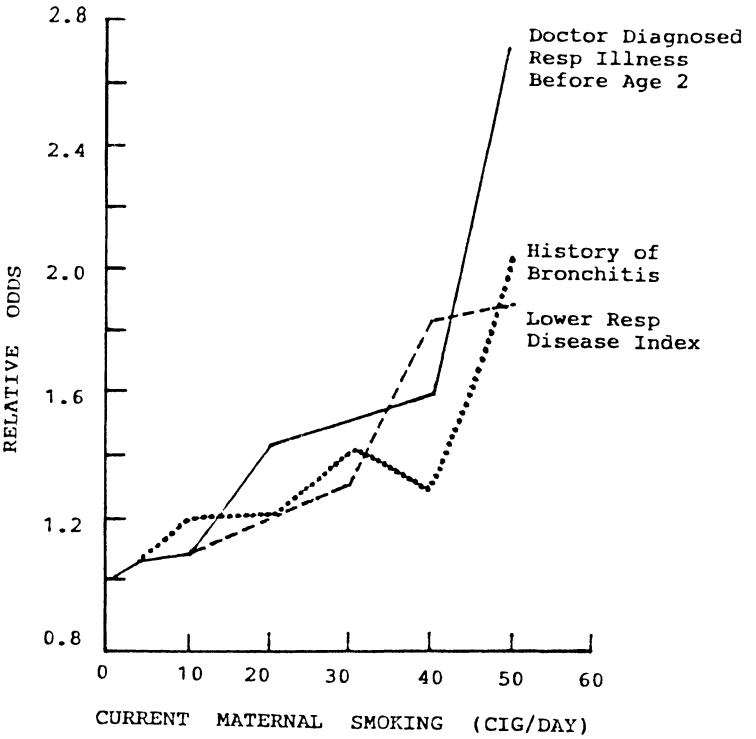

Fig. 1. Relative odds of respiratory illness or symptoms versus average daily cigarette smoking by the child's mother. (From [6])

Regardless of the mechanism, the exposure of young children to smoking in the home puts them at increased risk of respiratory illnesses.

Parental smoking may have a small effect on their children's lung function as measured by forced expiratory volume (FEV_1). This effect appears as a small reduction in the expected increment in FEV_1 which takes place during normal growth and development. Although an annual decrease of 0.5% or even less from the expected rate is unlikely to be clinically significant, it could reflect pathophysiologic changes relevant to the development of chronic airflow obstruction in adult life.

Nonpulmonary Effects: Nonsmoking pregnant women exposed to smoking spouses or other sources of daily ETS exposure are at increased risk of delivering infants of slightly lower birthweight than comparable unexposed women. A best estimate of the average difference in birthweight between neonates with in utero ETS exposure and those without such exposure is 24 grams. A dose response relationship between number of cigarettes smoked by the fathers and birthweight of the neonates of nonsmoking mothers has been reported.

Other adverse effects of ETS include increased rates of chronic ear infections and middle ear effusions among children with household exposure to ETS.

It must be emphasized that for all postnatal health effects in children, it is often not possible to differentiate the effect of in utero exposures to ETS from subsequent childhood exposures.

Health Effects in Adults

Lung Cancer: Exposure to ETS increases the incidence of lung cancer in nonsmokers. Estimates of the magnitude of the increased risk vary. Among studies of various populations in Europe, Asia and North America, the risk of lung cancer is roughly 30% higher for nonsmoking spouses of smokers than for nonsmoking spouses of nonsmokers. There is consistency among the studies in that the 30% increased risk is included within the 95% confidence interval for each study. Patterns and extent of ETS exposure may vary in different communities and countries. The estimate of the increased risk from the American studies is lower than the average for all studies combined, although this difference is not statistically significant. These risk estimates are mostly derived from the comparison of nonsmoking persons identified as ETS exposed, or unexposed, on the basis of their spouse's smoking habits.

Two types of bias in epidemiologic studies are likely:

1) Misclassification of current smokers and exsmokers as nonsmokers. This bias acts to artificially increase the observed relative risk.
2) Misclassification of persons as unexposed who truly have workplace or other exposures to ETS. This bias acts to artificially reduce the observed relative risk.

When correction is made for both types of bias, the resulting estimate of risk for lung cancer among nonsmokers exposed to ETS approximates the 30% excess observed in the epidemiologic studies.

Tables 2 and 3 illustrate data from selected case control and cohort studies, respectively. Except for Garfinkel, 1981, each study shows increased lung cancer risk with increasing number of cigarettes smoked by the spouse. Figure 2 shows the overall risk

Table 2. Risk of lung cancer in nonsmokers according to cigarette consumption of spouse: case-control studies. (From [5])

Authors	Exposure	Relative risk*
Trichopoulos et al. 1983	Exsmoker	1.0
	Cig/day 1–20	2.4
	21+	3.4
Garfinkel et al. 1985	Cig/day 1–19	0.84
	20–39	1.08
	40+	1.99
	Cigar/pipe	1.13
Akiba et al. 1986	Cig/day 1–19	1.3
	20–29	1.5
	30+	2.1

* Relative risk for nonsmokers married to nonsmokers is 1.0

Table 3. Risk of lung cancer in nonsmokers according to cigarette consumption of spouse: cohort studies. (From [5])

Authors	Exposure		Relative risk[a]
Hirayama 1984	Cig/day	1–19	1.45
		20+	1.91
Garfinkel 1981	Cig/day	1–19	1.27[b]
		20+	1.10[b]

[a] Relative risk for nonsmokers married to nonsmokers is 1.0
[b] Mortality ratios, not relative risks

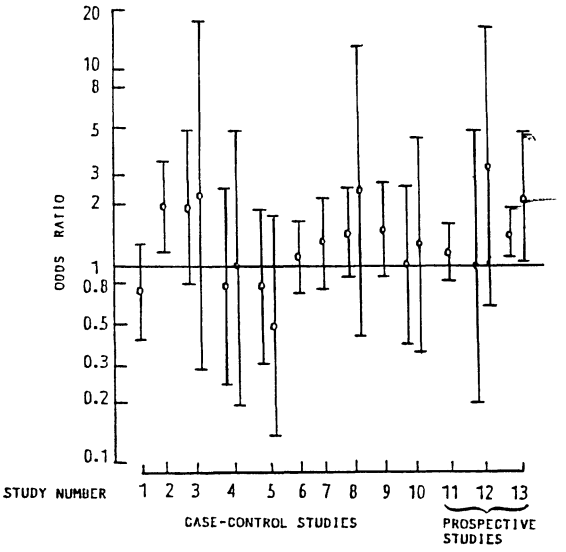

Fig. 2. ETS exposure by nonsmokers and lung cancer. (From [5])

estimates and 95% confidence intervals from each of 13 studies (selected on the basis of meeting minimum methodologic criteria). For only two of these studies does the 95% confidence interval exclude unity, but for most of the studies the 95% confidence intervals are very broad. Figure 3 shows the risk estimates for all 13 studies combined and for various subsets of them. These summary estimates of risk are consistent with a 30% excess lung cancer risk among nonsmokers exposed to ETS.

Cancers Other Than Lung Cancer: Uncertainty exists concerning the possible risk of cancers other than lung for nonsmokers exposed to ETS. Epidemiologic studies have been few and the results inconsistent. Other cancers known to be associated with active smoking should be obvious targets of inquiry. In addition, studies of cancers not traditionally associated with active smoking are reasonable candidates for study, since ETS is known to contain carcinogens, some of which are different from those in MS. The primary prerequisites for any such studies must be adequate numbers of subjects, good quality exposure data and information on potential confounders.

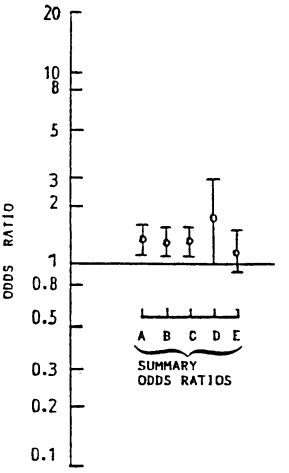

Fig. 3. ETS exposure by nonsmokers and lung cancer. (From [5]) A = all studies; B = all studies with at least 20 expected cases; C = only female studies; D = only male studies; E = all U.S. studies

Table 4. Relative risk estimates, wife who smoked compared with wife who did not smoke, for men who never smoked, MRFIT, 1973–1982. (From [2])

Endpoint	Relative risk*	P value	95% confidence interval
Death from any cause	1.94	0.08	0.91–4.09
Coronary heart disease death	2.23	0.17	0.72–6.92
Fatal or non-fatal coronary heart disease event	1.61	0.07	0.96–2.71

* Adjusted by Cox proportional hazards regression for age, baseline blood pressure, cholesterol, weight, drinks per week, and education

Cardiovascular Disease: Studies of acute ETS exposure in healthy children and adults have shown no statistically significant alterations in heart rate or blood pressure either during resting conditions or during exercise. Studies of ETS exposure in persons with preexisting atherosclerotic heart disease have been inconclusive. Important questions about ETS exposure and the induction of angina, electrocardiographic abnormalities, and cardiac arythmias are unanswered.

A priority area for population-based research is to resolve uncertainties about chronic ETS exposure and morbidity from cardiovascular disease. A recent report by Svendsen et al. [2] using data from the Multiple Risk Factor Intervention Trial, provides substantial evidence on adverse effect of ETS. All cause mortality, death from coronary heart disease, and nonfatal coronary events exhibited higher rates and relative risks among nonsmoking men with smoking spouses than among nonsmoking men with nonsmoking spouses (see Table 4). These findings are also substantiated by a second recent report from Washington County, Maryland, USA [3].

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Increased Risk of Lung Cancer in Non-smokers Married to Smokers: A Result of ETS Exposure or of Bias?

P. N. Lee

Summary

Combined evidence from at least 15 epidemiological cohort and case-control studies appears to indicate non-smokers married to smokers have a risk of lung cancer 30%–40% higher than that of non-smokers married to non-smokers. This increase is surprisingly large, given the very low level of exposure to smoke constituents of non-smokers compared with that of smokers. The possibility that it results wholly or in part from bias, rather than as a direct effect of exposure to environmental tobacco smoke (ETS), must be considered seriously. Weaknesses of much of epidemiological evidence and the various possible sources of bias are discussed in detail.

One serious potential source of bias arises if even a small proportion of smokers are misclassified as non-smokers. Data from a series of studies specifically designed to determine accuracy of statements on current smoking habits (by salivary cotinine measurements) and on past smoking habits by repeated questionnaires) suggests that such misclassification might cause bias large enough to explain a major part, and perhaps all, of the apparent increase in lung cancer risk related to spouse smoking. Whilst evidence from a detailed review of the available literature on misclassification of smoking habits, is consistent with this view, there is a need for more research on this issue. Future epidemiological studies on passive smoking and lung cancer need to obtain more objective and reliable information on the subject's smoking habits and exposure to ETS. Bias can also arise if positive studies are more likely to be reported than negative studies and research is needed to attempt to estimate the extent of this bias.

Data currently available do not permit reliable conclusions to be drawn concerning the relationship of ETS exposure to lung cancer risk.

The Association

Since the early studies of Hirayama (1981) and Trichopoulos et al. (1981) reporting that never smokers married to smokers have a higher risk of lung cancer than those married to non-smokers, further epidemiological evidence has accumulated. Table 1 summarizes evidence from 16 published studies, 1–3 being prospective studies and 4–16 case-control studies. Wald et al. (1986), based on results from studies 1–13, reported an overall significant relative risk of 1.35, with 95% confidence limits of 1.19–1.54. This estimate is in broad agreement with other estimates of 1.30 (Lee 1984), 1.41 (Wells 1986) and 1.2–1.5 (Doll 1986). It would not be materially affected by including results from studies 14–16 of Table 1 since they are all small, and have relative risks that vary either side of the average.

While the overall evidence, which is based on a total of almost 1,200 lung cancer deaths in never smokers, predominantly in females, suggests a statistically significant

H. Kasuga (Ed.) Indoor Air Quality

Table 1. Summary of epidemiological studies of risk of lung cancer in never smokers in relation to environmental tobacco smoke exposure

Study number	Authors	Study location	Sex	Number of lung cancers[a]	Relative risk	Significance[b]
1	Hirayama (1981, 1984)	Japan	F	163	1.63	Yes
			M	64	2.25	Yes
2	Garfinkel (1981)	USA	F	153	1.17	No
3	Gillis et al. (1984)	Scotland	F	8	1.00	No
			M	6	3.25	No
4	Trichopoulos et al. (1981, 1983)	Greece	F	77	2.11	Yes
5	Chan and Fung (1982)	Hong Kong	F	84	0.75	No
6	Correa et al. (1983)	USA	F	22	2.07	(Yes)
			M	8	2.00	No
7	Buffler et al. (1984)	USA	F	41	0.78	No
			M	11	0.52	No
8	Kabat and Wynder (1984)	USA	F	24	0.79	No
			M	12	1.00	No
9	Koo et al. (1984, 1987)	Hong Kong	F	88	1.64	No
10	Garfinkel et al. (1985)	USA	F	134	1.31	(Yes)
11	Akiba et al. (1986)	Japan	F	94	1.50	No
			M	19	1.80	No
12	Lee et al. (1986)	England	F	32	1.00	No
			M	15	1.30	No
13	Pershagen et al. (1987)	Sweden	F	67	1.20	No
14	Wu et al. (1985)	USA	F	29	1.20	No
15	Ziegler (in Delager et al. (1986))	USA	M	16	<1	No
16	Humble et al. (1987)	USA	F	20	1.80	No
			M	8	>1.80	No

[a] Among never smoking subjects

[b] Yes = significant at 95% confidence level in comparison of exposed and non-exposed subjects; (Yes) = significance only in trend analysis or in subjects exposed to heavy smokers

association, it is not at all clear that it represents a causal effect of exposure to environmental tobacco smoke.

Before coming to any conclusion it is necessary to consider two important questions:

(a) Is the magnitude of the association plausible, in view of what is known about the epidemiology of active smoking and the relative levels of smoke constituents to which smokers and non-smokers are exposed?

(b) Is the epidemiological evidence open to any serious bias which might affect relative risk estimates in specific studies, or generally?

Table 2. Comparison of relative risks of lung cancer in relation to passive and active smoking

Study number	Authors	Sex	Relative risk		Ratio of excess risk
			Passive	Active	
1	Hirayama (1981, 1984)	F	1.63	3.81	0.22
		M	2.25	4.91	0.32
3	Gillis et al. (1984)	F	1.00	1.53	0.00
		M	3.25	5.92	0.46
4	Trichopoulos et al. (1981, 1983)	F	2.08	2.90	0.57
5	Chan and Fung (1982)	F	0.75	3.07	−0.12
6	Correa et al. (1983)	F	2.07	18.51	0.06
		M	2.00	18.27	0.06
7	Buffler et al. (1984)	F	0.78	5.37	−0.05
		M	0.52	5.26	−0.11
9	Koo et al. (1984, 1987)	F	1.64	3.80	0.23
11	Akiba et al. (1986)	F	1.50	3.36	0.21
		M	1.80	3.55	0.31
12	Lee et al. (1986)	F	1.00	4.75	0.00
		M	1.30	12.91	0.03
14	Wu et al. (1985)	F	1.20	4.50	0.06

Plausibility

Table 2 compares relative risks of lung cancer in relation to passive and active smoking. The passive smoking estimates compare risk in never smokers according to whether or not they are married to a smoker, while the active smoking estimates compare ever smokers and never smokers. Exceptionally, in studies 1 and 3, the comparison is in relation to current rather than ever smoking. The table also shows the ratio of excess risk in relation to passive and active smoking. Nine of the 16 ratios suggest an effect of passive smoking 6% or less than that of active smoking, while seven suggest an effect 20% or more. Overall the epidemiological data appear to be indicating that passive smoking has 10–15% of the effect of active smoking. Most studies of active smoking suggest a linear relationship between lung cancer risk and number of cigarettes smoked per day, though a quadratic relationship has been proposed (Doll and Peto 1978). It follows that if the epidemiological data are unbiased one would expect that the average dose received from passive smoking is at least 10%–15% of that from active smoking.

Many workers have used the (virtually) tobacco specific marker cotinine as an indicator of exposure of passive and active smokers. Table 3, based on an extensive UK study by Lee (1987) which will be referred to in more detail below, found that the increase in salivary cotinine in relation to passive smoking was less than 1% of that in relation to active smoking. Similar findings have been reported by other workers (e.g. Jarvis et al. 1984). The only study reporting relative levels much higher than this (Matsukura et al. 1984) has been questioned (Adlkofer et al. 1985; Pittenger 1985).

Since lung cancer risk in smokers is generally thought to be related to particulate matter rather than nicotine, it can be argued that an index of relative exposure of passive

Table 3. Salivary cotinine levels in relation to active and passive smoking

Exposure	Sex	Salivary cotinine (ng/ml)		
		Exposed	Non-exposed	Differences
Active smoking	M	319.2	0.85	318.3
	F	310.6	0.40	310.2
Spouse smoking (among non-smokers)	M	2.9	0.6	2.3
	F	1.0	0.3	0.7
Ratio of differences		Male 0.7%		
		Female 0.2%		

Table 4. Smoking related particulate levels in US smokers and non-smokers

Measure	Sex	Smoking related particulates (mg/day)		
		Active smoker	Non-smoker	Ratio
Inhaled dose	M	477.3	0.63	0.1%
	F	366.5	0.30	0.1%
Retention		80%	11%	
Retained dose	M	381.8	0.069	0.02%
	F	293.2	0.033	0.01%

and active smokers based on particulate matter would be more relevant. Table 4, based on Arundel et al. (1986), gives estimates for the US population of relative inhaled and retained particulate matter doses of non-smokers and active smokers. The ratios in Table 4 have to be adjusted upwards by a factor of 2 or 3 to make them comparable with the data in Tables 2 and 3, since (see Table 3) the difference between exposed and non-exposed non-smokers is two to three times the average level of non-smokers. This brings the inhaled dose estimates broadly in line with the cotinine estimates, though the retained dose estimates are about an order of magnitude lower. The lower figure for retained particulate matter is based on the work of Hiller et al. (1982a,b) who found that the collection efficiency of particles in environmental tobacco smoke is 11%, in contrast to the substantially higher figure of 80% for mainstream smoke. Robins (1986) also calculated that non-smokers take in the equivalent of an extremely small number of cigarettes per day in terms of respirable particulates. He noted that estimates of cigarette equivalents based on cotinine may be misleadingly high, since, whereas nicotine is in the particulate phase in mainstream smoke and will be absorbed mainly through the lungs, nicotine in ETS is mainly in the vapour phase, and, being water soluble, can be absorbed through the mucous membranes without ever reaching the lungs.

There appears to be a *huge discrepancy,* of two or perhaps three orders of magnitude between the claimed relative effects of passive and active smoke exposure and the much smaller relative exposure of passive and active smokers. What might explain this huge discrepancy?

One might argue that studies of active smoking, by including exposed and non-exposed non-smokers in their comparison group, underestimate the effect of active smoking so that the ratios in Table 2 are too high.

This is irrelevant for three reasons:

(a) the comparison between Tables 2 and 3 is in fact direct and not affected by this false baseline problem,
(b) failure to take the false baseline into account would have virtually no effect if risk was proportional to exposure and exposures in passive smokers are so low and
(c) it ignores a bias in the opposite direction due to failure to take into account the fact that smokers obviously have greater passive smoke exposure than do non-smokers.

Another point to be considered is duration of smoking. Since, in active smokers, risk of lung cancer is approximately related to the 4th power of duration of smoking (Doll and Peto 1978), one might infer that failure to take account of differences in duration might cause relative bias by a factor of 3.2 ($= 60_4/45_4$) when comparing a 60 year old non-smoker exposed to passive smoke from birth and a 60 year smoker who started at age 15. Actually, the relative bias will be much less than this for two reasons. First, by no means all passive smokers will have been exposed since birth. Second, the "duration to a power" formula is only a valid approximation at smoker doses. Assuming a multistage model, it can easily be shown that at low doses the excess risk in relation to passive smoking becomes approximately linearly related to duration of smoking.

Neither of the above points really affect the huge discrepancy for which an explanation is being sought. If one is still wishing to accept the epidemiology as valid, one would have to seek an explanation either in a greater toxicity of ETS than mainstream smoke or in a greater susceptibility of non-smokers. While there is evidence that sidestream smoke has higher concentrations of some toxic chemicals than mainstream smoke, the relevance of this finding to environmental tobacco smoke which is aged, vastly diluted, chemically altered sidestream smoke, is not at all clear. There does not appear to be any direct evidence that ETS is particularly noxious. Nor is there any direct evidence that active smoking reduces susceptibility to relevant effects of ETS.

Limitations of Epidemiology

While it is not possible to completely rule out such explanations, the obvious alternative explanation – that the epidemiology is in some way biassed – seems on the face of it much more plausible. While the claimed effect of passive smoking may be large when viewed against the magnitude of effect predicted on dosimetric grounds, it is actually quite small when viewed against the magnitude of effect it has proved possible in the past to reliably identify using epidemiological methods. Alderson (1983) has suggested that a well designed case-control study should be able to confirm a two fold difference in risk but that, for differences less than this, the power of the study design may be inadequate. While case-control studies are particularly susceptible to a variety of sources of potential bias, this conclusion may well be true for any non-randomised epidemiological study (Lee 1988a).

In trying to assess whether bias might have arisen in the epidemiological evidence it is necessary to consider potential limitations of the available data. A number of general points can be made:

Unrepresentativeness

Although it is clear that the combined study population in Table 1 is not fully representative of non-smokers, this does not appear to be a serious issue, since studies have been carried out in the US, UK, Greece, Sweden, Japan and Hong Kong, and Wald et al. (1986) found no evidence of significant heterogeneity of relative risk estimates.

Sample Size

While none of the studies considered in Table 1 concern particularly large numbers of non-smokers with lung cancer, chance can hardly be the total explanation of the association between passive smoking and lung cancer since the overall relative risk estimate quoted by Wald et al. (1986) of 1.35 is quite highly statistically significant, with 95% confidence limits of 1.19–1.54.

Confounding

Not all the studies considered have taken into account the possible confounding effect of factors known or suspected to be related to lung cancer, such as occupation or nutrition. Although it would perhaps be expected that non-smokers married to smokers might to some extent share the tendency of smokers to work in dirtier jobs, standardisation for occupation, or indeed any confounding factor, has never been found in practice to explain any material part of the association between lung cancer and passive smoking. It does not seem likely that failure to take confounding factors into account has materially affected the issue.

Inappropriate Choice of Controls

General scientific principles demand that like should be compared with like as far as possible. In a number of studies, there were clear exceptions to this. One example is the study of Trichopoulos et al. (1981, 1984) in which controls came from a different hospital. This may cause bias if patients came from different catchment areas with different smoking characteristics. Another example is the recently reported study of Humble et al. (1987), in which virtually all the interviews with controls were conducted directly while much of the data for cases came from surrogates. While inappropriate choice of controls may have materially biassed a few studies, it does not seem very likely, however, that it is a major explanation for the huge discrepancy.

Inaccuracy of Disease Classification

It is well known that diagnosis of lung cancer is imperfect and studies such as those by Garfinkel et al. (1985) which took pains to check and review all available evidence are to be preferred to those that did not do so. However, random misclassification of diagnosis would be expected to reduce the observed association between lung cancer and passive smoking, not increase it, and differential misclassification of diagnosis does not seem very likely, inasmuch as the doctor making the diagnosis is likely to have been blind to the

patient's ETS exposure in most cases, and not to have been affected by it even if he was, given most diagnoses were made before the first study on the issue was published in 1981.

Non-reporting Bias

A problem in combining results from various studies to come to an overall assessment of the evidence, by so-called "meta-analysis", is the possibility that the studies being combined are not representative of all those that have been carried out. In particular, overall estimates of relative risk may be biassed upward if a scientist is less likely to submit for publication, or a journal is less likely to publish, studies which show no significant relationship of disease to the factor of interest or a significant trend in the direction opposite to that expected in advance. Convincing evidence of bias resulting from this in the context of randomised controlled trials has recently been collected by Chalmers et al. (1987) and the problem may generally be greater in epidemiological studies. One can easily imagine an investigator running a range of statistical analyses, finding a few significant associations of interest, and then publishing papers on those, ignoring the non-significant relationships. One can also imagine journals not being too keen to given space to a paper on a new null association and one must inevitably wonder whether the reason the first two studies published on passive smoking and lung cancer (Hirayama 1981; Trichopoulos 1981) found a significant association was because first published papers on any association tend to be positive. Indeed, there seems a case for carrying out meta-analysis giving most weight to studies showing no association and least weight to studies published first.

Although it is obviously important to conduct research into the problems of non-reporting bias in epidemiological studies, it is difficult to claim that it is the full explanation of the overall association between passive smoking and lung cancer. The reasons for this view are two-fold. Firstly, the overall association remains significant (though the relative risk estimate reduces to 1.20), even after eliminating the Hirayama and Trichopoulos results. Secondly, the fact that lung cancer and passive smoking has been a very "hot" issue in recent years suggests researchers should now be able to publish results from studies showing no association between passive smoking and lung cancer risk.

Lack of Objective Measure of ETS Exposure

A limitation of all the published epidemiological evidence is lack of objective measurement of exposure to ETS. Subjects are classified mainly by whether or not they are married to a smoker and occasionally by reported degree of exposure outside the home, but there are no data available either on ambient levels of tobacco smoke constituents at home or at work or on levels in body fluids such as blood, urine or saliva. While (e.g. see Table 3) it can be shown that marriage to a smoker is indeed associated with increased levels of cotinine, the relatively crude method used for determining exposure leads to possibilities of bias in case-control studies where knowledge of disease may consciously or subconsciously affect reporting of ETS exposure. While this may have caused upward bias of the reported relative risk in some case-control studies, it can hardly explain the whole association, since it would not be expected to cause upward bias in prospective studies and the association seems as strong in prospective as in case-control studies.

Table 5. Hypothetical example of bias due to misclassification of 5% of smoking subjects as non-smokers

Smoking habit*		Assumed		Observed			
Subject	Spouse	N	Risk	N	Risk	Passive effect	Active effect
NS	NS	60	1	60 + 2 = 62	1.61	1	
NS	S	40	1	40 + 3 = 43	2.33	1.44	
NS	Total	100	1	100 + 5 = 105	1.90		1
S	NS	40	20	40 − 2 = 38	20		
S	S	60	20	60 − 3 = 57	20		
NS	Total	100	20	100 − 5 = 95	10		10.5

Assumed concordance = $(60 \times 60)/(40 \times 40) = 2.25$
Observed concordance = $(62 \times 57)/(43 \times 38) = 2.16$

* NS, non-smoker; S, smoker

Lack of Objective Measure of Active Smoking Status

Although considered last, this appears to be the most serious problem affecting the epidemiological evidence on passive smoking and lung cancer. As will be shown in the next section, completely erroneous conclusions can be reached when the "non-smokers" being studied actually include a small proportion of misclassified true smokers.

Misclassification of Active Smoking Habits as a Major Source of Bias

As shown in Table 5, misclassification of a small proportion of smokers as non-smokers, coupled with a tendency for smokers to be married to smokers ("concordance") can create an apparent positive effect of passive smoking when no actual effect exists. It also leads to an underestimation of the active smoking effect and of the concordance. The passive smoking bias depends critically on the assumed relative risk for active smoking, the degree of concordance and on the level of misclassification of subject smokers as non-smokers. This source of bias will also produce an artificial dose response relationship when the "non-smoking" subjects are divided according to the amount smoked by the spouse. It can be shown (Lee 1988b) that misclassification of non-smoking subjects as smokers and of smoking spouses as non-smokers causes a degree of bias that is minor compared with that resulting from misclassification of smoking subjects as non-smokers.

In an attempt to determine the extent to which smokers misreported their smoking habits and to which smokers tend to be married to smokers, Lee (1987) carried out three separate studies. In the first study, which concerned accuracy of reported current habits, 1775 British subjects were asked about their smoking habits and use of other nicotine products in a non-health context likely to minimize underreporting of smoking. They were then (with no prior warning) asked to provide saliva for cotinine analysis and 1537 agreed to do so. As shown in Table 3 there was in general a very marked difference between the cotinine levels of tobacco users and non-users. Using 30 ng/ml as a cut-off,

1.1% of self-reported non-users could be classified as occasional users, with levels of to 100 ng/ml, while 1.4% could be classified regular users, with levels above 100 ng/ml.

The second study, which aimed at obtaining information, on accuracy of past smoking habits, followed up in 1985 540 subjects previously interviewed in 1980 about their smoking habits. Ten% claiming on one occasion never to have smoked made inconsistent statements on the other occasion, with inconsistent smokers being more often men, old, smokers of fewer cigarettes and long term ex-smokers.

The third study, which aimed at obtaining information on smoking habit concordance, involved 8857 subjects aged 16+ interviewed regarding their own smoking habits and that of their spouse. The concordance ratio, 3.55 in men and 3.07 in women, was found to be rather greater than that assumed in the example in Table 5. Concordance rose with amount smoked. Thus, the chance of having a spouse who was a manufactured cigarette smoker was 22% for subjects who reported no such smoking, and 45%, 52% and 59% respectively for subjects who reported smoking 1–17, 18–22 and 23+ manufactured cigarettes per day.

From the data obtained, Lee (1987) concluded that misclassification could bias relative risk estimates in relation to passive smoking upwards by a factor of 1.31 in men and 1.24 in women, not significantly different from the pooled estimate of risk in relation to passive smoke exposure.

At about the same time as Lee presented his findings, Wald et al. (1986) used similar techniques to estimate the bias from misclassification, but based on a number of smaller, and less representative studies, not specifically designed for the purpose. They estimated this misclassification would have less effect, reducing the pooled estimate of risk only from 1.35 to 1.30, i.e. it had only caused upward bias by a factor of 1.04.

Examination of the detail of how the estimates of bias of Wald et al (1986) and of Lee (1987) were arrived at reveals three reasons for the difference. The first was that Wald et al. (1986) used an assumed relative risk of 8 for the effect of active smoking observed in women whereas Lee (1987) used 10. The second was that the calculations of bias by Wald et al. (1986) were mathematically inaccurate, due to confusion between true relative risks in relation to active smoking and those observed (which are affected by misclassification). These are less important than the third reason, which is that Lee et al. (1987) found that 1.4% (10/808) self-reported non-smokers were current regular smokers, whereas Wald et al. (1986) only found 0.14% (1/705) such cases.

In an attempt to reconcile this difference, I have recently conducted a detailed literature review of the evidence on misclassification of smoking habits, which will be published as a book early in 1988.

Despite the various study designs and populations involved a number of clear conclusions were reached:

(1) Even in circumstances that are apparently similar quite a wide variation in the extent of misclassification can be found.
(2) The proportion of "non-smokers" subsequently found actually to be smokers is markedly higher in smoking cessation studies than in studies where the respondent is under no special pressure not to smoke.
(3) The proportion of "non-smokers" subsequently found actually to be smokers is also markedly higher in lung cancer patients than in the general population. This is not surprising in view of the overall *a priori* expectation that a lung cancer patient actually is a smoker.
(4) Studies of "non-smokers" without lung cancer and under no special pressure not to smoke suggest that around 4% are likely actually to be current smokers. While not all

studies provide information on the extent to which such misclassified smokers smoke, and those that do indicate many of them are occasional smokers, it seems that 1 to 2% of self-reported non-smokers are regular smokers.

(5) In addition to these misclassified current smokers there are a somewhat larger number of ex-smokers misclassified as never smokers. Available information suggests that these tend to have smoked less and a longer time ago than average ex-smokers.

(6) None of the studies have investigated whether the extent to which smokers deny smoking depends on whether their spouse happens to smoke, which is of theoretical importance as it could materially affect estimates of bias.

(7) There is even now virtually no information on the extent to which smoking habits might be misclassified in Japan and Greece, from whence came the early epidemiological evidence on passive smoking and lung cancer. The only study in Japan, by Akiba et al. (1986), provided data suggestive of substantial misclassification of smoking habits. Here, of 187 men who reported not smoking in 1964–68, as many as 96 (51%) reported in 1982 that they had smoked.

While there is an obvious need for further research on misclassification of smoking habits the results of the review[1] suggested strongly that Wald et al. (1986) had seriously underestimated its importance.

Overall Conclusion

It has clearly been shown that there is a huge discrepancy between the relative doses of smoke constituents to which passive and active smokers are exposed and the much larger relative effect claimed from epidemiological evidence. The most likely explanation for this discrepancy seems to be a persistent bias affecting all the studies due to a small proportion of smokers being wrongly classified as non-smokers in the epidemiological studies.

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[1] Supported by a recent large study by Coultas et al. (American Review of Respiratory Diseases, 1987, 136, 305–309) who found 63 subjects with salivary cotinine >20 ng/ml among a sample of 1,360 New Mexicans reporting they were not current smokers.

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An Introduction to the Study of Smoking Using Urinary Hydroxyproline

H. Kasuga

Summary

The indicators used to identify the effects of environmental tobacco smoke (ETS) and exposure to low level nitrogen dioxide (NO_2) on the respiratory system are so weak that they can not be detected using traditional markers such as the increased prevalence of respiratory symptoms and a decrease in lung function. After studying urinary hydroxyproline (HOP) starting in 1977, we first reported the significant relationship between HOP and smoking, ETS and NO_2 in the air, in 1981. Since then, the coherent association between urinary HOP and the established pathological and biological development of lung diseases has been studied. Bias problems based on confounding factors, misclassification of nonsmokers and over- or underestimation of ETS effects also have been discussed.

Among articles presented by us during the past 4 years, several papers and some arguments for and against this study on urinary HOP were introduced:

1) The effect of cessation from smoking on the urinary excretion of hydroxyproline [19].
2) A prospective repeated cross-sectional study on the possible health effects caused by automobile exhaust and passive smoking [20].
3) Impact of smoking on the concentration and activity of alpha-1-antitripsin in serum, in relation to the urinary excretion of hydroxyproline. Matsuki H, Kasuga H et al., 1988.
4) Behavior of urinary hydroxyproline and effect of cigarette smoking in silicosis. Osaka F, Kasuga H, Matsuki H et al., 1985.
5) Opinions contrary to the relationship between urinary hydroxyproline and smoking, ETS and NO_2.

Introduction

Hydroxyproline (HOP) is one of the essential constituents in collagen and elastine and is an unique one which is not found in other tissues. Therefore, urinary HOP is regarded to be a potential candidate for the study of the breakdown of lung tissue due to smoking and environmental tobacco smoke (ETS).

As is generally known, the index symptom such as "a persistent cough and phlegm" based on the BMRC Questionnaire [1] is used frequently as a clinical marker, but it is not applicable for ETS effects because prevailing concentrations of ETS are estimated to be less than 1% of an undiluted mixture of sidestream and second-hand mainstream smoke. Therefore, urinary HOP as a biochemical marker for ETS effects appeared on the stage, and a causal relationship between smoking including ETS and its health effect was

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reported by Matsuki et al. [2] in 1981. However, some confounding factors which influence the excretion of HOP into urine have been found. Accordingly, it is very important to control these factors, including growth and age [3], disorders in hormone secretion, various collagenosises, outdoor or indoor air pollution with nitrogen dioxide (NO_2), pregnancy, and abnormalities in collagen metabolism in other sites than the lung. For details on this problem, we refer to our reports [4–9] so far; our method for HOP analysis [10] is recorded in the manual [11] for passive smoking, IARC, WHO, 1987. Our improved method is suitable for routine determination of HOP in urine at concentrations up to at least 400 ng/ml. The limit of detection is about 50 ng/ml. The autoanalyzer can handle 40 samples per hour. It is very difficult to obtain 24-h urine samples from many individuals, but the ratio of hydroxyproline to creatinine in a spot urine sample, particularly collected after fasting, is representative for the quantity of hydroxyproline in 24-h urine. Determination of urinary creatinine is performed routinely.

The amount of HOP excreted in urine is affected by the gelatin content of food, except in case of urine collected after fasting. Even if gelatin is ingested the day before urine sampling, its influence on urine HOP can be avoided by discarding the urine collected in the early morning after a 10–12-h overnight fast and collecting a fasting urine sample 2 h later.

As the first step of the study on smoking effects, it is necessary to classify the selected subjects according to the amount of exposure to cigarette smoke, directly or indirectly. In case of smokers, they can report their own smoking habits in the response to the question by means of interview and questionnaire. But in order to express the personal exposure levels to ETS for non-smokers, we are forced to ask for the smoking habits of potential smokers who supply the ETS. Since such answers are apt to be biased it may cause misclassification of the non-smoking subjects. Therefore, some biochemical markers have been used to assess the exposure to cigarette smoke including ETS. Among them, urinary cotinine has shown to be the most reliable marker for active and passive smoking. But it is not always easy to use this complicated measurement for hundreds or thousands of subjects in epidemiologic surveys. Therefore, a new questionnaire [12] has been developed. The questions in the old questionnaire were revised and enlarged by inserting only a phrase "How many cigaretts did you smoke *in the presence of non-smoking spouse and child* at home a day?". This new questionnaire showed a significantly high correlation between urinary cotinine levels and the number of cigaretts smoked in the presence of nonsmokers [12] (Table 1).

On the other hand, it may be necessary to use much more detailed questionnaires for studying the relationship between ETS and lung cancer, as Dr. Wynder mentioned. The interview with such a questionnaire is now used in an international survey sponsored by the IARC [13], to provide information on past and current active and passive smoking status. This troublesome questionnaire with as many as 20 sheets may be needed for studying lung cancer because it has been suggested that exposure to cigarette smoke during childhood may cause lung cancer later in life, and its incubation period may be more than ten years.

Since our study using urinary HOP aims at detecting preclinical signs of COLD (chronic obstructive lung diseases) except asthma, it may be possible to abbreviate most of the question sheets. In an actual epidemiological survey, it may be a practical way to examine all the subjects with such an improved questionnaire, and to check for report bias by measuring urinary cotinine. Originally the ETS effect is so weak that we can not always obtain a significant result according to circumstances, e.g. studies carried out by Verplanke et al. [14] in Holland and by Matsuki et al. [15] on Chinese women in Hong Kong were unsuccessful. So, it is necessary to use a sufficient number of subjects on

Table 1. Correlation coefficients among urinary cotinine level and involuntary smoking. (From [23])

Winter	Child Co/CR	Mot. Co/CR	Fam. Cig/day	Fam. Cig house/day
Child Co/CR	–	0.396*	0.494**	0.626**
Mot. Co/CR	–	–	0.799**	0.820**
Fam. Cig/day	–	–	–	0.851**
Fam. Cig house/day	–	–	–	–
Summer	**Child Co/CR**	**Mot. Co/CR**	**Fam. Cig/day**	**Fam. Cig house/day**
Child Co/CR	–	0.250	0.389*	0.526**
Mot. Co/CR	–	–	0.426*	0.730**
Fam. Cig/day	–	–	–	0.854**
Fam. Cig house/day	–	–	–	–

* $p<0.05$, ** $p<0.01$

Remarks: Child Co/CR: Cotinine to creatinine ratio in children, Mot. Co/CR: Cotinine to creatinine ratio in mothers, Fam. Cig/day: Familial smoking per day at home, Fam. Cig house/day: Familial smoking at home per day in the presence of non-smokers

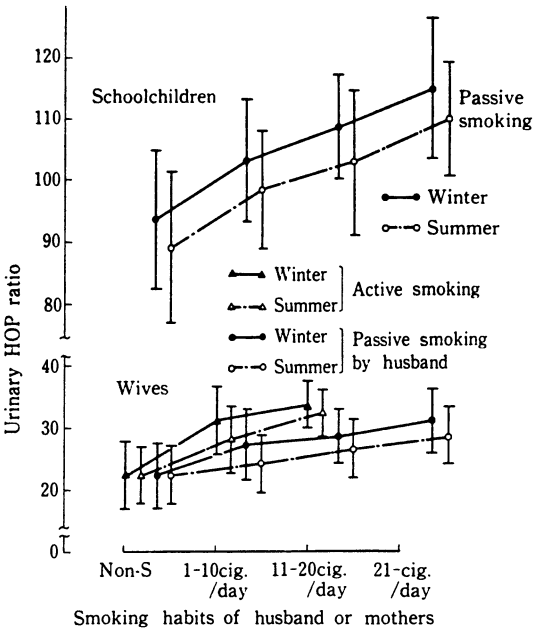

Fig. 1. Seasonal variation of urinary hydroxyproline to creatinine ratio

condition that each bias and confounding factor is under control, and to find a potential internal and external consistent trend by a prospective way, even though each association in the subgroup is weak. Several interventional studies [16–18] with rodents were conducted recently for smoking effects but these ended in failure to show an increase in

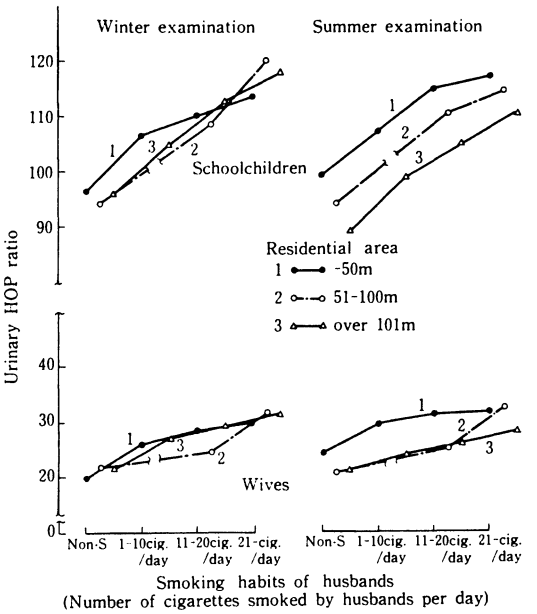

Fig. 2. Passive smoking effects with HOP-ratio by distance from heavy traffic road

urinary HOP. It seems that a major part of the failure can be ascribed to a defective experimental plan using the short term exposure with low-level ETS. Furthermore, nonsmoking workers are exposed to ETS at offices frequently but measurement of ETS at offices is more difficult than at home. Therefore, at present it may be advisable to select non-smoking, non-working, housewives and schoolchildren as the study subjects. And such an investigation carried out in summer time may be a problem that requires careful consideration because the high level ETS is hard to be formed due to well-ventilation at home in summer [4] (Figs. 1, 2). On the contrary, health effects induced by NO_2 in automobile exhaust should be measured in a summer period because they are masked by higher levels of indoor air pollution which often results from kitchen and space heating in the winter season.

In conclusion, although we have made a gratifying progress in this field, there still remains much to be done. Opinions presented so far may be summarized in some studies conducted during four years after the review [9] on this problem stated at the International Symposium on Effects of Indoor Air Pollution with Special Reference to Nitrogen Oxides and Smoking sponsored by Tokai University and WHO, in 1984, as follows.

The Effect of Cessation from Smoking on the Urinary Excretion of Hydroxyproline [19]

The increased urinary HOP levels due to smoking decrease with time, after discontinuation of smoking, and approached to the lower levels found among non-smokers. This observation must be useful for supporting the positive dose-effect relationship between urinary HOP and smoking. Furthermore, it is important from a public health and

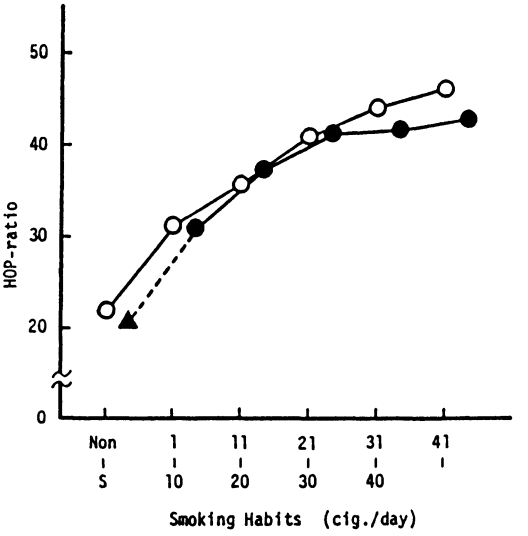

Fig. 3. HOP-ratio of a smoking cessation clinic group and a fathers group of schoolchildren in the same area; ●——● Smoking cessation clinic group (just after cessation); N: 49, Age: 49.0 ▲ control (non-S) group; N: 6, Age: 30.7 ○——○ father group; N: 345, Age: 42.3

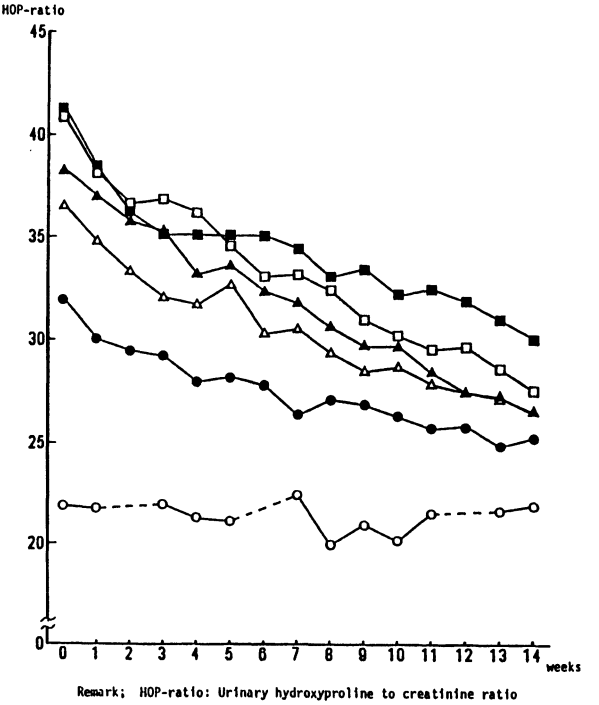

Fig. 4. Arithmetic means of HOP-ratio by amount of cigarette smoking after cessation from smoking;
■——■ 41 cig./day;
□——□ 31–40 cig./day;
▲——▲ 21–30 cig./day;
△——△ 11–20 cig./day;
●——● 1–10 cig./day;
○——○ non-smokers

Table 2. Calculated proportional and rate constant, correlation and time to reach non-smokers HOP-ratio levels for each group of ex-smokers

Ex-smoking (cig./day)	k (week)	lnA	r	No.	Time (weeks)
1–10	−0.0751	2.279	0.431**	4	61
11–20	−0.0673	2.630	0.613***	17	73
21–30	−0.0754	2.821	0.611***	11	68
31–40	−0.0709	2.925	0.819***	10	74
41–	−0.0429	2.853	0.391**	7	120

** $p<0.01$; *** $p<0.001$

model: $\ln (C_i\text{-}Co) = \ln A + kt_i + e_i$

where C_i is the HOP-ratio of i-th sample, t_i is the time (week) of the i-th sample, e_i is the error of the i-th sample and has a normal distribution with mean 0 and a variance σ^2, Co is the mean HOP-ratio value of the non-smokers

pathogenic point of view, to determine the time course of recovery from the increased HOP-ratio. That is, this study was carried out with the object of bringing out a coherent association between urinary HOP and smoking and a consistence of availability of urinary HOP as marker.

The effect of cessation from smoking was assessed in 49 smokers who participated in an anti-smoking course using the urinary HOP: creatinine ration (HOP-ratio). Urine samples were collected daily at the beginning of the course for five days and during the subsequent 14 weeks, two times a week. The subjects were divided into five groups depending on the number of cigarettes smoked daily before cessation: 1–10, 11–20, 21–30, 31–40 and >41 cigarettes. The urinary HOP-ratio immediately after cessation of smoking was proportional to the mean daily number of cigarettes smoked in the past. This result was in agreement with that of a similar survey undertaken in adult men, in the same district in the same year (Fig. 3). All subgroups showed decreasing HOP-ratios with an increasing period of abstinence. Half of the total observed decrease in the HOP-ratio after the 14 weeks was reached within 5 or 6 weeks (Fig. 4). When using the Brinkman Index to adjust for the number of smoking years, half of the maximum decrease in all subgroups was reached within four weeks. In an exponential decay model fitted to the data (Table 2), the halflife time to reach the non-smokers urinary HOP levels was nine to ten weeks for all subgroups. And it was estimated that the HOP levels of smokers who smoked less than 41 cigarettes before cessation reached the HOP levels of the control group after 61–74 weeks. The period needed for the most heavy smokers subgroup was estimated to be 120 weeks. The results suggest that the urinary HOP-ratio is useful as a biochemical marker for the short-term breakdown of lung collagen and lung elastin.

Influence of Automobile Exhaust and ETS (Environmental Tobacco Smoke) in Areas Alongside Main Road [20]

This present study is a critical assessment of the effects on health of ETS and NO_2 generated from main roads. A hydroxyproline:creatinine ratio (HOP-ratio) was used as the representative measure of the health effects. The associations between the HOP-ratio and ETS, and the HOP-ratio and low concentration NO_2 are essentially very weak; for

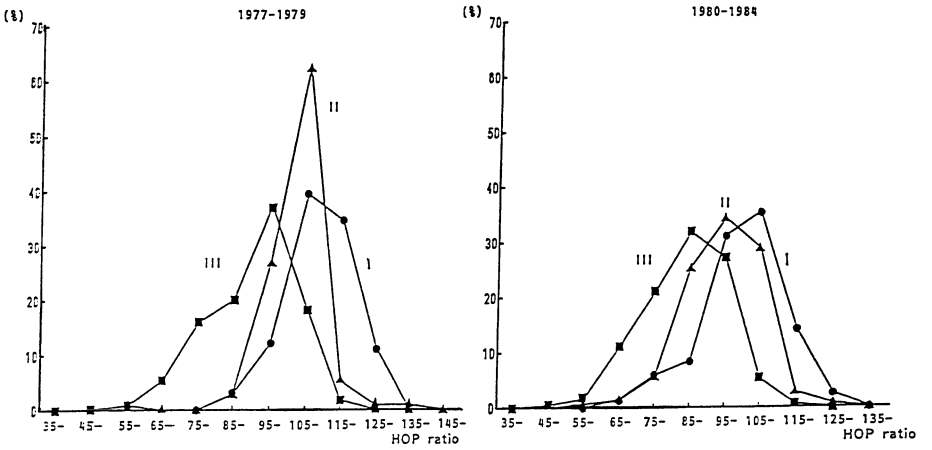

Fig. 5. Distribution of HOP-ratio by area in non-passive smokers
Remarks: Area I: within 50 m from roadside.
Area II: 51–100 m from roadside.
Area III: over 101 m from roadside

this reason, being able to control the confounding factors and their resulting bias was a major priority in the study. In order to ascertain the consistency and strength of these associations and coherence of the evidence repeated cross-sectional study was performed each year in May over an eight-year period from 1977 to 1984. 4,375 schoolchildren from F primary school area acted as subjects for the study. The school area was a typical urban residential area adjoined by main roads with a daily traffic of 3,000 vehicles or more such as C highway, but excepting these, it was a typical residential area with no other significant NO_2 generating sources as large-scale factories. The area was divided into three according to the distance from the main roads. (Area I: areas within 50 m from the roadside, Area II: within 50–100 m, Area III: over 101 m.) Subjects were divided in four groups according to levels of ETS exposure through passive smoking in the home, which were represented by the number of cigarettes smoked per day at home, by all members of the family, (NPS group: non-passive smoking, LPS group: 1–10 cig./day, MPS group: 11–20 cig./day, HPS group: 21 or more cig./day).

The association between ETS and the HOP-ratio was investigated as that of pupils living in Area III which was free of any direct influence from automobile exhaust diffusion. The area and HOP-ratio association was observed using the NPS group which was free of ETS influence.

1) The HOP-ratio increased as the level of ETS exposure increased and was greatest in schoolchildren who lived in the area nearest the main roads. The strength of the association was considered statistically significant based on the magnitude of the HOP-ratio, the correlation coefficient, a two-way layout and relative risk. This, with the coherence of the measurements for each area in each year, seemed to suggest without exception a strong causal relation. The influence of ETS and area distinctions on the HOP-ratio were totally independent and showed virtually no interaction.
2) Lowered ventilation rates in the winter heating period tended to produce high levels of NO_2 indoor air pollution and often overrode the influence of the roads (according to

Table 3. Annual trend of HOP-ratio by ETS and by area

Area	Year	N-PS			L-PS			M-PS			H-PS			Total		
		N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.
I	1977	30	114.86$^{\#\#}$	9.44	16	119.24$^{\#\#}$	8.85	25	124.55$^{\#\#}$	7.59	27	133.61$^{\#\#}$	9.50	98	123.21	11.57
	1978	33	115.68$^{\#\#}$	8.24	13	116.84$^{\#\#}$	11.13	22	127.07$^{\#\#}$	7.61	22	130.72$^{\#\#}$	13.69	90	122.31	12.08
	1979	44	110.79$^{\#\#}$	7.71	21	117.61$^{\#\#}$	4.67	22	121.58$^{\#\#}$	5.32	17	122.22$^{\#\#}$	5.64	104	116.32	8.10
	1980	16	101.73$^{\#\#}$	13.63	8	112.85$^{\#\#}$	17.88	16	114.67$^{\#\#}$	12.94	13	119.32$^{\#}$	21.86	53	111.63	17.87
	1981	19	108.06$^{\#\#}$	13.14	7	112.42$^{\#\#}$	19.95	22	114.91$^{\#\#}$	12.69	32	122.91$^{\#\#}$	14.71	80	116.26	15.56
	1982	20	108.56$^{\#\#}$	11.46	6	116.26$^{\#\#}$	5.77	17	115.18$^{\#\#}$	9.37	16	116.41*	7.42	59	113.38	10.01
	1983	35	106.34$^{\#}$	5.38	12	107.94$^{\#}$	5.36	21	111.06$^{\#\#}$	5.10	20	115.45$^{\#\#}$	6.37	88	109.76	6.61
	1984	28	96.90$^{\#}$	11.64	12	102.82$^{\#}$	7.48	24	103.40$^{\#}$	12.56	16	106.37$^{\#}$	11.76	80	101.63	12.01
	Total	225	108.55	9.73	95	113.82	10.25	169	116.68	9.57	163	122.20	12.21	652	114.84	11.840
II	1977	27	106.54$^{\#\#}$	9.06	23	111.30	8.98	23	124.77$^{\#\#}$	16.02	19	125.66$^{\#\#}$	5.59	92	116.23	10.78
	1978	39	108.21$^{\#\#}$	9.55	23	113.52$^{\#\#}$	3.57	16	118.24$^{\#\#}$	5.24	12	127.45$^{\#\#}$	9.99	77	113.98	10.87
	1979	48	104.85$^{\#\#}$	4.22	12	111.37**	3.63	17	111.25$^{\#\#}$	4.11	16	119.31$^{\#\#}$	5.31	93	109.35	6.89
	1980	22	97.16$^{\#\#}$	10.41	6	98.51	17.23	16	105.28	14.68	11	112.27**	19.54	55	102.69	15.87
	1981	30	97.39$^{\#\#}$	12.30	11	101.02	13.89	23	103.65	20.06	17	108.18*	19.96	81	101.93	17.23
	1982	6	106.08$^{\#\#}$	6.27	2	103.02	2.57	5	106.16	4.81	6	106.00	7.81	19	105.75	6.22
	1983	43	100.49$^{\#\#}$	6.24	25	101.46	6.94	32	104.51$^{\#\#}$	4.63	22	106.41$^{\#}$	4.38	122	102.81	5.74
	1984	44	97.19$^{\#\#}$	11.26	13	100.86	6.84	13	109.40$^{\#\#}$	13.45	23	106.05$^{\#}$	9.00	93	101.60	11.60
	Total	259	102.02	9.03	102	105.76	8.83	145	110.47	12.50	126	113.62	11.27	632	106.88	11.22

III	1977	198	98.06	10.94	79	108.18**	9.33	71	110.51**	9.09	36	114.62**	7.63	384	104.00	10.03
	1978	372	91.75	14.12	93	97.93**	13.54	107	103.64**	7.77	61	109.69**	9.77	633	97.00	14.23
	1979	185	98.44	6.12	50	98.42	5.14	64	102.17**	4.74	43	111.15**	3.89	342	100.73	6.92
	1980	180	84.01	14.77	45	89.31*	13.19	52	100.93**	11.71	60	109.23**	14.36	337	91.82	17.26
	1981	311	86.19	10.09	109	94.51**	10.93	131	97.50**	15.70	107	100.43**	17.53	658	92.14	14.19
	1982	126	92.03	7.93	24	98.20**	7.36	28	108.30**	4.90	29	111.59**	7.49	207	97.69	10.84
	1983	140	94.28	9.83	59	98.87**	6.09	66	100.91**	5.70	60	103.38**	5.80	325	98.14	8.62
	1984	115	91.18	11.77	32	97.00**	8.64	30	95.37	13.57	28	98.79**	10.38	205	93.74	11.84
	Total	1627	91.56	11.45	491	98.15	10.30	549	102.09	10.59	424	106.37	11.96	3091	96.51	12.64
Total	1977	255	100.94	12.02	118	110.29**	9.93	119	116.21**	12.62	82	123.43**	11.48	574	109.24	11.69
	1978	444	94.97	15.37	116	101.39**	14.52	145	108.80**	11.68	95	116.81**	14.45	800	101.00	16.50
	1979	277	101.51	7.71	83	105.15**	9.77	103	107.81**	9.22	76	115.35**	6.74	539	105.23	9.53
	1980	218	86.64	15.44	59	93.44**	16.60	84	104.38**	13.62	84	111.19**	16.86	445	95.52	18.50
	1981	360	88.28	11.87	127	96.06**	12.66	176	100.48**	17.03	156	105.89**	19.47	819	95.46	16.44
	1982	152	94.76	10.35	32	101.88**	9.81	50	110.43**	7.59	51	112.44**	8.16	285	101.47	12.23
	1983	218	97.44	9.76	96	100.68**	6.91	119	103.67**	6.51	102	106.40**	7.30	535	101.12	8.19
	1984	187	93.45	11.98	57	99.10**	8.40	67	100.97**	14.28	67	103.09**	10.91	378	97.34	12.45
	Total	2111	94.65	12.41	688	101.44	11.59	863	106.36	12.55	713	111.27	13.72	4375	100.74	13.99

Remarks: *N-PS:* no smokers in the family, *L-PS:* smokers with 1–10 cig./day at home, *M-PS:* smokers with 11–20 cig./day at home, *H-PS:* smokers with more than 21 cig./day at home.
Compared non-passive smoking group with each passive smoking group. * $p<0.05$, ** $p<0.01$.
Compared III group (over 101 m from roadside) with I (within 50 m) and II (51–100 m) group. # $p<0.05$, ## $p<0.01$.

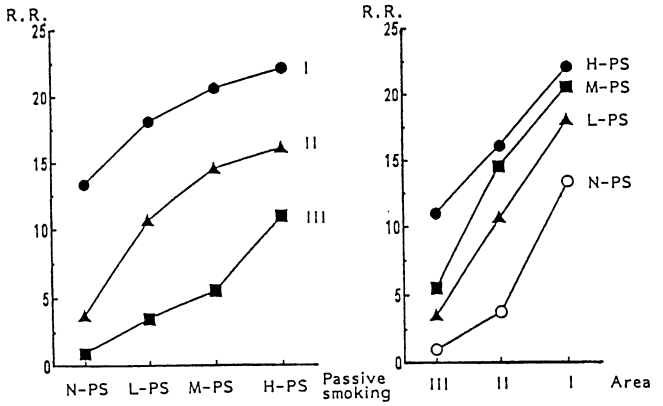

Fig. 6. R. R. of ETS and automobile exhaust (1977–1984).
Remarks: I: within 50 m from roadside, II: 51–100 m from roadside, III: over 101 m from roadside. *N-PS:* no smokers in the family, *L-PS:* smokers with 1–10 cig./day at home, *M-PS:* smokers with 11–20 cig./day at home, *H-PS:* smokers with more than 21 cig./day at home

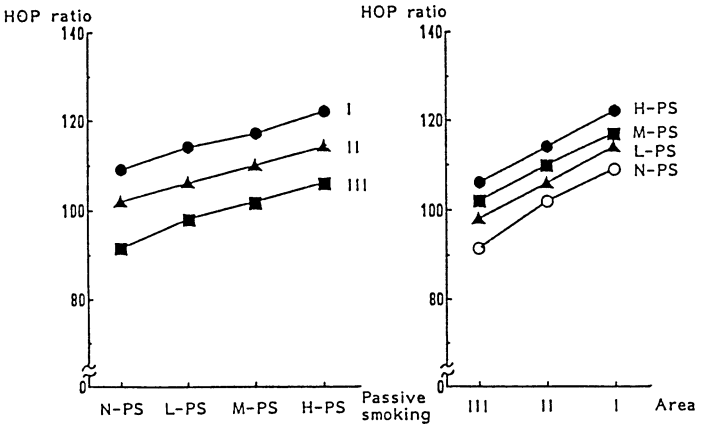

Fig. 7. HOP-ratio of ETS and automobile exhaust (1977–1984)

filterbadge measurements of NO_2 exposure levels). In addition, this not only eliminated difference in HOP-ratios according to area distinction but also produced the indoor ETS and increased ETS exposure opportunities as evidenced by the urine cotinine levels measured. It thus became clear that the survey of ETS and area distinction influence would have to be conducted during the summer months.

3) In order to control any bias, all pupils were subjected to a prior medical check-up and those with any confounding factors in HOP-ratios were eliminated from the study. However, the changes in patterns of indoor smoking from 1980 onwards were not sufficiently accounted for by the former interview and questionnaire surveys so we introduced an additional bias, namely misclassification of pupils. Subsequently,

the possibility to cause underestimation of ETS influence was suggested, thereby establishing the need for a revision of the relevant questionnaires.

However, we cannot offer any conclusion on the possibility that these changes in the HOP-ratios may in the future have morbid effects to cause the development of chronic bronchitis, or emphysema of the lungs.

Impact of Smoking on the Concentration and Activity of Alpha-1-Antitrypsin in Serum in Relation to the Urinary Excretion of Hydroxyproline [21]

This study aims at assessing the coherent association between smoking and urinary HOP, in the light of the "protease and antiprotease balance theory" by Eriksson. Alpha-1-antitrypsin (α_1-AT) is the most important inhibitor of proteases in human serum and is essential in preventing autodigestion of the lung by inhibiting elastase and collagenase. Oxidation renders this inhibitor inactive. Cigarette smoke contains many potent oxidants which can reduce the functional activity of α_1-AT and turn the existing balance with lung proteases into an imbalance resulting in the degradation of connective tissue in the lung.

The data suggest that active smoking has significant impact on the concentration and activity of α_1-AT in serum as well as on the urinary excretion of HOP. The data concerning passive smoking reveal less consistent results, except for the urinary excretion of HOP (Fig. 8).

The impact of active and passive smoking on the serum levels of α_1-AT, the trypsin inhibitory capacity (TIC), the trypsin inhibitory activity (TIA) and the urinary hydroxyproline to creatinine ratio (HOP-ratio) was studied. The subjects used in the

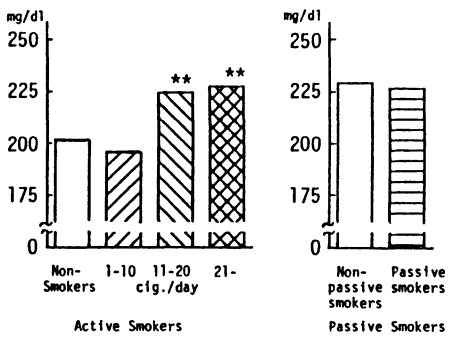

Fig. 8. Serum α_1-antitrypsin concentration in active and passive smokers; **$p<0.01$: compared with non-smokers or non-passive smokers

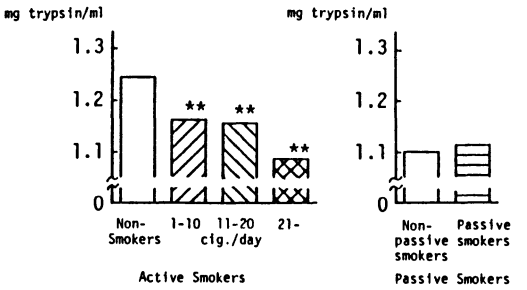

Fig. 9. Trypsin inhibitory capacity in active and passive smokers; **$p<0.01$: compared with non-smokers or non-passive smokers

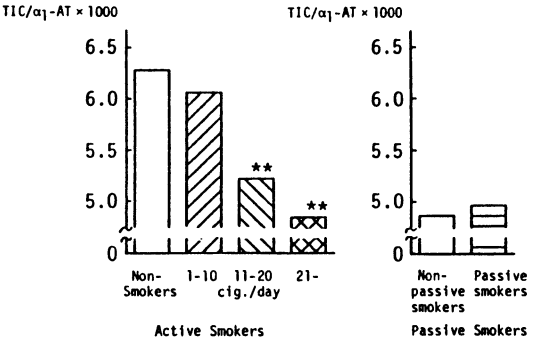

Fig. 10. Trypsin inhibitory capacity to α_1-antitrypsin ratio in active and passive smokers; **$p < 0.01$: compared with non-smokers or non-passive smokers

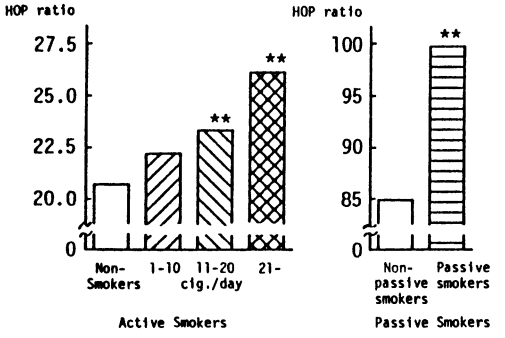

Fig. 11. Urinary hydroxyproline to creatinine ratio in active and passive smokers; **$p < 0.01$:compared with non-smokers or non-passive smokers

study on active smoking were 167 healthy adult men and in the study on passive smoking 189 healthy primary school children. Serum levels of α_1-AT in active smokers were significantly higher than those in non-smokers (Fig. 8). The TIC as well as the TIA in active smokers decreased with increasing number of cigarettes smoked (Figs. 9, 10). The urinary HOP-ratio increased significantly with increasing number of cigarettes smoked. On the other hand, in the case of passive smokers a significant difference was obtained only for the HOP-ratio. The associations between all markers in active smokers were significant. Less strong associations were found in the case of passive smokers (Fig. 11). These results suggest that the urinary excretion of hydroxyproline can be considered as a marker for the imbalance between proteases and antiproteases as a result of smoking.

Behavior of Urinary Hydroxyproline and Cigarette Smoking Effect in Silicosis [22]

It is common knowledge that symptoms of pneumoconiosis deteriorate rapidly with smoking. But many problems, demanding solutions from a viewpoint of epidemiology, still lie before us. It seems that the behavior of urinary HOP holds the key for them.

This study was conducted through regular pneumoconiosis examination according to the law on 1,096 employees of medium and small-sized ceramic enterprises in the Tokai district in 1981–82.

Interview examination with the BMRC questionnaire, X-ray examination and measurements of the urinary hydroxyproline to creatinine ratio (HOP-ratio) were carried

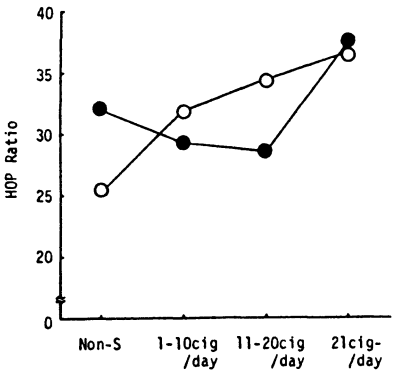

Fig. 12. Relations between urinary HOP-ratio and smoking or grade with X-ray photo. Grade with X-ray photo: ○, 0; ●, 1–4

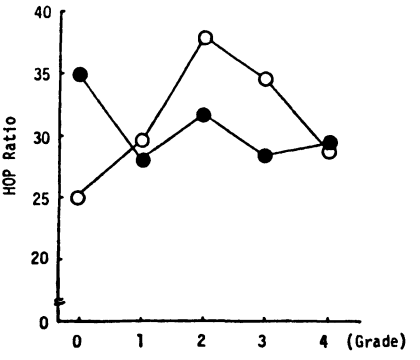

Fig. 13. Relations between urinary HOP and smoking or grade with X-ray photo. ○, non-smokers; ●, smokers

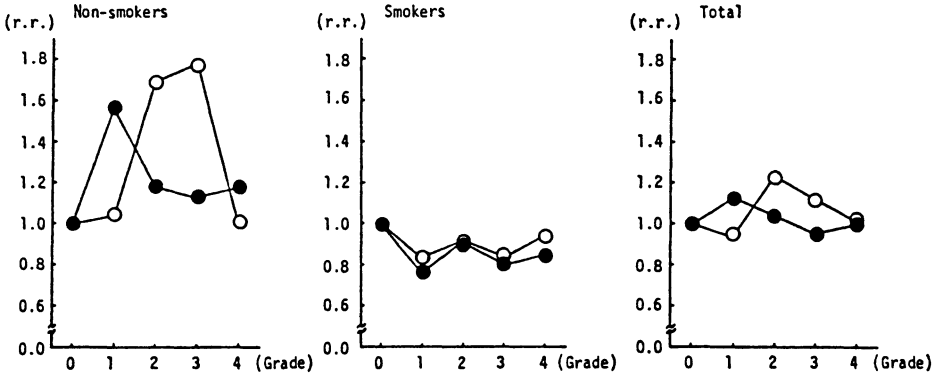

Fig. 14. Turning point of HOP-ratio by grade with X-ray photo. ○, without symptoms; ●, with symptoms

out in order to elucidate the relationship between silicosis and urinary HOP-ratio and to demonstrate the effect of smoking on pneumofibrosis. The grades of silicosis were classified into five types (0 to 4) with increasing severity of the symptoms based on the Japanese Classification of Radiographs of Pneumoconioses. Index symptoms of respiratory diseases were recorded using BMRC questionnaire [9]. In healthy subjects (type 0), the urinary HOP-ratio increased with the number of cigarettes smoked (Fig. 12).

In smokers, the collagen metabolism was rapidly repressed and fibroplastic conditions developed, although smoking itself did not seem to induce pneumofibrosis.

In the non-smoking group, the HOP-ratio was the lowest in type 0 and it increased in the order of type 1 and 2. The turning point was at type 2 and the HOP decreased type 3 and 4, by turns (Fig. 13). Further analysis of the data showed that the turning point for non-smokers without index symptoms was found at type 3, whilst the turning point for

non-smokers with index symptoms was at type 1 (Fig. 14). Shifting of the turning point suggests that index symptoms also promote fibroplastic activities.

Contrary Opinions Against the Relationship Between Urinary HOP and Smoking, ETS and NO_2

Intervention Studies

Intervention studies of urinary HOP levels in rodents were conducted by Mullenae et al. [16], Read and Thornton [17] and Higashi et al. [18]. These studies were generally performed using an extreme short exposure term combined with an extreme small number of subjects, and they ended in failure to show a positive result.

If an exposure level of NO_2 as in actual air pollution is used, a prolonged exposure experiment with numerous subjects shall be needed from a pathological viewpoint. In addition to our study, Mizoguchi and Yoshida [23] also reported in 1986 that urinary HOP-ratios in schoolchildren living in three areas with different ambient NO_2 concentrations in Tokyo increased with the NO_2 concentration.

Opinions Presented by Adlkofer [24, 25]

1) Adlkofer stated in 1983 as follows: even though smoking was originally regardless of the HOP excretion, the HOP: creatinine ratio increased with smoking because the creatinine excretion was positively correlated with the number of cigarettes smoked.
2) He raised another objection to our studies in 1987.
   - The urine volume in smokers was larger than that in non-smokers.
   - HOP excreted into urine was reabsorbed to some extent but tubular reabsorption of HOP was interfered by the increasing urine flow.
   - In contrast with HOP, urinary creatinine was not reabsorbed at all. Therefore, he concluded that the HOP: creatinine ratios in smokers were higher, irrelevant to the higher HOP excretion.
3) In the same paper, he stated as follows; HOP in 24 h urine of smokers was found to be larger than that in non-smokers, but after standardizing for body surface, the urinary HOP excretion was almost completely unaffected by tobacco uptake.

Answers

1) If his opinion was right, it would be impossible to apply the cotinine ratio in random urine as a substitute of cotinine in 24-h urine. It is not too much to say that the usefulness of urinary cotinine: creatinine ratio was established by the report on involuntary smoking by Surgeon General U.S.A. in 1986 [28]. Urinary HOP: creatinine ratio which was developed in the 1960 s by Allison et al. [26] and Whitehead [27] is prevailing now in the field of epidemiology, and it was also included in the manual on passive smoking, IARC, in 1987.
2) His syllogistic conclusion does not seem to be supported with high reliability and consistency. The possibility of his opinions is only very slight.
3) Excretion of HOP decreases with aging, and body surface increases with aging [3]. In conclusion, I think that there is no need to adjust for body surface, in this case but, it is necessary to adjust for growth or age.

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Chapter 1: Environmental Tobacco Smoke Measurement

The Aging of Sidestream Tobacco Smoke Components in Ambient Environments

R. R. Rawbone, W. Burns, and G. Haslett

Summary

A large number of sidestream smoke components have been measured over a 50-min time period in a well-defined experimental room. The results show a variable rate of decay following smoking which would suggest that extrapolation from a single measured "marker" to other potential smoke components should be performed with caution.

Introduction

Environmental tobacco smoke is a dynamic aerosol and its characteristics, both physical and chemical, depend on a number of factors; these include the elapsed time since its formation, whether the smoke plume is allowed to fully form before dispersion and the more general dilution within the ambient environment [1]. In terms of a single point sampling site the resultant measurement value will therefore not only depend upon the characteristics of the environment and the number and manner of cigarettes being smoked but also upon both temporal and spatial factors of the sampling position relative to the smoking.

This dynamic nature of the aerosol results not only in a loss of volatile components, including nicotine, from the particles to the vapour phase, but also in a complex and variable behaviour of the individual chemical components which manifests in their exhibiting different decay characteristics. This is of importance in the interpretation of ambient air studies which are generally limited to the measurement of one or two environmental tobacco smoke markers.

The objective of this paper is to demonstrate this variability in decay patterns for a series of chemical measurements over a 50-min period following smoke generation in a well defined experimental room.

Materials and Methods

Smoke was generated using a modified smoking head from a Battelle rotary smoking machine [2] in a specially constructed room with a volume of about 48,000 litres. The internal walls, ceiling and floor were coated with a sealant paint and there was a single door with no windows, other than a sealed observation port; all other access, including that for electricity supply and air sample collection, was through sealed ducting. During the current studies there was no active ventilation in the room and furniture was kept to a minimum. Temperature and humidity were monitored continuously.

H. Kasuga (Ed.) Indoor Air Quality

At the start of each experiment 16 cigarettes, with a standard mainstream delivery of 17 mg tar (PMWNF), were smoked on the rotary smoker to the reference conditions of one 35 ml puff of 2 s duration every minute. The mainstream smoke was ducted away and the sidestream smoke, after formation of the plume, mixed into the room by a series of fans. In order to maintain a constant carbon monoxide level in the room throughout a 50-min-study period, as a standard condition, single cigarettes were smoked subsequent to the initial 16 cigarettes being extinguished. The time at which the initial cigarettes were extinguished was also taken as time zero for the commencement of chemical measurement.

Ambient chemistry in the room was measured using the following techniques which have also been employed, for comparative purposes, in a benchtop collection device [3] for the measurement of freshly generated sidestream smoke:

Carbon monoxide was measured continuously using a non-dispersive infra-red analyser (Analytical Development Co., Model RFA/1).

Nicotine, which is distributed between the particulate and vapour phases, was measured as total nicotine by collection into a Tenax trap over 5-min-sampling periods, with subsequent thermal desorption and gas chromatographic analysis (Perkin Elmer, ATD50).

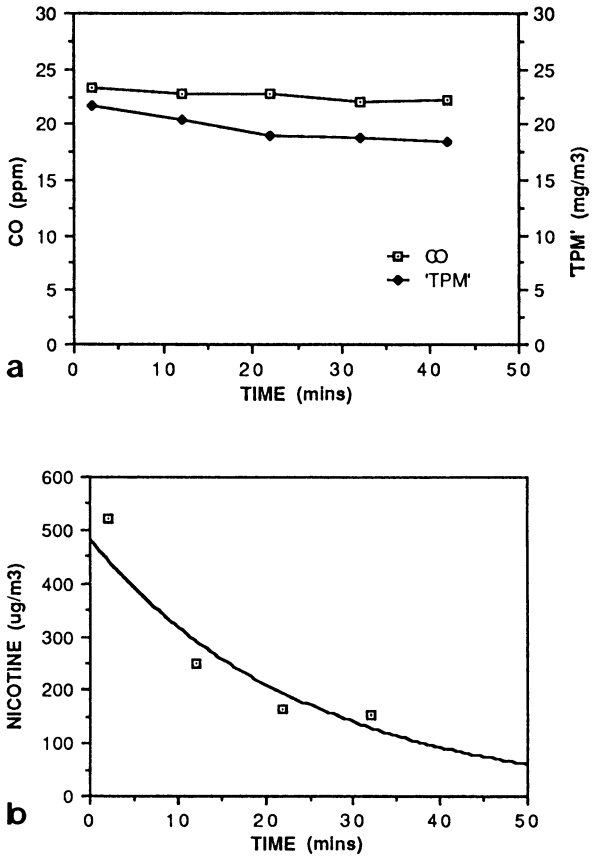

Fig. 1. a Changes in ambient concentrations of carbon monoxide and "Miniram" particulates. b Changes in ambient concentration of nicotine

Particulates were measured using the MINIRAM (Miniature Real-time Aerosol Monitor, GCA Corporation, Model PDM-3), a light scattering device which samples over 10-s-time periods. This instrument gives a quantitatively high result because of its sensitivity to particle size distribution and its dependence upon a relevant calibration [4].

Ammonia was measured continuously using a selective ion electrode.

A "whole smoke" gas chromatographic profile was obtained by actively drawing the ambient atmosphere through standard Perkin Elmer ATD50 tubes packed with Tenax TA, 60–80 mesh for a 15-min-period at a flow rate of 300 ml/min. The Tenax was then thermally desorbed in two stages onto a 50 m mixed Ucon phase capillary column. Values for 33 distinct peaks were calculated as the peak area relative to that of the Internal Standard (Dimethyl Furan), these included Acetone, Acrolein, Acetonitrile, Pyridine and 3-vinyl pyridine.

A "phenolic profile" was obtained by drawing the atmosphere through a small Cambridge filter pad for 10 min at a flow rate of 20 l/min. The pad was then silylated using BSTFA and Digol was added as an Internal Standard. This was then heated for 1 h at 80 °C and run on a 25 m SE54 capillary column. Values for 26 peaks, including Catechol, Glycerol, and Hydroquinone were calculated with reference to the Internal Standard.

Results

Figures 1a and 1b show the results for nicotine, carbon monoxide and Miniram particulates. The carbon monoxide levels remain constant at the relatively high level of 22 ppm throughout the 50-min-study period, this being consequent upon the defined

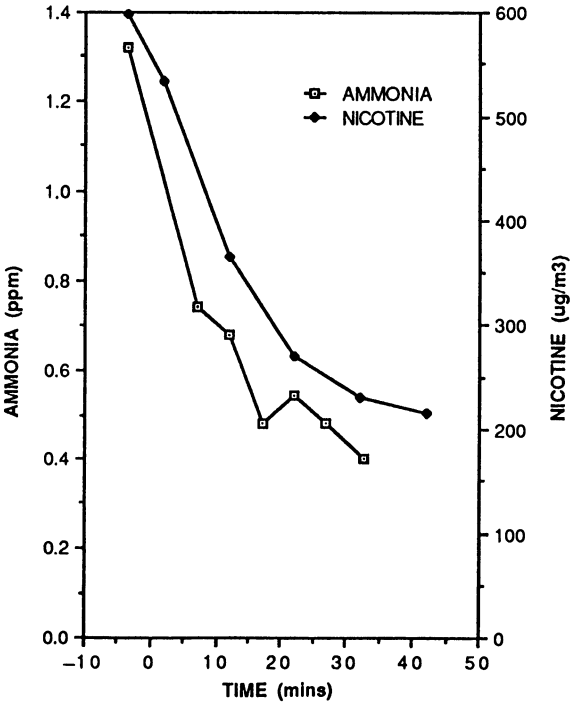

Fig. 2. Changes in ambient concentration of nicotine and ammonia

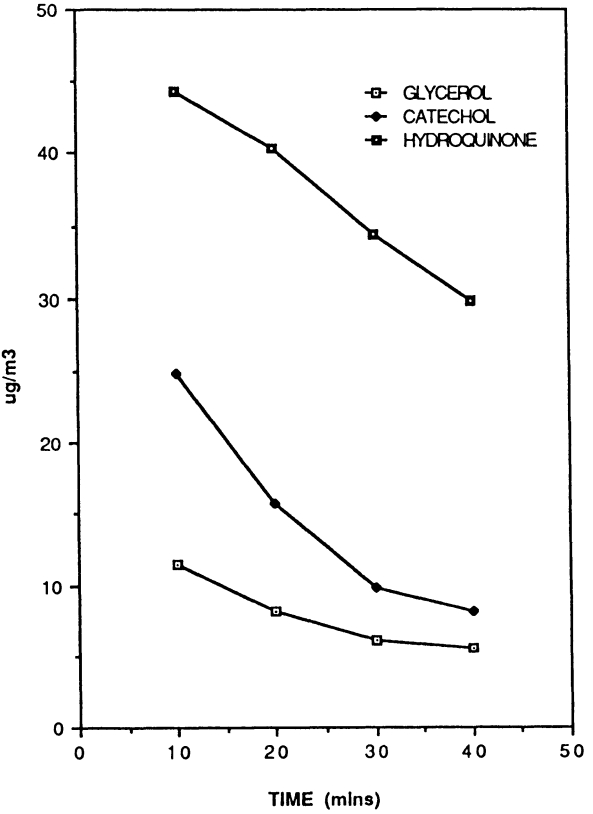

Fig. 3. Changes in ambient concentration of Catechol, Glycerol, and Hydroquinone

smoking regimen. The particulate levels can be seen to fall by about 15% and this is most likely accounted for by the loss of volatile materials to the ambient atmosphere. In contrast to this relatively small decline in particulate levels however is the rapid fall in airborne nicotine levels which decay to less than 20% of their initial value.

Figure 2 shows that the levels of ammonia exhibit a similar rapid decay to that seen for nicotine.

Examples from the analysis of the "phenolic profile" are given in Fig. 3 which illustrates the decay of Catechol together with Glycerol and Hydroquinone. These results draw attention to the fact that whilst the majority of components appear to show an exponential decay pattern this is not invariable and as an example Hydroquinone appears to decay over this time period in a linear fashion.

Because of the longer periods over which the "whole smoke" profile samples are obtained it is not possible to display the changes graphically. Comparing the time periods 0–15 min with 30–45 min gives some idea of the variability in rates of decay. These are illustrated in Table 1 where the percentage change of individual peak areas between the two periods can be seen to range from 0% to 40%.

Of the 50 plus components of sidestream smoke examined in these studies in no case was any component found to increase over the 50-min-time period.

Table 1. Levels of major components in the "whole smoke" profile of an ambient air sample and their % change over a 45-min-time period

Peak No.	Identification	15–30-min-value	45–60-min-value	% change
1		1.51	1.64	− 5
2		0.62	0.61	−13
3		4.40	3.94	−22
4		0.65	0.74	0
5		0.52	0.46	−22
6		0.36	0.30	−27
7	Acetone	0.77	0.87	0
8	Acrolein	0.34	0.38	− 3
9		1.28	1.22	−16
10	Pyridine	1.05	1.10	− 8
11	Acetonitrile	0.67	0.68	−11
12		0.68	0.58	−25
13	Benzene	2.66	2.36	−22
14		0.52	0.53	−10
15	*Int. Standard*	1.00 (33.5)	1.00 (29.4)	
16	Toluene	4.51	5.20	0
17		0.79		
18		2.31	1.93	−27
19		2.29	1.73	−34
20	3-Vinyl pyridine	0.70	0.76	− 5
21	Phenol	1.99	2.28	0
22		2.25	1.75	−32
23		0.89	0.75	−26
24		1.20	1.00	−27
25		1.31	1.23	−17
26		3.53	3.00	−25
27		1.92	1.90	−13
28		1.45	1.40	−15
29		1.83	1.56	−25
30		2.01	1.68	−27
31		1.64	1.25	−33
32		1.02	0.74	−36
33		0.65	0.44	−40

Values presented were calculated by the (peak area of component)/(peak area of Internal Standard). Values in brackets were the actual peak areas. The % change between the results allows for the differences in value for the Internal Standard

Discussion

The results presented in this paper clearly demonstrate the variability in the decay pattern for individual components of environmental tobacco smoke. Although the measurements were made in an experimental situation at a relatively high ambient smoke level this variability would certainly be encountered in the real-life situation.

It is thus clear that to make extrapolations from the measurement of a single marker to the behavior of other smoke components involves an assumption which is likely to be

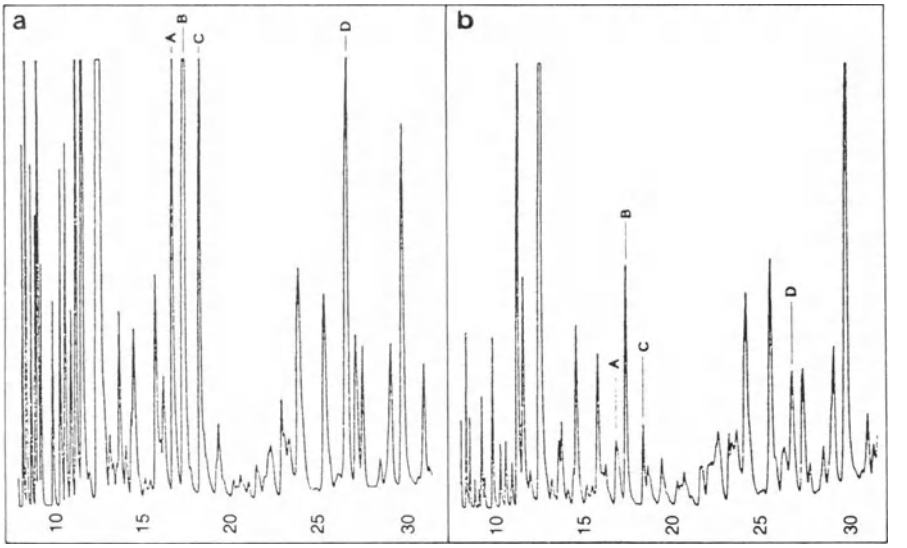

Fig. 4 a, b. "Whole smoke" chromatographic profiles of (a) freshly generated sidestream smoke in a benchtop apparatus and (b) environmental tobacco smoke following the dispersion of sidestream smoke from 16 cigarettes

invalid. One further point can be noted from a comparison between fresh sidestream smoke measured in a benchtop apparatus and sidestream generated in the experimental room. This is illustrated in Fig. 4 which presents the whole smoke profiles obtained in a Keith apparatus with that taken in the experimental room immediately following the smoking of the 16 cigarettes. The four components labelled A, B, C and D, which have been provisionally identified as Furan, Acetone, Acrolein and Acetonitrile, are among those which can be seen to have greatly reduced levels in the room relative to those in the benchtop collection device. Although these components appear in fresh smoke their apparent decay is so rapid that they may not be seen to any significant extent in room air.

Conclusions

1) Environmental tobacco smoke is a dynamic aerosol which exhibits both temporal and spatial variation.
2) Each of the components of smoke measured has its own decay rate and pattern.
   Relative to carbon monoxide and particulates, nicotine and ammonia have rapid decay rates.
   Other components, which probably include Acrolein, decay at an even faster rate and high airborne levels are probably never achieved.
3) Extrapolations from benchtop sidestream measurement to room air based on simple dilution calculations is unlikely to provide valid information.
4) Extrapolations from a measured "marker" in ambient air studies to other potential smoke components should be performed with caution.

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Indoor Air Quality: The Contribution of Environmental Tobacco Smoke

R. Perry, J. N. Lester, M. Hunter, P. W. W. Kirk, and S.-O. Baek

Summary

An extensive 30-week survey of environmental tobacco smoke has been undertaken in Great Britain. The survey consisted of over 2,900 sampling operations according to a scheme which covered a range of situations to which the public are exposed during their travel and leisure as well as at home and work. Sampling took account of population distribution as well as geographical and seasonal effects.

Three components of tobacco smoke – particulate matter as measured by Minirams, carbon monoxide and nicotine – have been determined in smoking and non-smoking situations, whilst the reported presence or absence of smoking within 2 h prior to sampling was used to distinguish between non-smoking and smoking environments. The survey was structured around 30 min sampling periods, using unobstrusive, portable sampling equipment capable of detecting each of the three components at less than 5% of their individual (occupational exposure limit (OEL) is the UK recognized workplace safety level).

Overall mean Miniram particulate matter was 0.56 mg m^{-3}, with a smoking location mean of 0.81 mg m^{-3} and a non-smoking mean of 0.31 mg m^{-3}. These results, as determined by the Miniram light scattering device are, however, known to be an overestimate when compared to methods based on the measurement of particulate mass, such as the Piezobalance. Subsequent studies in a variety of locations have shown the Miniram to over-estimate by at least a factor of 2.5 in the presence of tobacco smoke.

The overall mean carbon monoxide level was 2.4 ppm with a mean of 2.7 ppm in smoking locations and 2.1 ppm in non-smoking locations. With the limitations of the carbon monoxide monitors, this difference is not thought to be significant.

In calculating the mean results for nicotine, a value of 6.8 μg m^{-3} (i.e. half the limit of detection) was assumed whenever the nicotine level was below the limnit of detection. This has almost certainly led to an over-estimation of nicotine, particularly in non-smoking situations, where nicotine was rarely detected. Applying this factor the mean overall nicotine concentration was 14 μg m^{-3} with a mean of 21 μg m^{-3} in smoking locations and 8 μg m^{-3} in non-smoking locations. No nicotine concentrations exceed the OEL set at 500 μ m^{-3} and 95% of all readings were below 10% of the OEL.

Introduction

Considerable effort has been expended over the last 15 years attempting to control emissions of air pollutants into the atmosphere from sources such as power stations, factories and automobiles [1]. More recently, increasing public awareness has prompted

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concern regarding the quality of indoor air, particularly as the majority of the population spend up to 80%–90% of their lives indoors [2].

There are many sources of indoor pollutants (both gaseous and particulate) including the use of gas stoves and fires, coal, coke, and wood fires, house plants, cooking, cleaning, painting, and the adoption of a variety of household and office products including cleaning agents, glues, correction fluids, plastics and varnishes [3, 4]. In addition, the simple act of movement resuspends particulate matter [5] whilst building materials and furnishings, especially when new, may release a variety of organic materials into the indoor atmosphere [6]. Release of formaldehyde from cavity wall insulation, furniture and fabrics are all examples of such indoor air pollutants and are of considerable public concern.

Specific interest has been directed towards pollutants associated with emissions from gas cooking and other problems such as radon build up, "sick-building" syndrome and environmental tobacco smoke (ETS) [1, 7]. Probably the most emotive issue is that of ETS, largely with respect to considerations of irritation and discomfort, but more especially in the light of recent epidemiological studies alleging risks to the health of the exposed non-smoker.

The contribution ETS components make to the indoor air environment is difficult to quantify for a number of reasons. Environmental tobacco smoke has not yet been sufficiently characterized such that its nature can be clearly defined. The concentration of any individual ETS compound or group of compounds in an enclosed space is dependent upon its generation rate from the tobacco, the source consumption rate, ventilation, the concentration of the constituent in the incoming ventilation air, dimensions of the room, the degree of mixing, the rate of removal by adsorption or chemical transformation and the effectiveness of any air cleaning devices such as air conditioning systems [8].

One major problem when attempting to define the contribution of ETS to air quality is that in real life situations ETS normally exists in association with a complex mixture of air contaminants from other sources, particularly those from other combustion sources [1]. Indeed, these may not necessarily originate from indoor situations. Pollutants such as carbon monoxide for example, readily pass from the outdoor to the indoor environment without significant change in concentration [9]. However, indoor pollutants can give rise to high local concentrations, but are greatly diluted on passing to the outdoor environment. In contrast, reactive gases such as ozone and sulphur dioxide are rapidly removed in the indoor environment and levels are normally only a fraction of those commonly encountered outdoors [10], thereby indicating the complex relationship between indoor and outdoor air.

To date the major short-fall of studies examining ETS in the failure to adequately quantify the actual ETS dose received by the non-smoker. Environmental Tobacco Smoke is a complex and greatly diluted mixture of sidestream (commonly defined as the smoke which issues from the product between puffs), mouthspill (smoke released from the mouth before inhalation) and exhaled smoke, the proportions of which will vary depending on the smoking behaviour of the individual smokers. In realistic circumstances ambient concentrations depend on sidestream smoke and the exhaled mainstream smoke [11, 12]. In order to quantify ETS components therefore, any component determined should ideally be unique to tobacco smoke, present in sufficient quantity to be easily detectable, similar in emission rate for a variety of tobacco products and be present in a fairly consistent ratio to other smoke components of interest [9]. Furthermore, it is apparent that in order to evaluate the contribution of tobacco smoke to indoor air quality, non-smoking as well as smoking situations need to be studied under as wide a variety of actual conditions as possible.

Consequently the objectives of this study were

- to assess indoor air quality in home, work, leisure and travel situations;
- to evaluate the ETS components of indoor air;
- to compare smoking and non-smoking environments.

Materials and Methods

Markers for ETS

Three main components of tobacco smoke were identified as markers within the study, namely, nicotine, carbon monoxide and Miniram particulate matter (TPM).

Nicotine fulfils most of the criteria for a suitable marker being a major component of, and almost exclusive to, tobacco smoke and also is detectable in small quantities of air at low concentrations [11, 13, 14]. Moreover, nicotine has been measured in the majority of existing studies [1].

Carbon monoxide is a commonly measured constituent of indoor tobacco smoke in field surveys since it is a major component of cigarette smoke and is relatively easy to measure, although there are many other sources of indoor carbon monoxide besides tobacco smoke [9, 11, 16].

Total suspended particulate matter can be defined as particles (generally $< 15\,\mu m$) suspended in the atmosphere, as collected for subsequent gravimetric determination. An alternative generalised measurement of particulates utilizing a light scattering technique was used and subsequently calibrated against piezobalance and gravimetric methods.

Survey Design

A 30-week field survey was designed to study four types of indoor environment; workplaces (W), homes (H), leisure (L) and travel (T). Monitoring was evently distributed between each type and performed by an independent research laboratory (Hazleton Laboratories UK Ltd., UK). The study was designed to evaluate a total of 30 locations representing a wide variety of exposures throughout the United Kingdom which were considered in three major regions according to population density (Table 1).

These figures were derived from recent statistics [17], by a market research group (MAS Survey Research Ltd., UK) to represent the geographical regions, urban and social status of the UK.

Homes were randomly selected after reclassification by local authority area according to these criteria. Work situations were randomly selected within each classification according to type and size (number of employees) of business to reflect any particular location based on a quota system. Leisure and travel situations were identified and arranged around work and home samples to maintain flexibility.

A balance of timing with respect to days of the week, start times, and times of the year was arranged so as to cover the spectrum of normal life exposure (Fig. 1). The study was divided into three 10-week-periods, each area being sampled completely over any 10-week-period. Each operative subsequently rotated to a different area during the following 10-week-period. A staggered pattern of start times and days enabled extended coverage of time of day and days of the week. These were repeated by succeeding operatives.

Table 1. Allocation of sampling locations in the United Kingdom

Area No.	Location	Population %	Total regions	Conur-bations	Large urban	Small urban/rural	
						H[a]	L[b]
1	South East	30	9	4	1	3	1
2	South West, Wales, Midlands, East Anglia	34	10	1	2	3	4
3	North, Yorkshire, Humberside, North West, Scotland	36	11	6	2	1	2

[a] H – high density
[b] L – low density

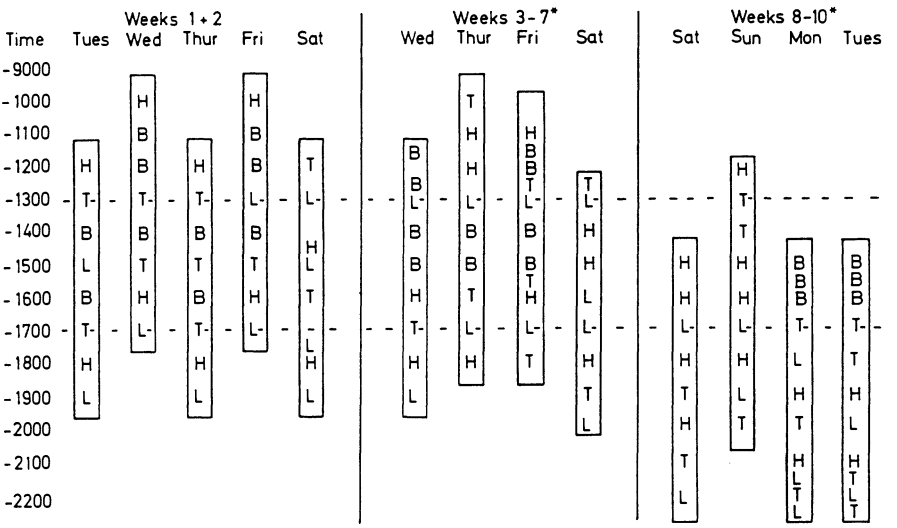

Fig. 1. Typical operative work schedule during any 10-week-period. *H:* house call; *B:* business call; *T:* travel call; *L:* leisure call; * Residual T & L performed where possible after arrival at new locality

Equipment Selection and Analytical Procedures

The equipment used was potable, robust and discretely operable, being reliable and precise. Four integrated kits were assembled and tested in field trials prior to the study. Each kit consisted of a carbon monoxide dosimeter (General Electric 15 ECCICO2; MDA Scientific, UK), a Miniram PDM-3 particulate dosimeter (GCA Corp., USA), a

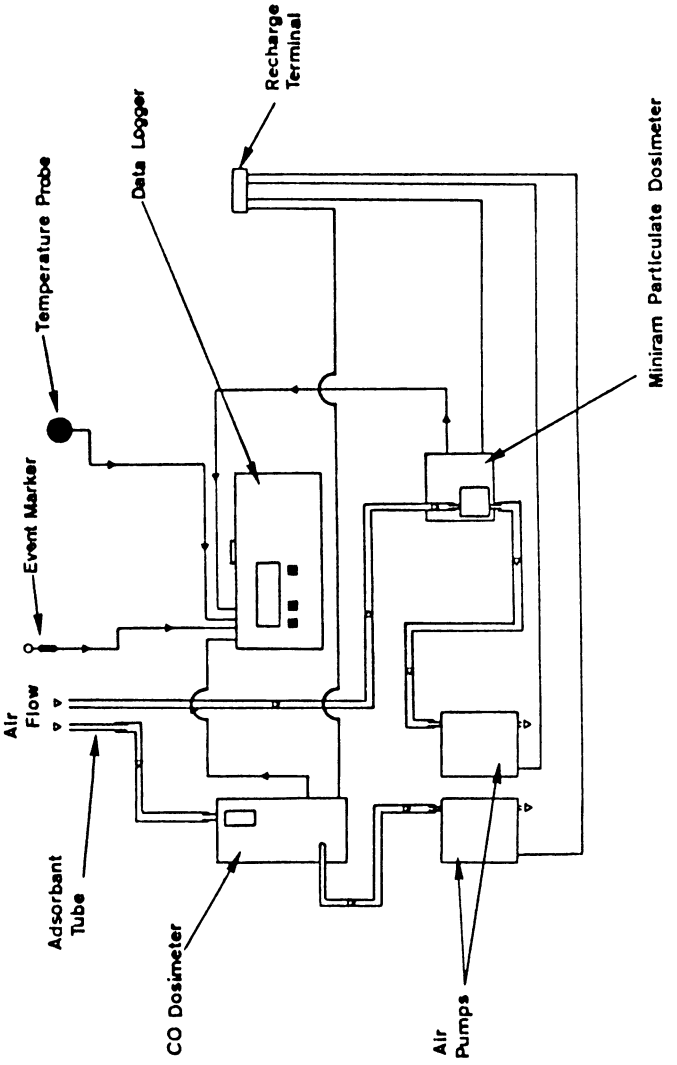

Fig. 2. Schematic of the portable sampling equipment

temperature probe and an electrical event marker interfaced to a data logger. Air flow through CO and TPM dosimeters during sampling was maintained at rates of 0.006 m^3 h^{-1} and 0.015 $m^3 h^{-1}$ respectively using two Alpha pumps (DuPont Ltd., USA) illustrated in Fig. 2.

Each sampling event lasted for a period of 30 min, CO, TPM and temperature readings being logged every 2 min. Concurrently, nicotine samples were obtained by adsorption onto 200 mg of Tennax TA adsorbent (Chromopak, UK) contained in open ended steel tubes which were placed on the CO line. Readings of relative humidity were recorded manually along with relevant site details in the operators diary. Nicotine

samples were analysed using 2-stage thermal desorption followed by capillary gas chromatography (Perkin Elmer, 8320) fitted with FID.

A total of 5% of samples were validated in the field by Imperial College staff in parallel with Hazleton field operatives. Instrument cross checks were also performed with all kits between each 10-week-work-period.

Miniram TPM dosimeters were retrospectively subject to a separate calibration exercise in comparison with piezobalance and gravimetric methods.

Results

Summary data for the complete 30-week-study is given in Table 2 along with corresponding percentile values. In each table a smoking sample is one in which smoking is known to have taken place during sampling or within the 2 h prior to sampling.

Carbon monoxide had an overall mean concentration of 2.4 ppm for some 2,657 measurements throughout the survey. In smoking situations the mean carbon monoxide level was 2.7 ppm (49.6% of samples) and in non-smoking situations it was 2.1 ppm. In 95% of cases where smoking was taking place, carbon monoxide concentrations were less than 7.2 ppm compared with 5.9 ppm in non-smoking situations (Table 2). The distribution of CO values indicated the relatively high proportion of readings within the ranges 0–2 and 2–4 ppm (Fig. 3). Similarly mean CO values observed in each activity confirmed these low levels, travel locations having greatest means at 2.9 ppm and 2.7 ppm for smoking and non-smoking situations respectively (Fig. 3). However, differences between these situations remained small regardless of activity or smoking status.

When comparing the difference in particulate levels between smoking and non-smoking situations the values quoted should be assessed with caution due to the likely over-estimation of the Miniram for particulate levels in mixtures of ETS and particulates from other sources. Indeed, comparative assessments of Miniram TPM, piezobalance and gravimetric methods revealed overall overestimates of 2.5 over piezobalance data and 2.0 over gravimetric data. These also varied according to smoking status. The mean overall Miniram TPM reading determined from 2801 readings was 0.56 mg m^{-3}. In places where smoking occurred a mean of 0.81 mg m^{-3} was found whereas a mean of 0.31 mg m^{-3} occurred where no smoking was recorded. Smoking and non-smoking related uncorrected Miniram TPM values in 95% of all cases were less than 2.42 and 0.88 mg m^{-3} respectively. A similar distribution of data was observed with low numbers of high readings although this was less marked in smoking situations (Fig. 3). The highest mean TPM values were observed in smoking locations particularly in leisure areas with a value of 0.91 mg m^{-3} and in travel locations with a mean of 0.79 mg m^{-3} (Fig. 3).

Of the 2912 sites sampled for nicotine, 49.6% represented smoking situations. Across these samples the mean nicotine concentration was 14 μg m^{-3} (median N.D.) compared with 21 μg m^{-3} in smoking locations only and non-detectable in non-smoking situations (Table 2), their distribution is shown in Fig. 3.

Nicotine was not detected in 77.5% of all samples taken. Concentrations found were less than 49.8 μg m^{-3} in 95% of all samples whereas in smoking situations 95% were below 74 μg m^{-3}. Where no smoking occurred within 2 h of sampling, 95% of samples were below 16 μg m^{-3}, and nicotine exposure was consistently very low across all activities. Where smoking occurred travel and leisure activities appeared to be associated with highest nicotine readings, mean nicotine values being 24 and 22 μg m^{-3} respectively (Fig. 3).

Nicotine, carbon monoxide and miniram TPM samples recorded during the 5% validation programme, initially randomly chosen and subsequently selected, were

Table 2. Summary and percentiles for 30-week-study

Activity		Temp. °C	R.H [%]	CO (PPM)			TPM (MG/M3)*			Nicotine (UG/M3)**		
				SM(T)	SM(Y)	SM(N)	SM(T)	SM(Y)	SM(N)	SM(T)	SM(Y)	SM(N)
Travel	mean	20	44	2.8	2.9	2.7	0.62	0.79	0.42	17	24	7
	sd	5	8	2.8	2.5	3.1	0.64	0.75	0.36	31	40	4
	min	1	22	0.0	0.0	0.0	0.00	0.00	0.07	7	7	7
	max	34	75	17.4	13.1	17.4	4.98	4.98	1.83	414	414	42
	data	545	308	518	283	235	538	297	241	564	313	251
Work	mean	20	45	2.1	2.2	2.1	0.41	0.61	0.31	10	14	9
	sd	4	9	2.7	3.3	2.4	0.42	0.59	0.26	12	18	7
	min	8	23	0.0	0.0	0.0	0.00	0.07	0.00	7	7	7
	max	30	75	31.9	31.9	21.9	5.78	5.78	2.20	167	167	99
	data	723	721	671	221	450	704	224	480	733	238	495
Home	mean	20	46	1.9	2.3	1.8	0.36	0.70	0.27	10	19	8
	sd	3	9	2.3	2.9	2.1	0.36	0.52	0.23	17	33	6
	min	10	5	0.0	0.0	0.0	0.00	0.07	0.00	7	7	7
	max	30	71	26.2	26.2	25.4	3.15	3.15	2.05	292	292	82
	data	766	763	688	139	549	748	156	592	774	162	612
Leisure	mean	20	45	2.7	2.8	2.2	0.84	0.91	0.33	20	22	8
	sd	3	8	2.7	2.7	2.6	0.82	0.85	0.26	29	31	6
	min	8	17	0.0	0.0	0.0	0.07	0.07	0.07	7	7	7
	max	32	75	28.7	28.7	18.9	6.22	6.22	1.24	450	450	66
	data	819	578	780	676	104	811	703	108	841	729	112
Total	mean	20	45	2.4	2.7	2.1	0.56	0.81	0.31	14	21	8
	sd	4	9	2.7	2.8	2.5	0.63	0.77	0.27	24	32	6
	min	1	5	0.0	0.0	0.0	0.00	0.00	0.00	7	7	7
	max	34	75	31.9	31.9	25.4	6.22	6.22	2.20	450	450	99
	data	2,853	2,370	2,657	1.319	1,338	2,801	1,380	1,421	2,912	1,442	1,470

Note *: Particulate matter measured by miniram
**: Nicotine data below detection limit included as 6.8 UG/M3

Table 2 (continued)

Percentiles	CO(PPM)			TPM(MG/M3)			Nicotine(UG/M3)*		
	SM(T)	SM(Y)	SM(N)	SM(T)	SM(Y)	SM(N)	SM(T)	SM(Y)	SM(N)
Minimum	0.0	0.0	0.0	0.00	0.00	0.00	N.D	N.D	N.D
01% value	0.0	0.0	0.0	0.07	0.07	0.07	N.D	N.D	N.D
05% value	0.0	0.0	0.0	0.07	0.15	0.07	N.D	N.D	N.D
10% value	0.0	0.0	0.0	0.15	0.22	0.15	N.D	N.D	N.D
25% value	0.5	0.8	0.3	0.22	0.37	0.15	N.D	N.D	N.D
50% value	1.9	2.1	1.6	0.37	0.59	0.22	N.D	N.D	N.D
75% value	3.4	3.8	3.1	0.66	1.02	0.37	N.D	23.3	N.D
80% value	3.9	4.2	3.5	0.81	1.17	0.39	15.2	28.4	N.D
90% value	5.1	5.6	4.5	1.24	1.68	0.59	30.7	48.5	N.D
95% value	6.8	7.2	5.9	1.68	2.42	0.88	49.8	74.4	16.4
99% value	11.5	12.6	11.5	3.07	3.81	1.46	112.4	146.0	36.1
Maximum	31.9	31.9	25.4	6.22	6.22	2.20	449.9	449.9	98.5
No of data	2,657	1,319	1,338	2,801	1,380	1,421	2,912	1,442	1,470

* Note: 77.5% of data is below detection limit

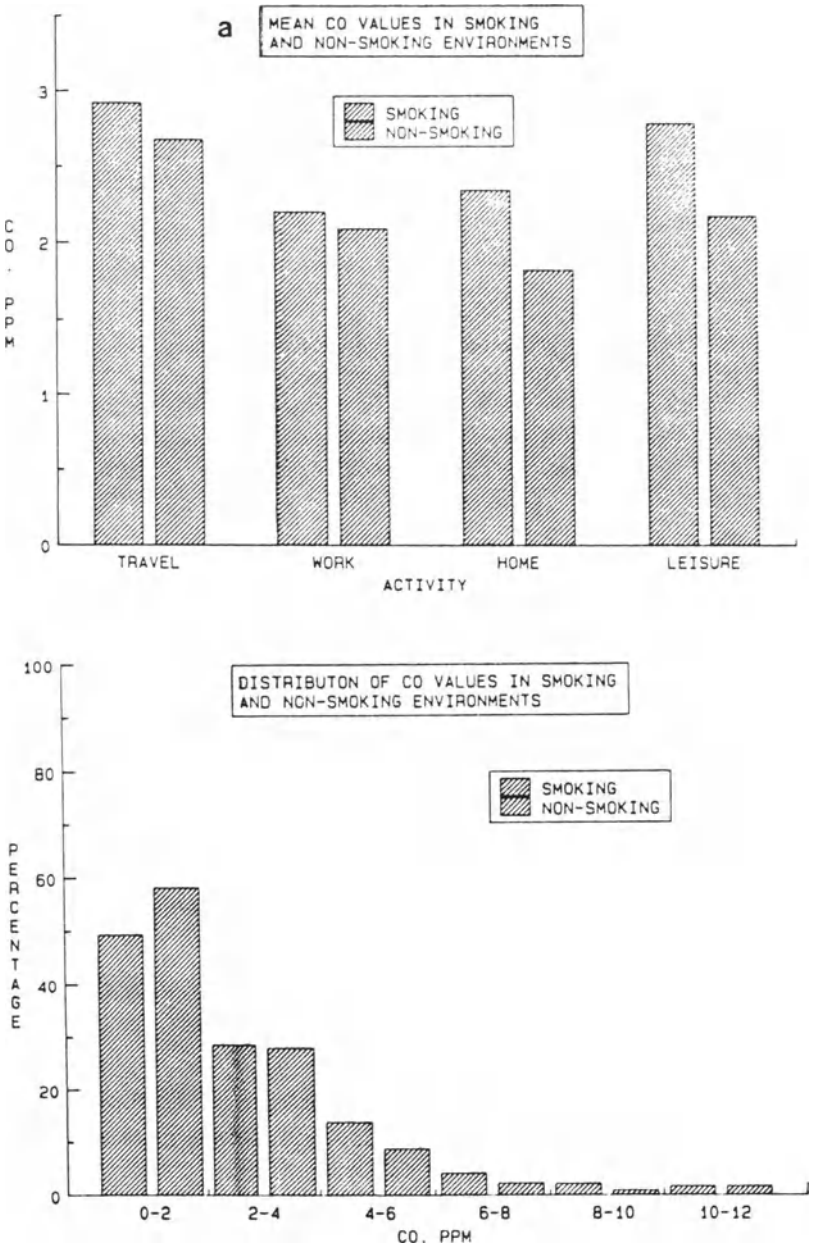

Fig. 3a–c. Mean values and distributions of CO (**a**), nicotine (**b**), and TPM (**c**)

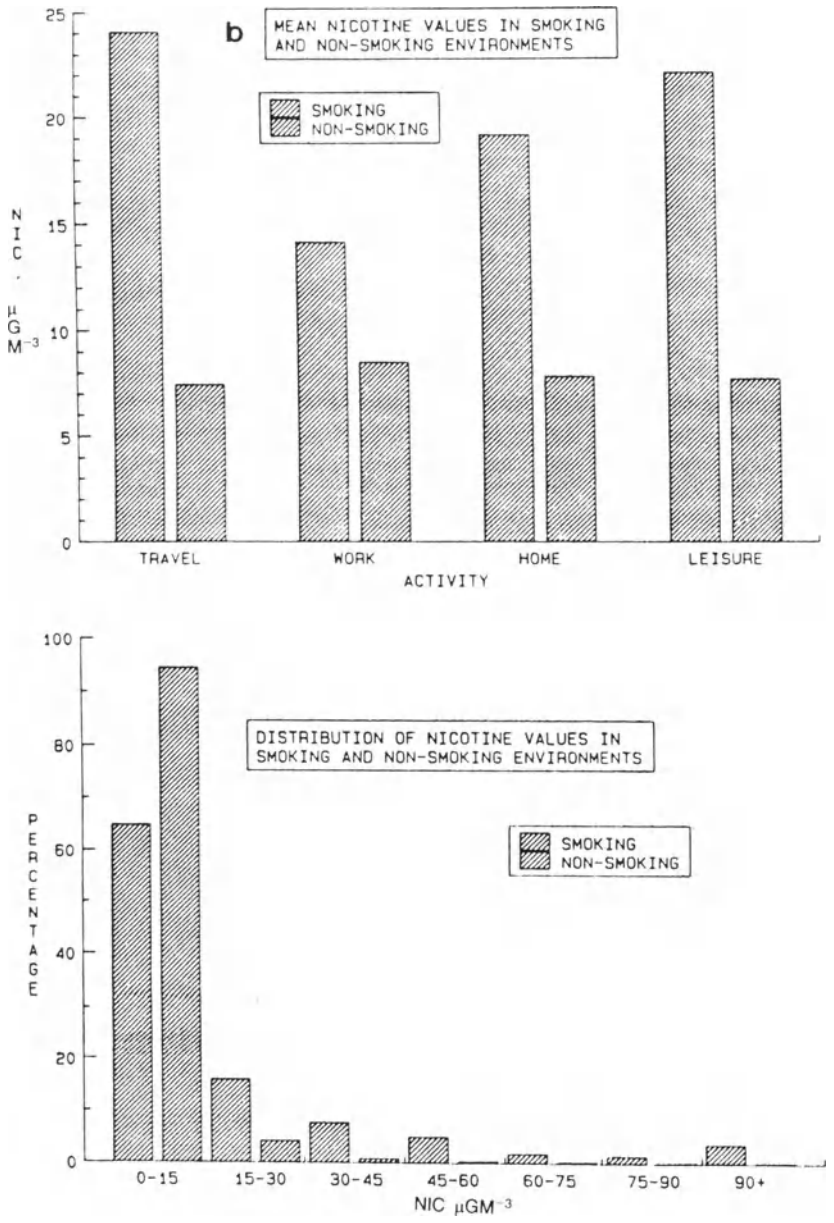
b
MEAN NICOTINE VALUES IN SMOKING AND NON-SMOKING ENVIRONMENTS
SMOKING
NON-SMOKING
NIC. μGM⁻³
25
20
15
10
5
0
TRAVEL
WORK
HOME
LEISURE
ACTIVITY
DISTRIBUTION OF NICOTINE VALUES IN SMOKING AND NON-SMOKING ENVIRONMENTS
SMOKING
NON-SMOKING
PERCENTAGE
100
80
60
40
20
0
0-15
15-30
30-45
45-60
60-75
75-90
90+
NIC μGM⁻³

Fig. 3b

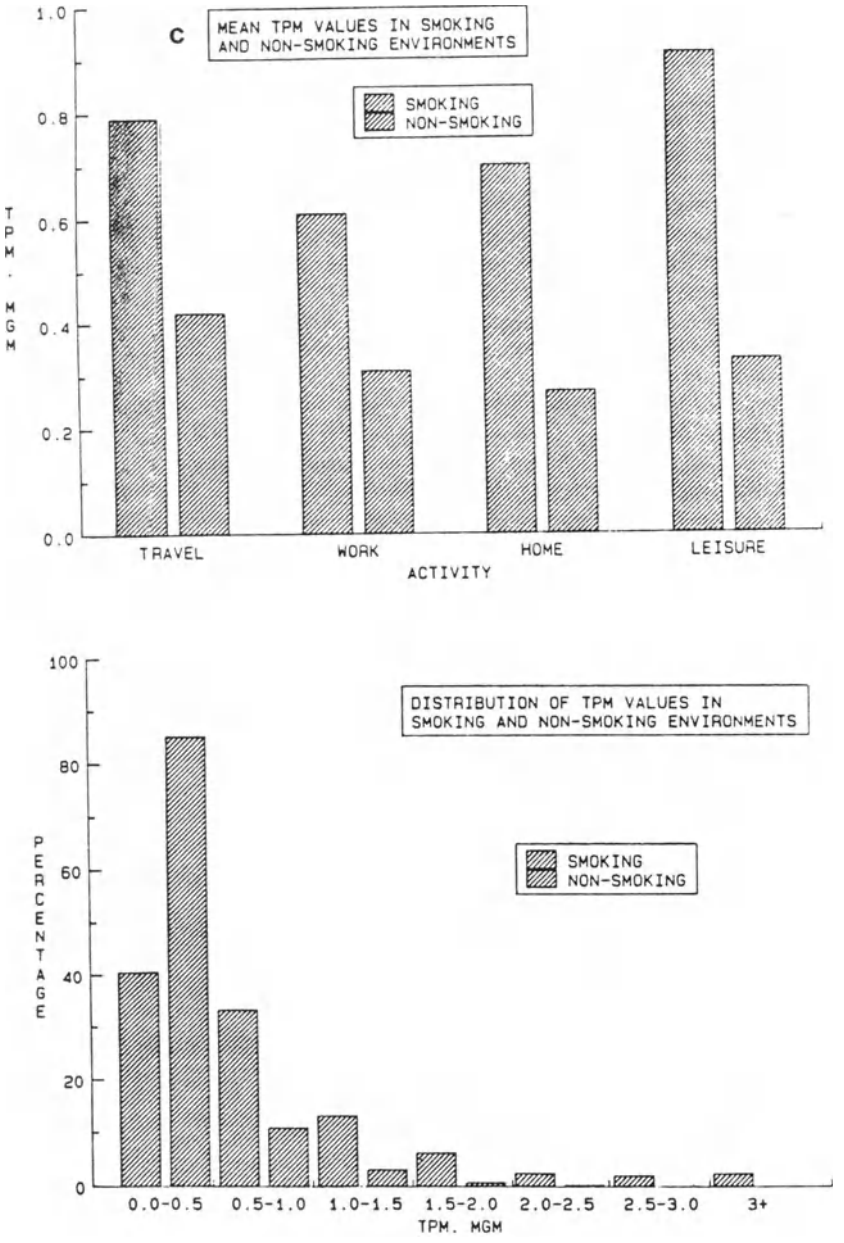
C
MEAN TPM VALUES IN SMOKING AND NON-SMOKING ENVIRONMENTS
SMOKING
NON-SMOKING
TPM. MGM
1.0
0.8
0.6
0.4
0.2
0.0
TRAVEL
WORK
HOME
LEISURE
ACTIVITY
DISTRIBUTION OF TPM VALUES IN SMOKING AND NON-SMOKING ENVIRONMENTS
SMOKING
NON-SMOKING
PERCENTAGE
100
80
60
40
20
0
0.0-0.5
0.5-1.0
1.0-1.5
1.5-2.0
2.0-2.5
2.5-3.0
3+
TPM. MGM

Fig. 3c

subjected to paired t-test analysis. No significant differences were observed ($p = 0.05$) between Imperial College and HUK collected data for any parameter. Of the manually collected relative humidity and temperature readings which were t-tested, only temperature readings were found to be significantly different ($p = 0.05$). However, the difference (0.7°C) was negligible, subsequent tests performed in the laboratory confirmed the kits to be within 0.1°C of each other. Cross checks involving all kits between 10-week-periods also revealed no significant differences ($p = 0.05$) between paired nicotine, carbon monoxide and miniram TPM data.

Discussion

Several authors have previously indicated the inherent difficulty associated with the assessment of human exposure to ETS as a consequence of the number of variables involved [11, 15]. Apart from human behaviour and environmental factors, experimental design and analytical considerations are also important. In this study reported values are based on arithmetic means of large numbers of individual results and hence may reflect any imbalance that exists in the number of observations in each sampling category. The incidence of smoking and non-smoking samples within each category and activity may not reflect the "natural" relative incidence. Therefore an average exposure to ETS in all situations over both smoking and non-smoking samples require certain assumptions to be made prior to evaluation.

In terms of the survey as a whole the sampling locations within each activity were selected at random and therefore the relative incidence of smoking to non-smoking situations should reflect the "natural" incidence due to the large number of data points. Overall 49.5% of all locations were smoking samples. As one examines the sampling locations within each activity in more detail, however, the incidence of smoking to non-smoking may not reflect the "natural" incidence. For example, assessing the exposure to ETS in a bus in all situations is difficult since smoking occurred during or prior to 75% of the samples ($n = 113$). Over all travel locations, however, smoking had occurred in 56% of all samples ($n = 537$) a proportion which is more likely to be representative. Care must therefore be exercised when examining the data in detail.

No ambient air quality standard exists for nicotine in air in the United Kingdom but an OEL of 500 $\mu g\ m^{-3}$ has been set by the Health and Safety Executive for long term industrial exposure in terms of an 8 hour time weighted average. Of all the locations sampled in this study, 95% were less than 10% of this OEL, furthermore, the overall respective non-smoking and smoking nicotine means of 8 and 21 $\mu g\ m^{-3}$, were regarded as higher than anticipated in reality. These high mean values were attributable to non-detected nicotine readings, in non-smoking and smoking environments, being recorded as 6.8 $\mu g\ m^{-3}$ accounting for a reasonable distribution of data below the 13.6 $\mu g\ m^{-3}$ detection limit.

The mean overall nicotine value of 14 $\mu g\ m^{-3}$ was lower than that observed by Maramatsu et al. [18] who found a mean nicotine concentration of 20.3 $\mu g\ m^{-3}$ (max 83 $\mu g\ m^{-3}$, $n = 91$) in various work, leisure and travel locations. However, Sterling et al. [1] in a summary of 230 studies undertaken in buildings in the United States reported a median nicotine concentration of 8.5 $\mu g\ m^{-3}$ where smoking was permitted. Similarly, nicotine values associated with different activities are compatible with previous findings. For example, mean nicotine concentrations in offices of 19 $\mu g\ m^{-3}$, with maximum of 48 $\mu g\ m^{-3}$ from 10 samples and in railway workshops of 5.1 $\mu g\ m^{-3}$, maximum 41 $\mu g\ m^{-3}$ from 14 samples, have been measured [14]. An early study had

suggested a mean nicotine concentration of 1.1 $\mu g\ m^{-3}$ for 160 samples with a maximum of 16 $\mu g\ m^{-3}$ [19].

Occupational Exposure Limits to carbon monoxide in the United Kingdom are 50 ppm as an 8 h time weighted average for long term exposure and 400 ppm as a 10 min time weighted average for short term exposure [16]. In this study carbon monoxide values were relatively low throughout and no individual 30 min mean carbon monoxide concentration exceeded the OEL of 50 ppm, and 95% of all locations were below 14% of this OEL. In 95% of cases where smoking was taking place, carbon monoxide concentrations were less than 7.2 ppm compared to 5.9 ppm in no smoking situations and the distribution data would indicate significant contributions from other combustion sources at the higher levels of carbon monoxide. Sisovic and Fugas [9] suggested that, during summer months, indoor carbon dioxide levels in shops can be significantly affected by proximity and density of traffic.

Particulates were determined by light scattering methods which must be related to standard gravimetric or piezobalance measurements due to difficulties in Miniram calibration related to particle size and particulate colour. Despite such calibration considerations the Miniram was the only instrument capable of the field monitoring required in this survey due to its portability, robust nature and logging capability. Comparative assessment of particulates were consistent with the findings of Rawbone et al. [20], who suggested a reduction factor of 2.5 for Miniram readings. Assuming a correction factor of 2.5, all particulate concentrations in the survey were below the OEL of 5,000 $\mu g\ m^{-3}$ set for "respirable dust" [21]. Furthermore, 95% of all samples would be less than 14% of the OEL and 95% of all smoking samples would be less than 19% of the OEL. The findings observed compare favourably with other studies when the correction factor is applied. Typical values for particulates in indoor air have been reported to range between non-detectable levels and 700 $\mu g\ m^{-3}$ in the United States with a median value of 37 $\mu g\ m^{-3}$ [1]. In a comparison of sampling methods for respirable suspended particulates ($<3.5\ \mu m$) undertaken by the Reynolds Tobacco Company, Conner et al. [22] reported gravimetric particulate data up to 306 $\mu g\ m^{-3}$ in a restaurant where smoking was taking place.

Summary and Conclusions

- An extensive 30-week-survey of indoor air quality in the UK has been undertaken.
- Travel, work, home and leisure activities were evaluated approximately 3,000 times.
- Components of ETS monitored were: CO, Miniram particulate matter and nicotine in smoking and non-smoking situations.
- Ventilation and building design can affect ETS.
- TPM was significantly higher in smoking versus non-smoking situations although both are consistently less when determined by piezobalance and gravimetric methods.
- CO readings were all background level and significantly less than outdoor air. Fifty percent were below 2 ppm in smoking and non-smoking situations.
- More than 50% nicotine values in smoking and 90% in non-smoking environments were below the 14 $\mu g\ m^{-3}$ detection limit, 77.5% overall.
- Travel and leisure ETS exposures were consistently higher than home and work exposures.
- Home and work exposures to nicotine, 5% or less than UK long term occupational exposure limits (OEL), whereas travel and leisure were within 10% of UK OEL of 500 $\mu g\ m^{-3}$.

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Personal Exposure to Ambient Nicotine in Different Seasons

S. Umemura, Y. Ishizu, and M. Muramatsu

Summary

To evaluate the difference in the exposure of nonsmoking women to environmental tobacco smoke (ETS) between winter and summer, exposure levels of ambient nicotine in both seasons were measured by a personal nicotine monitor carried by the nonsmoking subjects throughout the whole day. Housewives and working women were selected as the nonsmoking subjects.

The average amount of nicotine inhaled by housewives during their smoking husbands' holiday was estimated to be 93.2 μg/day in winter and 34.3 μg/day in summer. The winter and summer values were 2.22 and 2.01 times higher, respectively, than those determined during their husbands' workday.

The average amounts of nicotine inhaled during a workday by working women with a smoking husband and without a smoker in their family were estimated to be 75.1 μg/day and 68.8 μg/day in winter, and 50.8 μg/day and 51.6 μg/day in summer, respectively. These values in winter and summer for the women with a smoking husband were 1.24 and 1.14 times higher, respectively, than the values determined during their holiday. On the other hand, the value during a holiday for the women without a smoker in their family was negligibly small regardless of season. Thus, the daily exposure to ETS was found to be generally higher in winter than in summer. The difference in the exposure levels between winter and summer was particularly significant for housewives.

Introduction

It is indispensable to quantify the exposure level of nonsmokers to ETS in order to assess the health effects of exposure to ETS. Various ETS components such as acrolein [1, 3, 10], aromatic hydrocarbons [1], CO [1, 3, 10], nitrogen oxides [3, 11] and respirable particulate matter [2, 8] have been measured under realistic conditions as markers of the exposure to tobacco smoke. The major limitation of using these components is that they do not all originate from tobacco smoke as there are other sources of them in the environment [9].

Nicotine, however, is a specific indicator for ETS exposure. Therefore, nicotine has been extensively used as an excellent marker for ETS exposure [1, 2, 4–7, 11]. The authors have developed a personal nicotine monitor to enable measurement of individual exposure levels of nonsmokers to ETS in their daily lives, and have measured personal exposure of nonsmokers to ambient nicotine in various living places [6, 7]. In the present work, the difference between winter and summer in the personal exposure of nonsmoking women to ambient nicotine has been measured by the personal nicotine monitor as a part of a series of studies evaluating exposure levels to ETS.

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Experimental Methods

Eleven nonsmoking women, i.e., five housewives with smoking husbands, three working women with smoking husbands and three working women without smokers in their families, were selected as the subjects.

A personal nicotine monitor, which consists of a sampler tube and a small sampling pump [6], was carried by the subjects throughout the whole day, in summer and winter. Ambient nicotine was collected in the sampler tube by drawing air at 40 ml/min. The sampler tube was exchanged every 8 h.

After collection, n-propanol solution containing 400 ng of 7-methylquinoline (7-MQ) was injected into the sampler tube as an internal standard. Then the sampler tube was placed in a cylindrical furnace heated to 280°C and connected directly to a gas chromatograph (GC) equipped with a nitrogen-sensitive detector. By passing the carrier gas through the sampler tube, the collected nicotine and 7-MQ were desorbed onto a GC column and analyzed. A glass column (2 m × 3 mm i.d.) packed with Chromosorb W (AW-DMCS, 30/60 mesh) coated with 10 wt% of PEG-20M and 2 wt% of KOH was used for the analysis. To improve the desorption efficiency of nicotine, a small amount of ammonia vapor was added into the carrier gas during the thermal desorption period. Further details of the personal nicotine moniter and analytical methods have been reported in the previous papers [6, 7].

Results and Discussion

Figure 1 shows the comparison of the exposure level of ambient nicotine between winter and summer for housewives with smoking husbands. The exposure level was significantly

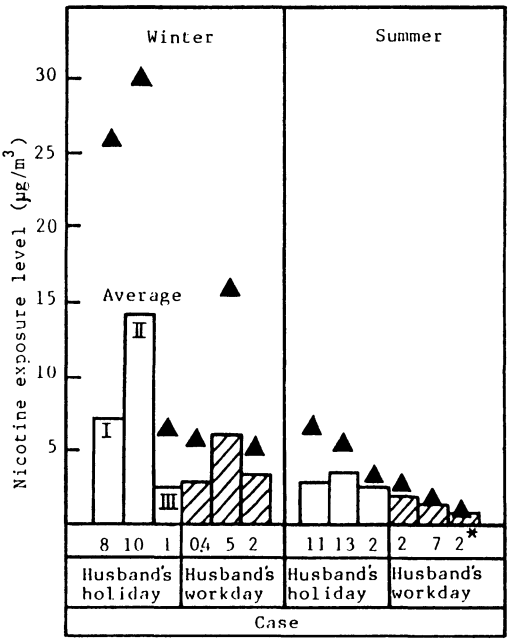

Fig. 1. Comparison of personal exposure of housewives with smoking husbands to ambient nicotine between summer and winter. ▲: Max; I: 8:00–16:00; II: 16:00–24:00; III: 0:00–8:00; *: Number of cigarettes smoked by husband at home

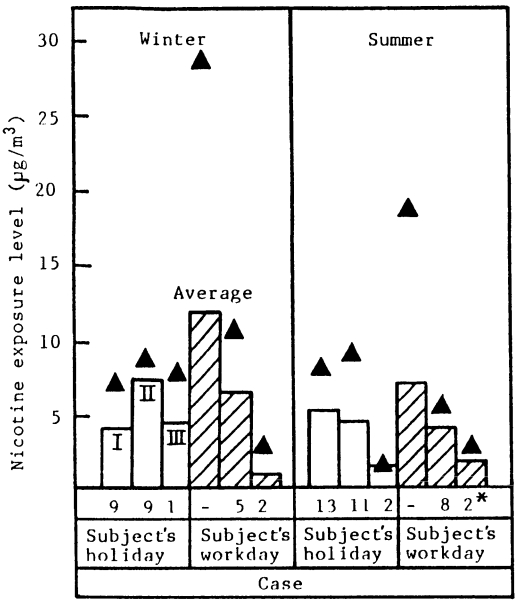

Fig. 2. Comparison of personal exposure of working women with smoking husbands to ambient nicotine between summer and winter. ▲: Max; I: 8:00–16:00; II: 16:00–24:00; III: 0:00–8:00; *: Number of cigarettes smoked by husband at home

higher in winter than summer and also during the husband's holiday than his workday. The highest average of nicotine exposure for housewives was observed between 16:00 and 24:00 on their husbands' holiday in winter. The average exposure in this case went up to 14.2 $\mu g/m^3$, which was about twice as high as the level for the comparable time period during their husbands' workday in winter. According to the results of questionnaire answered by the subjects, windows were usually closed in winter, while they were more often opened in summer. This indicates that the rooms were naturally well ventilated in summer and this, in turn, would significantly contribute to reducing the exposure level to nicotine in summer.

Figure 2 shows the comparison of nicotine exposure levels between winter and summer for working women with smoking husbands. The exposure level was somewhat higher in winter than in summer, but not so significantly different as the case for housewives with smoking husbands shown in Fig. 1. The highest average of nicotine exposure for these women was observed between 8:00 and 16:00 of their workday regardless of season. This result indicates that these subjects are more exposed to ETS in their working places than in their homes. The average exposure level to nicotine during the same period of a workday was 11.3 $\mu g/m^3$ in winter and 7.4 $\mu g/m^3$ in summer.

Figure 3 shows the comparison of the nicotine exposure levels between winter and summer for working women without a smoker in family. As can be seen from Fig. 3, nicotine exposure level was very small during their holiday and between 0:00 and 8:00 on their workday. The average exposure level between 8:00 and 16:00 on their workday reached 12.4 $\mu g/m^3$ in winter and 11.2 $\mu g/m^3$ in summer. Such a small difference in the exposure level between winter and summer will be attributed to the fact that their working places were air-conditioned throughout all seasons.

The results shown in Figs. 1, 2 and 3 are in fair agreement with those of Hinds and First [5], Badre et al. [1], Weber and Fischer [11], First [2], and Hammond et al. [4]. For

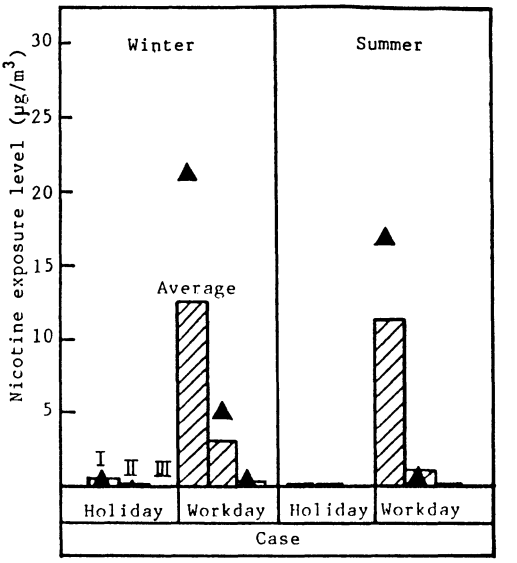

Fig. 3. Comparison of personal exposure of working women without a smoker in family to ambient nicotine between summer and winter. ▲: Max; I: 8:00–16:00; II: 16:00–24:00; III: 0:00–8:00

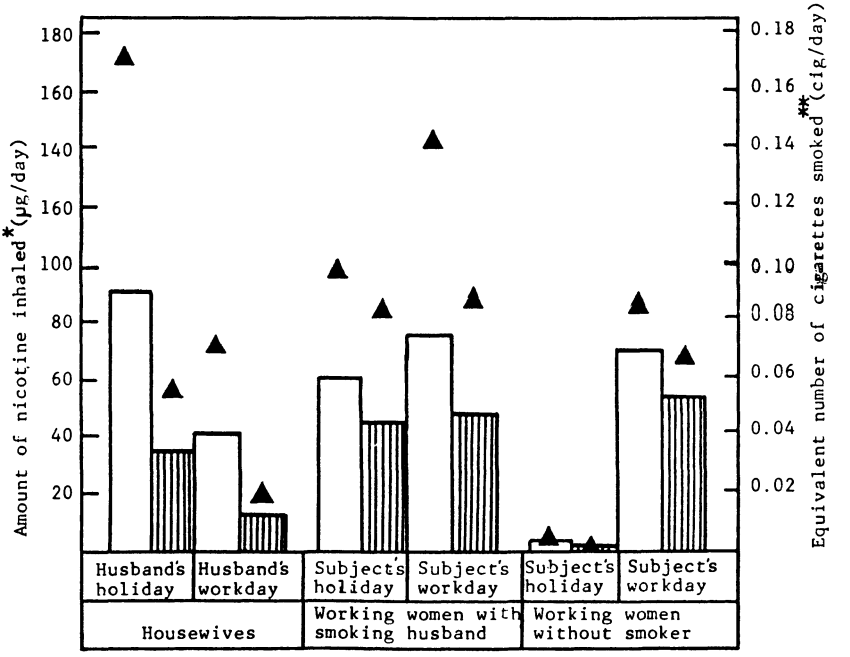

Fig. 4. Personal exposure to nicotine in different seasons. □: Winter; ▥: Summer; ▲: Max; *: Respiration volume was estimated to be 8l/min; **: Number of cigarettes smoked by husband at home

example, Hammond et al. have recently reported that the exposure level of office workers to nicotine was in the range from 9 to 28 $\mu g/m^3$.

Figure 4 illustrates the estimates of "daily amount of nicotine inhaled" and "equivalent number of cigarettes smoked" by passive smoking. The former was estimated by multiplying the nicotine concentration ($\mu g/m^3$) by a respiration volume of 11.5 m^3/day, and the latter was obtained by dividing the "daily amount of nicotine inhaled" by the nicotine amount (1 mg) inhaled through active smoking of one cigarette.

The average of the daily amount of nicotine inhaled by housewives during their husbands' holiday was estimated to be 93.2 μg in winter and 34.3 μg in summer. The values for winter and summer were 2.22 and 2.01 times higher, respectively, than for their husbands' workday. The averages of the daily amount of nicotine inhaled during the workday by working women with smoking husbands and without a smoker in their families were estimated to be 75.1 μg and 68.8 μg in winter, and 50.8 μg and 51.5 μg in summer, respectively. The values in winter and summer for working women with smoking husbands were 1.24 and 1.14 times higher, respectively, than those values obtained during their holiday. The daily amount of nicotine inhaled by women without a smoker in family was negligibly small regardless of season. Thus, Fig. 4 clearly shows that the amount of nicotine inhaled is larger in winter than in summer. This may largely result from good ventilation owing to leaving the windows open more often in summer as mentioned above.

In this study, the highest nicotine exposure was observed for a housewife whose husband smoked 31 cigarettes/day at home during a holiday in winter. In this case, the daily amount of nicotine inhaled by this woman throughout the day was estimated to be 177 μg, which is only equivalent to the amount of nicotine inhaled by active smoking of 0.177 ordinary cigarettes containing 1 mg of nicotine in mainstream smoke. Therefore, the amount of nicotine inhaled by nonsmoking women in their daily lives is considered to be far smaller than that inhaled by a smoker through active smoking.

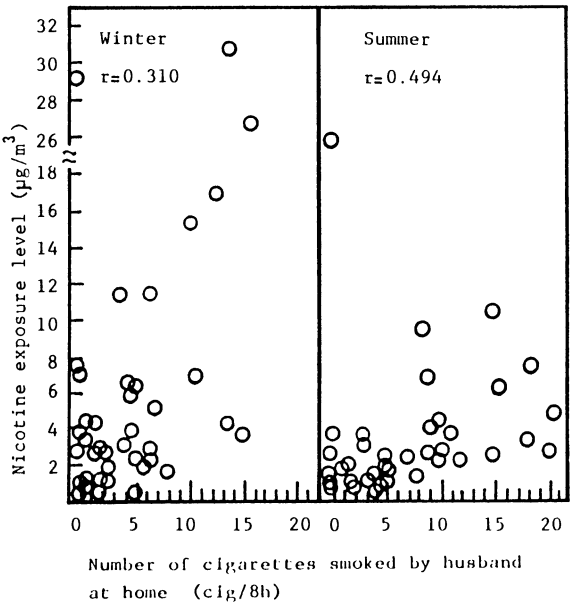

Fig. 5. Relation between the nicotine exposure level and number of cigarettes smoked by husband at home

Figure 5 shows the relationship between the 8-h average of nicotine exposure for women with smoking husbands and the number of cigarettes smoked by the husband at home in the corresponding period. As one might expect, the correlation is not good enough to be able to evaluate the exposure level of a nonsmoking woman to ETS according to the number of cigarettes smoked by her husband. This is because the exposure level to ETS depends not only on the smoking habits of the spouse but also on other factors such as the smoking habits of fellow workers, ventilation conditions of environment, the life style of the subject, and so on.

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The Measurement of ETS Through Adsorption/Desorption Procedures

C. Proctor and H. Dymond

Introduction

Environmental tobacco smoke (ETS) has received increasing attention in recent years, yet there is still no clear way of precisely measuring ETS. This is due to several compounding factors. ETS is an extremely complex mixture of compounds [1], it is much diluted and integrated with the ambient air and hence any compounds present from other sources, and it is not a stable entity [2]. Because of the dilution factor and the complexity involved one must use a highly sensitive and selective analytical technique that can determine the presence of chemicals specific to tobacco smoke. The alternative is to measure an environment with and without tobacco smoke present, but this is rarely possible in realistic situations [3]. Furthermore the technique must take account of the fact that ETS is continuously changing; it is analytically a moving target. This paper presents a method that allows the acquisition of chromatographic profiles of ambient air.

ETS originates from the combination of the sidestream smoke of a burning cigarette, the exhaled mainstream smoke and any smoke spilled from the mouth during draw (mouthspill). Its concentration and composition will depend on many factors, including the type of tobacco product smoked, the number smoked, the air movement conditions in the environment, and the type of adsorbent surfaces such as walls and furnishings present. It will consist of chemicals in both the gaseous, the vapour and the particulate phases. Moreover, it is a dynamic aerosol and some compounds traditionally associated with the particulate phase of smoke are found in the vapour phase of aged ETS as the particles tend to lose volatiles with time [4]. Associated with this phenomena is the fact that different compounds in ETS will have different decay rates.

Some constituents of ETS may be measured directly by portable and sensitive equipment [5], but this generally is only applicable to gases such as carbon monoxide which are non-specific to tobacco smoke and will be produced by other forms of combustion [6]. More specific chemicals, such as nicotine, when in the low concentrations found in ETS require concentration steps in the analytical method. An appropriate method for achieving this, and at the same time producing chromatographic profiles of the ambient atmosphere is described here.

Collection of the Sample

Adsorption traps have become increasingly more accepted in methods aimed at measuring concentrations of chemicals in ambient atmospheres [7]. The general principle is very simple. A known volume of air is drawn through a chemical support with adsorbent properties. If the correct adsorbent is used and concentrations are not so high as

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to cause breakthrough, then sampling can take place over several hours. The longer the sampling period, the better the sensitivity of the analysis. However, this should be balanced by the fact that the measurement is an average over a period of time and does not account for short-term temporal variations, though this may also be desirable.

In assessing the capability of an adsorbent system it is necessary to investigate one compound at a time. The obvious choice for ETS is nicotine. This is because it is specific to tobacco smoke, it is in high concentration relative to other volatile components and because it has been traditionally a measure of mainstream smoke. Numerous analytical methods for the determination of ambient nicotine have already been published [8]. All use an initial trap for concentration of the sample. The National Institute for Occupational Safety and Health Administration (NIOSH) recommend that the nicotine is trapped on Amberlite XAD-2 resin [9]. The sample can then be eluted with a quantity of ethyl acetate and quantified by gas chromatography. Liquid desorption, however, introduces a considerable dilution factor to the analysis and thus does not allow the attainment of very low limits of detection. The sensitivity of the method is much improved if thermal desorption of the adsorbent is used as then the total sample is analysed in one go.

Adsorbents applicable to thermal desorption must fulfill several criteria:

- the adsorbent must be efficient in trapping the chemical under consideration, whether that compound is in the particulate or the vapour phase;
- the efficiency should be such that there is no breakthrough of compound during long sampling periods;
- the adsorbent must however be able to release all of the compound after thermal desorption for a short period of time and at a temperature below that likely to degrade the sample;
- the adsorbent itself must be chemically inert and thermally stable (to avoid leaching of compounds associated with the support complicating the analysis);
- the adsorbent must be able to trap the sample for some length of time without degradation to allow for the transfer time between the sample being collected and the eventual analysis time.

We found that the adsorbent Tenax TA, which is a polymer of 2,6-diphenyl-p-phenylene oxide [10], satisfied all of these criteria when considering the collection of nicotine. Several experiments were run before coming to this conclusion. In all experiments a weight of 0.4 g Tenax TA (35–60 Mesh) was packed into a stainless steel tube as described in Fig. 1.

The first experiment was to assess the collection efficiency of the trap to ambient smoke particulates. This was done using a Malvern LASX Laser Aerosol Spectrometer. This instrument is limited to a lower size range limit of 0.09 to 0.11 μm. Samples of 40 cc of both fresh sidestream smoke and aged ETS were collected and introduced into an inert bag containing 2,000 cc of nitrogen. The samples were then analysed by the spectrometer with and without a trap between sample and analyser. The experiment showed the trap to have a collection efficiency for all particulates of 96% for "fresh" smoke and 93% for aged smoke. This efficiency was consistent over the range of particles observed from 0.09 to 2 μm. A similar experiment, but using the adsorbent Supelcoport 100/120 mesh containing 5% OV17 in the trap, gave trapping efficiencies for all particulates of 99.6% for "fresh" smoke and 99% for aged smoke. Even though the Tenax efficiency is not as good, further factors make it useful.

The second series of experiments set out to determine the collection efficiency of vapour phase constituents. Nicotine is thought to be almost entirely in the vapour phase in

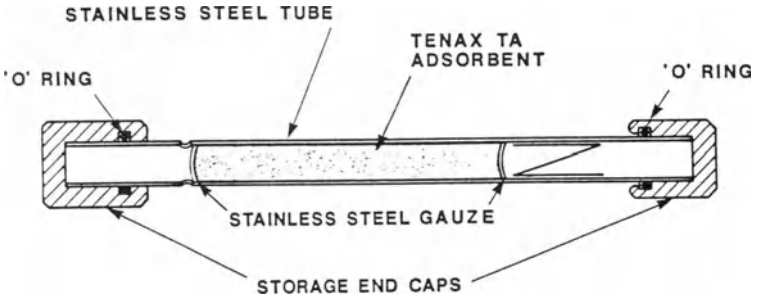

Fig. 1. Schematic diagram of the sampling tube used for adsorption

aged smoke [2] and so it was used for this check. By sampling ETS produced in a controlled room through two tubes in series it was determined that the first tube was 99% efficient.

The good thermal stability of Tenax is well documented, and so the third experiment investigated the retention of nicotine on the tube during thermal desorption. By injecting liquid standards of nicotine in propanol both onto the Tenax and directly into the analysis system, and by analysis of ETS samples, it was determined that a desorption of 15 min at 150°C released 99% of the nicotine for subsequent analysis.

Storage of trapped samples was also considered, and it was found by taking samples of ETS in parallel that there was no deterioration in nicotine content over two week refrigerated storage [11].

There has been much data published on the effectiveness of Tenax as an adsorbent for a wide range of volatile materials [12]. Within the regime of using 0.4 g of Tenax and typically sampling 1,000 cc of air at a rate of 10 cc per minute, the tubes will be efficient for the majority of volatile compounds present in ambient air.

Analysis of the Sample

Such complex mixtures as found in ambient air require a powerful separation stage in order to resolve the individual components. In order to attain good resolution the sample must be presented to the chromatographic column as a discrete sample. Therefore, direct thermal desorption (which requires 10 to 15 min for complete release) will result in a poorly resolved chromatogram. This can be overcome by the introduction of a cryofocusing step in the procedure. The sample of trapped and concentrated ambient air is swept off the trap by being heated at 150°C for 15 min whilst a flow of helium gas flushes the desorbed components through the system and into a cold trap containing a small amount of Tenax (approximately 0.05 g) maintained at −30°C. This secondary, cryofocusing trap is then rapidly heated electronically in order to "inject" the collected compounds onto the chromatographic column.

Our instrumental set-up is illustrated in Fig. 2. A Perkin-Elmer ATD-50 is used for the two stage desorption. The carrier flow can be split both before and after secondary trapping. The head of the chromatographic column is positioned directly after the cold trap. A heated transfer line containing the column then links the trap to a Perkin-Elmer Sigma 3 gas chromatograph. The exit of the column is fed directly into the ion source of

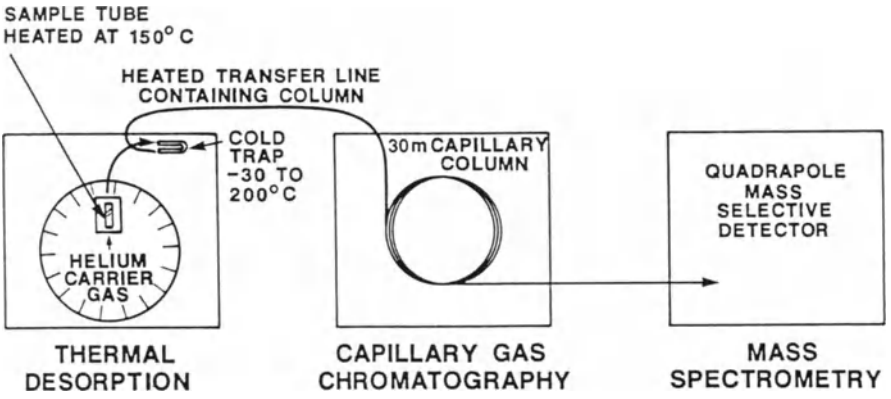

Fig. 2. Schematic diagram of the analytical instrumentation used to analyse the adsorbed samples

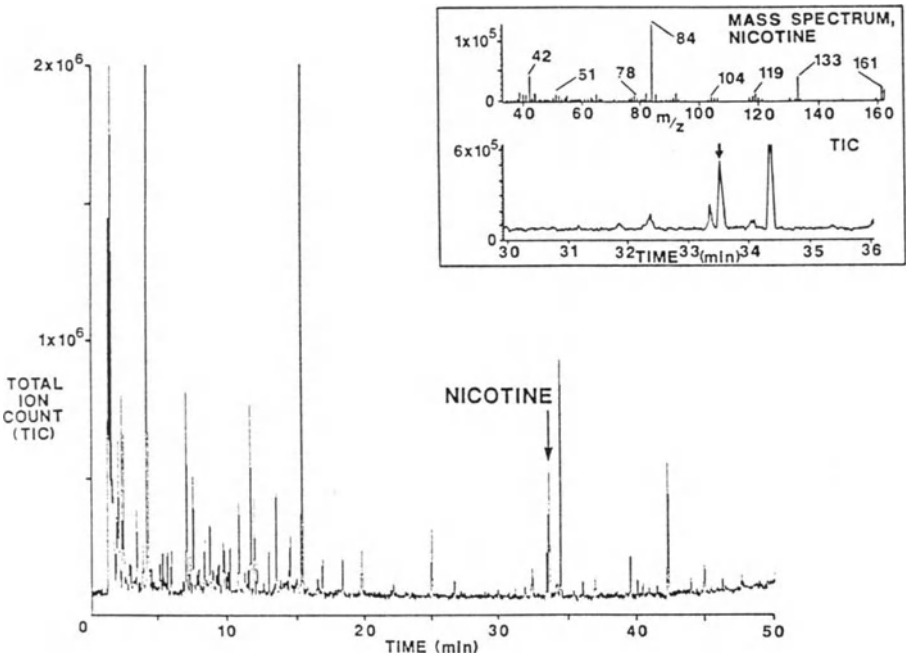

Fig. 3. Chromatographic profile of the ambient atmosphere in a bar in a public house

a Hewlett-Packard mass selective detector. This combination of analytical techniques allows introduction of the concentrated sample, followed by high resolution separation of the individual components, followed by identification and quantification of each compound by the mass spectrometer.

Breakthrough of compounds through the cold trap can be monitored by running the mass spectrometer during primary desorption. When using the apparatus to measure ETS samples, this is rarely a problem. Tenax is hydrophobic and so any moisture collected during sampling will not cause analytical problems such as freezing of the cold trap.

The mass spectrometer is a very selective and sensitive device. From the fragmentation patterns produced by electron impact most compounds can be uniquely identified. The sensitivity of the device allows the measurement of sample in sub nanogram concentrations.

Examples of Chromatographic Profiles of Ambient Atmospheres

The following are examples of the type of chromatographic profiles that may be obtained with the analytical system described. In each case sample air volumes of between 1 and 2 litres were taken at approximately head height from a static position and no attempt was made to avoid close contact with smokers. Sample flow rate was 0.6 l/h for each sample. Analysis of samples was achieved in every case with a primary desorption of 15 min at 150 °C onto a cold trap maintained at −30 °C. Secondary desorption heated the cold trap from −30 to 200 °C, thus introducing the sample to a 30 m, 0.25 μm Supelco SPB-5 capillary column. The mass spectrometer was run in total ion mode with a multiplier set at 2000 V.

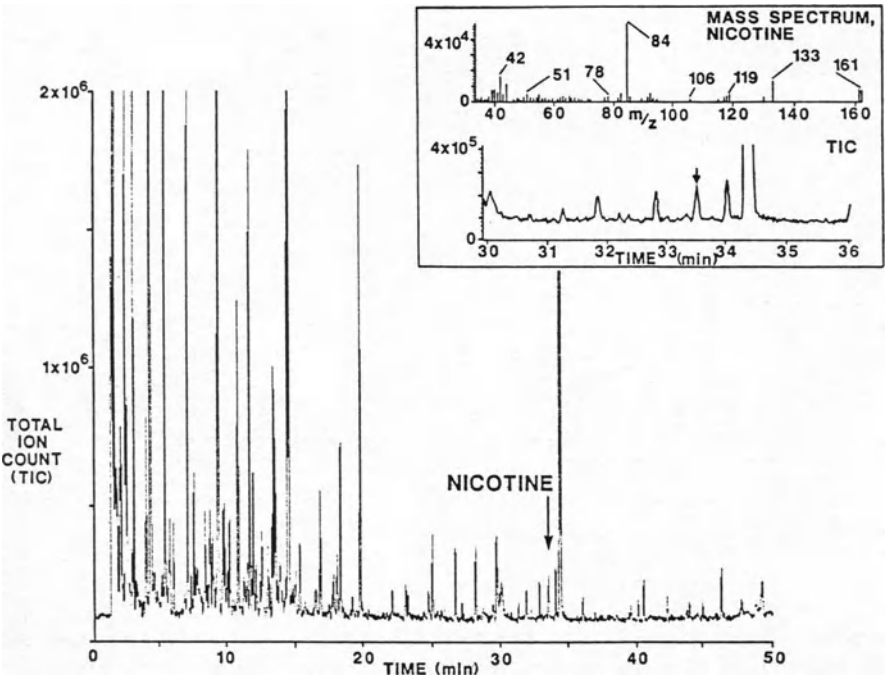

Fig. 4. Chromatographic profile of the environment in the living room of a private house

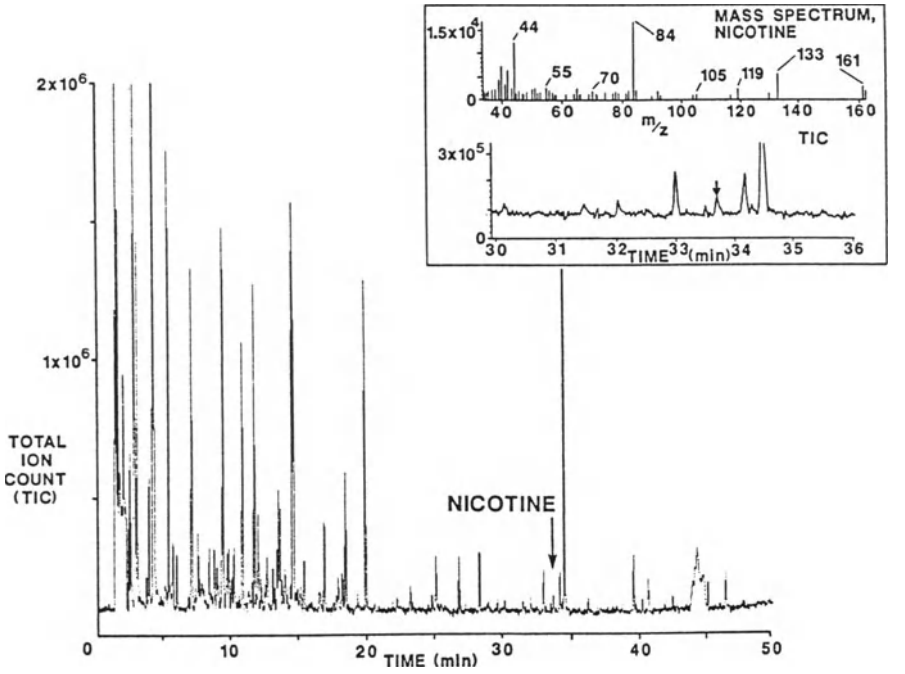

Fig. 5. Chromatographic profile acquired in the kitchen of a private house during cooking in an electric oven

The first example was taken in the bar of a public house during a lunchtime period. There were more than six active smokers present, three of which sat close to the monitoring point. Figure 3 shows the chromatographic profile for this sample. The nicotine peak corresponds to an ambient concentration of 38 $\mu g/m^3$ of nicotine. There are clearly a large number of compounds present in this atmosphere. For example, the large peak at 15.5 min retention time corresponds to dichlorobenzene. This presumably arises from the use of a cleaning agent in the pub.

Figure 4 shows the chromatographic profile corresponding to the ambient air in the living room of a private house. Two people smoked a total of six cigarettes during a 2-h-sampling period. The ambient nicotine concentration averaged over this period was 8 $\mu g/m^3$. Many of the other compounds observed were found to be aliphatic hydrocarbons. Figure 5 was acquired in the kitchen of the same house during the cooking of a meal using an electric oven. There the nicotine level was found to be 3 $\mu g/m^3$. The majority of the chemicals identified were common to both environments.

The ambient atmosphere in a car during a 2-h-motorway (high speed) journey is illustrated in Fig. 6. Five cigarettes were smoked by the driver during the trip, the sample was taken in the position of a front seat passenger, and the air ventilation devices and windows remained closed for the majority of the journey. The average ambient nicotine content was found to be 8 $\mu g/m^3$. Again the profile is complex and contains many compounds.

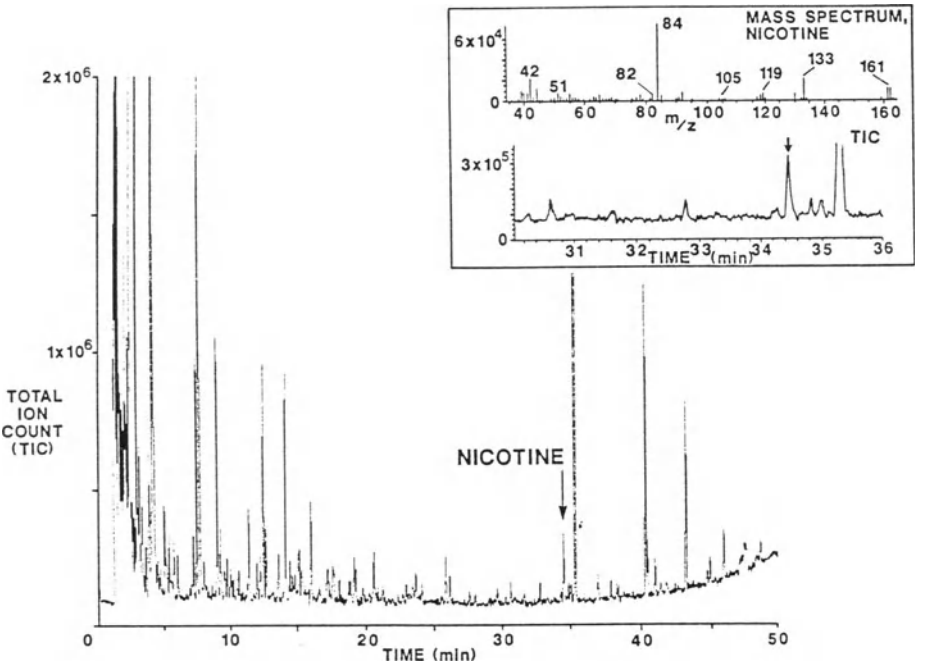

Fig. 6. Chromatographic profile of the ambient air in a car during a 2-h-journey

Finally, Fig. 7 presents the profile of the atmosphere in an Indian restaurant during a meal taken by two smokers over the period of two hours. Three other people were noticed to be smoking during the same period. Nicotine level was found to be 12 $\mu g/m^3$. More than 200 other chemicals were observed in the analysis, many of them being volatile "flavour" type compounds.

Conclusions

This work has demonstrated that adsorption/thermal desorption procedures can be used to measure volatile compounds present in ambient atmosphere. However, the chromatographic profiles given as examples make it clear that ambient air consists of a complex mixture of compounds. Moreover, the analysis of several realistic environments, all of which contained ETS, shows large differences in the individual chemicals present in different atmospheres. As ETS is common to the experiments, these differences presumably arise from the contribution of various sources other than tobacco smoke.

Therefore, any measurement of ETS, whether it takes nicotine or some other compound specific to tobacco smoke as a marker, must use analytical methodology capable of high resolution of the mixture. It should also use a detection technique capable of specific identification of the compound because, as has been shown in this paper for the case of nicotine, the peak of interest is likely to be small relative to signals arising from other volatile compounds.

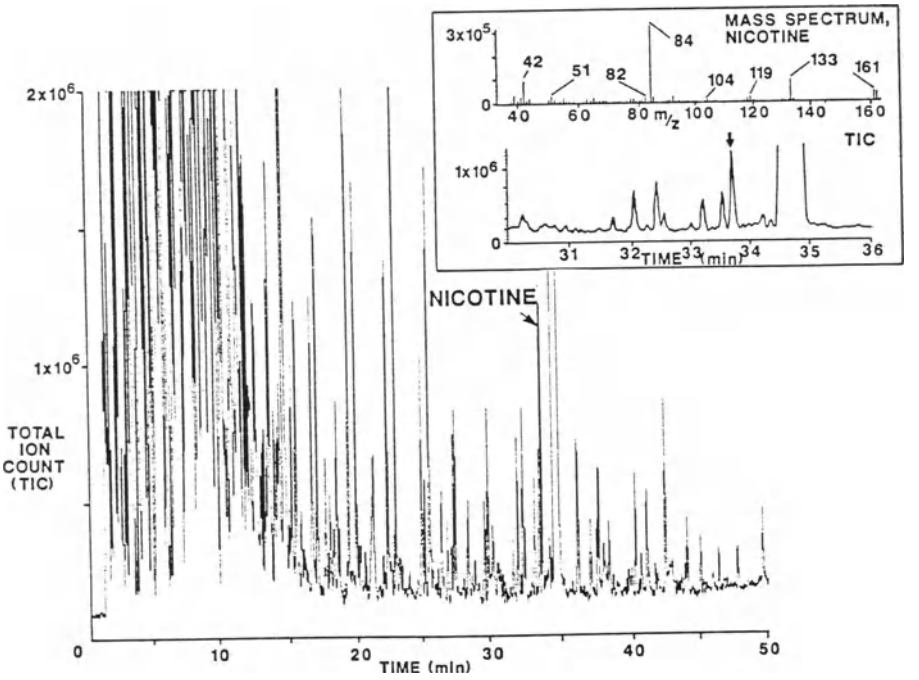

Fig. 7. Chromatographic profile of the atmosphere of an Indian restaurant

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Removal of Cigarette Smoke Particulates from Room Environment*

H. Emi, C. Kanaoka, and Y. Otani

Summary

Performance of commercial room air cleaners for the removal of cigarette smoke was evaluated experimentally by measuring the change in the cigarette smoke concentration in a closed room. As a result, the rate of decrease in particulate concentration increased with an increase in the product of the volumetric flow rate and the collection efficiency of the room air cleaner. The combination of electret filters and corona charger appeared to be the most effective for the removal of cigarette smoke in room environment. The change in the particulate concentration in a closed room was well described by mass balance equation for cigarette smoke in both the presence and absence of smoke generation.

Introduction

As more and more of our time is spent in a closed environment, the adverse health effect of cigarette smoke on nonsmokers is of great concern from both mental and physiological aspects. In order to protect nonsmokers from cigarette smoke exposure, economic versions of a room air cleaner with disposal cartridge filters have been commercialized and installed in air-conditioned offices and houses. However, since cigarette smoke consists of submicron particles which are not easily removed by the conventional air filters, there is great doubt about the effectiveness of these air cleaners for cigarette smoke removal. In the present work, the fractional and overall collection efficiencies of two types of commercial room air cleaners were measured and compared with those of remodelled air cleaners equipped with different filter media. Then, the effectiveness of the room air cleaners for the removal of cigarette smoke was evaluated by operating them in a closed room filled with cigarette smoke.

Experimental Procedure

Measurement of Collection Efficiency of Room Air Cleaners

Figure 1 shows the two types of commercial room air cleaners studied in the present work. Type I utilizes electrostatic force to collect particles. Particles entering the cleaner are first charged by a corona charger and then filtered by an electret filter. The electret

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H. Kasuga (Ed.) Indoor Air Quality

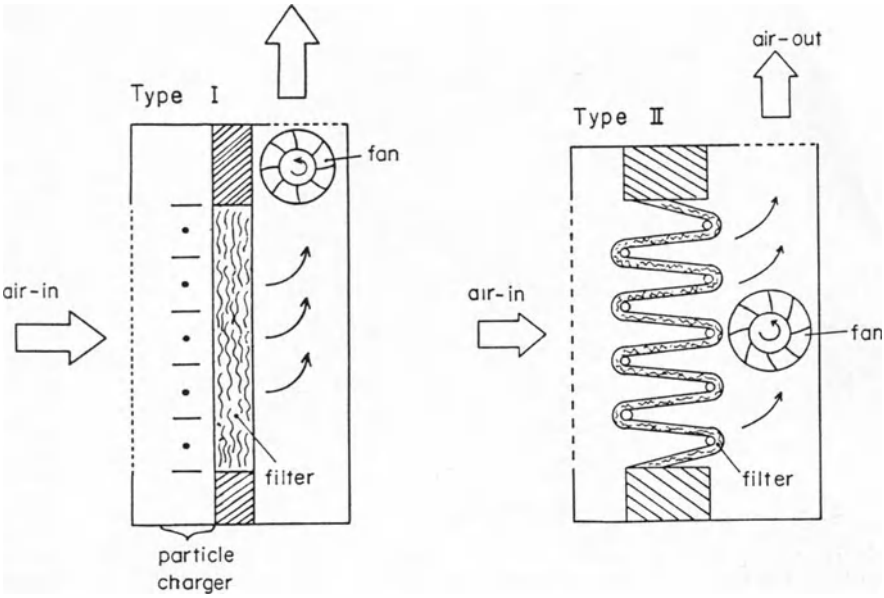

Fig. 1. Structures of room air cleaners

filter consisted of permanently charged fibers with average diameter of $d_f = 38\,\mu m$ and the packing density of $\alpha = 0.049$. The filtration area was $45 \times 25\,cm^2$ and the volumetric flow rate, Q, was either $1.0\,m^3/min$ (filtration velocity $u = 15\,cm/s$) or $2.5\,m^3/min$ ($u = 38\,cm/s$). Although the thickness of the filter, L, was 2.7 mm, the pressure drop was only 7 and 20 Pa at $u = 15$ and 38 cm/s, respectively, because of the large fiber diameter.

In order to elucidate the effects of charged filter and charging particle on the removal of cigarette smoke, the performance of remodelled version of Type I was also measured. The remodelled Type I was equipped with a "medium" performance filter in place of the electret filter and could be operated with and without the corona charger. The medium performance filter ($L = 0.548$ mm, $d_f = 3.52\,\mu m$, $\alpha = 0.044$) had pressure drop of 20 Pa at $u = 15$ cm/s and 68 Pa at 38 cm/s.

The Type II room air cleaner was equipped with a "high" performance glass fiber filter ($L = 0.330$ mm, $d_f = 1.82\,\mu m$, $\alpha = 0.047$). Since the high performance filter was made of fine glass fibers with a high pressure drop, the Type II was designed to have a large filtration area ($150 \times 22\,cm^2$) and thus a low filtration velocity, by the use of pleated filter. However, the pressure drop was 35 Pa at $u = 6\,cm/s$ ($Q = 1.2\,m^3/min$) and 52 Pa at 10 cm/s ($2.0\,m^3/min$), which was much higher than that of electret filter at a given Q.

The overall collection efficiency of the room air cleaner was measured by a piezo balance mass monitor (Respirable Aerosol Mass Monitor, Kanomax Model 51-1111) by using cigarette smoke particles (Japanese cigarette brand, "MILD SEVEN"). The fractional efficiency was measured with the indoor aerosol particles or the cigarette smoke by a condensation nucleus counter (TSI Model 3020) after classifying them into monodisperse particles with an electrostatic classifier. In the measurements, ducts with sampling tubes were attached to the inlet and outlet of the cleaner in order to separate influent and effluent airs of the cleaner. Further, because these commercial room air

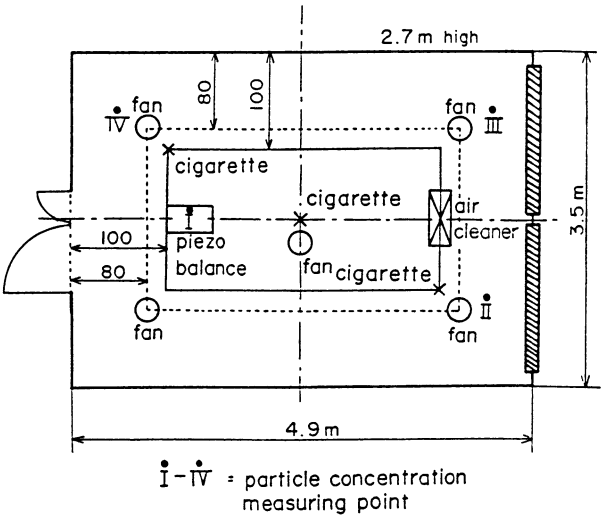

Fig. 2. Arrangement of apparatus in experimental room

cleaners had simple structures and were manufactured with little attention to the leakage of air, a large portion of influent air did not flow through the filter. Therefore, the leakage of air was avoided by sealing the possible passages of air with a silicone sealant.

Measurement of Cigarette Smoke Concentration Change in a Closed Room

The air cleaner was placed in a closed room filled with cigarette smoke particles, and the change in the cigarette smoke concentration was measured.

Figure 2 shows the arrangement of experimental room. The volume of the room is $3.5 \times 4.9 \times 2.7\,m^3$ and windows and doors were sealed with masking tape to ensure a "closed" room. The piezo balance mass monitor, cigarettes and room air cleaner were placed on a table (1.52 m wide, 3.04 m long, and 0.70 m high). Fans were placed at five locations, and the uniformity of the smoke concentration was assessed by measuring the concentrations at four different locations with a light scattering photometer (I to IV

Table 1. Overall of collection efficiencies of room air cleaners

Air cleaner	Type I				Type II	
Flow rate Q [m^3/min]	1		2.5		1.2	2.0
Corona charger	on	off	on	off		
Overall efficiency						
Electret filter	0.96	0.29	0.94	0.21		
Medium performance filter	0.61	0.05	0.42	0.03		
High performance filter					0.40	0.31

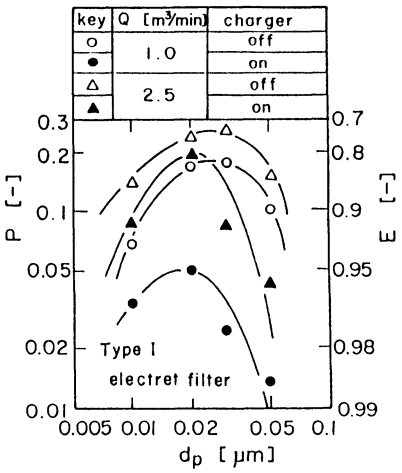

Fig. 3. Fractional collection efficiency of room air cleaner of Type I with electret filter, measured with indoor aerosol particles

shown in Fig. 2). Three cigarettes (the cigarette brand, "MILD SEVEN") were lit and placed at each of three locations, a total of nine cigarettes were burned to fill the room with the sidestream smoke. The concentration change in the room was measured with and without the smoke generation. In the measurement with smoke generation, one or two lit cigarettes were placed at the center of the table after the burn-out of the first nine cigarettes.

The mass median aerodynamic diameter of the cigarette smoke (sidestream of cigarette brand, "MILD SEVEN") measured by an Andersen Air Sampler was 0.64 μm, and the geometric standard deviation was 1.87.

Experimental Results

Collection Efficiency of the Room Air Cleaner

Table 1 shows the overall collection efficiency of cigarette smoke measured with the piezo balance mass monitor. The overall efficiency varies widely from 0.03 to 0.96 depending on the operating condition of the air cleaner. The table shows that the volumetric flow rate has little influence on the collection efficiency but that the activation of the corona charger changes the efficiency drastically. The increase in the collection efficiency of the Type I with medium performance filter by the activation of the corona charger resulted from the electrostatic image force which is exerted between charged particle and uncharged fiber. For the Type I with electret filter, the uncharged particle is captured by electrostatic induced force, whereas, when particles are charged, the Coulombic force is also exerted on the particle in addition to the image and induced forces, thus giving the very high collection efficiency of over 90%. The strong electrostatic effect on the particle collection is clearly seen from the fractional collection efficiency. Figure 3 shows the fractional collection efficiency of room air cleaner of Type I with electret filter measured with the indoor aerosol, and Fig. 4 is the fractional efficiency of Type II measured with sidestream cigarette smoke. In Fig. 3, when the corona charger is activated, the penetration curve is very sharp and the maximum penetrating particle size exists at about

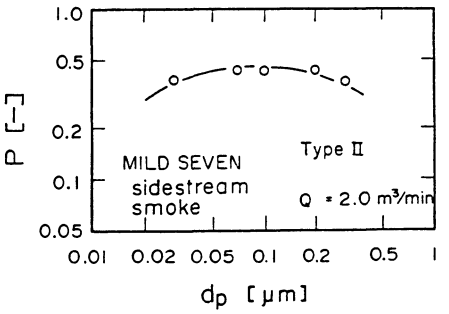

Fig. 4. Fractional collection efficiency of room air cleaner of Type II with high performance filter, measured with cigarette smoke particles

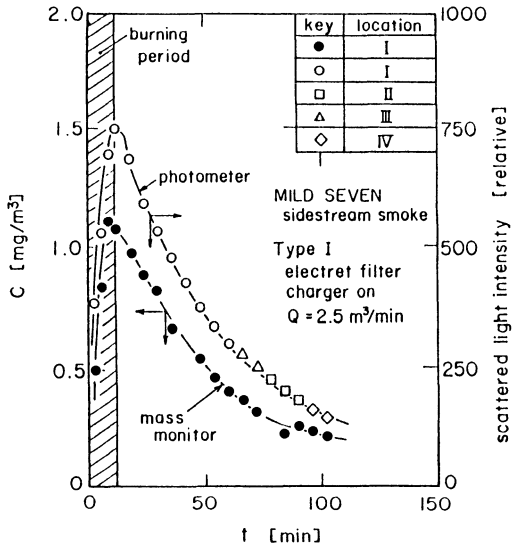

Fig. 5. Change in cigarette smoke concentration in a closed room

$d_p = 0.02\,\mu m$. Since the average diameter of the cigarette smoke particles is 0.64 μm which is much larger than the maximum penetrating particle size, the cigarette smoke is removed at very high collection efficiency. On the other hand, the Type II has a flat penetration curve, and maximum penetration exists at $d_p = 0.1\,\mu m$ which is close to the average size of the cigarette smoke. Consequently, the Type II is operated near the minimum collection efficiency of the filter, resulting in a very low overall efficiency for cigarette smoke.

Concentration Change of Cigarette Smoke in a Closed Room

Figure 5 shows the change in the cigarette smoke concentration after lighting nine cigarettes. The room air cleaner installed was Type I with electret filter ($Q = 2.5\,m^3/min$, corona charger is on). The solid circles are the data measured with the piezo balance mass monitor and the open symbols are those measured with the photometer at different

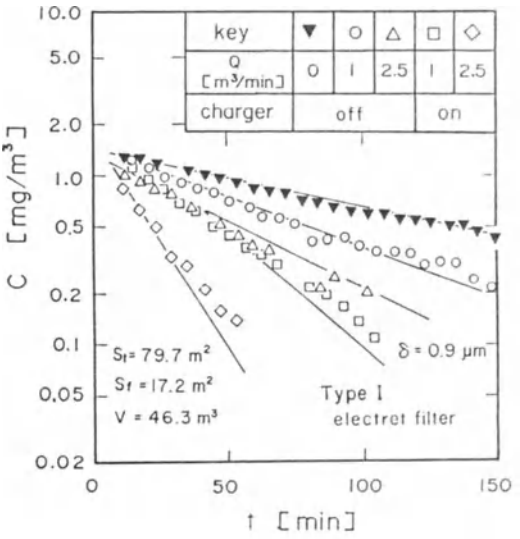

Fig. 6. Cigarette smoke concentration change under the operation of room air cleaner of Type I with electret filter in the absence of smoke generation

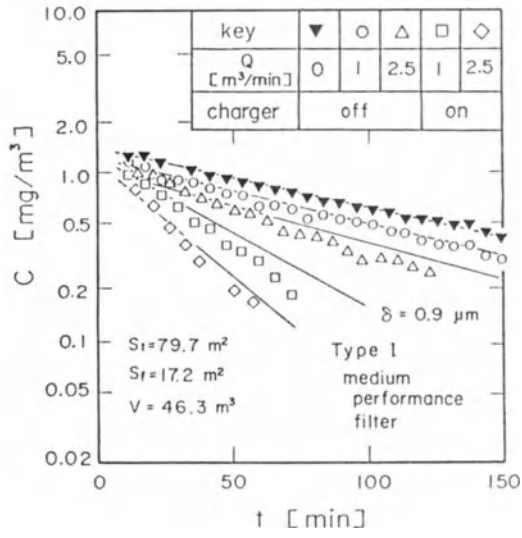

Fig. 7. Cigarette smoke concentration change under the operation of room air cleaner of Type I with medium performance filter in the absence of smoke generation

locations. Since the data measured at different locations fall on a single curve, particle concentration is considered to be uniform in the experimental room.

The change in the particle concentration under various operating conditions of room air cleaner Type I is compared in Fig. 6 (with electret filter) and Fig. 7 (with medium performance filter) and those for the Type II are compared in Fig. 8. These figures show that the particle concentration decreases linearly on semi-logarithmic paper, i.e., decreases exponentially with time. Furthermore, since the rate of particle removal by a room air cleaner is proportional to the collection efficiency, E, and volumetric flow rate

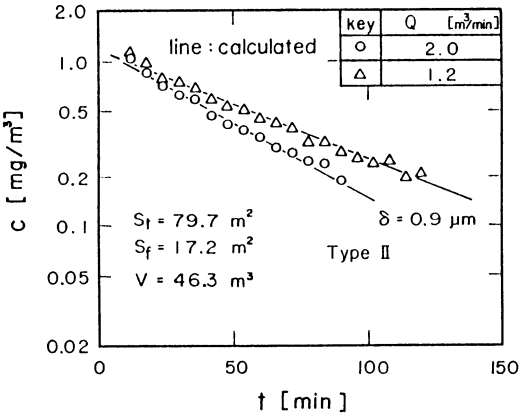

Fig. 8. Cigarette smoke concentration change under the operation of room air cleaner of Type II in the absence of smoke generation

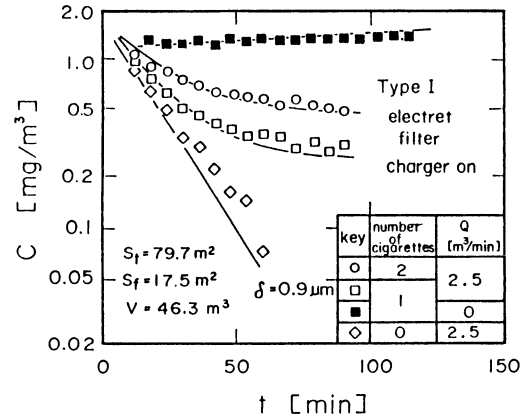

Fig. 9. Cigarette smoke concentration change under the operation of room air cleaner Type I with electret filter in the presence of smoke generation

of the cleaner, Q, the rate of decrease of particle concentration is higher as the product of EQ increases (see Table 1). When the room air cleaner is not operated, the particle concentration reduces gradually because of the gravitational and diffusional particle deposition onto the surface of the room.

The influence of particle generation on the concentration is shown in Fig. 9. When one cigarette is continuously burned and the air cleaner is off, the particle concentration does not decrease because one burning cigarette supplies more particles than those removed by the wall deposition. However, if the room air cleaner is on, the concentration reduces to a constant value.

Discussion

When particle concentration is uniform throughout the closed room, the change in particle concentration may be estimated by accounting the mass balance of particles. The mass balance equation is

$$V\frac{dC}{dt} = M - Cu_gS_f - C\frac{D}{\delta}S_t - CEQ \tag{1}$$

where V is the volume of the room, C the particle concentration, t the time, M the rate of particle generation, u_g the gravitational settling velocity of the particle, D the diffusivity of the particle, δ the concentration boundary layer thickness, S_f and S_t are the floor and total surface areas of the room. Integrating E_q. (1) with the initial condition of $C = C_0$ at $t = 0$,

$$C = C_0 \exp\left(-\frac{a}{V}t\right) + \frac{M}{a}\left[1 - \exp\left(-\frac{a}{V}t\right)\right] \tag{2}$$

where

$$a = EQ + u_gS_f + \frac{D}{\delta}S_t \tag{3}$$

Eq. (2) gives the steady state concentration. Letting $t \to \infty$,

$$C = \frac{M}{a} \tag{4}$$

If there is no generation source of particle ($M = 0$), then Eq. (2) reduces to

$$C = C_0 \exp\left(-\frac{a}{V}t\right) \tag{5}$$

Eqs. (2)–(5) explain all the observed dependence of particle concentration on time as shown in Figs. 7–9, in both presence and absence of a particles generation source.

In the prediction of concentration change of cigarette smoke, u_g and D are calculated from the measured size distribution of cigarette smoke. However, since the concentration boundary layer thickness δ depends on the mixing condition of air in the experimental room, $\delta = 0.9\ \mu m$ was obtained empirically from the data without smoke generation and room air cleaner, equating the experimental slope and $-(u_gS_f + DS_t/\delta)$. The value of $\delta = 0.9\ \mu m$ is about one order of magnitude less than the value reported for monodisperse polystylene latex particles (Harrison 1979), but is in agreement with the value reported for cigarette smoke particles (Yoshida et al. 1979).

The lines shown in Figs. 7–9 are predicted lines by Eqs. (2) and (5) with the value of $\delta = 0.9\ \mu m$. The predicted lines well describe the experimental data under any operating condition of the room air cleaner in the presence and absence of smoke generation.

Through the results obtained in the present work, the rate of decrease in the cigarette smoke concentration becomes higher as the product of volumetric flow rate and collection efficiency of room air cleaner increases. However, an increase in a volumetric flow rate brings up both an increase in pressure drop and an decrease in collection efficiency. The conventional filter, which collects cigarette smoke particles mostly by Brownian diffusion, is not suitable for air cleaner installation, unless the cleaner is designed to have a large filtration area (this, of course, leads to an increase in size of air cleaner). Combination of electret filter and corona charger is more advantageous for the removal of cigarette smoke particles because cigarette smoke particles which are hardly

removed by diffusion and other mechanical collection mechanisms, are effectively captured by electrostatic forces.

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Results from Surveys of Environmental Tobacco Smoke in Offices and Restaurants

G. B. Oldaker III, P. F. Perfetti, F. C. Conrad Jr., J. M. Conner, and R. L. McBride

Summary

Surveys were conducted in several major cities in order to estimate the exposures of occupants in offices and restaurants to environmental tobacco smoke (ETS). Concentrations of ETS were estimated by measuring vapor phase nicotine and ultraviolet particulate matter, an empirically derived parameter providing an upper limit for the contribution of ETS to respirable suspended particles (RSP). Area samples were collected with portable air sampling systems (PASS), which are battery-powered devices contained in otherwise ordinary briefcases, a design allowing sampling to be performed unobtrusively. Nicotine was determined with gas chromatography and nitrogen specific detection. UV-PM was determined spectrophotometrically by analyzing methanolic extracts of RSP collected after separation at 3.5 μm with an inertial impactor. For offices, mean concentrations of nicotine, UV-PM, and RSP were 4.8, 27, and 126 $\mu g/m^3$, respectively. Mean concentrations of nicotine, UV-PM, and RSP for restaurants were 5.1, 36, and 126 $\mu g/m^3$, respectively.

Within the past decade, environmental tobacco smoke (ETS) has emerged as a major issue within the general subject area of indoor air quality. The issue has acquired increased attention owing to recent reports by the U.S. Surgeon General [28] and the National Academy of Sciences [5]. Reviewing results from epidemiological investigations, these two bodies concluded that there exists a causal relation between exposure to ETS and incidence of lung cancer. This conclusion has elicited controversy for several reasons: results of the investigations vary in terms of epidemiological and statistical significance and overall quality; relative risks indicated are low within the context of epidemiological associations; consistent "dose"-respose relationships are not observed (with dose inferred from questionnaires regarding spouses' smoking behavior); and the experimental designs of the investigations admit the strong possibility of influence by biases and confounding. A scientifically rigorous approach to clarify controversial issue calls for quantifying exposures and doses of the subject populations either included in or affected by epidemiological investigations [4]. Toward this goal, scientists with the tobacco industry have been engaged in developing and applying sampling technologies and analytical methodologies for assessing exposures to ETS in indoor environments. This paper summarizes progress in connection with surveying exposures in offices and restaurants, two important, public environmental categories. Results from one of the several surveys conducted have been presented earlier by Conner et al. [7].

H. Kasuga (Ed.) Indoor Air Quality

Experimental Method

Surveys were performed in four major cities in the U.S. and Canada during the spring, summer, and autumn months. The cities all have populations greater than 100,000. At least 30 samples were acquired for each environmental category in each city. Offices were surveyed in all cities; restaurants were surveyed in three cities. Sampling was conducted either by scientists with the tobacco industry or by independent contractors.

Selection of Sampling Sites

Offices were selected based upon the criterion that they be shared by two or more persons of whom at least one smoked. Office managers were informed of this criterion and given a description of guidelines regarding appropriate sampling locations. These guidelines were contained in a protocol prepared as part of the overall project effort. Based upon these, managers selected offices to be sampled. Sampling was performed during normal business hours. None of the offices had smoking restrictions.

Restaurants were selected from listings contained within telephone directories. Sampling was performed during normal lunch and dinner hours. None of the restaurants had smoking restrictions.

Selection of Sampling Locations

Sampling locations within offices and restaurants were selected based upon a protocol's guidelines, which were derived from those described by Nagda and Rector [19]. The protocol was prepared in response to recommendations of the American Chemical Society [1] and, in addition, was patterned after quality Assurance Project Plans required by the U.S. Environmental Protection Agency for projects conducted by them [21].

Sample Collection

Area samples were collected with Portable Air Sampling Systems (PASS) [16], which from the outside appear to be ordinary briefcases. During operation the PASS remains closed. An on-off switch is located beneath the briefcase's handle, and inlet and exhaust ports are fashioned of brass to match the briefcase's normal hardware. With these battery-powered devices, integrated samples are obtained for determining concentrations of vapor phase nicotine, respirable suspended particles (RSP), and ultraviolet particulate matter (UV-PM), an empirically defined measure providing an upper estimate of the contribution of ETS to RSP. Eudy et al. [9] and Eatough et al. [8] have reported that at least 90% of nicotine associated with ETS is in the vapor phase. The PASS is also equipped with three monitoring devices including a carbon monoxide monitoring system, a thermistor, and a pressure transducer, the latter two which enable volumetric results to be adjusted to actual conditions of temperature and pressure. Data provided by monitoring devices are stored in a data logger. (Efforts to reduce and interpret carbon monoxide data are in progress; consequently, carbon monoxide measurements are not discussed further here.)

The PASS's nicotine sampling system includes a sorbent tube containing XAD-4 resin connected with a short section of rubber tubing to a constant flow sampling pump

operated at 1 l/min. The major components of the sampling system for particulate matter species are an inertial impactor separating at 3.5 μm, a filter assembly housing a Fluoropore membrane filter, and a constant flow sampling pump operated at 2 l/min. The inertial impactor is sized to correspond to that employed in piezoelectric balances manufactured by TSI, Inc., St. Paul, MN.

Samples were collected for a minimum of 1 h in order to provide adequate material for the gravimetric determination of RSP.

Analysis

Nicotine was analyzed with a method representing an enhancement of the method employed by the U.S. National Institute of Occupational Safety and Health (NIOSH) [20]. This enhanced method, which entails gas chromatography and nitrogen specific detection, has been described by Ogden et al. [22]. The gravimetric method for determining RSP was derived from the method described by Treitman et al. [27]. UV-PM was quantified according to the method described by Conner et al. [6]. For this method, filters employed for the RSP determination are extracted with methanol and the absorbance of the methanolic extract is measured spectrophotometrically at 325 nm. Masses of UV-PM are then interpreted with a standard calibration curve obtained from generating known concentrations of ETS in an environmental chamber [12]. The methods for determining RSP and UV-PM have been shown to be unbiased relative to piezoelectric balances [14].

To ensure further the quality of results, collaborative tests were conducted involving laboratories engaged in the surveys. Results from these tests have been reported by Ogden and Conner [23].

Results and Discussion

Data from determinations of nicotine, UV-PM, and RSP for restaurants and offices associated with each city were analyzed statistically. These analyses indicated that each data set associated with each city was distributed log-normally. Moreover, these analyses

Table 1. Summary of results for measurements of ETS in offices and restaurants. Concentrations in $\mu g/m^3$

	Nicotine	UV-PM	RSP
Offices			
Mean	4.8	27	126
Range	0–69.7	0–287	0–1,088
	(n = 156)	(n = 125)	(n = 131)
Restaurants			
Mean	5.1	36	126
Range	0–23.8	0–184	0–685
	(n = 170)	(n = 82)	(n = 83)

showed that no statistically significant differences existed among the data sets for the cities. Consequently, results for each analyte were pooled and geometric means were computed. Results for offices and restaurants are summarized in Table 1.

Offices

For offices, nicotine results are consistent with those previously reported. Hammond et al. [11] found concentrations of nicotine in offices that ranged from 3.1 to 28.2 $\mu g/m^3$. These researchers used personal sampling devices that collect nicotine on Teflon-coated glass fiber filters treated with sodium bisulfite. Muramatsu et al. [17, 18] employ personal sampling devices utilizing Uniport-S coated with silicon OV-17 for the collection of nicotine. They reported average nicotine concentrations ranging from 5.9 to 22.2 $\mu g/m^3$ for 8-h-samples collected in three offices. Weber and Fischer [29] reported much lower concentrations of nicotine in offices. These researchers, however, employed Cambridge filters to collect nicotine, and as Badre et al. [3] have observed, substantial losses of nicotine occur with this procedure.

The mean concentration of RSP, 126 $\mu g/m^3$, as well as the range of concentrations, 0 to 1,088 $\mu g/m^3$, are comparable to results reported by Weber and Fischer [29]. Using a piezoelectric balance, these researchers reported mean and maximum RSP concentrations of 170 and 1,130 $\mu g/m^3$, respectively, for samples collected in 44 workrooms. This same measurement technique was used by Quant et al. [25] who reported average concentrations of RSP ranging from 36 to 89 $\mu g/m^3$ during daytime periods in three offices.

The UV-PM results strongly suggest that a substantial portion of the RSP measured originates from sources other than ETS. Thus, based upon comparisons of the tabulated means, UV-PM represents about 20% of the RSP. This observation points to RSP's lack of specificity and therefore its general inappropriateness for use as an indicator of ETS in settings outside of the laboratory.

Restaurants

Results associated with restaurants are also consistent with results previously reported. Muramatsu et al. [17] collected eight 1-h-samples in five restaurants; they reported mean and maximum nicotine concentrations of 14.8 and 27.8 $\mu g/m^3$, respectively. (Hinds and First [13] used Cambridge filters to collect nicotine and reported much lower concentrations of nicotine in restaurants. However, as was noted above, their results are presumed to be biased owing to low collection efficiencies of the filters.)

Survey results for RSP are comparable to results reported by Repace and Lowrey [26], who surveyed RSP with a piezoelectric balance in 10 restaurants. RSP concentrations ranged from 29 to 414 $\mu g/m^3$ for 13 sampling periods of times ranging from 2 to 40 min. These researchers attempted to assess the contribution of smoking to indoor concentrations of RSP and to demonstrate the validity of a model for estimating such contributions based upon number of occupants and room volume. A mean RSP concentration of 42 $\mu g/m^3$ was found in no-smoking sections and places where smoking was not seen to occur. In places where smoking occurred, a mean RSP concentration of 171 $\mu g/m^3$ was found. Although smoking was observed in all the restaurants surveyed by us, smoking was not continuous. Thus, mean results would be expected to fall between these two means, as indeed is the case.

The UV-PM results for restaurants are similar to those of offices. Thus, relative to the tabulated mean RSP, UV-PM makes about a 30% contribution.

Estimation of Exposure to ETS

The results of these surveys show mean nicotine and UV-PM concentrations to be low. In order to place these results in a more convenient form for discussion and interpretation, many researchers have employed the cigarette equivalent concept [13, 17, 24, 26, 29]. Assumptions atttending use of this concept have been described [28]. Here, exposures are estimated from the mean nicotine concentrations reported in Table 1. (Exposures estimated from mean nicotine concentrations are higher than those computed from UV-PM results, with the assumption made that UV-PM is equivalent to "tar" as defined by the Federal Trade Commission.) Also assumed for estimation of exposures are a breathing rate of 8.61/min, which corresponds to miscellaneous office work [2], and a U.S. sales weighted average "equivalent cigarette" delivering 0.88 mg nicotine [10, 15]. Accordingly, estimated mean exposures for an eight-hour work day in an office is 0.02 cigarette equivalent and for a 1-h meal in a restaurant, 0.003 cigarette equivalent.

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Strategy for Future ETS Exposure Measurements Relative to Its Transient Nature and Other Indoor Air Pollutants

I. O'Neill

Introduction

From the outset, it has not been possible to relate exposure to individual components of mainstream (MS) and environmental tobacco smoke (ETS)[1] with important biological outcome in humans. We do know from the extensive studies by Spengler et al. (1985), Wallace et al. (1985), Hirayama (1981), both that ETS is a main indoor source of airborne particulates and volatile carcinogens, and also that passive exposure to tobacco smoke seems associated with increased risk of lung cancer. Following on the IARC evaluation of ETS carcinogenicity[2] (IARC, 1986), there are substantial problems in devising the appropriate strategy for exploring the relationship between ETS pollution and the biological outcome in humans. Looking at this another way, there is a fundamental gap between the epidemiological and experimental approaches to this problem. Discussed below are the key problems of the multiplicity of pollutants in indoor air and the potential importance of active although transient components; this discussion is related to some IARC activities in this field.

Biologically Active Components of Indoor Air Pollution

Since most people spend 75% to 90% of their time on average breathing indoor air (NRC 1981), and building design has changed greatly in recent years (Mage and Gammage 1985), a number of recent studies have examined the biological activity of indoor air and substances infiltrating from outside. Mutagenicity of indoor air has been compared to indoor activities in studies in the Netherlands (Van Houdt et al. 1984), USA (Lewtas 1982), Finland (Salomaa 1987) and Norway (Lofroth et al. 1983). It is notable, however, that the levels of airborne particulate found, for example, by Spengler et al. (1985) in the USA are much lower than those arising from unventilated combustion of biomass in non-industrialized countries (WHO 1984) where respiratory illness is often a major contributor to mortality for women who are almost entirely nonsmokers. Hence, there

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[1] The Sixth World Conference on Smoking and Health (Tokyo, 9–12 November, 1987) resolved that ETS is a misnomer implying a natural component of the environment. In the absence of any proposed alternative, ETS, however, is used in this paper.

[2] This IARC working group evaluation included the following statement: "The observations on nonsmokers that have been made so far are compatible with either an increased risk from "passive" smoking or an absence of risk. Knowledge of the nature of sidestream and mainstream smoke, of the materials absorbed during "passive" smoking, and of the quantitative relationships between dose and effect that are commonly observed from exposure to carcinogens, however, leads to the conclusion that passive smoking gives rise to some risk of cancer".

H. Kasuga (Ed.) Indoor Air Quality

Table 1. Detailed methodology for contaminants of indoor air in IARC Manual series (volume 12)

	Air	Biological monitoring
Radon and radon daughters	+	−
Asbestos	+	+
HCHO and Aldehydes	+	−
Nitrogen oxides	+	−
N-nitroso compounds	+	−
E.T.S.	Volume 9	+
Particulate - mutagens	+	−
- organics	+	Volume 8
Volatile organics - aromatics	+	Volume 10
- halogenated alkanes	+	Volume 7
Pesticides	+	−
Carbon monoxide	+	−

are a wide range of biologically-active components of indoor air (Table 1) and care must be taken to set the findings from ETS exposures in an appropriate context.

Exposure to Biologically Active Components of ETS

Exposures to ETS components that have established biological activities, including carcinogenesis, have been measured in many indoor environments (Repace 1987; US Surgeon General 1986). Although measurements for nicotine in the breathing zone or of its metabolite, cotinine, in urine, have been developed as tobacco-specific markers (Van Vunakis et al. 1987; Muramatsu et al. 1984), the relationship is poorly known between the levels of airborne nicotine and substances having biological activity. For example, a recent report (Thawborne et al. 1988) indicates that nicotine has a short half-life in indoor air so that exposures extrapolated from nicotine can consequently be underestimated. The relationship of concentrations between nicotine and carcinogens in sidestream smoke is markedly different from that in mainstream smoke; it is from the effects of the latter exposure by active smokers that many workers have tried to extrapolate the effects of passive smoking. Using exposures to nicotine or carbon monoxide (two substances easily measured in both the environment and biological fluids) leads to major underestimations for exposures to some carcinogenic substances, especially aromatic amines and NDMA which are much richer in sidestream smoke (Table 2). Some studies, for example that of Hugod et al. (1978), have attempted to quantify exposure to ETS components in terms of "cigarette equivalents", but since we do not know which are the biologically critical components of mainstream smoke, such comparisons can be misleading at present.

One way through these problems would be to make parallel measurements firstly in human tissue of appropriate macromolecular adducts, or biological effects arising from several tobacco-related substances having known adverse biological effects, and secondly of urinary cotinine or breathing zone nicotine. This should establish whether nicotine-based markers can indicate the likely DNA damage that is a consequence from the co-occurring carcinogens; such possibilities are presently limited. Bryant et al. (1988) have shown that 4-aminobiphenyl (4-ABP) adducts in nonsmokers are in the range of 10–30% of the smoking-related levels in smokers; however, it is not yet clear whether there may be other

Table 2. Enrichment of substances of biological interest in sidestream smoke compared to amounts in mainstream smoke, relative to nicotine and particulate matter[a]

	Enrichment relative to nicotine	Enrichment relative to particulate matter
Particulate matter	0.5	1.0
Nicotine	1.0	2.0
CO	1.1	1.6 to 3
Benzene	3.3	6
NDMA	7 to 33	12 to 60
NNK	0.3 to 1.3	0.6 to 2.4
4-Aminobiphenyl	10	19
Benzo(*a*)pyrene	1	1.6 to 2.2
2-Naphtylamine	10	18
Acrolein	3 to 5	5 to 10

[a] See Environmental Carcinogens: Methods of Analysis and Exposure Measurement, Volume 9

Table 3. Reviews on aspects essential to measurement and control of environmental tobacco smoke (volume 9) and indoor air (volume 12) of IARC Manual series

	E.T.S. (11 classes)	INDOOR AIR (12 classes)
Health effects/cancer epidemiology	+	+
Biological effects	+	+
Sources	−	+
Generation (S.S.-M.S. differences)	+	−
Air and biological monitoring, field surveys	+	+
Back-up questionnaire (international)	+	+
Concentrations already found	+	+
Controls and validation measurements	−	+

environmental sources of this bladder carcinogen, although its use has been prohibited for many years. Although Bos et al. (1983) found an increase in excreted urinary mutagenicity by passive smokers under experimental conditions, later studies have not been able to find reliable differences that could be used as a marker for exposure under real conditions. Morimoto et al. (1984) found a small increase of mitomycin C-inducible S.C.E. in lymphocytes but Husgavfel-Pursiainen et al. (1987) could not find SCE difference between groups of non-smokers having large differences in ETS exposure.

Cotinine/creatinine ratios are being investigated in an IARC study to compare exposures in 13 centres world-wide (Riboli 1987) and now have shown there to be a substantial difference in mean exposures to ETS between populations which also have different ventilation and room volumes of their dwellings (results being prepared for publication). Therefore, it would be surprising not to find a range of relative risks for passive smoking being reported from studies in different countries, and it would seem a necessary clarification to measure several tobacco-related indicators and 4-ABP adducts, S.C.E.'s and possibly hydroxyproline (Kasuga et al. 1987) in these populations. As one

approach for resolving the technical difficulties and interpretations of exposure determination, we are preparing two volumes on ETS and Indoor Air in the IARC series "Environmental Carcinogens – Methods of Analysis and Exposure Measurement" for which the background information contained is listed in Table 3.

Especially of note for considering the consequences of polluted indoor air, is that ETS may display synergism with radon daughters (Bergman and Axelson 1983; US Surgeon General 1986) of which the latter is known to cause lung cancer from occupational studies. Different studies (Repace and Lowrey 1985; NCRP 1984) have estimated attributable risks for these two agents to be of the same order in the USA, although these estimates are far less proportionally than ascribed to pollution by carbon monoxide and biomass combustion in other countries (WHO 1984; Cha and Cho 1988).

Transiently Active Substances and Oxidative DNA Damage for Tobacco Smoke

Present approaches to monitoring ETS and most other airborne exposures do not envisage the presence of biologically active substances having a very short lifetime; however, Hirayama (1984) has advanced an hypothesis based on his extensive field observations during the large-scale prospective study (Hirayama 1981) that freshly generated ETS (the term "neighbour tobacco smoke" or "NTS" has been coined by him) is of crucial importance. Experimental data by Sonnenfeld et al. (1985) show that 95% of the cytoxicity to cultured mammalian cells exposed to sidestream smoke is lost after only 10 s; they showed this activity to be principally in the gaseous phase. Pryor et al. (1983) have shown substantial concentrations of fast-decaying free radicals in the gaseous phase but also a lower concentration of more persistent radicals (Church and Pryor 1985). Nakayama et al. (1985) showed that DNA single strand breaks are produced in cultured human cells by aqueous extracts of cigarette tar and that this damage was inhibited by superoxide dismutase (SOD) thus implying an oxygen-dependent radical-mediated process. Borish et al. (1987) have subsequently shown that DNA synthesis and repair is blocked by tar-induced lesions and that these are consistent with radical-mediated damage caused by the semí-quinone radicals which are the principal radical type in cigarette tar. In light of these experimental observations on shortlived entities, the empirical hypothesis of NTS by Hirayama (1984) could be meaningful and also would provide a disproportionate effect for small rooms and poor ventilation.

There is also another transient aspect which can be inferred from the work of Ahotupa et al. (1987) who have shown that administration of NDMA leads to a short-lived burst of lipid peroxidation in rats; such processes could lead to oxidative damage for DNA which has been advanced (Ames 1988) as a potential source of carcinogenesis. (It should be noted that NDMA is very prominently enriched in sidestream smoke compared to mainstream smoke). Added to these effects is the fluctuation in ETS exposure for which cotinine in urine measurement can only indicate a time-weighted mean, and not peaks of exposure to freshly generated ETS containing transiently-stable compounds. Together, these findings call into question the fundamental basis of using conventional monitoring procedures, namely that the substance of importance either persists in the air or that its measurable biological effect persists. Until further investigations are undertaken, the markers of ETS in air and biological fluids cannot be used to compare the biological activities of different exposures, although they may serve as a basis for exposure to tobacco products, to which future data on transient substances might later be linked with care.

Table 4. Substances from tobacco smoke for which exposure methodology is available (IARC Manual, volume 9)

(a) Carcinogens or co-carcinogens	(b) Tobacco-related substances
Volatile *N*-nitroso compounds	Nicotine
Tobacco-specific *N*-nitroso compounds	Carbon monoxide
Polycyclic aromatic hydrocarbons	Nitrogen oxides
Aromatic amines	Cotinine (in urine)
Phenols	Thiocyanate (in urine)
Aldehydes	Hydroxyproline (in urine)

Need for Standard Methods for Exposure Ascertainment

The need for standard validated methods has long been recognized as a principal requisite for comparing exposures in order to establish causal relationships and was the reason for establishing the IARC Manual series; this problem was brought to the fore when it was not found possible to directly link the incidence of human liver cancer with aflatoxin exposures because different analytical procedures giving incomparable data had been used in different studies and countries. Measurement of ETS levels and exposures will require methods that are universally accepted as having both sufficient accuracy and relevance. Hence, substances presently recognised as having biological activity in ETS, or that may serve as surrogates, are dealt with in detail in the recently published IARC volume (IARC 1987). These are listed in Table 4.

This volume also contains background information that can help interpretation and design of studies as well as epidemiological questionnaire use in the on-going IARC study on passive smoking. A similar treatment of indoor air pollutants (Table 1) is contained in the volume in preparation.

Conclusions

The recognition that indoor air and ETS may present problems for human health is relatively recent, and the scientific basis for distinguishing the mechanisms of biological hazard remains to be established. The problems arising from multiple pollutants and transiently-present substances require urgent attention due to the major consequences for altering life-style, building ventilation, and heating/cooking practises for a large fraction of the world's population.

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Assessment of ETS Impact on Office Air Quality

J. J. Piadé, C. Gerber, and W. Fink

Summary

The contribution of environmental tobacco smoke (ETS) to indoor air quality was investigated by quantifying the concentration of some of its constituents in the course of a series of strictly controlled experiments.

One brand of commercial cigarettes was smoked by trained smokers following a prescribed protocol both in a test-chamber and in an office of a modern, air-conditioned building. The ETS components investigated were CO, NO, NO_2 and nicotone. The concentration of respirable suspended particles (RSP) was also monitored using three different methods.

The concentrations of these ETS constituents and their ratios are reported, together with background and outdoor levels. In addition, the influence of room ventilation, smoke generation rate, wall deposition effects, etc., is discussed.

Introduction

The indoor air concentration of ETS components has been surveyed by many authors in real-life measurements, but with little or no information on smoke generation. In other reports, mostly for exposure studies, both smoke generation and air concentration of several ETS components were carefully monitored, but with often unrealistic smoke levels [1, 2].

This paper is the first part of a study aimed at investigating ETS chemistry in real-life situations, but with a strictly defined smoke generation and investigating a wide array of components. It comes as a continuation of previous investigations on sidestream smoke (SS) generated in a test-chamber [3]. In this study the effects of smoke generation patterns, room ventilation and air mixing should be assessed, with an emphasis on the time variation of the measured concentrations and their ratios. This paper reports on early results establishing the experimental concept, checking methods and evaluating the impact of various indoor environmental factors.

Experimental Procedures

Smoking Sessions

The office used for this study has a surface of $12\,m^2$ and a volume of $35\,m^3$, with a door and a large window. Its walls are plastered, the floor is carpeted and it is furnished with a desk, three chairs and a cupboard. It is situated in a modern building

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with central air conditioning. The ventilation was checked to ensure 3.5 air changes per hour.

Smokers normally consuming about 1 pack per day were trained to take 2-s puffs per minute in a reproducible way, as checked by consistent puff-counts per cigarette. They were asked to smoke commercial cigarettes according to a pre-determined, realistic protocol. All smokings took place in the same room, but ventilation was turned on or off with possible additional air mixing.

Analytical Methods

For each session, the concentrations of CO, NO, NO_2 and respirable suspended particles (RSP) were measured continuously. Nicotine concentration was measured periodically.

Samplings were done using feed-back flow control pumps (SKC Aircheck Sampler 224-36) drawing air from near the center of the room at an height of about 1.2 m.

Carbon monoxide was measured continuously by non-dispersive IR (Dasibi 3008) and nitrogen oxides by chemiluminescence (Tecan CLD 502).

Nicotine was sampled by pumping air through XAD-4 tubes (SKC 226-30-11-04) which were extracted with 1 ml of ethyl acetate (0.01% triethylamine) and analysed by capillary gas chromatography according to [4]. Quinoline was used as an internal standard.

RSP concentration was simultaneously measured by three different methods:

- Filter gravimetry, by pumping air at 2 l/min through a filter pad (Fluoropore, Millipore FALP03700), possibly after passing through an impactor (TSI 3.5 μ cut-off) retaining particles that would not be inhaled [5], according to [4]. The weight change was measured with a microbalance (Mettler M3).
- Portable piezobalance (TSI model 5500).
- RAM nephelometric detector (GCA RAS-1).

Instrument Calibration for RSP Determination

The gravimetric determination is a direct method which is well established [4, 6]. It is precise down to about 30 $\mu g/m^3$ for 1-h samplings and the coefficient of variation of replicate analyses is about 4%. It only provides time-averaged answers, whereas the RAM gives almost real-time readings and the piezobalance provides a result every 3–5 min.

The TSI 5,500 is factory calibrated and gives direct readings of RSP levels (mg/m^3). It has been used in many ETS studies [7] and its performance has been questioned by several authors [2]. The manufacturer reports it to underestimate tobacco smoke by 15% [9] and in a recent study significant differences between the responses of two identical instruments were reported [8]. The response of the TSI 5,500 we used to SS (between 0.09 and 1.2 mg/m^3) was compared to gravimetric determinations in a series of experiments performed in our test-chamber. The difference between both determinations was consistently smaller than the variability of the methods, provided that the sampling flow rate of the piezobalance was kept at exactly 1 l/min and that its sensor was washed after each determination.

In contrast to the piezobalance, the RAM has to be calibrated before use with the aerosol studied [10]. This is due to its sensitivity to the particle size distribution of the

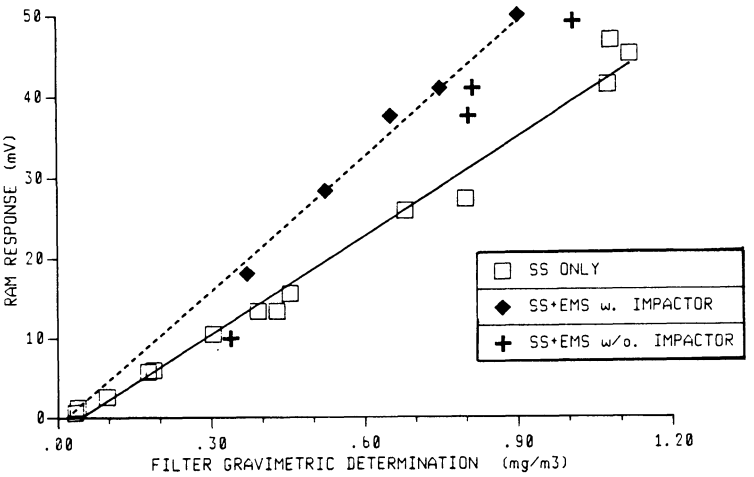

Fig. 1. Calibration of RAM vs. gravimetric determinations

sample. To this aim, the time-averaged RAM output was compared to gravimetric results in a series of experiments where smoke was generated in the test-chamber by SS only (machine smoking, mainstream smoke (MS) exhausted out of the room), or by SS plus exhaled MS (human smoking). Determinations were made for total airborne particulate matter or for RSP only (by sampling through 3.5 μ impactors).

The results are given in Fig. 1. They reveal two possible sources of systematic error:

- If the RAM is calibrated using SS only for ETS measurements, RSP results will be significantly over-estimated.
- It is obvious that omitting the impactor will result in over-estimating the air burden if one should perform a direct gravimetric determination. But since the RAM response is practically not affected by the adjunction of an impactor, it is essential that the calibration be made by comparison with *RSP only* (i.e. using 3.5 μ impactors at the filter and RAM inlets).

Results and Discussion

For each smoking session of this first set of office ETS studies, the smoke generation protocols and the environmental conditions are given in Table 1.

In experiment 3, five cigarettes were smoked simultaneously, and the room ventilation was left on. Time zero was set at the moment when the cigarettes were extinguished. Figure 2 shows the plot, as a function of time, of the CO concentration together with that of RSP as measured with the RAM and with the piezobalance and the time-averaged concentration of nicotine. These values are all background corrected.

Figure 2 shows that the CO concentration decreases exponentially. The calculated decay rate is almost equal to the measured air changes per hour in the room. Thus CO is a good tracer that can be used to offset the effects of room ventilation.

The RSP concentration as measured by the RAM also decreases exponentially, a little faster than the CO. Thus the RSP to CO ratio does not remain constant with time.

Table 1. Smoke generation protocol and environmental conditions

Experiment code	Number of cigarettes smoked	Generation rate	Room ventilation
1	1	at time 0	on
2	2	at time 0	on
3	5	at time 0	on
4	9	every 15 min	on
5	2	at time 0	off
6	4	every 15 min	off
7	4	every 15 min	off, fans on

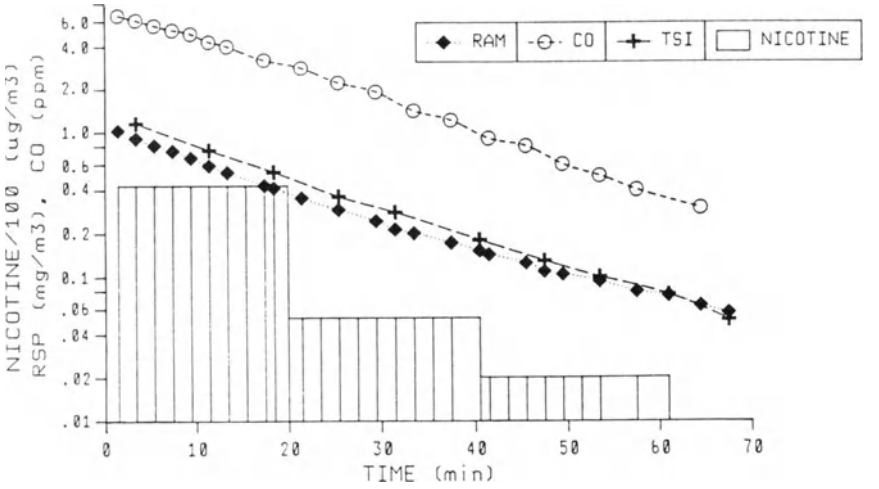

Fig. 2. RSP, CO, and nicotine decay after smoking 5 cigarettes

Actually, the decay rate of the RSP/CO ratio reflects the kinetics of wall impaction and sedimentation of the particles.

If we now consider the piezobalance determinations, they are slightly higher than the RAM measurements for unaged ETS. After about 40 min both curves coincide. An explanation for this discrepancy may be sought in changes in the smoke particle size during the early aging phase [11].

The plot of the nicotine concentration shows that it decays much faster than RSP immediatly after smoking. After 1 h, the level drops much more slowly, actually even more slowly than the CO. This is probably due to the fact that nicotine is mostly present in the gas phase [12], and wall effects become very important. Of course the nicotine/RSP ratio is far from remaining constant.

Figure 3 shows the time variation of NO and $N0_2$ concentrations. The decay of the NO concentration appears to be exponential. Considering the NO/CO ratio, which offsets the effect of room ventilation, evidences the contribution of what seems to be a pseudo-

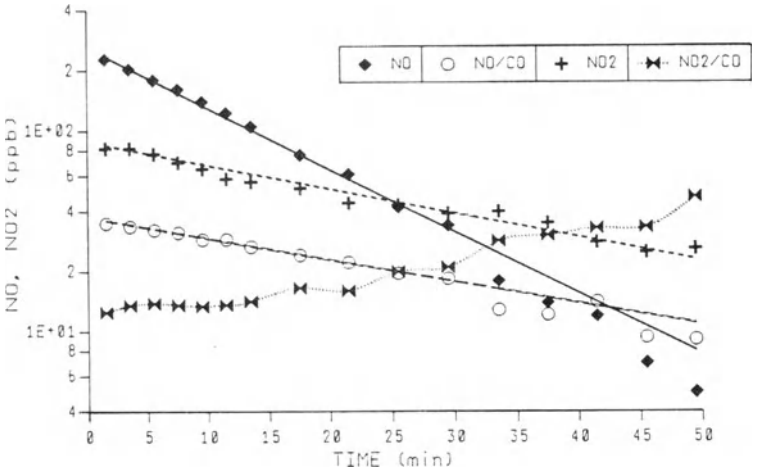

Fig. 3. NO, NO/CO, NO_2, and NO_2/CO decay after smoking 5 cigarettes

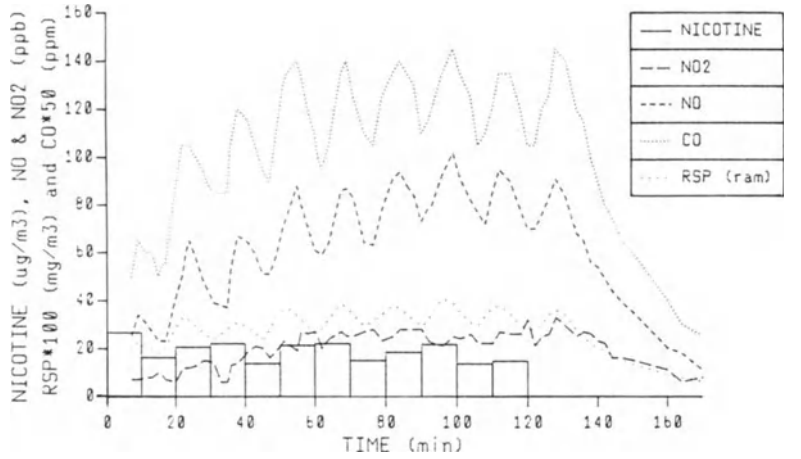

Fig. 4. RSP, CO, NO, NO_2, and nicotine concentration; 9 cigarettes smoked at 15-min-intervals

first order chemical decay. It should be noted that the NO decay was recently reported to be pseudo-first order in MS gas phase, but pseudo-second order in the whole MS [13]. The time increase of the NO_2/CO ratio, on the other hand, reveals a chemical generation of NO_2 in the early phase of ETS aging. Of course, the NO_2 level decreases in absolute value after a few minutes.

A steady-state situation can be created with a constant smoke generation rate. This is what is obtained in experiment 4, where a cigarette is smoked every 15 min with the room ventilation left on. The corresponding profiles are shown on Fig. 4.

Table 2. Time averaged RSP and nicotine concentrations

Experiment code	RSP		Nicotine	
	Sampling time (min)	Concentration (mg/m^3)	Sampling time (min)	Concentration ($\mu g/m^3$)
1	90	0.089	40	8.6
2	96	0.189	40	18.6
3	79	0.391	40	25.6
4	150	0.478	40	21.4
5	121	0.350	40	25.3
6	128	0.508	40	28.7
7	130	0.486	40	16.8
Indoor background		0.033		0.7

Each time a cigarette is smoked, there is a rise and subsequent decay of the CO, NO and RSP concentrations, and after about 1 h a steady-state concentration is achieved. Even the nicotine level becomes fairly constant after a brief initial peak. This kind of experiment could be very useful in determining how environmental conditions may affect the ratio between the concentrations of two ETS components.

The effect of changes in the environmental conditions can also be quantitatively evaluated when the time-averaged nicotine and gravimetric RSP concentrations obtained for all the situations investigated are compared. These results are gathered in Table 2 and perusal of this table allows the following comments to be made:

Comparing the RSP and nicotine averaged concentrations in experiments 1, 2 and 3, it appears that these values are not proportional to the number of cigarettes smoked, even in this strictly controlled set of experiments. This is even more true for the nicotine values and thus the nicotine to RSP ratio is fairly different in these three experiments. The drastic effect of room ventilation is obvious when comparing the results of experiments 2 and 5 or, in the case of continuous smoke generation, 4 and 6. Again, the impact of room ventilation is quite different whether one considers RSP or nicotine. Eventually, the effect of an increased air turbulence in the room is apparent when comparing the results of experiments 6 and 7. It appears that the average concentration of nicotine is much more reduced by air turbulence than that of RSP, pointing at the large influence of wall effects on nicotine concentration.

Background Indoor and Outdoor Levels

In average, the indoor background levels were about 0.6 ppm for CO, 10 ppb for NO, 50 ppb for NO_2, 30 $\mu g/m^3$ for RSP and 0.7 $\mu g/m^3$ for nicotine

In addition to indoor analyses, and in order to put these results in perspective, the outdoor concentration of CO, NO and NO_2 was measured, at the same time as the smoking sessions were held, by extending probes 1 m outside the window. The levels monitored over a 24-h period are plotted on Fig. 5. For nitrogen oxides, these values are at times higher than any level obtained in the course of our experiments. This is due in part to the proximity of a highway.

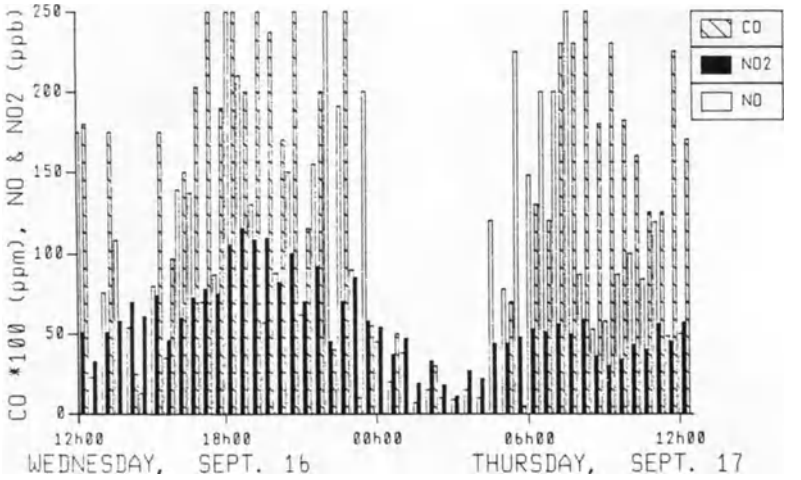

Fig. 5. Outdoor CO, NO, and NO_2 concentrations

Conclusion

This study constitutes a first part of a program we have initiated on the analytical investigation of ETS in indoor air. Much more work is needed to obtain a good understanding of the main processes governing ETS aging. This initial study outlined some possible flaws in RSP measurement. It showed that a careful examination of the time variation of the measured concentrations and their ratios may yield valuable insights into ETS aging processes. As these ratios are not constant, it appears that no component can readily serve as a marker for other ETS components. In particular, nicotine was found to be quite outstanding in its behaviour, making it a poor marker of ETS exposure. Eventually the large impact of indoor environment factors such as air mixing, room ventilation, wall surfaces etc. on ETS was outlined.

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ETS in Offices and When Smoking Is Restricted to Designated But Not Separately Ventilated Areas*

T. D. Sterling and B. Mueller

Summary

Nicotine, respirable suspended particles (RSP), carbon monoxide (CO), and carbon dioxide (CO_2) levels were measured in the smoking and nonsmoking sections of two cafeterias, a smoking lounge, and several offices.

Smoking in the offices was regulated by one of three methods:

1) smoking permitted *ad lib*,
2) smoking prohibited except in designated areas which were not separately ventilated, and
3) smoking prohibited except in designated areas which were separately ventilated.

Nicotine levels in the nonsmoking offices which received recirculated air from a designated smoking area were less than 1.0 $\mu g/m^3$. There was no difference in average RSP, CO, and CO_2 concentrations between nonsmoking offices that received recirculated air from designated smoking areas and nonsmoking offices that did not receive recirulated air. The results indicate that the provision of a designated, but not separately ventilated smoking area can effectively eliminate or drastically reduce most components of environmental tobacco smoke from non-smoking offices.

Introduction

Policies to regulate smoking in offices have been developed and implemented by private companies and some government agencies in response to concerns of health effects from involuntary exposure to environmental tobacco smoke (ETS). Several North American municipalities have passed bylaws to regulate smoking in all public buildings and the Canadian and American federal governments are currently developing methods to regulate smoking in workplaces under their jurisdiction. Most of the current or proposed bylaws establish no smoking as the workplace norm, except for specially designated areas where smoking is permitted.

Four options are available to regulate smoking in the office-work area:

1) Outright prohibition of smoking in all building locations;
2) Restricting smoking to designated areas that are separately ventilated;

* Part of the costs of this project came from a special grant from the council for Tobacco Research Inc.

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3) Restricting smoking to designated areas that are not separately ventilated;
4) Providing some framework by which an adjustment between smoking and non-smoking workers can be achieved, without directly regulating the placement of smokers.

The third option, that of providing a designated but not separately ventilated smoking area, appears to be the most frequently adopted procedure. The first option, an outright ban on smoking throughout a building, is usually an unsatisfactory solution because a certain proportion of building occupants are smokers who demand a location where they can be allowed to smoke. Smokers are found not only among employees but also among members of the public who are waiting for services. Buildings such as prisons or hospitals have full-time residents, some of whom are smokers. The second option, restricting smoking to designated areas that are separately ventilated, is often not a viable alternative because installing separate ventilation in an existing building may be physically impossible or very expensive. The fourth option is infrequently adopted because of objections by non-smokers or because of existing municipal regulations. Thus, the least disruptive and least costly solution for many buildings is to restrict smoking to designated, but not separately ventilated, areas. However, it is necessary to determine if the third option can reduce ETS constituents to acceptable levels.

This report presents the results of two separate field studies of ETS levels in Canadian offices under conditions of normal occupancy, smoking and ventilation.

The two studies were designed to provide data on two questions:

1) What is the contribution of smoking to ambient levels of four substances: CO_2, CO, nicotine, and RSP in offices?
2) How does restricting smoking to specially designated, but not separately ventilated areas, affect the levels of these four substances in nonsmoking offices?

Methods

Series I

In the first study, the number of office occupants and number of cigarettes smoked were observed while ambient levels of nicotine, CO and CO_2 were measured on the 7th and 11th floors of a government office building. (Measurements of RSP were also taken but, unfortunately, turned out to be inappropriately analyzed.) Smoking was permitted *ad lib* on the 11th floor but was restricted on the 7th floor to a 22.5 m^2 (242 ft^2) coffee/smoking lounge where smoking was permitted at all times. The layout and design of the two floors were almost identical, with an open-area office of approximately 780 m^2 (8,400 ft^2) surrounding a 114 m^2 (1,230 ft^2) mechanical/service core.

Each floor had it's own independent ventilation system which recirculated between 80% to 85% of the air returned from each floor and provided at least 20 cfm (cubic feet per minute) of fresh air per person. Except for leakage through elevator shafts and stairwells, no mixing or recirculation of air between floors occurred. The coffee/smoking lounge on the 7th floor was on the same ventilation system as the rest of the 7th floor.

Series II

In the second study, the number of office occupants and cigarettes smoked were observed while ambient levels of RSP, nicotine, CO and CO_2 were measured in two adjacent buildings (A and B) containing a mixture of open-area offices, private offices and public waiting/service areas.

Building A was a sealed, mechanically ventilated four storey office building with two levels of underground parking. Each of the four floors contained approximately 1,390 m^2 (15,000 ft^2) of office space. Smoking was prohibited in all areas of the building except for a smoking section, in the fourth floor cafeteria, which was not separately ventilated. The ventilation system mixed indoor air from all parts of the building before recirculation.

Building B was a 12-storey unsealed office building where most areas were passively ventilated by building leakage. Few areas had a separate ventilation system, and these systems were not connected to other ventilation systems. Consequently, there was no mechanical mixing of air from different floors or offices. Smoking was prohibited in all areas of the building except in the smoking section of a basement cafeteria. Heated/cooled air was supplied separately to the cafeteria and exhausted through windows.

Sampling Methods

Nicotine: In Series I, eight 1-h nicotine samples were collected in the designated smoking room, ten 1-h samples in the non-smoking offices on the 7th floor, and ten 1-h samples in the smoking-permitted offices on the 11th floor. In Series II, six 1-h nicotine samples were collected in each of the smoking and non-smoking sections of the cafeterias of Buildings A and B; two samples on each of the four floors in the non-smoking offices of Building A and two samples in non-smoking offices of Building B. Of the samples obtained in the non-smoking offices of buildings A and B, six collected air for 2 h, three collected air for 4 h and one collected air for 8 h.

Ambient nicotine was sampled with a portable air sampling pump housed inside a briefcase. The sampling apparatus was designed to collect samples unobtrusively because of the previously noted effect of observation on occupant behavior (Health and Welfare Canada 1985a). Nicotine samples were collected by pumping air at 1 l/min through sorbent tubes containing XAD-4 resin, a styrene divinylbenzene copolymer. The sorbent tubes contained 80 mg of resin in the front (primary) section and 40 mg in the rear (secondary) section. After sampling, the sorbent tubes were refrigerated until analysis.

The analytical procedure for nicotine was based on NIOSH (1977). Resin beads from the primary section of sorbent tubes were transferred to gas chromatograph autosampler vials containing 1 ml of ethyl acetate as the extraction solvent, 5 mg/l quinoline as an internal standard and 0.01% by volume of triethylamine to prevent adsorptive losses of nicotine onto the glass autosampler vials. Samples and spiked standards were placed on an automatic shaking device and shaken for 30 min. A Hewlett-Packard Model 5880A or Model 5830A gas chromatograph equipped with a nitrogen-phosphorous detector, an autosampler and a GC terminal were used to determine peak areas of the nicotine samples and standards. The assayed nicotine was corrected for the desorption efficiency (usually 94%) of the particular lot of XAD-4 resin used in sampling. The final weight of nicotine detected was divided by the volume of air sampled to give results in $\mu g/m^3$. The rear (backup) sections of sorbent tubes were analyzed separately and, except for one case,

gave nicotine determinations less than the detection limit, indicating no break-through of nicotine past the primary resin section.

RSP: RSPs were measured in Series II during the entire period of nicotine sampling and were averaged over each sampling period. RSP (particles less than 5 μm diameter) levels were measured with a Sibata Scientific Technology P-5H digital dust indicator which senses light side-scattered by suspended particles. The unit was calibrated at the factory to monodispersed stearic acid particles with a mean diameter of 0.3 μm. The digital counts of particles per sampling time were converted to RSP levels in $\mu g/m^3$.

CO and CO_2: Co and CO_2 levels were measured over 3–4-min-periods approximately midway into the 1- or 2-h nicotine sampling periods and at least twice during the 4- or 8-h nicotine sampling periods. CO was measured using a direct reading electrochemical analyzer (Nova 310L) housed in a flight-case. CO_2 was measured using extra low range CO_2 Gastec detector tubes and a manual sampling pump.

Other Observations: During each sampling period, the number of occupants and the number of cigarettes smoked in each predefined observation area were recorded. The observation areas were defined by the ability to survey the area. For purpopses of comparison, the average number of persons per 10 m^2 and cigarettes smoked per hour per 10 m^2 were calculated.

Results

Series I

Table 1 presents the average concentrations of nicotine, CO and CO_2, the average number of persons per 10 m^2, and the number of cigarettes smoked per hour per 10 m^2 (where applicable) for the smoking-permitted and non-smoking floors and the designated smoking area.

Although the three areas differed substantially in the number of cigarettes smoked per hour per 10 m^2, only ambient nicotine levels responded in a similar fashion. For example, the average smoking intensity (cigarettes per hour per 10 m^2) was 10.8 times greater in the smoking designated area than in the smoking-permitted floor. Similarly, the average ambient nicotine level was 15.6 times greater in the smoking designated than the smoking-permitted areas. Corresponding ratios for CO_2 and CO were only 1.3 and 1.7 respectively.

Table 1. Comparison of ETS related air quality variables (averages) in smoking prohibited and permitted work areas and in designated smoking areas, site 1

	Nicotine ($\mu g/m^3$)	CO (ppm)	CO_2 (ppm)	Persons per 10 m^2	Cigarettes/ h/10 m^2
Smoking permitted	4.8	2.5	720	0.79	0.36
Smoking prohibited	<1.6	2.1	680	0.61	NA
Designated smoking	75	4.2	960	0.97	3.9

Smoking was not observed on the non-smoking floor. The average ambient nicotine concentrations were below the limit of detection (i.e. less than $1.6\,\mu g/m^3$) for the 1-h sampling periods used. CO and CO_2 levels were slightly lower on the non-smoking floor than on the smoking-permitted floor.

Table 1 also lists the average person densities for each of the three sampling areas. The average person density was 30% higher on the smoking-permitted floor and 60% higher in designated smoking area than on the non-smoking floor. Corresponding ratios calculated for CO and CO_2 show a similar pattern and range.

Series II

The data for the smoking and non-smoking cafeteria sections of Buildings A and B were combined because there were only very small differences in the results for each building.

Figs. 1 through 4 summarize the ambient CO_2, CO, RSP and nicotine concentrations, in four areas under different smoking and ventilation conditions: the smoking sections of the two cafeterias, the non-smoking sections of the two cafeterias, the non-smoking offices of Building A which received recirculated air from other areas of the building, and the separately ventilated non-smoking offices of Building B which did not receive recirculated air from other areas of the building. In each figure, the height of the bars give the average concentration, n gives the total number of samples on which the average is based. The range of observed values is given by the vertical line.

Figure 1 shows that there was little difference between the CO_2 levels in the smoking prohibited offices of building A and building B, whether or not they received recirculated air. The smoking and non-smoking sections of the cafeterias had slightly elevated, but not statistically significant, CO_2 concentrations when compared to the non-smoking offices. These small increases in CO_2 levels could have been partly due to occupant density which was twice as high in the cafeteria sections than in the non-smoking offices.

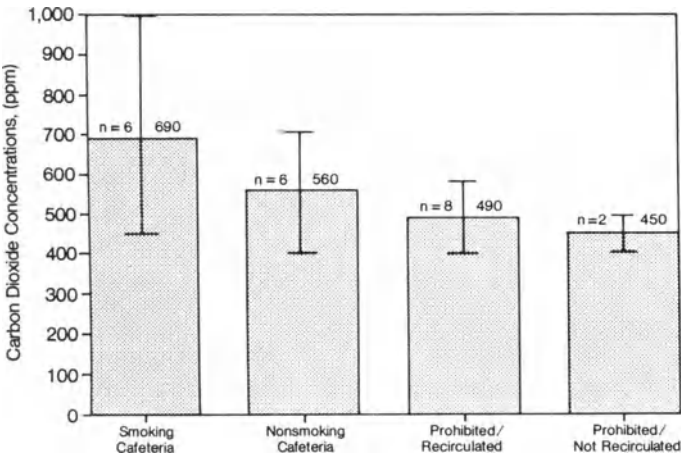

Fig. 1. Comparison of averages and ranges of CO_2 concentrations for different smoking regulations, series II

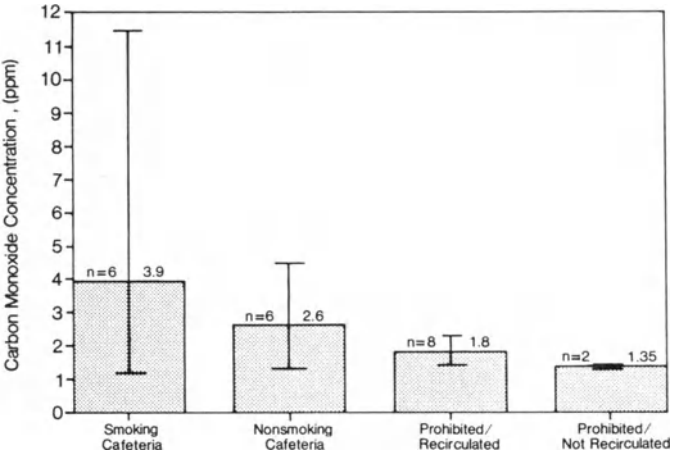

Fig. 2. Comparison of averages and ranges of CO concentrations for different smoking regulations, series II

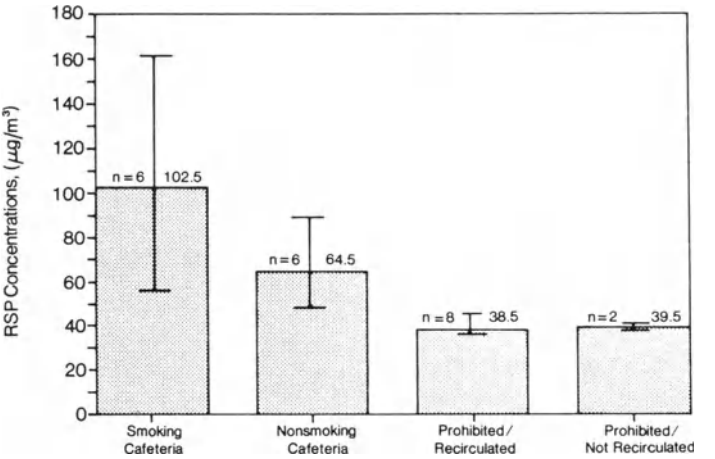

Fig. 3. Comparison of averages and ranges of RSP concentrations for different smoking regulations, series II

The distribution of mean ambient CO levels is similar to that for CO_2, as shown in Fig. 2. Although mean CO levels were higher in both cafeteria sections than in the non-smoking offices, none of the differences were statistically significant.

There were no differences in RSP concentrations between the non-smoking offices with and without recirculated air, as shown in Fig. 3. However, the mean RSP level in the smoking section of the cafeterias was 2.6 times that in the non-smoking offices while the mean level in the non-smoking section of the cafeterias was about 1.7 times that found in non-smoking offices.

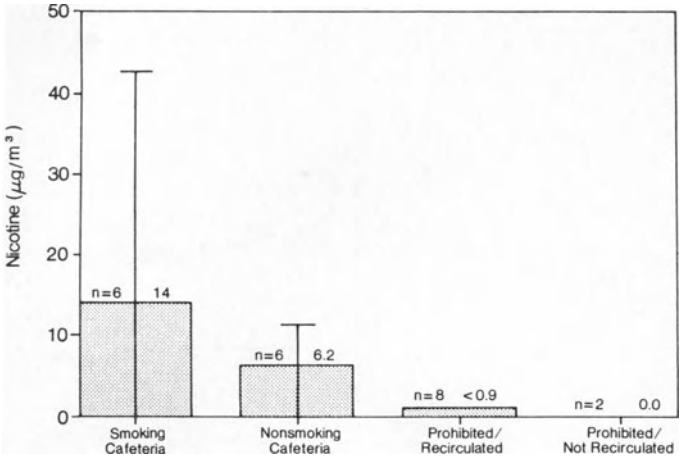

Fig. 4. Comparison of averages and ranges of nicotine concentrations for different smoking regulations

Figure 4 gives average ambient nicotine concentrations. In some instances the nicotine levels in the cafeteria sections were below the detection limit of 1.6 $\mu g/m^3$. The mean nicotine concentration measured in the smoking sections of the cafeterias was more than twice that in the non-smoking sections of the cafeterias and at least 15 times that in the non-smoking offices which received recirculated air.

The lower detection limit for nicotine is dependent upon the amount of air that is sampled. For the method used in this study, the lower detection limit was 0.8 $\mu g/m^3$ for a 2-h sample, 0.4 $\mu g/m^3$ for a 4-h sample, and 0.2 $\mu g/m^3$ for an 8-h sample. Two-, four- and eight-hour samples were taken in non-smoking offices in Building A which received recirculated air. None of four 2-h samples were above the detection limit; one of three 4-h samples was above the detection limit and gave a determination of 1.0 $\mu g/m^3$; the single 8-h sample was also above the detection limit and yielded a determination of 0.8 $\mu g/m^3$. These results indicate that the ambient nicotine concentration in these non-smoking offices was not larger than the maximum positive result of 1.0 $\mu g/m^3$.

Two 2-h nicotine samples were taken in non-smoking offices in building B which did not receive recirculated air. Nicotine was below the detection limit of 0.8 $\mu g/m^3$ in both samples.

Discussion

The Series I results suggest that ETS contributes little to ambient CO_2 levels. The differences in CO_2 concentrations between the smoking-permitted, prohibited and designated smoking areas were small compared with the observed differences in smoking intensity (cigarettes smoked per hour per 10 m^2) and ambient nicotine levels. However, the sample sites with higher CO_2 levels in Series I and II also had higher person densities. This suggests that people were the primary source of CO_2.

Ambient CO concentrations increased with smoking (Table 1 and Fig. 2) but did not closely follow smoking intensity or nicotine concentrations. Other indoor and outdoor

sources of CO must also contribute to CO levels, as indicated by the background level of 1.35 ppm in the non-smoking office without air recirculation. Part of the higher CO level in the cafeteria could also be due to cooking activities.

RSP are produced both by smoking and by many other processes. The background RSP level, as indicated by the results for the non-smoking office without recirculated air, are about 39 $\mu g/m^3$.

Not surprisingly, of the four substances measured, nicotine shows the strongest association with smoking. There are few if any significant sources of nicotine in the non-industrial indoor environment other than smoking and it follows that nicotine is an accurate marker of ETS exposure. Improvements in nicotine measurement technology could result in the widespread use of nicotine as an indicator of ETS exposure (HWC 1987).

Restricting smoking to specially designated areas which are not separately ventilated appears to effectively prevent high ETS levels in adjacent non-smoking areas. Both RSP and nicotine concentrations declined sharply from the smoking to the non-smoking sections of the cafeterias in Buildings A and B (Figs. 3 and 4). The recirculation of air from the smoking and non-smoking sections of the Building A cafeteria further diluted ETS to the extent that the levels of CO, CO_2, and RSP in the non-smoking offices of Building A were approximately the same as those levels in the non-smoking office in building B, which did not receive recirculated air.

Nicotine levels were at or below 1 $\mu g/m^3$ in non-smoking offices which receive recirculated air from smoking designated areas. This level of exposure is very low. For example, breathing air which contains 1.0 $\mu g/m^3$ of nicotine for 1 h at an average respiration rate for office activity of 0.48 m^3/h (ASHRAE 1986) is approx. equal to 1/1,900th of the 900 μg of nicotine inhaled by a smoker from the mainstream smoke of one cigarette (Muramatsu et al. 1984).

There are few published studies of nicotine levels in non-smoking offices. The nicotine levels observed by Bayer and Black (1986) are, unfortunately, not comparable with the results given here because their results are given in $ng/m^2/min$. Nevertheless, they did not detect nicotine in two of three non-smoking offices.

Other office studies have also found low RSP levels in non-smoking areas close to smoking designated areas that are not separately ventilated (Lee 1985). These findings are reinforced by Health and Welfare Canada (HWC 1985a) who measured RSP, CO and CO_2 concentrations before and after the implementation of a no smoking policy in offices that received recirculated air from a designated smoking area. After the no smoking policy was implemented, mean RSP levels decreased by 8 $\mu g/m^3$, from 26 $\mu g/m^3$ to 18 $\mu g/m^3$ (HWC 1985a).

Another Health and Welfare Canada study (HWC 1985b) measured RSP and CO_2 on three floors of an office building before and after the implementation of a no smoking policy. This study differed from the previous HWC study in that smoking was restricted to a separately ventilated area. Table 2 gives mean RSP concentrations for the three floors before and after the implementation of the no smoking policy. The average RSP concentration on the three floors decreased from 28.1 $\mu g/m^3$ to 21.1 $\mu g/m^3$, for a net reduction of 7 $\mu g/m^3$.

The results of the Series II and the HWC (1985a) studies indicate that recirculated air from designated smoking areas contributes less than 8 $\mu g/m^3$ of RSP to non-smoking offices which receive such air. HWC (1985b) further suggests that *ad lib* smoking in offices under normal ventilation and occupancy conditions contributes about 7 $\mu g/m^3$. These findings are substantially different from the widely quoted estimate by Repace and Lowrey (1980) that smoking increases RSP levels in offices by 170 to 200 $\mu g/m^3$. This

Table 2. Comparison of RSP mean concentrations on office floors before and after a no smoking policy was implemented (extracted from HWC, August, 1985)

	RSP ($\mu g/m^3$)	CO_2 (ppm)
Before no smoking policy		
Floor A	29.3	663
Floor B	30.0	614
Floor C	25.0	606
Overall average	28.1	627
After no smoking policy		
Floor A	22.7	591
Floor B	19.8	551
Floor C	20.8	503
Overall average	21.2	551

estimate, also accepted by Health and Welfare Canada, is based on modelling exposures. However, Repace and Lowrey's estimate is up to 21 to 29 times greater than the observed effect of smoking on RSP levels in the two HWC studies and, in fact, is 5.3 to 6.3 times larger than the average RSP concentration of 31.8 $\mu g/m^3$ from all sources found in smoking designated areas in the HWC study (1985b). These results further verify the results of a comparison of air pollutant measurements in a large number of buildings with and without smoking regulations (Sterling et al. 1987). The study found only small differences in airborne particles (combined total and respirable particles).

While smoking regulations are here to stay and will affect most offices under federal, provincial or municipal control in Canada, the haste to regulate smoking may have been based on the unrealistic modelled estimates of Repace and Lowrey or on "worst case" measurements in poorly ventilated workplaces, instead of on actual measurements of RSP levels in typical offices.

The provision of a designated smoking area appears to effectively reduce ETS constituent levels in non-smoking offices, even if the designated smoking area is not separately ventilated. However, we should caution that an exclusive reliance on regulating smoking while ignoring other sources of indoor pollution in the non-industrial work environment may accomplish little in meeting indoor air quality problems, especially in so-called "Sick Buildings" (Sterling et al. 1987).

Acknowledgements: We thank Mr. C. Collett for his help in arranging for sampling sites. We are beholden to Dr. C. Nystrom for help with some of the equipment used for Series 1.

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Chapter 2: Biological Effects Associated with Exposure to Environmental Tobacco Smoke

Environmental Tobacco Smoke and Lung Cancer – Recent Aspects on Confounders and Dose Levels

R. Rylander and L. C. Koo

Summary

To explore possible relations between exposure to environmental tobacco smoke (ETS) and lung cancer the control of confounders is important. This review describes the mechanisms by which substances taken into the body by the oral route may cause lung cancer. Two major possibilities are metabolism in the gut with subsequent absorption of carcinogenic compounds or selective accumulation of agents in the lung and local metabolism, particularly in the epithelium. It is suggested that these mechanisms may account for some anemalous findings in earlier studies on ETS and that exposure via the oral route may be the most important cause for low risk lung cancers in the population.

Introduction

A variety of occupational and environmental agents has been associated with increased risk for lung cancer. When trying to identify causal relationships, intervening or confounding exposures must be taken into consideration. Regarding the possible role of environmental tobacco smoke (ETS) as an agent related to lung cancer, such confounding factors have usually been identified as industrial exposures or sources of indoor air pollution in the home, such as cooking or heating stoves, and other airborne contaminants originating from combustion (Nat. Res. Council 1986).

The concept that the risk for development of lung cancer is related only to airborne agents, which are inhaled and deposited in the airways of the lungs, needs to be widened. It is now recognized that the lungs can be the site for uptake, accumulation and metabolism of numerous substances, which are administered to the body through the oral route or by injection. Examples of such substances are drugs, polycyclic aromatic hydrocarbons and other chemicals.

In the following, the different mechanisms through which substances taken up by other routes than inhalation may be of importance for cancer in the lungs will be examined followed by an assessment of the possible importance of these other exposure routes in comparison to inhalation of, for example ETS.

Metabolism in the Gastrointestinal Tract

It is now recognized that the microbiological flora in the intestinal tract, has a large metabolic capacity which in certain aspects is similar to that of the liver (Scheline 1973). This microbiological flora plays in important role when metabolizing endogenous compounds, for instance cholesterol bile acids and steroid hormones or exogenous compounds to form

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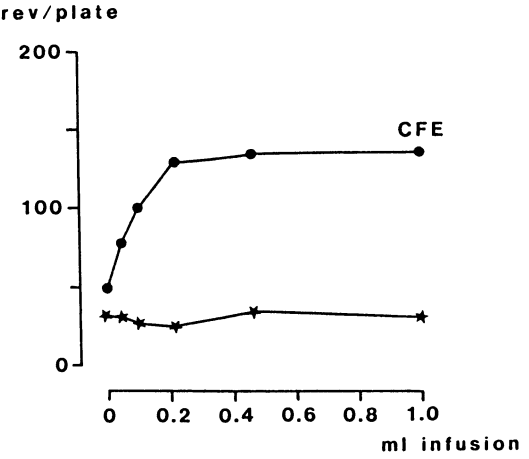

Fig. 1. Revertants (TA98) induced by tea extract, mixed with S-9, with and without extract from cecal bacteria (CFE)

metabolites with carcinogenic properties (Love et al. 1977). Compounds which have been partly metabolized in the liver can be further metabolized in the intestinal tract by bacteria. Certain of these metabolites may be reabsorped and enter in the entero-hepatic circulation (Gustafsson et al. 1981). Among the various substances, known to be metabolized by the intestinal bacteria, are polycyclic hydrocarbons, extracts from different vegetable fibers and nitrates. Carcinogenic and mutagenic substances can also be generated by metabolizing azodyes, and certain pharmaceutical preparations. An example from our own research work will be given in the following.

Several researchers have reported a suspected association between the drinking of tea and the development of various types of cancer (Bogovski and Day 1977; Heilbrun et al. 1986; Kaiser 1967). In order to further assess this hypothesis, experiments were undertaken where extracts of different kinds of teas were studied regarding their mutagenicity using the Ames' Salmonella assay. Extracts of tea were liophylized and incubated with strains TA98 and TA100 in the absence and presence of cell-free extract of cecal bacteria from rats (CFE). As an example, the results of one type of tea are demonstrated in Fig. 1.

It can be seen that only the tea extracts which were incubated with CFE, caused an increase in the number of revertants in comparison to background values. This experiment illustrates the transformation of a substance, normally considered innocuous, into a potential carcinogenic compound through the metabolism that occurs by bacteria present in the intestinal tract.

Uptake and Transportation

Extensive information is available regarding uptake of various pharmaceutical preparations given by oral, intramuscular, intraperitoneal or intervenous route and its transportation to the lungs. A specific accumulation in the lungs with subsequent toxic action has been reported for around 40 different compounds (Cooper et al. 1986). Such compounds have been found to accumulate in the alveolar macrophages, pulmonary neutrophils, fibroblasts, alveolar type 2 cells, lymphocytes or subepithelial glands. Diseases related to the compounds are hypersensitivity lung disease, capillary damage with following edema, fibrosis and effects on the immune lung system. Comparatively little information is available on the pulmonary uptake of potentially carcinogenic substances.

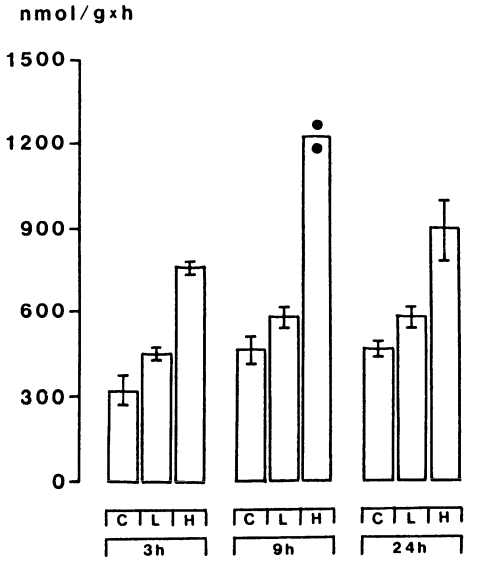

Fig. 2. Pulmonary microsomal induction by i.p. injection of 300 ng (L) and 1 mg (H) of benz-a-pyrene compared to solvent control (C) at various times after exposure

Experiments were undertaken where the effect of an intraperitoneal injection of benzo(a)pyrene (B(a)P) on the microsomal cytochrome P450-dependent B(a)P hydroxylase in the lungs was assessed (Haussmann and Walk unpublished). Male Sprague Dawley rats received an intraperitoneal injection of 300 ng or 1 mg B(a)P per kilo body weight. The microsomal B(a)P hydroxylase activity was estimated using fluorescence analysis after HPLC separation and expressed as micromoles 3-OH-B(a)P per gram protein and per hours.

Figure 2 illustrates the induction of the microsomal enzyme system in the lungs after an intraperitoneal administration of B(a)P.

Using a perfused rat lung preparation, Fotu et al. (1984) demonstrated that the covalent binding of benzo(a)pyrene to DNA, RNA and protein was higher after perfusion than after intratracheal instillation.

These findings show that carcinogenic substances administered through non-inhalation routes can influence enzyme reactions in the lung ever more than when the substances are inhaled.

Uptake and Metabolism in the Lung

The lungs have several important characteristics that facilitate the absorption of substances from the blood. The venous drainage from practically the entire body, flows through the alveolar-capillary unit, which has an extensive endothelial surface. The epithelial layer is in very close contact with the blood which allows for rapid absorption of lipophilic agents from the circulation. This is illustrated by the capacity of the lung to regulate the systemic concentration of biologically active endogenous compounds by selective removal metabolism. Certain polypeptides, prostaglandins, vasoactive amines and hormones, are handled in this manner (Bend et al. 1985). Substances with chemical characteristics, similar to those agents, will also be taken up when the blood passes through the lung.

Several researchers have demonstrated a metabolism of substances which accumulate in the nasal and respiratory epithelium (e.g. review by Brittebo et al. 1986). Generally, the drug metabolizing system of the epithelium transforms substances into non-toxic excretable products. In certain cases, however, relatively inert compounds may be metabolically activated to form reactive intermediates which, in turn, can bind to tissue macromolecules, such as DNA.

Using studies involving whole body autoradiography, the metabolism of nitrosonornicotine was studied by Brittebo et al. The highest amount of tissue bound metabolites was found to be present in the nasal subepithelial glands but metabolites were also found in other parts of the respiratory epithelium (Löfberg et al. 1982). Other nitrosamines show a similar pattern. This deposition correlate with findings from clinical and epidemiological investigations that exposure to nitrosamines causes tumors in the nasal mucosa.

An intravenous injection of 1,2-dibromoethane (EDB), which is used as a herbicide and as a lead scavenger in gasoline, resulted in high levels of non-volatile metabolites in the mucosa in the entire respiratory system of mice for up to four days. Again, this finding parallels observations of an increased frequency of tumors in the nasal cavity of mice exposed to the same agent. The rapid localization of the non-volatile metabolites in the mucosa of the respiratory tract suggests a local metabolism of the substance in these tissues. These examples demonstrate the organotropic property of carcinogens and could be a possible mechanism for the previously described association between consumption of salted fish and nasal tumors in rats (Huang et al. 1978) or nasal-pharyngeal cancer in humans (Yu et al. 1986).

A metabolism in the respiratory epithelium has also been demonstrated for pharmaceutical preparations, such as phenacetin, and endogenous substances such as steroid hormones. The importance of these substances as risk factors for lung cancer has not been studied.

Perspective on ETS Risk Estimations

The review on the metabolism and accumulation in the lung of potentially carcinogenic substances, administered by other routes than inhalation, demonstrates the need to take into account a wider variety of agents when evaluating confounding factors in studies on the relation between ETS and lung cancer. A practical example is given in an investigation on tea-drinking habits, ETS exposure and lung cancer among females in Hong Kong based on the material from a previously published case-control study (Koo et al. 1984). The data are illustrated in Fig. 3.

It can be seen that a risk of 1.3 was found for black tea and 2.4 for green tea drinkers. The relation remained the same when smoking habits were statistically controlled. This review exemplifies that it is necessary to investigate potential agents other than inhalants in understanding lung cancer risks. When examining the relationship between ETS and lung cancer, it is thus prudent to investigate a series of potential agents which may be administered the oral route. It is even likely that a reexamination of earlier data with this in mind, may explain some puzzling findings, such as the very high incidence of lung cancer in non-smoking females in the rural area of Japan as reported by Hirayama (1981).

Before calculating lung cancer risk estimates for ETS exposure, the importance of the above factors must be taken into consideration. The previously suggested increases in the relative risk of lung cancer with relation to ETS exposure, reflect dose levels which were present 20 to 30 years ago. As ETS dose levels today may be substantially different, a possibility exists that exposures through the oral route as discussed here, and/or other well known environmental carcinogens, such as radon, may be the largest contributors to the risk of lung cancer in the non-smoking population.

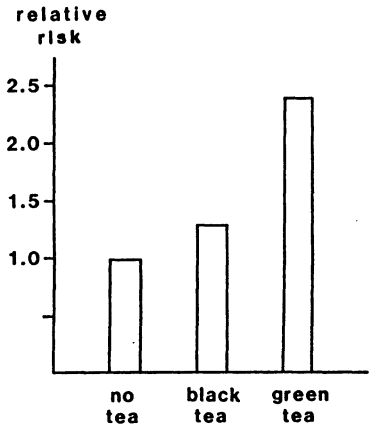

Fig. 3. Lung cancer risk for tea drinking Chinese females – odds ratio adjusted for age and cigarette smoking

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Urinary Mutagenicity, Hydroxyphenanthrene, and Thioether Excretion After Exposure to Environmental Tobacco Smoke

G. Scherer, K. Westphal, and F. Adlkofer

Summary

In two controlled studies 10 non-smokers each were exposed for 8 h to environmental tobacco smoke (ETS) equivalent to 10 ppm CO (Experiment 1) and 25 ppm CO (Experiment 2). During the control and the exposure period the room air was monitored for CO, NO, NO_2, nicotine and formaldehyde. Biomonitoring included determination of carboxyhemoglobin (COHb), cotinine in serum and urine, and urinary excretion of five different monohydroxyphenanthrenes (OH-PHE), thioethers and mutagenic activity (as detected by the Salmonella typhimurium TA 98/microsome assay). The observed increases in COHb indicate that ETS exposure in Experiment 1 was substantially higher than in a real-life situation, whereas that in Experiment 2 bore no relation to common passive smoking. This is mainly due to the fact that high ETS exposure in a real-life situation is usually much shorter than 8 h per day. Urinary excretion of OH-PHE and mutagenicity was not significantly increased after both experimental ETS exposures. In contrast to this, excretion of thioethers was elevated after ETS exposure in Experiment 1 ($P = 0.07$) and Experiment 2 ($P < 0.001$). Our results suggest that non-smokers in real-life situations take up very low doses of ETS constituents, which in case of potentially genotoxic substances are likely to be detoxified.

Introduction

There has been much controversy in the scientific literature about the health risk to non-smokers due to passive smoking [8]. Since epidemiology which provides most of the evidence for a positive correlation between ETS exposure and chronic diseases is extremely sensitive to bias and confounding factors in low risk associations [24], solid risk assessments should not be based on epidemiological data alone. Toxicological data have to be considered as well in order to come to firm conclusions. Dosimetry of ETS exposure is clearly a prerequisite for risk evaluations. Nicotine, cotinine and thiocyanate in body fluids as well as COHb are normally used as biochemical markers for ETS exposure [10]. While in fact these markers permit comparing tobacco smoke exposure during active smoking with that during passive smoking to some limited extent, they do not allow direct estimates of the non-smoker's body burden by toxic and, in particular, genotoxic substances. This is due to the quantitatively different composition of mainstream smoke (inhaled by the smoker) and sidestream smoke (breathed in highly diluted form by the non-smoker) [12], the different aging time-related toxicities of both smoke types [21], and the different patterns of inhalation between active and passive smoking resulting in different deposition rates and distributions in the respiratory tract [6, 19].

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In order to get some more insight into the exposure doses of potentially genotoxic substances after ETS exposure, we extended the biomonitoring in two controlled ETS exposure experiments to the excretion of five different monohydroxyphenanthrenes (used as marker for exposure to polycyclic aromatic hydrocarbons (PAH)), the excretion of thioethers (used as a marker for exposure to electrophilic substances), and the excretion of mutagens in the urine.

Material and Methods

Subjects

Twenty-four healthy male subjects (14 non-smokers and 10 smokers) aged 18 to 44 years (mean age 22.0 years) volunteered to take part in either one or both experiments. After admission to the laboratory on Friday evening they completed a questionnaire on socio-economic and life-style factors as well as on their ETS exposure during the last 48 h.

Protocol

Experiment 1: After admission to the laboratory at 8 pm, 10 non-smokers aged 18 to 29 (mean 23.8 ± 3.6) years were put on a defined diet low in polycyclic aromatic hydrocarbons during the course of the experiment. The following night and day (control day) any exposure to ETS was avoided. On the first day the subjects spent 8 h in an unventilated, ordinarily furnished room of 45 m^3, in order to simulate exposure conditions. On the second day (exposure day) the subjects were exposed to ETS at a level of approx. 10 ppm CO in the unventilated room for 8 h. The exposure session started at 8.30 am and was finished at 5 pm with a 30-min lunch break at noon. The subjects were only allowed to leave the room to go to the lavatory. The smoke was generated by two smokers smoking cigarettes, so that a CO level of about 10 ppm was maintained. Blood samples were taken before the subjects entered the room at 8 am and after they had left the room at 5 pm on both the control and exposure day. Each subject sampled his 24 h urines on two consecutive days. Sampling began after discarding the first morning urine at approximately 8 am on the control day. The subjects were dismissed from the laboratory on the morning after the exposure day.

Experiment 2 was carried out in the same way as experiment 1 except for the following changes: It was performed in two separate runs each of them comprising five non-smokers and five smokers. Six of the non-smokers had participated in experiment 1. The age of the subjects ranged from 19 to 28 (mean 23.7 ± 2.7) and from 24 to 44 (mean 32.4 ± 7.0) years for the 10 non-smokers and the 10 smokers, respectively. The smokers had to refrain from smoking after admission to the laboratory until entering the exposure room on the exposure day. After this they were free to smoke cigarettes of their own brand. The CO level on the exposure day varied between 20 and 25 ppm. The 10 smokers served as positive controls for the biological monitoring.

Room Monitoring

The air sampling tubes were installed in breathing height of a sitting person at the end of the room which was opposite to where the smokers sat. Carbon monoxide (CO) and nitrogen oxide/nitrogen dioxide (NO/NO_2) were measured continuously using a Carbon-Monoxide Analyzer, Model 8310 (Monitor Labs Inc., U.S.A.) and a Nitrogen-Oxide Analyzer, Model 8840 (Monitor Labs Inc., U.S.A.), respectively. Nicotine was sampled on Extrelut-filled tubes for 0.5 to 2 h (flow rate 2.4 l/min). The loaded tube was alkalized by ammonia and the alkaloid was eluated with 20 ml ethyl acetate. In the dried and concentrated eluate nicotine was determined by capillary gas chromatography [13]. Formaldehyde was measured according to the method of Kennedy and Hill [11]. The aldehyde was derivatized with N-benzylethanolamine to form N-benzyloxazolidine which was detected by capillary gas chromatography.

Biomonitoring

Carboxyhemoglobin (COHb) was measured by using a CO-Oximeter, Model 182 (Instrumentation Laboratories Ltd., U.S.A.) immediately after drawing the blood samples. Cotinine in serum and urine was detected by a radioimmunoassay as described by Langone et al. [14] and modified by Haley et al. [2]. Thioethers in urine were determined in the laboratory of Prof. M. Sorsa (Helsinki, Finland, according to established methods [3, 25]).

Extraction of urine samples for mutagenicity testing was performed according to the original method of Yamasaki and Ames [26], modified by Mohtashamipur et al. [17]. Briefly, aliquots of 400 ml filtered urine samples were adjusted to pH 8.0 (NaOH) and loaded on a XAD-2 column (0.7 × 8 cm). After washing with 3 ml water the column was extracted with 40 ml methanol. The first drops were discarded until the brownish eluate appeared. The eluate was evaporated to dryness under reduced pressure at 65–70 °C. The residue was dissolved in 2 ml DMSO. This procedure is reported to lower the histidine concentration in the extract to undetectable levels [17]. The urine concentrates were tested for mutagenicity by the Salmonella (TA98) microsome (S9-mix derived from aroclor treated rats) assay. Each sample was determined in triplicate using 10, 25, 50 and 75 µl urine concentrate, corresponding to 2, 5, 10 and 15 ml of original urine. The slope of the linear part of the dose-response obtained by linear regression technique was used to calculate the mutagenic activity in the 24 h urine. In each case the steepest of the three slopes was used for further analyses.

1-, 2-, 3-, 4- and 9-Hydroxyphenanthrene (OH-PHE) in urine was determined in the laboratory of Prof. Grimmer by gas chromatograph [4]. Aliquots of 10 individual 24-h-urine samples were used in experiment 1, whereas pooled urines of five smokers and five non-smokers each were used in experiment 2.

Statistical Analysis

The one sample t-test for differences (exposed minus non- exposed) was applied.

Table 1. Average levels of ETS components in indoor air during control and exposure days of Experiment 1 and Experiment 2[a]

	Control day[b]		Exposure day of			
			Experiment 1		Experiment 2	
	Morning	After-noon	Morning	After-noon	Morning	After-noon
Total number of cigarettes smoked	–	–	19	23	47	53
CO (ppm)	2– 3	2– 3	10	10	20	22
NO (ppm)	10–15	10–15	160	160	350	280
NO_2 (ppb)	15–20	15–20	20– 30	10– 15	130	170
Formaldehyde ($\mu g/m^3$)	20	15	40	40	30	50
Nicotine ($\mu g/m^3$)	20	20	40–100	50–100	150	120

[a] Figures indicate time-weighted averages.
[b] Average of the three control days.

Results

The results of the air monitoring during the control and exposure days in both experiments are summarized in Table 1. A total of 42 cigarettes were smoked during Experiment 1 whereas during both sessions of Experiment 2 the total number of cigarettes smoked amounted to 100 each. The doubling of the amount of tobacco consumed from Experiment 1 to Experiment 2 is also reflected in the increases in CO and NO, but is not observed for the other air monitoring variables. NO_2 was more than proportionately increased, whereas formaldehyde and nicotine were less than proportionately elevated.

The averages of the biochemical markers before and after ETS exposure and active smoking are summarized in Table 2. COHb and cotinine in serum and urine were significantly elevated after both ETS exposure regimens. The increases however were low compared to those observed after smoking. Urinary excretion of OH-PHE was not significantly increased after exposure to ETS (Table 2, Fig. 1a). Smoking led to a small elevation of OH-PHE in urine.

Slightly higher amounts of thioethers were excreted by non-smokers after exposure in Experiment 1 ($p = 0.07$). Significantly higher excretion of thioethers in subjects exposed to ETS were observed in Experiment 2. This increase represents about 45% of that found after active smoking (Table 2, Fig. 1b). The mutagenic activity of urine extracts was found to be highly variable under controll and exposure conditions for both smokers and non-smokers (Fig. 1c). No significant increase in urinary mutagenicity was observed after ETS exposure in Experiment 1 and 2, whereas smoking clearly increased the mutagenic activities in the urine (Table 2, Fig. 1c).

Table 2. Biomonitoring in ETS exposed non-smokers and cigarette smokers. (Mean ± SD)

	Experiment 1		Experiment 2			
	Non-smokers (n = 10)		Non-smokers (n = 10)		Smokers (n = 10)	
	Control day	Exposure day	Control day	Exposure day	Control day (no smoking)	Exposure day (smoking)
COHb (%)						
before	0.34 ± 0.15	0.18 ± 0.02 } ***	0.63 ± 0.19	0.65 ± 0.32 } ***	2.44 ± 1.10	0.81 ± 0.44 } **
after	0.32 ± 0.13	0.87 ± 0.04 }	0.62 ± 0.13	2.69 ± 0.13 }	1.24 ± 0.40	7.87 ± 2.20 }
Serum cotinine (ng/ml)						
before	0 ± 0	0 ± 0 } ***	1.2 ± 1.7	0.4 ± 1.0 } ***	377.8 ± 129.7	145.7 ± 51.0 } **
after	0 ± 0	1.1 ± 0.3 }	0.9 ± 1.6	4.9 ± 0.9 }	242.3 ± 84.3	244.0 ± 84.4 }
Cotinine in urine (µg/24 h)	8 ± 8	23 ± 8	21 ± 13	67 ± 26	4,485 ± 1,795	3,584 ± 1,278
		**		***		*
Σ Hydroxyphenanthrenes in urine (µg/24 h)	5.63 ± 2.38	5.33 ± 2.05	4.60 ± 0.30	4.28 ± 0.80	4.82 ± 0.48	5.55 ± 0.44
		NS		(NS)[b]		(*)[b]
Thioethers (µMol/24 h)	40.0 ± 15.4	53.9 ± 22.8	69.3 ± 36.3	90.7 ± 44.8	89.1 ± 24.8	136.1 ± 38.9
		NS		**		**
Mutagenicity						
Rev./plate[a]	6 − 12	3 − 16	0 − 10	0 − 19	0 − 23	15 − 376
Rev./24 h	875 ± 371	1,069 ± 565	236 ± 358	548 ± 757	927 ± 510	13,819 ± 17,224
		NS		NS		**

Levels of significance are as follows: NS = not significant, $p > 0.05$; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

[a] Range of highest mean rates (minus spontaneous rate) of triplicate measurements observed after applying 10, 25, 50 and 75 µl urine concentrate (corresponding to 2, 5, 10 and 15 ml urine).

[b] Two pooled urine samples of five subjects each.

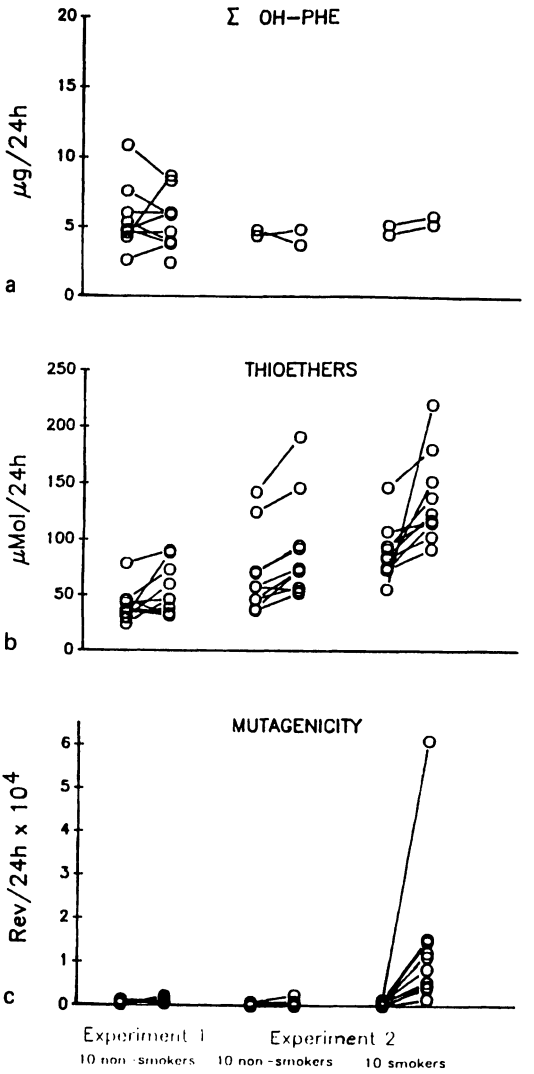

Fig. 1a–c. Individual changes in urinary excretion of **a** OH-PHE, **b** thioethers, and **c** mutagenicity. The lines connect the value before and after exposure for each individual. OH-PHE measurements in Experiment 2 were performed with urine samples pooled from five subjects

Discussion

Our indoor air measurements reveal that the concentration of ETS in Experiment 1 may correspond to real-life situations [13]. However, average daily exposure time is reported to be usually less than 8 h [15, 16], indicating that exposure conditions in Experiment 1 are higher than commonly achieved. This is confirmed by the observed increases in COHb levels in our Experiment 1 which were found to be 0.7% on the average. Field measurements of COHb in non-smokers working in ETS-polluted rooms result in much lower, if any, increases in COHb [9, 23]. Significant increases in serum and urine cotinine levels were found after ETS exposure in both experiments. However, since steady-state levels were not attained for cotinine in a single 8-h-exposure regimen, our data cannot be compared with cotinine concentrations measured under field conditions with repeated exposures.

For the first time, urinary excretion of 1-, 2-, 3-, 4- and 9-hydroxyphenanthrene was used as a marker of ETS-related PAH exposure. The limitations of these and other markers for this purpose have been discussed elsewhere [5]. Our results indicate that passive smoking and even smoking do not substantially contribute to the daily PAH burden. The diet might be of greater importance in this respect. In addition, findings of OH-PHE excretion in road paving and wood creosoting workers show that PAH exposure, at least at some workplaces, is about two orders of magnitude higher [4, 5].

An elevated urinary thioether excretion is an unspecific indicator of exposure to and detoxification of electrophilic substances. We, for the first time, observed increased excretions of thioethers after ETS exposure which reached statistical significance under the high exposure conditions. We assume that the strictly controlled dietary conditions in our experiments are a prerequisite for this finding. Sorsa et al. [22] were unable to find a change in thioether excretion after moderate ETS exposure (4 ppm CO, 5 h/d, for 2 days). Quite surprisingly, the increases measured in our ETS exposed non-smokers were not substantially lower than those observed after smoking. At least two points have to be considered when interpreting this result: 1) Non-smokers might have glutathione-S-transferase/glutathione (GST/GSH)-systems with higher detoxifying capacities than smokers; 2) breathing of ETS might lead to an uptake of higher amounts of substances detoxifiable by the GST/GSH-system than does inhaling of mainstream smoke.

All urine extracts of ETS exposed non-smokers were found to be negative in the mutagenicity test (Salmonella typhimurium TA 98/microsome assay) when applying the criterium of Ames (doubling of spontaneous mutation rate) [26]. A quantitative evaluation of the test (results expressed as revertants excreted in the 24 h urine) reveals a slight but statistically not significant increase in urinary mutagenicity in Experiment 2. This increase amounts to about 2% of that found after smoking (Table 2). This result is in agreement with that by Bos et al. [1] who reported that non-smokers exposed to similarly high concentrations as in our Experiment 2 excreted about 4% of the mutagenicity found in smokers. Both findings are at variance with the observation by Mohtashamipur et al. [18] according to which the urinary mutagenicity after high ETS exposure (19 ppm CO, 8 h) is similar to that found in smokers smoking 4 to 5 cigarettes. The reasons for this discrepancy are not yet clear and have been discussed elsewhere [20]. The situation becomes even more confused when considering the results by Sorsa et al. [22] who found an elevation of mutagenic activity in urine after moderate ETS exposure amounting to 70% of that after smoking. The same group [7], however, found no clear increase in urinary mutagenicity of ETS-exposed waiters and waitresses when compared with non-ETS-exposed office workers.

The lack of a measurable increase in urinary mutagenicity after ETS exposure in our experiments together with the fact that the Ames-assay is difficult to interpret when testing complex mixtures, leads us to conclude that this parameter is not suitable for assessing the risk due to passive smoking.

In conclusion, our results on the increase in thioether excretion show that non-smokers exposed to high ETS concentrations take up measurable amounts of electrophilic compounds. In our view, this observation as well as the absence of a detectable urinary mutagenicity favour the idea that the much lower amounts of electrophils non-smokers are exposed to under real-life conditions could be effectively detoxified.

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The Effects of Environmental Tobacco Smoke on Pulmonary Function

M. D. Lebowitz and J. J. Quackenboss

Summary

A community study in Tucson is underway to evaluate the effects of environmental tobacco smoke (ETS) exposure on acute and chronic pulmonary function, including bronchial reactivity. Study families (about 700) are part of a multi-stage stratified cluster sample. Monitoring for PM10 and PM2.5 in the houses showed a good correlation between amount of tobacco smoking in the home and measurements of concentration; distributions of PM by amount smoked do overlap somewhat. Further, PM10 and PM2.5 have a very close correlation ($R^2 = 85\%$).

In the first 400 subjects, some relationships have been found between proportions with significant durinal peak flow (PEF) and ETS (by amount smoked in the home), controlling for PM10 or PM2.5 ($\mu g/m^3$). These relations of PEF – bronchial lability in association with PM and ETS, some of which are definitely paradoxical, have to be explored further. So far, the acute changes are not reflected in any differences in chronic symptomatology. Further, the acute symptoms have not been associated with ETS-PM; one exception is non-specific, complaint symptoms, which are higher when both ETS and PM10 are highest ($p = 0.08$). It is possible that PEF changes have a similar mechanism. To study the relability and validity of such relationships, atmospheric nicotine and serum cotinine should be evaluated.

Environmental tobacco smoke has various chemical constituents that are either annoying, irritating, or biologically active (US Surgeon General 1975, 1984). Thus, there are different effects on the primary organ site, the lung (Stein and Weinbaum 1986): annoyance responses affect the lung only in suggestible individuals who may respond with increased airway resistance; a few asthmatics are like this. Irritants can produce several responses, that are dose-dependent. Constituent may be biologically active: they may attract defense and inflammatory cells which may lyse to release proteases, endotoxins, and chemotactic factors, and stimulate the production of mediators, leading potentially to inflammation (and bronchial reactivity), stimulate mucus glands, and/or affect immune responses. Certain constituents may alter dna or RNA within cells. Irritant responses may be greater in previously sensitized individuals. Biological activity will depend on host status and susceptibility (physiologically, biochemically, immunologically). Biological assays/markers help determine status/susceptibility.

Sensitivity/susceptibility is a function of age as well, and early exposures and infections are quite important (Lebowith and Burrows 1986). Some of the effects mentioned can be measured by pulmonary function responses, in individuals characterized by their susceptibility or sensitivity (Lebowitz et al. 1987). Acute and chronic effects, and the relationships between them, need to be considered.

H. Kasuga (Ed.) Indoor Air Quality

A new community study is underway in Tucson (USA) to evaluate these effects from environmental tobacco smoke exposure (ETS), especially in susceptible/sensitive people. This paper will discuss some initial findings from this study.

Methods

Study families (about 800) are part of a multistage stratified cluster representative sample, which has been described previously (Quackenboss et al. 1987a). Initial questionnaires provided information to stratify them by age and sex, presence of children, and likely exposure to various indoor, work, and outdoor pollutants. In the second stage, monitoring for PM10 & PM2.5 was conducted using impactors (Quackenboss et al. 1987b). Environmental inventory questionnaires obtained information about smoking in the house. Standard respiratory questionnaires obtained information about chronic respiratory history. Standard spirometry was used for all individuals ages five and older. Daily symptom diaries and peak flows provided the acute impact measurements related to exposures (Lebowitz et al. 1985, 1988). Outdoor monitoring, performed within clusters, was conducted by the pima county aqcd (Lebowitz et al. 1985).

Results

Monitoring, by cluster, show little relation between PM10 indoors and outdoors; the indoor levels are dependent on ETS (Fig. 1). Indoor PM10 and PM2.5 are highly related, within groups determined by the amount of smoking indoors; the distributions overlap (Fig. 1).

Screening by diurnal and daily peak flow measurements led to a classification of bronchial responsiveness ("reactivity"), which is the major determinant of susceptibility/

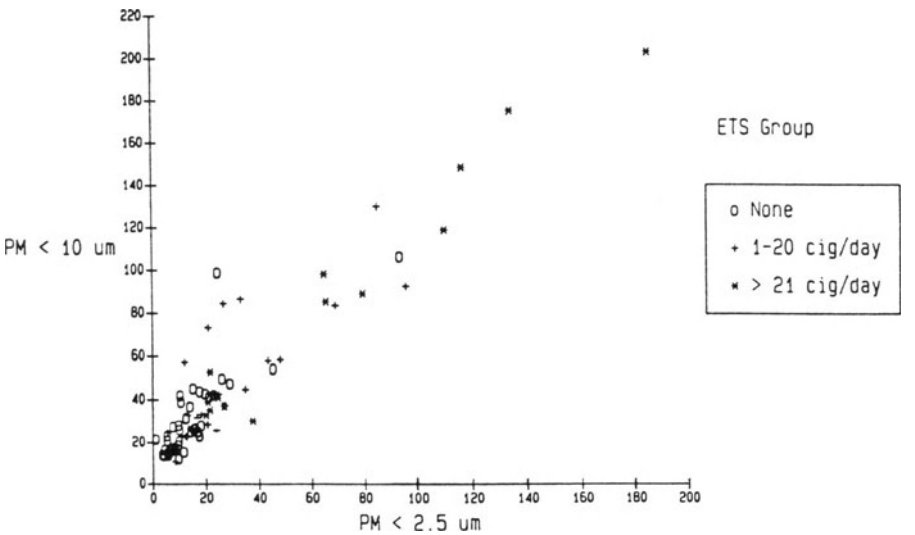

Fig. 1. PM10 and PM2.5 by smoking

Table 1. Prevalence rates (per 100 person-day) of diurnal bronchial "reactivity" (peak flow determination) by ETS and PM exposures in the home

ETS	None		≤ 20 cigs/day		> 20 cigs/day	
PM10 (μg/m³)	≤ 50	> 50	≤ 50	> 50	≤ 50	> 50
	46%	53%	50%	42%	25%	47%
p	ns		ns		ns	
PM < 2.5 (μg/m³)	≤ 15	> 15	≤ 15	> 15	≤15	> 15
	41%	63%	50%	45%	0	43%
p	p = 0.03		ns		n.d.	

Table 2. Prevalence rates (per 100) of daily bronchial "reactivity" all ages[a], for PM10 in the home[b]

	ETS			
	None	1–20 cigs/day	> 20 cigs/day	p
PM10				
≤ 50 μg/m³	27.3%	44.0%	38.9%	ns
> 50 μg/m³	34.7%	42.9%	68.0%	0.01

[a] No significant effects of age and sex.
[b] PM10 × ETS: p = 0.0004.
No significant effects of PM10 on "reactivity" independent of ETS.

sensitivity of respiratory responses to air pollutants (Quackenboss et al. 1987a, b; Lebowitz et al. 1988). As predicted by previous results, including comparisons of this "reactivity" to other measures of responsiveness (post broncho-dilator and -constrictor flows), children showed more "reactivity".

Initial analysis had shown that, for all subjects, there was a trend indicating an increased prevalence rate of diurnal "reactivity" associated with PM10 in homes with higher ETS; the diurnal and daily prevalence rates were significantly related to PM2.5 in homes without ETS (Table 1). Further analyses (in the first 216 subjects) has shown that the daily "reactivity" relation to PM10 was not influenced by age or sex, and there was no significant relationship between this rate and PM10 independent of amount of ETS. The prevalence rates of daily reactivity in homes with PM10 >= 50 μg/m³ were 34.7% without ETS, 42.9% with 1–20 cigarettes smoked in the home per day, and 68% with 21 or more (Table 2). The relationship was not significant in homes with PM10 < 50 μg/m³ though the prevalence rate was still higher in homes with ETS. (A log-linear analysis controlling for all other factors confirmed these findings.) Controlling for outdoor PM10 as well indicated that there was more daily "reactivity" related to indoor ETS on days when PM10 outdoors was below 50 μg/m³; higher outdoor PM10 appeared to relate "reactivity" more closely when there was little or no exposure to household ETS (<= 20 cigarettes per day). Diurnal variability was large, and there were no relationships of it to ETS after controlling for all other significant variables.

Table 3. Prevalence rates (per 100) of daily bronchial "reactivity" (peak flow determination) by ETS in house, children under age 15 (log linear model, controlling for age, sex, significant)

	ETS				
	None	1–20 cig per day	> 20 cig per day	Total	p
	30.6%	25.0%	61.1%	34.3%	0.0275
(N)	62	28 males: 57.1% females: 63.6%	18	108	

Table 4. Daily prevalence rates (per 100 person-days) of allergic-irritant symptoms, for all subjects, by PM10 in the home

		ETS				
		None	≤ 20 cigs/day	> 20 cigs/day	Total	p
PM10	≤ 50 μg/m^3	72.6%	60.8%	58.3%	67.6%	0.08
	> 50 μg/m^3	69.2%	36.0%	75.0%	56.9%	0.09

The prevalence rates of daily "reactivity" in children under age 15 (that is, in the age group with the greatest "reactivity") is shown to be significantly correlated with the amount of ETS in the home (Table 3); 61% of children in homes with >= 20 cigarettes per day exposure had such "reactivity" ($p < 0.0275$). Males and females had similar prevalence rates. The log linear model, controlling for age and sex was significant.

In addition, prevalence rates of daily symptomatology were analyzed in relation to household ETS. Symptoms were grouped into non-specific symptoms (primarily acute), allergic or irritant symptoms (acute and chronic), and acute respiratory illness symptoms (primarily acute).

There were no significant relationships between ETS and allergic/irritant symptoms, for the entire sample by gender or for any age group, either independent of or controlling for PM10 in the house. In fact, there was more reactivity in the homes without ETS and with PM10 < 50 μg/m^3 (Table 4). This implies that daily "reactivity" was not likely to be a reflection of responses by asthmatics, allergics, or others with underlying reactivity symptomatology; such individuals may avoid both ETS and other sources of PM10. Analysis of the 31 with diagnosed current asthma indicated that 58% live in homes without ETS; only four (13%) live in homes with >= 20 cig./day. There was no relationship of diurnal reactivity in this group with ETS. Likewise, asthmatics without diagnoses and/or diagnosed allergic subjects had low rates of ETS in their home and no relationship of diurnal reactivity with ETS.

There was a slight increase of about 15% in the prevalence rate of daily acute respiratory illness symptoms in those homes with both ETS and PM10 > 50 μg/m^3 (Table 5); the trend was reversed in the homes with PM10 < 50 μg/m^3. These trends could not be traced to any specific age-sex group.

Table 5. Daily prevalence rates (per 100 person-days) of acute respiratory illness symptoms, for all subjects, for PM10 $> 50\ \mu g/m^3$

None	≤ 20 cigs/day	> 20 cigs/day	Total	p
53.8%	32.0%	70.0%	50.0%	0.035

Table 6. Daily prevalence rates (per 100 person-days) of non specific symptoms, for children[a]

ETS				
None	≤ 20 cigs/day	> 20 cigs/day	Total	p
42.9%	51.7%	75.0%	50.0%	0.037

[a] For adults: males not significant with ETS; females significantly increased.

There was a significant increase in the daily prevalence rates of non-specific symptoms associated with ETS. Of those in homes with higher ETS, 75% of person-days had such complaints. There were 51.7% of person-days with such complaints in homes with some ETS and only 42.9% of person-days with such complaints in homes without ETS. These complaints (annoyance reactions and sensory irritation) were much greater in adult females, and were reported more frequently for children by their mothers (Table 6). There was no relationship between the prevalence rates for chronic symptoms and diseases and the presence or amount of ETS in the home.

Discussion

The lack of a relationship between ETS and chronic conditions is consistent with previous findings in Tucson (Lebowitz 1984). This further indicates the necessity of studying the effects of ETS on susceptible individuals (Lebowitz and Burrows 1986; Lebowitz et al. 1987), where such susceptibility is determined by biological tests performed for specific target organs (in this case, the lung).

We will determine in further analyses whether those who are defined as susceptible by the immunological markers we use are more sensitive to ETS. Further, to evaluate the reliability and validity of relationships of biological response to ETS, and to determine dose-response relationships quantitatively, we will have to measure atmospheric nicotine and serum cotinine as well. Further discussions about the biological roles of ETS should be conducted to determine future research goals.

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Are There Any Impairments of Maximal Expiratory Flow-Volume Curves by Passive Smoking?

M. Kentner and D. Weltle

Summary

Impairments of lung function are generally found more often in active smokers than in non-smokers. Thus, the question arises whether the passive inhalation of tobacco smoke may also cause such an effect.

To find an answer to this question, an investigation involving 1,364 white collar workers with healthy lungs was carried out. Information on tobacco smoke exposure was obtained by a standardized questionnaire. The group was divided into four subgroups: never smokers, passive smokers, ex-smokers and current smokers, each further subdivided according to sex. Bronchopulmonary function was tested by measuring the flow-volume curve. The following parameters were determined: forced expiratory vital capacity (FVC), peak expiratory flow (PEF) and the maximal expiratory flows (MEF 75, 50, 25, 15). These values were standardized for age, height and body weight on the basis of the measurements obtained in the never smokers group applying multiple regression.

Our findings confirmed, as expected, that *active smoking* causes an impairment of pulmonary function. In men MEF 50, MEF 25, MEF 15 and FVC showed a statistically significant ($P \leqq 0.05$) decrease, in women the same was true for all parameters. *Ex-smokers* showed no essential flow reductions with exception of MEF 25 and MEF 15 in men. In female *passive smokers* we found decreased flows for PEF and MEF 75. Male passive smokers had no impaired lung function. Altogether it has to be pointed out that only in active smokers was the decreased lung function out of the range of the normal variability.

From this it follows that average everyday passive smoke exposure in the office or at home does not lead to essential impairments of lung function in healthy adults.

Introduction

There is no doubt that active inhalation of tobacco smoke can cause a reduction in pulmonary function. This applies both to the ventilation with decreased forced expiratory vital capacity (FVC) and to forced expiratory volume in 1 s (FEV_1) [4, 14, 22, 26, 30, 49, 51, 55]. Furthermore obstructions of the small airways have been discovered in active smokers by other authors using end-expiratory flows of the flow-volume (MEFV)-curve [4, 9, 16, 29, 37, 44].

Our knowledge of the effects *passive smoking* on the bronchopulmonary system, however, is still far from being complete (Surveys in [2, 3, 15, 17, 21, 28, 32, 34, 35, 52]).

- The findings obtained in studies of children with smoking parents concerning *respiratory symptoms and diseases* are, for the most part, consistent. In *early childhood*

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bronchitis, pneumonia and other diseases of the lower respiratory tract are significantly more common in children exposed to passive smoking than in those who are not. Moreover, positive correlations were found between parental smoking habits and the frequency of acute respiratory diseases, chronic coughing, phlegm and persistent wheeze in *older children* (Survey in [57]).

- Relatively few studies have been published to date on the effects of involuntary smoking on *lung function in children.* Some studies demonstrate a significant negative effect of parental smoking [47, 48, 50, 56, 61], other results are inconsistent [18, 53, 54] and a number of investigations fail to find any associations between parental smoking habits and a decreased pulmonary function in their children [13, 33, 42, 46].
- In persons with *bronchopulmonary prior diseases,* i.e. bronchial hyperreactivity, chronic bronchitis or asthma, passive smoking can either aggravate or lead to a relapse of the illness as is reported in some studies [12, 41, 45, 59]. Other authors such as Lebowitz [31], did not find these effects.

In view of these partly contradictory findings the question arises to what extent passive smoking can impair *lung function in healthy adults.* Only a few studies have dealt with this question and their results are not uniform (Chap. 3). To obtain a better insight into this issue, we carried out a study involving a larger group of white collar workers in 1982–1983. While our evaluation at that time concentrated on the time-volume curve, our attention is focussed at present on the flow-volume curve.

Patients and Methods

A *total* of 1,351 subjects (951 men and 413 women) took part in the study. All of them were office workers and participated voluntarily under blind study conditions. The subjects filled out a standardized *questionnaire* containing among other questions regarding their smoking habits and bronchopulmonary prior diseases.

Table 1. Number of subjects examined, average age and bronchopulmonary prior diseases in the subgroups

	No. of subjects examined		Age in years (median values)		Broncho-pulmonary prior diseases (pneumonia, asthma, tuberc. of the lungs)		Chronic bronchitis	
	M	F	M	F	M	F	M	F
NS	146	66	42 (31–51)	41 (33–55)	21	7	3	2
PS	252	133	39 (28–52)	37 (23–51)	30	18	8	3
ES	301	60	43 (34–55)	39 (26–49)	42	8	9	3
CS	252	154	40 (30–53)	31 (22–43)	34	13	10	8
Su.	951	413	41 (31–53)	35 (26–50)	127	46	30	16

Table 2. Correlation factors for adjustment of the pulmonary function parameters

		Age (Years)	Height (m)	Weight (kg)	Const.
FVC	M	- 0.026	5.766	- 0.007	- 3.633
	F	- 0.029	4.493	- 0.008	- 2.220
PEF	M	- 0.021	8.410	- 0.040	- 2.221
	F	- 0.057	4.234	0.041	- 1.373
PEF-V	M	- 0.008	0.157	- 0.001	- 0.883
	F	0.003	0.134	- 0.003	- 0.541
MEF 25	M	- 0.021	5.854	- 0.039	1.015
	F	- 0.054	3.733	0.027	- 0.209
MEF 50	M	- 0.019	4.203	- 0.023	- 0.054
	F	- 0.049	2.398	0.020	0.578
MEF 75	M	- 0.015	2.345	- 0.010	- 0.973
	F	- 0.031	1.890	- 0.003	- 0.215
MEF 15	M	- 0.007	1.226	- 0.005	- 0.599
	F	- 0.023	2.071	- 0.005	- 1.414

Subsequently the overall group was divided into four *subgroups*:

- *Never smokers* (NS), defined as persons who have never been regularly exposed to tobacco smoke, either actively or passively.
- *Passive smokers* (PS), defined as subjects who have never actively smoked, but who are currently exposed to passive smoking.
- *Ex-smokers* (ES), defined as persons who had given up active smoking at least six months previously.
- *Active smokers* (CS) representing the group of persons who, at the time of the investigation were actively smoking cigarettes, cigars and pipes.

The size of the subgroups, sex rations, average age and prior diseases in the lower respiratory system are specified in Table 1.

As statistical analysis of associations between lung function in healthy subjects and persons with prior diseases such as pneumonia, asthma, tuberculosis of the lungs and chronic bronchitis showed no significant differences, subjects with prior illnesses were not excluded.

Lung functions tests were carried out using an electronic spirometer with a so-called spiroceptor[1]. Test subjects remained in a sitting position for the breathing exercises. The flow-volume curves were recorded by a xy-recorder[2] under BTPS-conditions.

Generally the respiration manoeuvres were repeated two to three times, with only the best curve (plausible figure, maximal values) being used for evaluation.

The following *parameters* were determined from the flow-volume curve:

- *Forced expiratory vital capacity* (FVC),
- *peak expiratory flow* (PEF) with the additional volume (PEF-V),
- *maximal expiratory flows* at 75, 50, 25 and 15% of the remaining FVC (MEF 75, MEF 50, MEF 25, MEF 15).

[1] Siregnost FD 10, Fa. Siemens, Erlangen, FRG.
[2] xy-Recorder E 2218, Fa. Siemens, Erlangen, FRG.

Normal values were determined for these parameters on the basis of the measurements obtained in the never-smoker group. For this multiple regression analysis was used by adjustment for sex, age, height and weight (Table 2). The confidence interval of standardized normal values for each subgroup is shown cross-hatched in Figs. 1–4.

The difference between real and nominal values was analyzed statistically by a matched pairs signed rank test [60]. Statistical significances are marked with one ($p \leqq 0.05$) or two asteriks ($p \leqq 0.01$), resp. (Figs. 1–4).

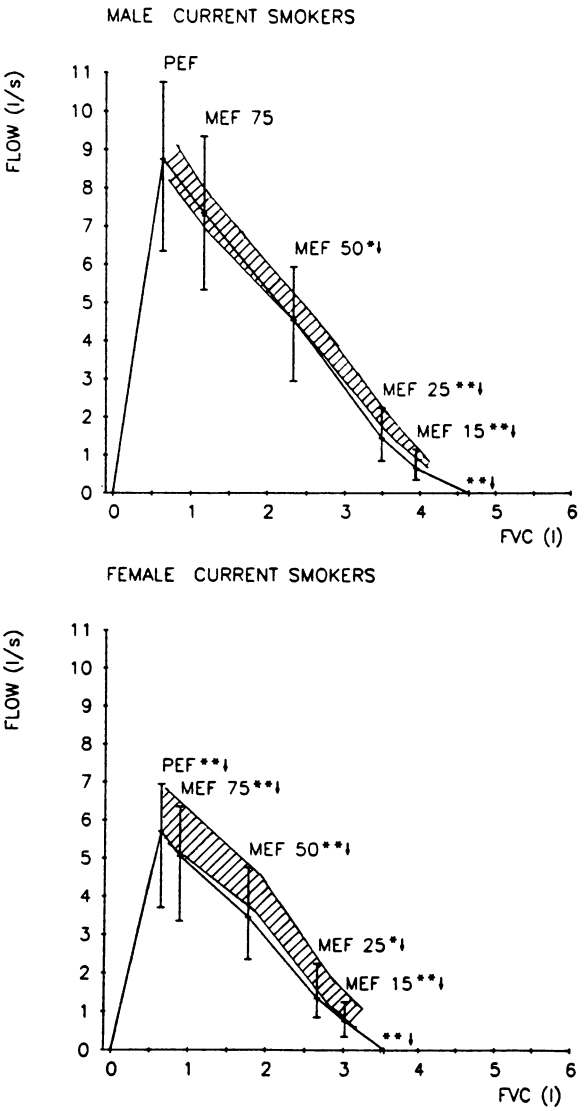

Fig. 1. MEFV-curve in male and female current smokers

Table 3. Smoking habits in ex-smokers and current smokers (median values and $66^2/_3$ confidence intervals)

		Cigarettes/day	Smoker years	Pack years	Ex-smoker years
ES	M	20.0 (9.0–37.5)	15.0 (7.5–22.5)	15.0 (3.5–42.0)	7.0 (1.5–12.5)
	F	14.0 (5.5–22.5)	9.5 (2.5–18.0)	6.3 (0.5–20.5)	4.5 (1.0– 9.5)
CS	M	19.0 (1.0–29.0)	17.5 (8.5–29.0)	16.6 (0.2–42.0)	–
	F	14.5 (6.5–24.0)	9.5 (4.5–19.0)	6.7 (1.5–22.8)	–

Results and Discussion

Results of Our Study

Active Smokers: The findings of our study support the thesis, mentioned in the introduction, that active inhalation of tobacco smoke leads to impairments of pulmonary function. A decrease in MEF 50, MEF 25, MEF 15 and FVC was found in male AS. Female AS even showed a degradation in all parameters (Fig. 1).

This means that in men the effect of tobacco smoke inhalation is predominantly reflected in a small airways dysfunction, whereas in women active inhalation shows more severe effects [36]. The depression of the entire flow-volume curve in female AS indicates more central bronchial obstructions [25].

The fact that women consume fewer cigarettes than men and also spend a shorter period as smokers shows the particular health hazard in women. While women reach 6.7 packyears (20 cig./day), men have a consumption of 16.6 packyears (Table 3).

Ex-smokers: We found no essential worsening of lung function in ex-smokers either in men or in women (Fig. 2). The only exception here is the decrease in MEF 25 and MEF 15 in men. On the other hand, PEF and MEF 75 in male ES show an increase.

Mean ex-smoker period in men was 7.0 years and in women 4.5 years (Table 2). Apparently during that time a restitutio ad integrum occurs, also in women, although the impairment of their lung function due to active smoking is more pronounced than in men.

Similar results have been obtained in intervention studies [5, 7, 8]. For example Buist et al. [8], by measuring lung function standard parameters, demonstrated a clear inprovement in ventilation after smoking cessation within a period of six to seven months.

Passive Smokers: Figure 3 shows no disturbance in lung function for male passive smokers. In women PEF and MEF 75 still lie within the normal confidence interval, but the statistical analysis reveals a reduction.

This finding is difficult to interpret. If these changes are to be attributed to passive smoke exposure, the results found for active smokers would lead us to expect a decrease in the other flow rates as well. A possible explanation for the isolated reduction of PEF in female PS might be the relatively high interindividual variability of the flow-volume curve. This may lead to erroneous correlations.

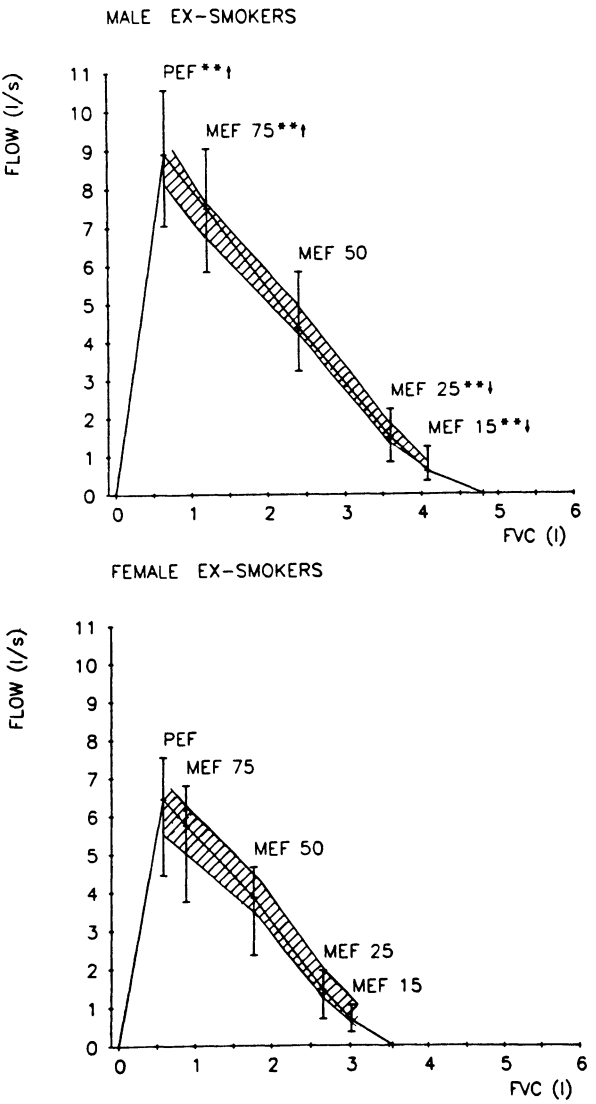

Fig. 2. MEFV-curve in male and female ex-smokers

Never Smokers: As the NS group also represents the reference population, no statistically significant alterations of their values can be expected (Fig. 4).

Findings by Other Authors

Up to now eight studies have been published on passive smoking and lung function in healthy adults (Table 4). These are exclusively cross-section studies.

Only in two studies the flow-volume curves were determined besides recording the time-volume curves. Whilst Brunnekreef et al. [6] found a statistically significant

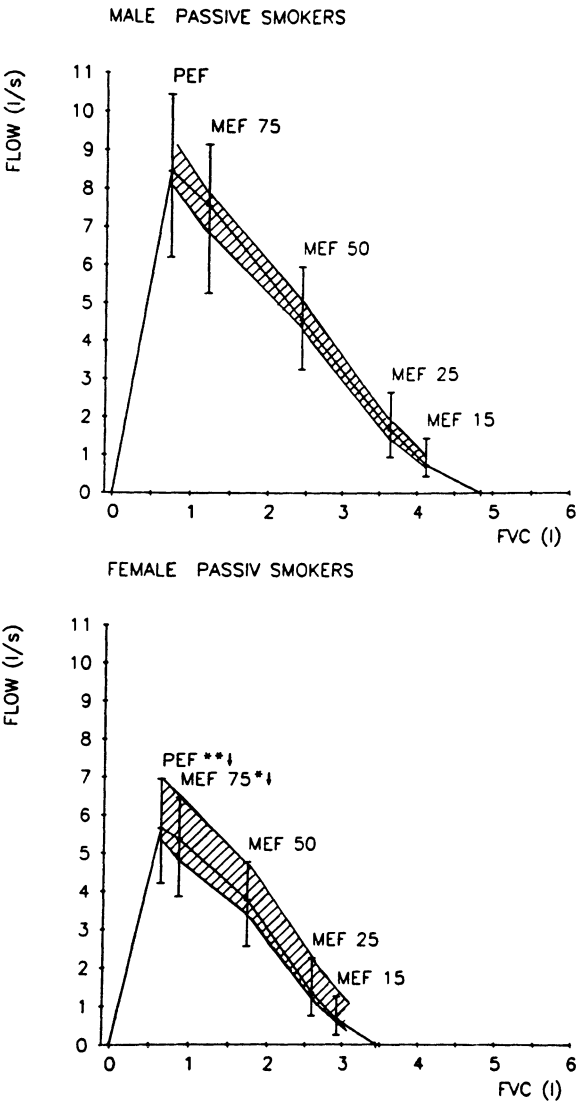

Fig. 3. MEFV-curve in male and female passive smokers

reduction of PEF and MEF 75 in PS in comparison to CS, Schilling et al. [42] were unable to establish such a relationship for any lung function parameter.

The remaining six studies which concentrated only on the time-volume curve did not show uniform results. Whereas three investigations confirm a reduction of lung function due to passive smoking [23, 38, 58], this relationship was not supported by the other three studies [11, 19, 27].

These investigations differ considerably in the methods applied. The discrepancies are mainly found in formation of subgroups, lung function procedures, standardization and, moreover, age structure of the participants. Therefore, any direct comparison can only be limited.

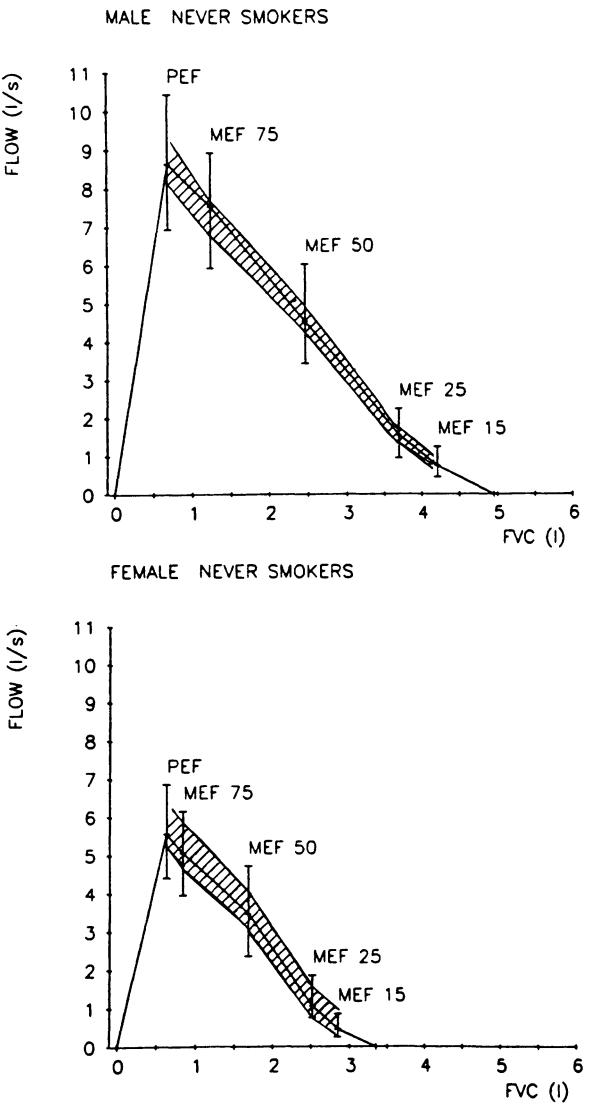

Fig. 4. MEFV-curve in male and female non-smokers

The best way to compare them is by calculating the differences in lung function parameters between NS or normal persons on the one hand and in PS on the other. The data available can be seen in Table 5. In female PS flow decreases for PEF and MEF 75 between 10 to 16% and 9 to 14%, resp. were found. For both male and female PS, decreases in FEF 25–75 and FEF 75–85 can be calculated which are between 6% and 9% or 5% and 15%, resp.

Reductions of this magnitude in our investigations were only found in comparing with NS and CS. Thus in female CS PEF was decreased by 19% and MEF 75 by 14%. For FEF 75–85 reductions were between 8% and 18% in CS [27].

Table 4. Review of the literature published so far with regard to the topic pulmonary function in healthy adult passive smokers

Authors	Subgroups (N)*	Pulmonary function parameters	Results
Schilling et al. (1977) [42]	M NS, F NS (138) M NS, F CS (40) M CS, F NS (74) M CS, F CS (78)	FVC, FEV_1, PEF, MEF 50, MEF 25	No statistically significant reduction of lung function in PS/H.
White and Froeb (1980) [58]	M NS (200), F NS (200) M PS/W (200), F PS/W (200) M CS (650), F CS (650)	FVC, FEV_1, FEF 25–75, FEF 75–85	FEF 25–75 and FEF 75–85 in MF PS/W show statistically significant lower values than in NS.
Comstock et al. (1981) [11]	M PS/H (369), F PS/H (49) M ES (179), F ES (17) M CS (472), F CS (142)	FEV_1, FEV_1/FVC	No statistically significant reduction of lung function in MF PS/H.
Helsing et al. (1982) [19]	MF NS (372) MF PS/H (189)	FEV_1, FEV_1/FVC	The presence of poor ventilatory function in PS/H showed only a very weak association (N.S.).
Petrovic et al. (1982) [38]	M NS/W, PS/W (434) F NS/W, PS/W (741)	FEV_1/VC	Statistically significant differences between the groups (exact study design was not available).
Kauffmann et al. (1983) [23]	M NS (849), F NS (826) M PS/H (65), F PS/H (1,158)	FVC, FEV_1, FEF 25–75	In the comparison of NS and PS/H aged 40 years or more statistically significant decrease appeared in women for FEV_1 and FEF 25–75.
Kentner et al. (1984) [27]	M NS (142), F NS (66) M PS/H(39), W(146), HW(36) F PS/H (18), W (61), HW (36) M ES (301), F ES (59) M CS (247), F CS (153)	FVC, FEF 25–75 FEF 75–85	No statistically significant reduction of lung function in MF PS/H, W, HW.
Brunnekreef et al. (1985) [6]	F NS (30, 16) F PS/H (27, 19)	FVC, FEV_1; IVC; PEF, MEF 75, MEF 50, MEF 25, MMEF	PEF and MEF 75 were statistically significant decreased in F PS/H.

* H = at home; W = at workplace; M = male; F = female. Other abbreviations see text.

This would mean that the strain put upon lung function impaired by passive smoking is comparable with that by active tobacco smoke inhalation. That this can not in fact be the case is underscored by estimating the doses of the most principal bronchial irritants found in tobacco smoke to which the passive smoker is exposed. At sedentary or easy physical work over an 8-h workshift cigarette equivalents of between 0.04 and 8 cigarettes

Table 5. Differences of lung function parameters in non-smokers with statistically significant association between passive smoke exposure and lung function reduction

Brunnekreef et al. (1985)	
- NS vs. PS/H (at present exposed aged 40–60 years, only women)	F PEF = 0.75 L/S (10%) F MEF 75 = 0.58 L/S (9%)
- NS vs. PS/H (exposed since about 15 years, aged 40–60 years, only women)	F PEF = 1.33 L/S (16%) F MEF 75 = 0.97 L/S (14%)
White and Froeb (1980)	
- Normal persons vs. PS/W	M FEF 25–75= 0.20 L/S (9%) F FEF 25–75= 0.19 L/S (7%) M FEF 75–85= 0.05 L/S (5%) F FEF 75–85= 0.12 L/S (15%)
Kauffmann et al. (1985)	
- NS vs. PS/H (aged 40 years or more)	F FVC = 0.09 L/S (3%) F FEV_1 = 0.09 L/S (4%) F FEF 25–75= 0.17 L/S (6%)

Table 6. Cigarette equivalents for passive smokers concerning respiratory membrane irritants (Henschler 1983)

Particulate matter	
- respirable particulates	0.04–0.24
Volatile substances	
- nitrogen oxides	ca. 8
- acrolein	0.80–4.00
- formaldehyde	?
- ammonia	?

may be taken into account, depending on the substances measured (Table 6). The substantial deviation is due to the great variability of the external exposure. This depends primarily on the amount of tobacco smoke emission and the ventilation of the room [39] while the internal exposure is mainly determined by the ventilations of the lungs.

Taking cigarette equivalents into consideration, the effects of passive smoking on lung function found by White and Froeb [58], Kauffmann et al. [23] and Brunnekreef et al. [6] are too high. A positive confounder in these investigations might be that persons having pre-existing impairments of lung function or bronchial hyperreactivity never take up smoking [51, 55] and so are over-represented in the PS group.

Furthermore, the question arises to what extent the described impairments of lung function due to passive smoking are of pathophysiological relevance. In 1984, the American Thoracic Society [1] published a diagram showing the various degrees of damages to the respiratory system from air pollution, which demonstrates a wide transitional field between physiological and pathophysiological alterations (Fig. 5). This applies particularly to lung function parameters [24].

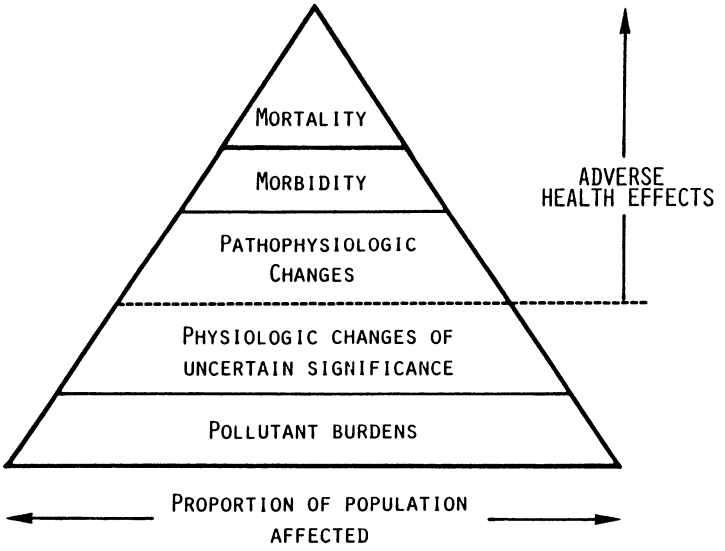

Fig. 5. Spectrum of biological response to pollutant exposure. (From [1])

In general it may be assumed that under normal everyday conditions passive smoke exposure does not induce relevant pathological changes of bronchopulmonary function in healthy adults in the sense of adverse effects.

Conclusions

From the findings available so far there is no evidence that average everyday passive smoke exposure in the office or at home leads to an essential reduction of lung function in healthy adults.

Under unfavourable conditions (forced and passive smoke exposure over many years, small rooms, heavy physical work, prior illnesses of the respiratory system) a reduction in lung function due to passive smoking might be possible, particularly in women.

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Effects of Light or Moderate Smoking on Birth Weight or on Serum Biochemical Components in Infants of Japanese Women

Y. Shimizu and T. Ishiguro

Summary

Smoking habits were studied in 1,545 Japanese pregnant women and the weight of delivered babies was compared to findings in the case of non-smokers. In all 120 of 1,545 women (7.8%) continued to smoke while pregnant, and 107 of those 120 women (89.2%) were light or moderate smokers who smoked less than 20 cigarettes per day. Birth weight differences between the infants of light or moderate smokers and those of non-smokers were 75 g. Serum biochemical components such as total protein, albumin, A/G, cholesterol, triglyceride, enzymes, electrolytes, urea nitrogen, creatinine and uric acid were studied in 32 infants, including 12 born to light or moderate smokers and 20 to non-smokers. Serum vitamin B12 levels were also examined in 15 infants of light or moderate smokers and 14 infants of non-smokers. The serum values of all these compounds were the same in both groups. Thus, light to moderate smoking is not an absolute risk factor, as related to intrauterine growth of the fetus.

Introduction

Since Simpson [14] first reported that the incidence of low birth weight ($< 2{,}500$ g) was almost twice as high among smoking women as compared with non-smoking women, the association between maternal smoking and reduced birth weight has been extensively investigated. Although most researchers [1–4, 8, 11, 12, 14] considered maternal smoking to be detrimental to fetal growth, some [5, 6, 13, 16] have argued that innate characteristics other than smoking were responsible for the reduced birth weight.

Fewer Japanese women smoke, as compared with their Western counterparts. According to Japanese literature published at the beginning of the 19th century (Edo period), the incidence of smoking among Japanese women in the 18th to 19th centuries was apparently higher than today. It was stated that "there were neither women who did not smoke nor priests who abstained from eating meat." Since the early 20th century, the number of women smokers began to decrease, and smokers, especially those who smoked over 20 cigarettes per day were few.

The present study was designed to investigate the epidemiological features of cigarette smoking in Japanese pregnant women and to study the effects of smoking on birth weight and on various biochemical components in sera of infants born to light or moderate ($\leqq 20$ cigarettes per day) smoking mothers.

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Material and Methods

Smoking habits and birth weight were studied in 1,545 pregnant subjects from two western areas of Japan: half being from large industrial cities and the remainder from the countryside.

Serum biochemical components were studied in 32 healthy infants born to mothers with an uncomplicated, term pregnancy. Twelve of the 32 mothers smoked fewer than 20 cigarettes per day and the remaining 20 were non-smokers. Sera were obtained from the umbilical cord vein immediately after delivery, and total protein, albumin, A/G ratio, cholesterol, triglyceride, glutamic-oxaloacetic transaminase (GOT), glutamic-pyruvic transaminase (GPT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), choline esterase (ChE), leucine aminopeptidase (LAP), electrolytes (Na, K, Cl), urea nitrogen, creatinine and uric acid were examined using a Hitachi 716 Automatic Analyzer. Vitamin B12 was also assayed by solid phase radioimmunoassay (Daiichi Radioisotope Lab. Ltd) in sera from 29 infants, including 14 from non-smokers and 15 from light or moderate smokers. The student's test was used to determine statistical significance.

Results

Incidence of Smoking and Number of Cigarettes Smoked Per Day by Pregnant Subjects

As shown in Table 1, 167 out of 1,545 women (10.8%) were smokers at the time of their first visit to the obstetrician. Forty-seven (28.1%) stopped smoking soon after they became pregnant, lowering the overall incidence to 7.8%.

Table 1. Smokers among Japanese pregnant women

	No.	[%]
Subjects	1,545	-
Smokers at the first examination by an obstetrician	167	10.8
Pregnant women who stopped smoking	47	3.0
Women who continued to smoke during pregnancy	120	7.8

Table 2. Number of cigarettes smoked per day by Japanese pregnant women

No. of cigarettes	Smokers	
	No.	[%]
$\leqq 5$	52	43.3
$6 \sim 10$	38	31.7
$11 \sim 20$	17	14.2
> 21	13	10.8
Total	120	100

Table 3. Average birth weight of infants and smoking habits of the mother. (All infants were delivered vaginally at 37 to 40 weeks of gestation. NS: not significant)

Sex of infants	Smoking mother		Non-smoking mother		Significance
	No.	Birth weight	No.	Birth weight	
Male	50	3,104 ± 335	283	3,211 ± 387	NS
Female	57	3,100 ± 347	286	3,142 ± 401	NS
Total	107	3,102 ± 348	569	3,177 ± 391	NS

The number of cigarettes smoked is shown in Table 2. Almost half the number of women smoked only five or fewer cigarettes per day, and heavy smokers who smoked over 21 cigarettes per day accounted for only 10.8%. The overall rate of such heavy smokers among all pregnant women was only 0.8%.

Average Birth Weight of Infants Born to Light or Moderate Smokers

Since most of the women were non-smokers, or only light or moderate smokers, women who smoke over 21 cigarettes per day were considered to belong to a special subpopulation different from the mean of Japanese women. Therefore, in the present study, infants born to heavy smokers were excluded, and birth weight was studied in infants of light or moderate smoking mothers, that is those who smoked fewer than 20 cigarettes per day. As case-controls, one to three non-smoking pregnant subjects were selected per smoking woman and all were matched according to age, parity, gestational weeks, body weight and residential location. All infants in the present series were born between 37 and 40 weeks of gestation. As summarized in Table 3, birth weight differences between the infants of non-smokers and those of light or moderate smokers were 107 g for males and 42 g for females. Thus, the overall weight reduction in the infants of smokers was 75 g, compared with those of non-smokers (no statistical significance).

Biochemical Components in Sera of Infants According to Maternal Smoking Habits

Table 4 shows total protein, albumin, A/G, cholesterol and triglyceride levels in sera of infants born to non-smoking and to smoking mothers. All of these parameters were slightly higher in infants of non-smoking mothers than in those of smoking mothers, but with no statistical significance. Various enzyme levels were also studied, and the findings are summarized in Table 5.

Although slight increases in GOT, GPT, LDH or LAP were evident in infants of smoking mothers, these differences were not significant. Concentrations of serum electrolytes, urea nitrogen, creatinine and uric acid are shown in Table 6, and there were no significant differences between the two groups.

Serum vitamin B12 levels are presented in Fig. 1. A lower concentration of the average serum vitamin B12 levels was present in the infants of smoking mothers (infants of

Table 4. Serum total protein, albumin, A/G ratio, cholesterol, and triglyceride in neonates

	Smoking mother	Non-smoking mother
Total protein (g/dl)	5.66 ± 0.49	5.75 ± 0.71
Albumin (g/dl)	3.70 ± 0.27	3.90 ± 0.38
A/G ratio	2.02 ± 0.76	2.26 ± 0.89
Cholesterol (mg/dl)	68.5 ± 18.6	70.4 ± 19.3
Triglyceride (mg/dl)	36.1 ± 12.5	38.2 ± 20.5

Table 5. Serum enzymes in neonates

	Smoking mother	Non-smoking mother
GOT (IU)	51.6 ± 35.4	46.9 ± 13.4
GPT (IU)	11.8 ± 8.4	10.6 ± 6.0
LDH (IU)	949.7 ± 382.8	789.5 ± 279.4
ALP (K-AU)	13.4 ± 3.0	14.4 ± 10.5
ChE (ΔPH)	0.60 ± 0.26	0.60 ± 0.27
LAP (IU)	101.0 ± 24.1	91.6 ± 23.3

Table 6. Serum electrolytes, urea nitrogen, creatinine, and uric acid in neonates

	Smoking mother	Non-smoking mother
Na (mEq/l)	134.7 ± 6.0	133.5 ± 16.0
K (mEq/l)	8.45 ± 2.43	8.35 ± 3.70
Cl (mEq/l)	107.0 ± 4.1	104.2 ± 10.2
Urea nitrogen (mg/dl)	10.4 ± 5.5	7.1 ± 2.2
Creatinine (mg/dl)	0.86 ± 0.18	0.75 ± 0.20
Uric acid (mg/dl)	5.37 ± 0.98	5.65 ± 0.95

smoking mothers: 1,058.9 ± 571.7 pg/ml, infants of non-smoking mothers: 1,444.2 ± 853.4 pg/ml). There was no statistical significance in these results.

Discussion

Although the incidence of smoking among males is higher in Japan than in western countries, smoking by Japanese women is less common. According to an annual study of The Smoking Research Foundation in Tokyo, the average incidence of male and female smokers in Japan is 62.5% and 12.6%, respectively (personal communication). The incidence of pregnant smokers is, as shown in the present study, less frequent than the average incidence of all female smokers, and the number of cigarettes smoked by Japanese pregnant women is usually fewer than 20 per day. Birth weight of infants born to such

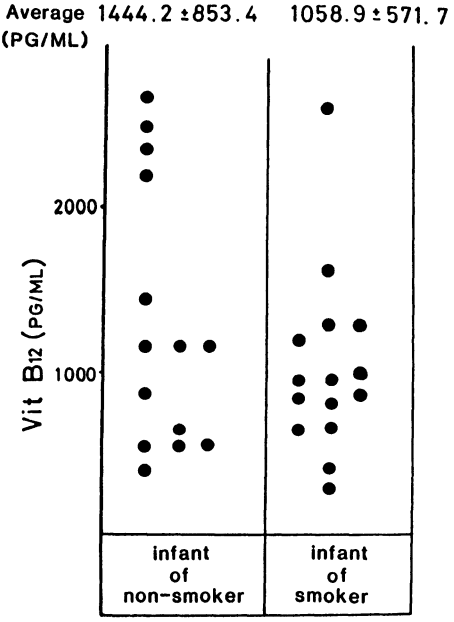

Fig. 1. Serum vitamin B12 level in neonates

light or moderate smokers was much the same as that of infants of case-controlled non-smoking women. The birth weight differences between the two groups were only 75 g.

Main metabolic factors associated with fetal growth *in utero* are protein and lipid metabolism. In the present study, we examined serum concentration of both total protein and albumin and of the A/G ratio, as indicators of protein metabolism. Cholesterol and triglyceride levels in fetal sera were also examined to assess the state of lipid metabolism. All these biochemical components were at the same levels in both infants of light or moderate smokers and in those of non-smoking mothers. There was no difference in the activities of various enzymes generally assumed to be indicators of liver function among infants of smoking and non-smoking mothers. Electrolytes (Na, K, or Cl) and catabolites (urea nitrogen, creatinine or uric acid) were also at the same levels in infants of smoking and non-smoking mothers.

Vitamin B12 is strongly associated with detoxication of cyanide inhaled by cigarette smoking [7, 15], and a lower concentration of serum vitamin B12 was noted in smokers than in non-smokers [15]. It was also reported that the serum vitamin B12 level was lower in pregnant women who smoke [10]. The serum vitamin B12 level in infants is usually higher than the normal level in adults (300–1,000 pg/ml), and lower concentrations of serum vitamin B12 were noted in infants of smoking women. However, this was not of statistical significance.

We did not examinethe effects of heavy smoking on fetal development or circulating biochemical components. Since almost all Japanese pregnant women are advised to stop smoking by their obstetrician, those who continue heavy smoking during pregnancy, despite such a recommendation, are expected to have risk factors. Factors such as occupation, nutrition, personal hygiene, or alcohol drinking among pregnant heavy smokers differ from those among the average Japanese women, and it is difficult to assess the influences of smoking apart from other risk factors.

These findings taken together suggest that smoking fewer than 20 cigarettes per day affects neither birth weight nor concentration of various biochemical components in the fetal circulation. According to our preliminary study [9], serum nicotine concentration 15 min after smoking one cigarette was less than 9 ng/ml in Japanese pregnant women, and it was assumed that the volume of smoke inhaled did not cause any significant increase in circulating nicotine.

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Psychophysiological Response to Environmental Tobacco Smoke in an Experimental Social Setting

G. Winneke, M. Neuf, A. Roscovanu, and H.-W. Schlipköter

Summary

Acute psychophysiological effects of environmental tobacco smoke (ETS), corresponding to carbon monoxide (CO) concentrations of 5 and 10 ppm and produced by an active smoker, were studied in 72 adult nonsmokers and compared to the effects of traffic noise (65 and 75 dB(A)) and of odorexposure (50 and 150 ppb of hydrogen sulfide). This sample represents the first block out of 126 subjects (Ss) for which data analysis was completed by November 1987. Experiments took place in an actively ventilated exposure chamber in a social setting. Objective measures, namely, heart rate, blood pressure, rate of respiration, eye blinks, and lacrymal flow as well as subjective measures of annoyance based on questionnaire items were taken four times during exposure; carboxyhemoglobin (COHb) was measured before and after exposure.

Whereas cardiorespiratory variables were not affected by ETS exposure, COHb, eyeblinks as well as part of the annoyance-data exhibited ETS-induced elevation, although not necessarily at the 5 ppm-level in each case. ETS-induced annoyance at 5 and 10 ppm dCO was comparable to noise-induced annoyance at 65 and 75 dB(A), respectively. Ss preclassified as either strongly or weakly annoyed by environmental conditions in their neighbourhoods (e.g. traffic noise or industrial odors), as assessed in a social survey covering 2,300 individuals, also did exhibit significant differential susceptibility in terms of ETS-induced annoyance. From these still preliminary findings the tentative conclusion is drawn for a no-adverse-effect-level (NOEL) for acute psychophysiological effects of ETS to be located near the 5 ppm-level in terms of dCO, and for annoyance to represent a more generalized, stable reaction-tendency rather than a reaction to a specific environmental condition.

Introduction

Most previous studies dealing with acute psychophysiological effects of environmental tobacco smoke (ETS) have used smoking machines to produce desired levels of sidestream smoke exposure (Weber et al. 1976, 1979, 1981; Muramatsu et al. 1983). In deviating from this typical procedure, which is consistent but lacks ecological validity, we conducted a pilot experiment, in which nonsmoking students were exposed to ETS by an active smoker in a social, experimentally controlled setting (Winneke et al. 1984). Objective measures, namely eyeblinks, lacrymal flow, blood pressure, heart rate and respiration, as well as subjective measures of annoyance based on questionnaire-items, were taken four times during exposure; in addition COHb-concentrations were measured before and after ETS-exosure. Significant effects of ETS-exposure were found for COHb, blinks, lacrymal flow, as well as for most of the questionnaire-based information. With

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the exception of some questionnaire-variables, exhibiting dose response-relationship, the majority of the dependent variables showed threshold-characteristics: The 15 ppm-condition only deviated significantly from the control level. From this finding the tentative conclusion was drawn for a no adverse effect-level for acute psychophysiological effects of ETS to be located between 5 and 15 ppm dCO.

In order (1) to substantiate this conclusion, (2) to compare acute psychophysiological effects of ETS to those elicited by noise- and odor-exposure, and (3) to gain information about the more specific or more generalized nature of the annoyance-response, the present extended study was conducted. The experimental part of this study, based on 126 Ss altogether, is finished whereas data-analysis is still preliminary. Partial results based on the first set of 72 Ss are given and discussed here.

Material and Methods

External Conditions

The experiments took place in a non-climatized but actively ventilated chamber with dimensions ($1 \times w \times h$) $238 \times 177 \times 230$ cm (9.7 cbm). Air exchange, as calculated from the measured dilution of H2S in the chamber (see below) was 80 cbm/h. Two experimental subjects (Ss) and the informed experimenter who, in case of ETS-exposure, was the active smoker, were sitting in the chamber around a table playing games (Memory). Temperature and humidity in the chamber increased during the experiment, namely from about 57 to 66% (humidity) and from about 18 to 20°C on the average, irrespective of the experimental condition.

Experimental Conditions

During the experiment Ss were exposed in three counterbalanced sessions to ETS, traffic noise and odor, but at only one out of three levels of exposure. In accordance with previous work (e.g. Muramatsu et al. 1983) carbon monoxide (CO) was measured as a convenient, non-specific marker of ETS- exposure by means of non-dispersive infrared (IR-)-spectroscopy (URAS III, Hartmann & Braun, Frankfurt). CO-levels, defined as dCO by taking pre-exposure levels into account, were <1, 5 and 10 ppm, respectively. Active smoking of 0, 4.2 and 7.2 cigarettes of the same brand was necessary on the average to reach these CO-levels.

Traffic noise was presented from calibratedtape-recordings at continuous equivalent sound levels of 65 and 75 dB(A), respectively; background sound pressure-level in the experimental chamber was 60 dB(A). Spot measurements were taken at random intervals by means of a portable sound level-meter (RC 345, Reten-Elektronic, Idstein).

Odor-exposure was done by controlled metering prediluted hydrogen sulfide (H2S) into the chamber from a pressure tank containing a calibrated gas-concentration of 100 ppm. Chamber-concentrations were set at 50 and 150 ppb and were monitored by means of the photometric molybdenum-blue method (VDI, 1974) after about 30 min sampling-time. The odor threshold of H2S is between 1 and 3 ppb; 50 and 150 ppb correspond to perceived intensities of "distinct/strong" and "strong/very strong" according to a six-point rating-scale (Winneke et al. 1979).

Dependent Variables

Before and after each experiment capillary blood-samples were taken from a fingertip for the determination of COHb by means of gaschromatography after methane conversion; CO-concentrations were converted to COHb by means of average Hb-concentrations for males and females, respectively. At the beginning and at three consecutive intervals during the experiment (15, 35 and 55 min) systolic and diastolic blood-pressure was taken by means of an electronic device (boso digital Standard). In addition the following measures were taken continuously during the experiment but evaluated at the four regular intervals given above for two minutes duration only: Eyeblinks by means of amplified potentials recorded from one eye by means of AgCl-electrodes, rate of respiration by means of thermistor-elements attached to the nose, and heart-rate by means of photo-electric couplers attached to one ear-lobe.

In addition to these objective measures an annoyance-questionnaire was given four times during the experiment, which consisted of 39 five-point statements covering descriptive (e.g. "The air is clean"), symptom-related (e.g. "My eyes are burning"), and emotional-reactive items ("I feel relaxed"). Response-categories ranged from "Don't agree at all" to "Fully agree", or from "Not at all" to "very strong". Part of the items were specific to each of the three conditions (ETS, noise, odor), whereas others covered all three of them. This was particularly true for the emotional-reactive items, as well as for an eleven-point annoyance thermometer with response-categories ranging from 0 (not at all disturbing) to 10 (unbearably disturbing).

Subjects: 72 nonsmokers of both sexes participated. 55% of them were females, and the mean age was 44.6 years with extremes ranging from 18 to 74 years. Four Ss with initial COHb exceeding 5% were treated as suspected smokers and excluded from further analyses, thus leaving 68 Ss for final statistical evaluation. Assignment of Ss to control ($N = 23$), medium ($N = 23$), and high ($N = 22$) intensities of exposure was random.

Statistical Procedures

Both descriptive and inferential statistics were applied. Questionnaire-data were tentatively treated as being of interval-quality. Analysis of variance (mixed model) was used for the testing of main- and interaction-effects (Winer 1962). Significance-levels of 5% and lower were taken to separate significant from non-significant effects.

Results

Objective Information

CO-uptake during ETS-exposure, as given by COHb-levels, did exhibit the expected alterations (Table 1). Whereas there was a slight, insignificant decrease of COHb for control-Ss during an experimental session on the average, ETS-induced, dose-dependent increase occurred during exposure ($F = 17.3$; $p < 0.0001$). The values given in the table correspond roughly to those of the pilot-study for comparable exposures (Winneke et al. 1984), but are well below limits of biological significance (Winneke 1978).

Cardio-respiratory variables, namely blood-pressure, heart rate and rate of respiration, did not exhibit significant ETS-induced changes (Table 2). There is, however, a tendency for respiration to become slower during exposure at the highest ETS-level.

Table 1. ETS-related COHb%. Means, standard deviations (SD) and ranges are given

Groups	Before exposure			After exposure			
	$\bar{x}$	(SD)	range	$\bar{x}$	(SD)	range	N[a]
Control	0.71	(0.23)	0.58–0.84	0.68	(0.19)	0.58–0.79	14
ETS 5 ppm	0.75	(0.21)	0.66–0.84	0.87	(0.19)	0.79–0.96	23
ETS 10 ppm	0.84	(0.23)	0.74–0.94	1.03	(0.22)	0.93–1.13	22

[a] COHb-analysis of blood taken after the experiment was done in only part of randomly selected control-Ss.

Table 2. Cardio-respiratory variables. Means ($\bar{x}$) and standard deviations (SD) are given. 0, 5 and 10 correspond to levels of ETS-exposure in terms of CO

	CO	0′		15′		35′		55′	
		$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD
Heart-	0	78.9	(8.3)	79.4	(8.5)	79.0	(8.3)	78.5	(9.0)
rate	5	78.1	(8.8)	78.8	(9.3)	77.2	(8.6)	76.9	(7.8)
	10	78.0	(10.4)	78.3	(10.2)	76.8	(10.3)	77.8	(11.0)
Rate of	0	18.7	(2.7)	18.2	(2.7)	18.6	(2.9)	18.1	(3.3)
respirat.	5	17.0	(3.4)	17.6	(2.8)	17.1	(2.9)	17.4	(2.5)
	10	17.7	(3.7)	17.0	(3.9)	16.5	(3.9)	15.6	(3.6)
Blood-	0	117.1	(14.6)	114.0	(13.8)	113.2	(15.6)	115.2	(19.7)
pressure	5	130.9	(20.3)	128.7	(20.1)	129.2	(21.6)	128.1	(20.3)
(systol.)	10	118.4	(21.4)	119.5	(24.4)	120.8	(28.1)	119.2	(25.9)
Blood-	0	116.9	(18.2)	111.9	(16.7)	111.4	(20.1)	114.1	(16.9)
pressure	5	133.1	(20.6)	127.9	(18.6)	131.3	(18.6)	127.2	(21.8)
(diast.)	10	121.6	(24.3)	118.2	(26.9)	116.9	(27.8)	117.9	(27.2)

The number of eyeblinks/minute increased during a one hour experimental session both under control- and exposure-conditions (Fig. 1). Comparatively, however, the rate of increase was faster at the high level of ETS-exposure than at control-level. The overall group- differences are not significant ($F = 1.92$; $p = 0.16$), although, as can be seen from the confidence-limits, the last three sampling-points of the 10 ppm-condition are significantly ($p < 0.05$) elevated. The slight elevation of the 5 ppm-curve is not significant for this sample size.

Subjective Information

Descriptive statements (e.g. "The air is clean") exhibited strong ETS-related change; typical examples are given in Fig. 2. These effects were, of course, highly significant ($p <$

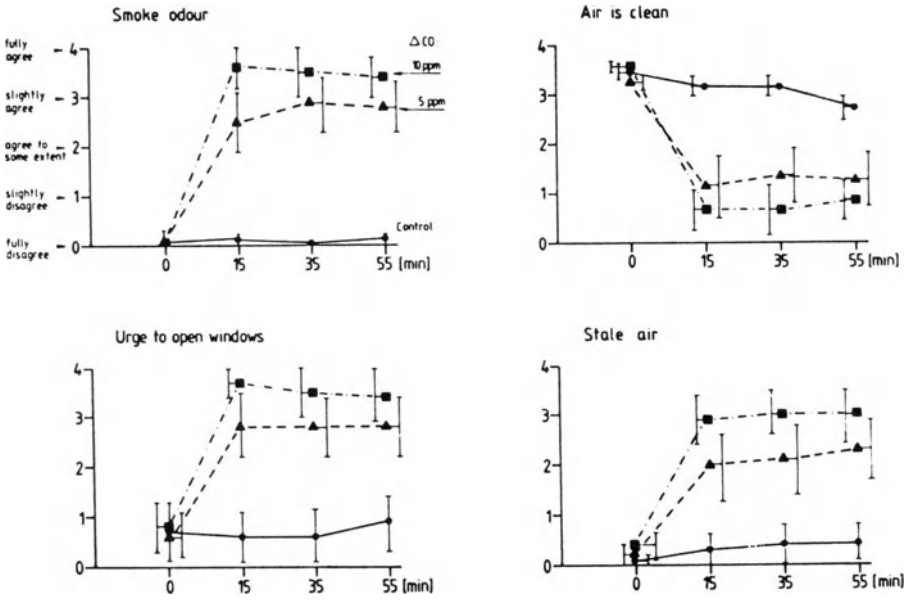

Fig. 1. Results from questionnaire-items describing the experimental situation for different levels of ETS-exposure. Means and confidence-limits (CL-95) are given

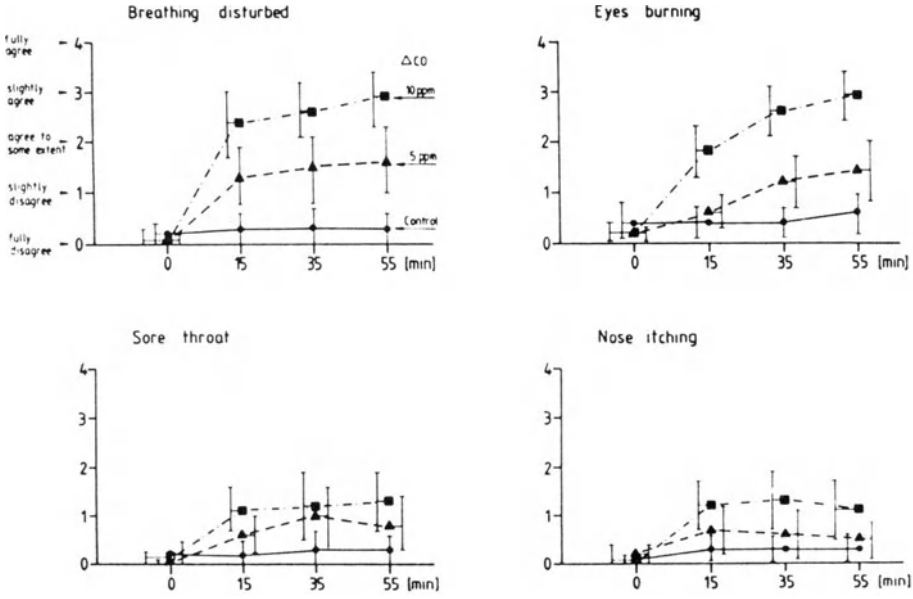

Fig. 2. Results from questionnaire-items related to perceived symptoms during different levels of ETS-exposure. Means and CL-95 are given

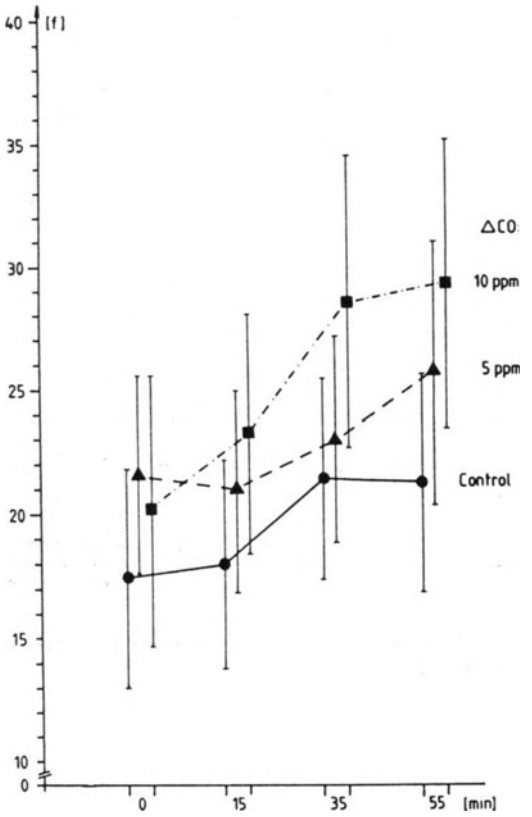

Fig. 3. Number of eyeblinks/minute during exposure for different ETS-levels. Means and CL-95 are given

Table 3. Symptom-related questionnaire-items. F- and p-values characterize the outcome of analysis of variance

	Main effect		Interaction	
	F	p	F	p
Burning eyes	19.45	0.000	20.03	0.000
Impaired breathing	19.50	0.000	14.90	0.000
Sore throat	3.43	0.040	3.84	0.001
Itching nose	4.52	0.015	2.65	0.017
Headache	1.17	0.310	2.96	0.009
Dry mouth	1.87	0.170	2.15	0.049

0.0001), both in terms of main effects (intensity of ETS-exposure) and interactions (intensity × time).

Typical examples for symptom-related effects are given in Fig. 3. The statistical results from analyses of variance for these as well as similar statements are shown in Table 3.

Table 4. Emotional-reactive questionnaire-items. F- and p-values characterize the outcome of analysis of variance

	Main effect		Interaction	
	F	p	F	p
Uncomfortable	9.26	0.000	7.50	0.000
Angry	3.93	0.024	3.42	0.003
Nervous	2.19	0.120	1.80	0.100
Cheerful	2.19	0.120	0.64	0.695
Relaxed	1.19	0.312	0.62	0.713
Merry	1.10	0.339	2.21	0.044
Concerned	0.87	0.424	1.07	0.382

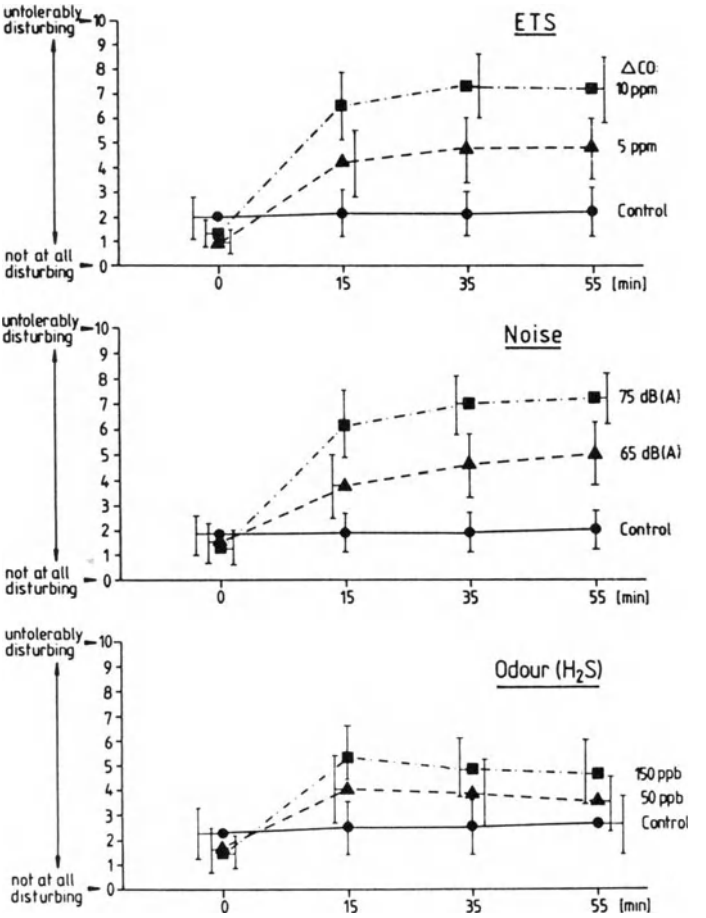

Fig. 4. Degree of annoyance during exposure to three levels each of ETS, traffic noise and hydrogen sulfide-odor. Means and CL-95 are given

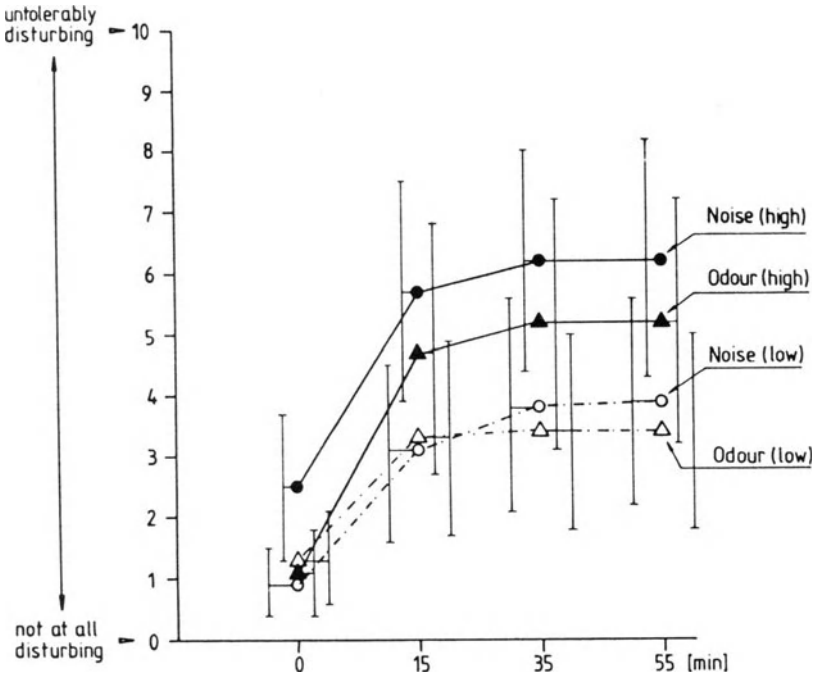

Fig. 5. Degree of annoyance during ETS-exposure for groups of Ss preclassified in terms of either high (upper curves) or low (lower curves) annoyance to environmental noise or odors, respectively. Means and CL-95 are given

Four out of eight items exhibit significant main effects (intensity), whereas for all of them significant interactions (intensity of exposure × time) were found as well. This means that the time-course is different for control- and exposure-conditions, respectively.

Only two out of seven emotional-reactive statements, namely those expressing feelings of discomfort ($F = 9.26$; $p = 0.000$) and of anger ($F = 3.93$; $p = 0.02$) did show significant main effects associated with levels of ETS-exposure, whereas additional time × exposure-interactions occurred for feelings of discomfort, anger and cheerfulness (Table 4).

For the purpose of comparing the annoying effects of ETS-exposure to that induced by either traffic noise- or odor-exposure data were taken from the eleven point annoyance-scale (see above). The results from that comparison are given in Fig. 4. These curves clearly show that for each of the three conditions highly significant ($p < 0.001$) exposure-related effects occurred which, except for the odor-condition, did exhibit pronounced dose-response-characteristics. It is interesting to note, furthermore, that the degree of annoyance produced by the two ETS-levels is roughly equivalent to continuous sound pressure-levels of 65 and 75 dB(A), respectively, whereas the degree of odor-annoyance induced by hydrogen sulfide is comparatively reduced. This, most likely, can be ascribed to olfactory fatigue or adaptation.

In order to ascertain if Ss, preclassified as either highly or weakly annoyed by either environmental noise or industrial odors in their respective neighbourhoods, these

extreme groups were compared for degree of annoyance across exposure-levels for the three experimental conditions. Ss preclassified as highly annoyed scored higher in terms of annoyance during ETS-exposure than did Ss preclassified as weakly annoyed (Fig. 5). This group-difference is statistically significant for ETS ($F = 2.80$; $p < 0.05$), but only borderline ($p < 0.12$) for either experimental noise- or odor-exposure. Perceived intensities at the different levels of exposure did not exhibit any group-differences, whatsoever ($0.95 > p < 0.55$).

Discussion

Carbon monoxide (CO) was used here and in our previous study (Winneke et al. 1984) to characterize the degree of ETS-exposure. Both because of its lack of specificity as well as its inconsistent temporo-spatial associations with other ETS-components CO cannot be considered a truely representative marker of ETS under real-life-conditions (Ball et al. 1987), particularly if, in addition to cigarettes, pipes and cigars contribute to ETS (Klus et al. 1987). No general agreement has, therefore, been reached so far as to which components or component-combinations could be used in order to characterize ETS-exposure in natural settings.

CO, on the other hand, has been shown to display consistent association with suspended particulates (TSP), both in decay-situations as well as in experimental steady-state- or dynamic conditions, in which both the number of cigarettes as well as the rate of air-exchange were varied (Leaderer et al. 1984). In addition correlation between CO-levels on the one hand and number of cigarettes as well as several gas-phase components of ETS, such as NO, aldehydes, acrolein, HCN or formaldehyde, have been reported both for extreme (Hugod et al. 1978) as well as for more moderated degrees of experimental ETS-exposure (Weber et al. 1976).

In the light of this evidence, and in order to be able to compare the outcome of our experiment with that of similar studies (Hugod et al. 1978; Muramatsu et al. 1983; Weber et al. 1976, 1979, 1981; Winneke et al. 1984) in a quantitative manner, the measurement of CO to characterize degrees of ETS-exposure in our experimental setting can be considered a reasonable compromise between describing the true complexity of ETS-exposure on the one hand and relying simply on the number of cigarettes smoked per unit time and volume on the other.

In taking CO as the basis for comparison our cardiovascular findings are consistent with those of others (Weber et al. 1976; Harke and Bleichert 1972), who, at even higher levels of ETS-exposure did not observe exposure-related increase of either heart-rate or blood-pressure. Nicotine-intake at such ETS-levels is likely to be too low for cardiovascular changes to be expected.

As for eyeblinks our data are somewhat at variance with those of Muramatsu et al. (1983), who describe significant elevation at ETS-levels below 3 ppm dCO, whereas both in our previous (Winneke et al. 1984) and in the present study no significant increase was observed at ETS-levels corresponding to 5 ppm dCO. It is still uncertain as to whether methodological differences can explain these different outcomes. Whereas Muramatsu et al. (1983) relied on intraindividual comparisons based on actual counting of videotaped blinks by observers at predetermined intervals during exposure, our findings are based on interindividual comparisons of a smaller number of Ss by means of continuous electrophysiological recordings of spontaneous blinking. Although the latter technique would generally be considered as having a higher ecological validity, final analysis of the full set of data will be needed to clarify, if

significant elevation of eyeblinks can in fact be expected to occur at ETS-levels at or even below 5 ppm dCO.

The most clearcut findings of the present study are those related to questionnaire-based annoyance. Descriptive and, to a lesser extent, symptom-related complaints display dose-related increase with some effects already significant at the lowest ETS-level. This was not true in our previous study. Part of this differential outcome is most likely due to the fact that in the present study control-conditions were improved by forced air-exchange. From these still preliminary findings the tentative conclusion is drawn for a non-adverse-effect-level (NOEL) for acute psychophysiological effects of ETS to be located near the 5 ppm-level in terms of dCO.

The present study is the first to compare ETS-induced annoyance – reactions to those associated with either noise- or malodor-exposure. The data presented here strongly suggest that such a comparative approach is feasible, and that ETS-exposure corresponding to dCO-levels of 5 and 10 ppm are equivalent to traffic-noise at sound pressure-levels of 65 and 75 dB(A), respectively. Comparison with odor-annoyance is less convincing because adaptation strongly attenuates perceived odor-intensity for hydrogen sulfide.

Another interesting finding of the present study relates to the observation that preclassification of nonsmoking Ss for environmental annoyance is related to the degree of annoyance under experimental exposure-conditions as well: Ss preclassified as being either strongly or weakly annoyed by environmental odor- or noise-exposure in their respective neighbourhoods, do exhibit strong or weak degrees of annoyance under conditions of ETS-exposure as well. From this the tentative conclusion is drawn for annoyance-responses to be more generalized reaction-tendencies rather than responses elicited by specific environmental conditions.

Acknowledgements: We would like to thank Dipl.-Ing. Jarmila Kotalik and Hans-W. Berresheim for analytical and technical support in setting up the experimental prerequisites and Hanne-Lore Krüll for her help in organizing the study and in collecting a substantial part of the data.

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Acute Cardiovascular Responses to Experimental Passive Smoking in Young, Healthy, Adult Men

M. Asano, C. Ohkubo, A. Sasaki, T. Irie, and H. Komine

Summary

Ten healthy adult men (20–40 years old) composed of five nonsmokers and five habitual smokers were subjected to measurement of changes in some selected parameters of cardiovascular function during passive smoking caused by experimental indoor air pollution due to the secondhand tobacco smoke. Every subject took part in two successive experiments in an exposure chamber: a control experiment was performed by sham smoking with non-lit cigarettes and an actual passive smoking experiment was done by smoking with standard cigarettes. All subjects participated in the experiments in groups of two nonsmokers and two smokers. Passive smoking conditions were prepared by successive smoking of three cigarettes by two smokers during a period of 1 h under poor ventilation (1 change/h). Concentrations of expired CO increased remarkably in all subjects along with the progress of actual passive smoking. The changes for nonsmokers reached values twice as high as the initial values, and those for smokers were about three times as high. Heart rates, systolic blood pressures, and Katz indexes increased appreciably for nonsmokers and markedly for smokers during actual passive smoking period. Finger skin temperatures tended to decrease in nonsmokers and decreased definitely in smokers concurrently with those changes. Although there existed an obvious difference between the extents of the changes observed, the nature of the nonsmokers' acute cardiovascular responses to passive smoking appeared to be the same as those of habitual smokers' responses to actual smoking.

Introduction

Exposure to or inhalation of environmental pollutants from tobacco smoke is referred to passive smoking, involuntary smoking or enforced smoking. Although health effects of passive smoking have been well documented especially in the epidemiological aspects of various chronic diseases, its acute effects upon the physiological function have reported less frequently (U.S. Dept. of H.H.S. 1986).

The present investigation has been aimed at elucidating acute effects of indoor air pollution due to cigarette smoking upon physiological functions, especially upon cardiovascular functions of healthy male adults under realistic conditions of laboratory experiments, with special regard to the smoking habit.

H. Kasuga (Ed.) Indoor Air Quality

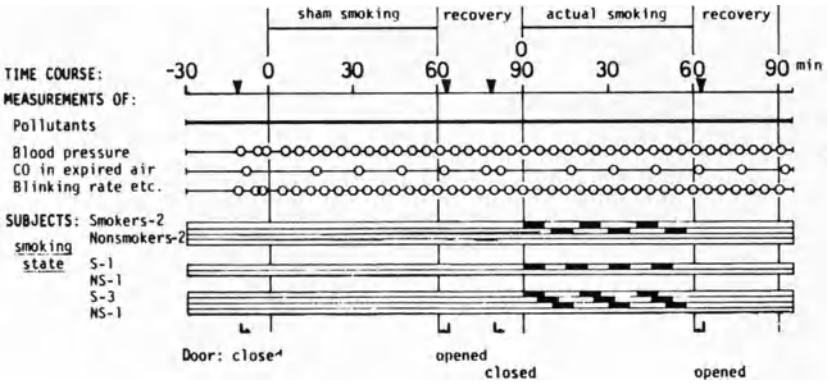

Fig. 1. Experimental procedure

Material and Methods

Subjects

Ten healthy, adult men volunteers (20–40 years old) were engaged in the present study. Five of them were habitual smokers and the remaining five were life-long nonsmokers.

Procedures (Fig. 1)

Every subject took part in two successive experiments, that is, a control experiment by sham smoking with non-lit cigarettes and an actual passive smoking experiment. The habitual smokers took part in both the experiments as passive smokers and active smokers. All subjects participated in the experiments in groups of two nonsmokers and two smokers.

The subjects spent three and a half hours in an exposure chamber of 16 m^3 at about 20° C of ambient temperature and about 60% of relative humidity. The air in the chamber was ventilated at a ventilation rate of 20 changes/h for the resting period during which the door was opened, and at 1 change/h for the smoking period during which the door was closed, respectively.

Throughout the experiments, air pollutants were monitored continuously and physiological parameters such as expired CO concentrations, systolic blood pressures, heart rates, Katz indexes (product of systolic blood pressure and heart rate), finger skin temperatures, and blinking rates were measured at appropriate time intervals.

For the air of the chamber, CO concentrations were monitored by an Ecolyzer (2,500), CO_2 concentrations by an infrared analyzer (model ZFP5, Fuji-Denki), NO, NO_2 and NO_x by a chemiluminescence apparatus (Monitor Lab 8440), and total particulate matter by a particulate monitor (model P-5H, Shibata-Kagaku-Kikai). Cardiovascular parameters were conventionally monitored with a polygraph and blinking rates were assessed by the same inspectors according to the visual counting.

Passive smoking conditions were prepared by the successive smoking of 3 cigarettes each by two smokers during a period of 1 h under poor ventilation, and thereafter the ventilation was switched to the higher rate in the recovery period. In addition to this two

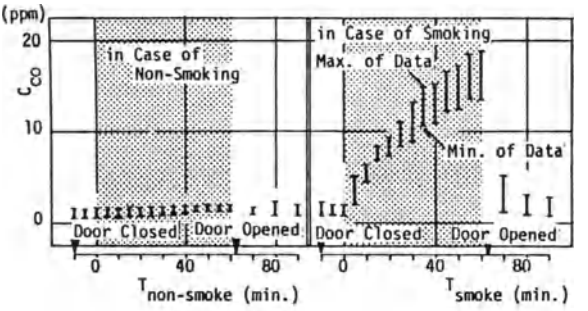

Fig. 2. Time course of changes in CO concentrations

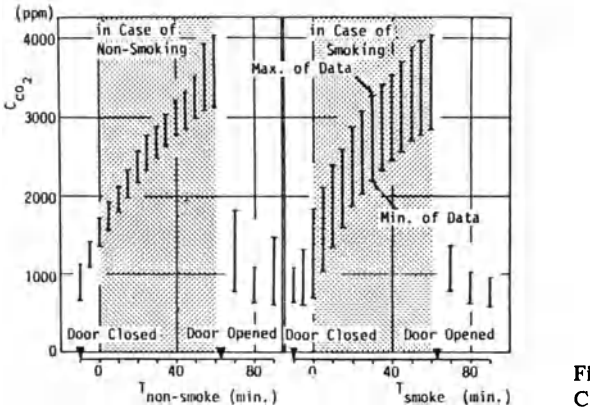

Fig. 3. Time course of changes in CO_2 concentrations

nonsmokers-two smokers session, one nonsmoker-one smoker and one nonsmoker-three smokers sessions were appropriately performed.

Content of nicotine and tar in the main stream smoke of a standard cigarette adopted was 0.9 mg and 14 mg, respectively.

Results and Discussion

Measurements of Air Pollutants

Chronological changes in averaged maximal and minimal values for each pollutant are presented according to sham and actual passive smoking sessions.

Figure 2 shows changes in CO concentrations during the experiments. The shaded area indicates the sham or actual smoking period of 1 hour. At the end of actual passive smoking period, CO concentration ranging 1–2 ppm at the initial level reaches the peak level ranging 14–19 ppm, while no appreciable change is noticed throughout the sham smoking period. The peak concentration of CO exceeds the concentration of 10 ppm and approaches 20 ppm, which is the Air Quality Standard of Japan for 8 h' exposure and 24 h' exposure, respectively.

Figure 3 illustrates changes in CO_2 concentrations of which overall trends for both the sham and actual passive smoking experiments are quite similar to each other. The initial

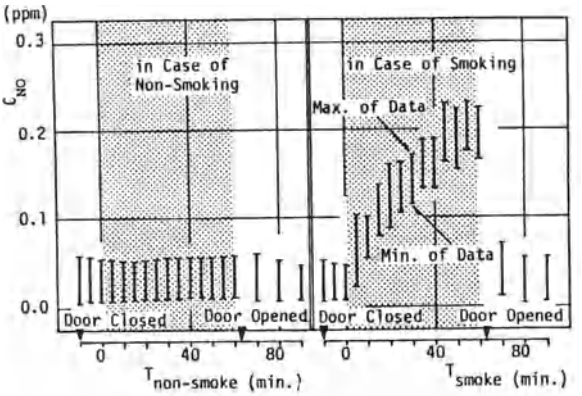

Fig. 4. Time course of changes in NO concentrations

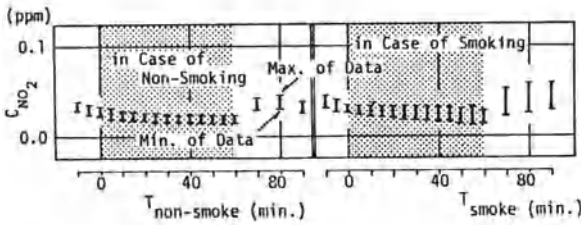

Fig. 5. Time course of changes in NO_2 concentrations

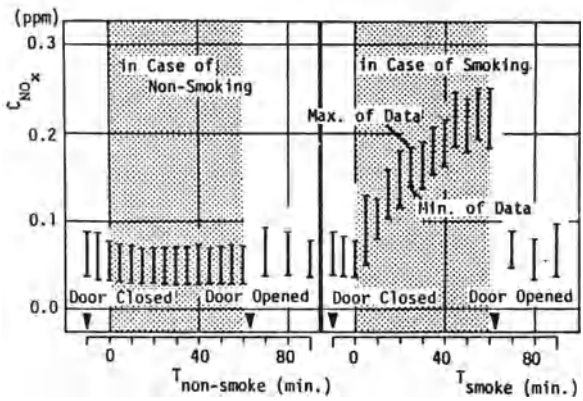

Fig. 6. Time course of changes in NO_x concentrations

levels around 100 ppm reach the peaks of 300–400 ppm for both the experiments. This similarity in the changes indicates that the quantity of CO_2 physiologically expired by 4 subjects is much larger than that in the secondhand smoke generated by two smokers.

Figure 4 demonstrates changes in NO concentrations. The initial level ranging 0.01–0.05 ppm reaches the plateau of peak concentrations around 0.2 ppm, 50 min after the start of smoking; maximum 0.23 and minimum 0.18 ppm.

Figure 5 presents changes in NO_2 concentrations. The overall trends for both the sham and actual passive smoking experiments are very similar to each other. Slight but definite decrease in NO_2 concentrations is noticed even during the sham smoking experiment. This similarity may indicate that the quantity of NO_2 in the secondhand

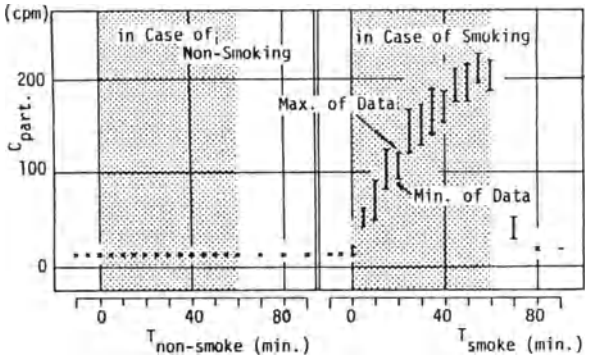

Fig. 7. Time course of changes in total particulate matter concentrations

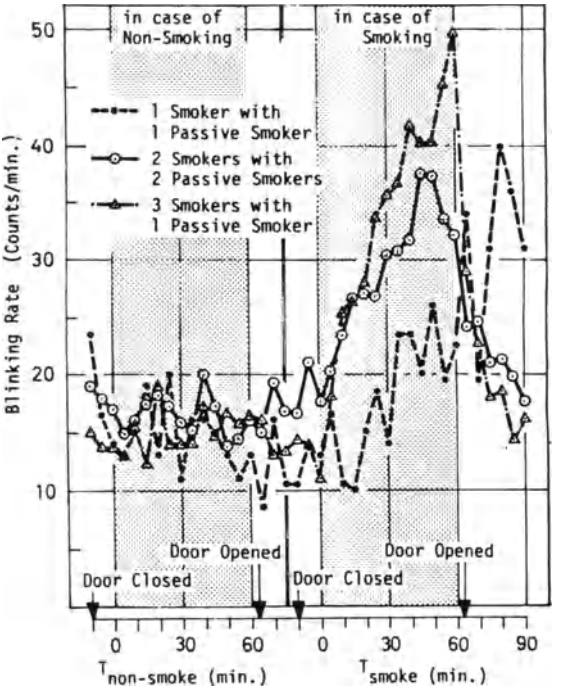

Fig. 8. Time course of changes in blinking rates of both smokers and nonsmokers according to three different conditions as annotated in the space of figure

smoke is quite small in comparison with the background levels. Moreover, the declining change during the experiment suggests the adsorption of NO_2 onto clothes of the subjects and surfaces of walls and others of the exposure chamber. The initial level of 0.03–0.04 ppm appears to be rather high as the background level, because the Air Quality Standard of Japan refers to the concentration within or less than 0.04–0.06 ppm.

Figure 6 demonstrates changes in NO_x concentrations of which the initial level ranging 0.03–0.08 ppm reaches a plateau around 0.2 ppm, 45 min after the start of smoking; maximum 0.26 and minimum 0.18 ppm. The trends of changes in both NO and NO_x are quite similar to each other and the concentration changes of NO_x run parallel

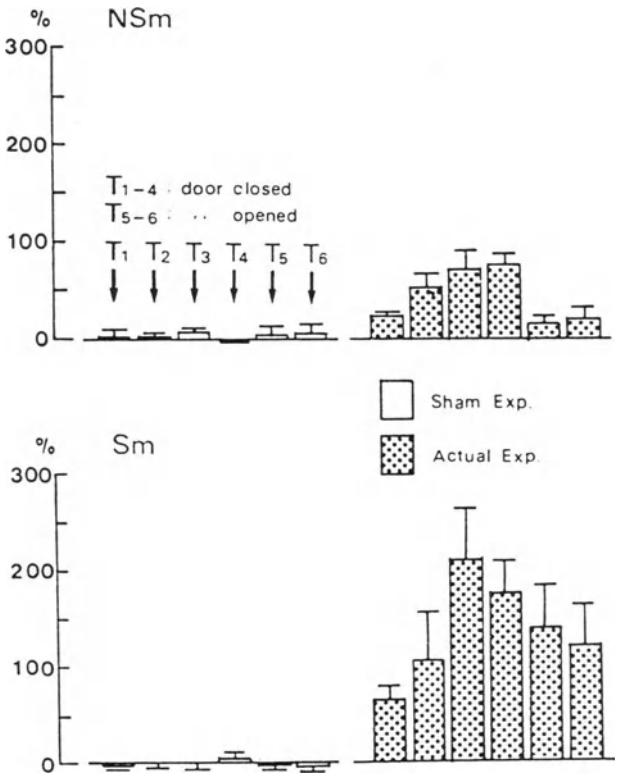

Fig. 9. Chronological changes in expired CO concentrations. NSm, nonsmokers; Sm, smokers (the same are employed in the subsequent figures). T_{1-6}; see explanations in the text

with those of NO only at high levels. Accordingly, the changes in NO_x concentrations might reflect mainly those in NO concentrations.

Figure 7 illustrates changes in total particulate matter (TPM) concentrations. The initial level of 18 counts/min, that means 0.18 mg/m^3, reaches the peak ranging 200–230 counts/min, i.e., 2.0–2.3 mg/m^3. The background concentration of TPM seems rather high compared with the Air Quality Standard, 0.10 mg/m^3 of less for 8 h' exposure and 0.20 mg/m^3 or less for 24 h' exposure. However, the obtained peak level of 2 mg/m^3 is about 20 times higher than the standard value for the shorter exposure.

Physiological Responses to Passive Smoking

All measurements, except for blinking rates, were averaged for 15-min-period and changes during the two experiments were expressed in per cent changes of the initial levels. The illustrated column and bar indicates mean and standard error, respectively. Reference marks of T_1 to T_4 indicate four sequential periods of the passive smoking experiment and T_5 and T_6 indicate two sequential periods of recovery.

Figure 8 demonstrates sequential changes of blinking rates of both smokers and nonsmokers for three different conditions of passive smoking; one nonsmoker-one smoker, two nonsmokers-two smokers and one nonsmoker-three smokers experiments. The blinking rates show remarkable increases along with the progress of actual passive

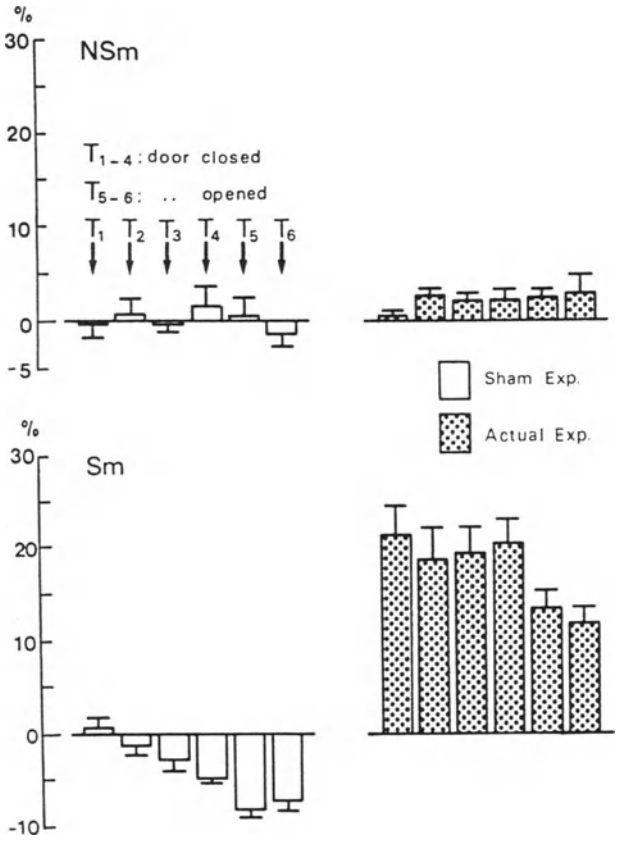

Fig. 10. Chronological changes in heart rates

smoking. It is evident that the more the number of smokers increases, the more the extent of blinking rates spreads. The trend of increasing rates in almost linear fashion with the increasing concentrations of pollutants, such as CO, CO_2, NO, NO_x, and TPM as shown in Figs. 2–4, 6 and 7, is quite consistent with the observations by Weber (1983) and by Muramatsu et al. (1985).

Figure 9 presents changes in expired CO concentrations of both nonsmokers and smokers which increase remarkably with the progress of passive and active smoking, respectively. While the changes are more pronounced for smokers who smoked actively and passively, the changes even for nonsmokers reach twice as high as the initial level. The peak level of expired CO concentrations for smokers is more than three times as high as the initial values.

Figures 10 and 11 respectively present appreciable increases in heart rates and systolic blood pressures for nonsmokers and marked increases in them for smokers through the actual passive smoking experiment. Although the changes in both the parameters for nonsmokers are much less pronounced than those for smokers, these findings indicate definite acute cardiovascular responses of nonsmokers to the passive smoking in the same direction as the responses of smokers to the active smoking.

Figure 12 presents changes in Katz indexes which increase appreciably for nonsmokers and remarkably for smokers throughout the actual passive smoking

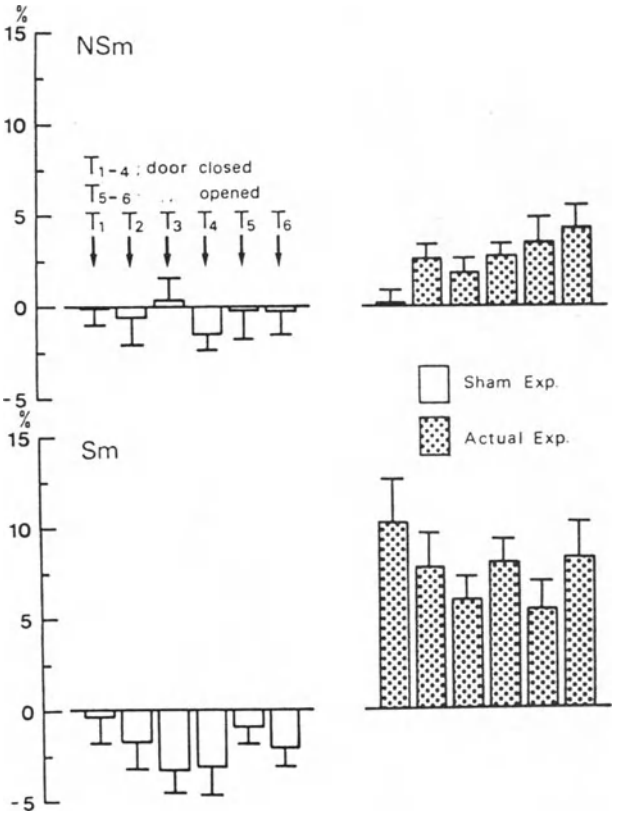

Fig. 11. Chronological changes in systolic blood pressures

experiment. Although the extent of changes in Katz indexes is much less for nonsmokers than smokers, this response of nonsmokers indicates an unnecessary and enforced load on their hearts because Katz indexes mean oxygen cost of the heart (Gerola et al. 1957).

Figure 13 demonstrates changes in finger skin temperatures of nonsmokers and smokers. The changes are relative decreases for nonsmokers and absolute decreases for smokers during the actual experiment as compared with those during the sham experiment, respectively. Although the extents of the changes in skin temperatures are different from each other, the falling trend of skin temperatures of nonsmokers indicates a constrictive response of the peripheral vasculature due to passive smoking in common with active smoking.

According to the analysis of variance, the extents of all the physiological responses of both nonsmokers and smokers to the actual passive or active smoking are significantly higher than those to the sham smoking experiment. The acute physiological responses to passive and active smoking under the present conditions are quite evident in nonsmokers and habitual smokers, respectively. Therefore, it is clear that the passive smoking under daily realistic circumstances can inevitably cause acute changes in some physiological, especially cardiovascular functions of nonsmokers, in addition to the annoyance and irritation (Weber 1983).

Moreover, the extent of the changes in blinking rates of smokers was much less than that of nonsmokers and the remaining responses of smokers to the actual active smoking

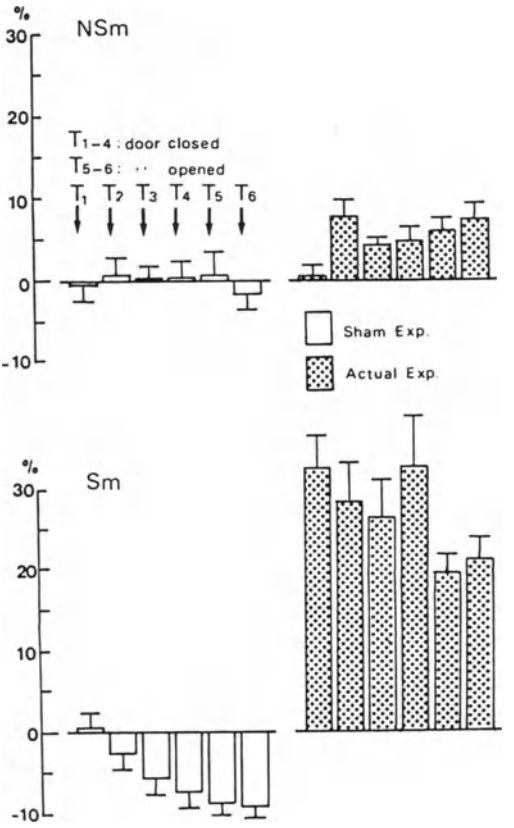

Fig. 12. Chronological changes in Katz indexes (systolic pressure × heart rate)

significantly differ from those of nonsmokers. This means that even the eyes of smokers must suffer from the irritation due to the secondhand tobacco smoke generated by themselves.

Conclusions

Under realistic conditions of the indoor air pollution caused by discharge of the secondhand tobacco smoke, even healthy young adults experience some physiological responses to passive smoking. Even if the cardiovascular responses to passive smoking could be underestimated from the clinical point of view at present (Pimm et al. 1978), the disturbance of normal physiological function which was typically evidenced by the increasing rates of eye blinking suggests that passive smoking can cause an infringement on the *amenity* of nonsmokers from the point of view of public health. Moreover, the cardiovascular responses imply definite, unnecessary physical and mental burdens on the homeostasis of the normal living body, and increased CO-Hb levels in blood, indicated by elevated concentrations of expired CO during and after passive smoking, may give warning on the chronic influences of concomitant inhalation of carcinogens in the secondhand tobacco smoke on the risk of lung cancer (Rylander 1983, U.S. Dept. of H.H.S. 1986).

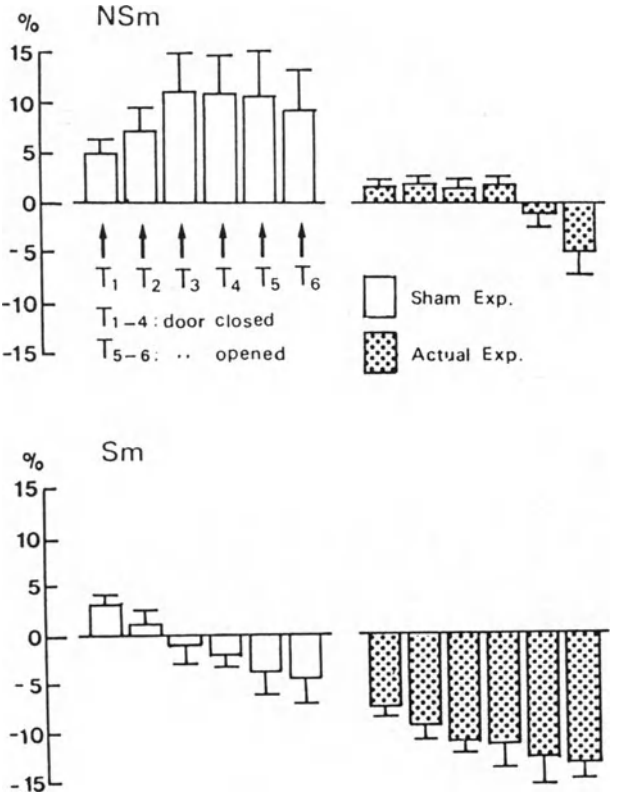

Fig. 13. Chronological changes in finger skin temperatures

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Involuntary Smoking and Urinary Cotinine

H. Matsuki, H. Kasuga, K. Misawa, and Y. Kawano

Summary

In epidemiological studies, involuntary smokers are generally classified using familial smoking habits based on questionnaires. However, this method is liable to give rise to misclassifications. Currently, the most promising method for estimating ETS exposure levels may be the measurement of cotinine in urine or serum. Therefore we compared questionnaires and cotinine levels in urine for the assessment of ETS exposure levels. Cotinine in urine was measured using an improved method of gas chromatography with a capillary column and flame thermionic detector. Subjects were 34 primary school children and their mothers. Data and urine samples were collected in February (winter) and July (summer) 1986. Urinary cotinine levels in both mothers and children were higher in winter than in summer. Correlation coefficients between number of cigarettes smoked by the family members in the same room and cotinine levels in winter in mothers and children were 0.820 and 0.626, respectively. It was suggested that the estimation of ETS exposure levels may be improved by asking for the number of cigarettes smoked at home per day.

Introduction

The risks associated with exposure to environmental tobacco smoke (ETS), frequently termed "Involuntary smoking" or "Passive smoking", have been the subject of several epidemiological studies [1–10]. These studies reported that involuntary smoking may increase the prevalence of respiratory infections and symptoms in children [9, 10] as well as the mortality of lung cancer [1–8]. In most of these epidemiological studies questionnaires were used to assess the level of personal exposure to ETS. ETS results from the combination of sidestream smoke and the fraction of exhaled mainstream smoke not retained by the smoker. ETS is diluted in a large volume of air and it ages prior to inhalation. Also the ETS exposure level depends on house structure, size of room and indoor ventilation rate. Therefore assessment of personal levels of ETS by questionnaires of familial smoking habits may lead to misclassification [11].

At present the most promising biochemical marker for ETS is cotinine [11], the major metabolite of nicotine. The half life of cotinine in biological fluids is longer than nicotine, and Beckett et al. [12] reported that cotinine in urine was less dependent on urine pH and flow rate than nicotine.

Urinary cotinine is mostly measured by radioimmunoassay [13–15] or by gas chromatography [16–18]. Since radioimmunoassay requires special devices and techniques the authors chose to use and improve an analytical method using gas chromatography with capillary column and flame thermionic detector (FTD). The

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purpose of this study was to compare the estimation of ETS exposure levels obtained from questionnaires and from actual urinary cotinine levels and also confirm the validity of ETS exposure levels obtained from questionnaire.

Methods

Subjects of this survey were schoolchildren of Hiranuma primary school and their mothers. This school was located in the Nishi Ward, a residential area in central Yokohama, Japan. All subjects were asked to fill in the ATS-DLD questionnaires. Out of the larger study population 34 families of which the mother was housewife were selected at random. These families were asked to complete detailed questionnaires concerning familial smoking habits. The questionnaires included questions about the number of cigarettes smoked per day by the household members and the number of cigarettes smoked in the presence of the mother and/or child at home per day. The subjects were asked to fill in a diary on their activities (time resolution 30 min). Personal nitrogen dioxide exposure levels [19] were measured on the same survey day. Collection of fasting urine samples was performed the next morning. The same subjects took part in winter and summer surveys.

The procedures for analysis of urinary cotinine by gas chromatography are summarized in Fig. 1. To 4 ml urine sample the internal standard 5-amino quinoline

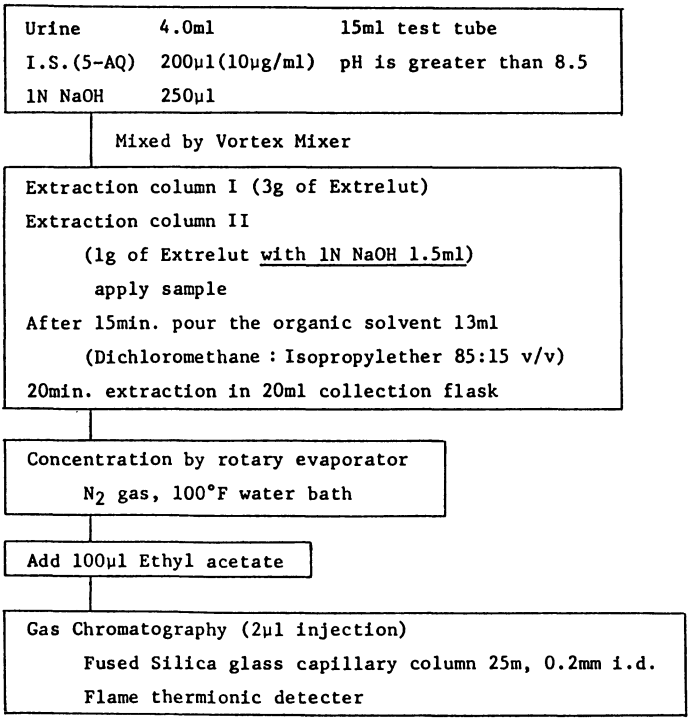

Fig. 1. Procedure of urinary cotinine analysis

200 µl (10 µl/ml) was added and the pH was adjusted with 1 N NaOH. After mixing on a vortex mixer, each sample was applied to two columns. Column I was packed with 3 g of Extrelut and column II was filled with 1 g of Extrelut and 1.5 ml 1 N NaOH. After 15 min, 13 ml of a mixture of organic solvents (dichloromethane:isopropylether 85:15 v/v) was added to the columns. The elute was concentrated by rotary evaporation. The residue was redissolved with 100 µl ethyl acetate. An aliquot (2 µl) of the redissolved solution was analysed by gas chromatography.

Gas chromatographic analyses were performed on a Shimadzu GC-16AM instrument equipped with flame thermionic detector (FTD). Fused silica glass capillary column (25 m, 0.2 mm i.d.) was used for gas chromatography. Column oven temperature was set with a two step increasing temperature program. Analytical time for one sample was about 15 min.

Detection limits for cotinine by this method was 2 ng/ml. The standard calibration curve was shown linear up to 2,500 ng/ml. The detection range made analysis of samples from active and involuntary smokers possible.

Urinary cotinine levels were expressed as the ratio of cotinine/creatinine. Urinary creatinine was determined according to the modified Jaffe's method [20].

Results

Complete sets of data were obtained for 33 out of 34 families. These sets were used in the statistical analysis. Fifteen households did not have smoking members: In 18 households one or more members smoked. In five households the mother was a smoker.

Total average cigarette consumption per day for the active smokers was 23.2 cigarettes in winter and 26.2 cigarettes in summer. The average number of cigarettes

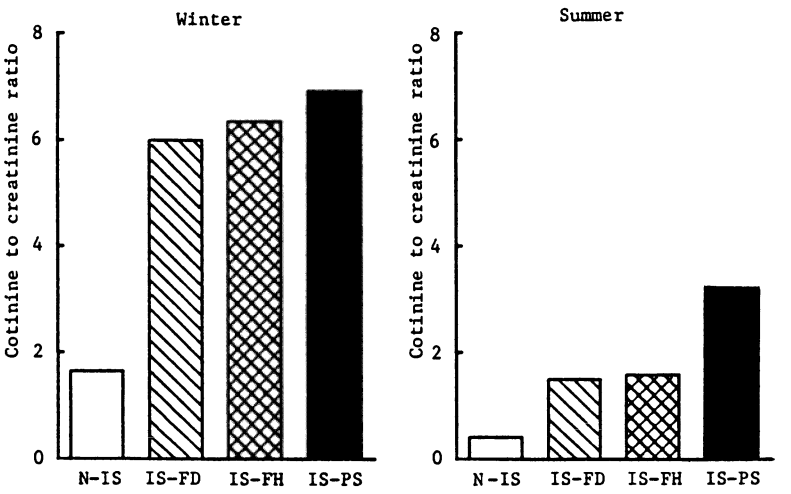

Fig. 2. Comparison of urinary cotinine level by familial smoking habits and by season (children). *N-IS:* Non-involuntary smokers; *IS-FD:* Involuntary smokers by familial smoking per day; *IS-FH:* Involuntary smokers by familial smoking at home per day; *IS-PS:* Involuntary smokers by parental smoking (father and mother) at home per day

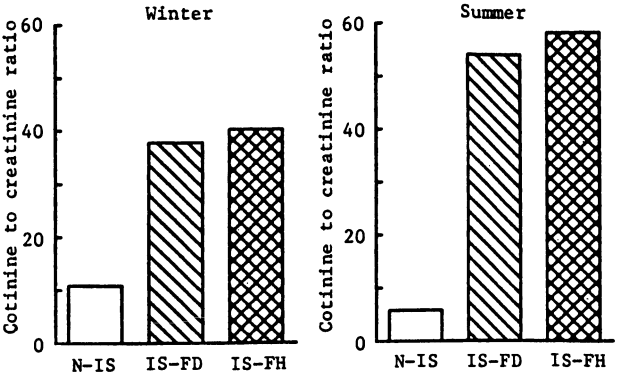

Fig. 3. Comparison of urinary cotinine level by familial smoking habits and by season (mothers). *N-IS:* Non-involuntary smokers; *IS-FD:* Involuntary smokers by familial smoking per day; *IS-FH:* Involuntary smokers by familial smoking at home per day

smoked in the house in presence of the involuntary smoker was 13.8 cigarettes in winter and 10.7 in summer. Matched pair testing showed that the seasonal differences in the number of cigarettes smoked were not significant.

Figure 2 shows the arithmetic means of urinary cotinine in the school children by season. In winter, the lowest value was obtained for the group of non-involuntary smokers (N-IS). The urinary cotinine/creatinine ratios in schoolchildren with one or two smoking parents (IS-FD) were almost four times as high as in the non-involuntary smokers. When only subjects of whom the parents were smoking at home (IS-FH) were considered, the cotinine/creatinine levels were slightly higher. The highest average cotinine/creatinine ratio was found in the group of involuntary smokers of which both parents smoked at home (IS-PS). A similar trend was found in the summer, but the arithmetic mean values were higher in winter than in summer for all groups. Significant seasonal differences were found in IS-FD group and IS-FH group ($p < 0.05$). Cotinine levels of the involuntary smokers whose family members smoked in the same room were about four times higher than the non-involuntary smokers in both seasons.

In the case of the non-involuntary and involuntary smoking mothers, the cotinine/creatinine ratios showed a similar trend as in the schoolchildren. Summer data of the IS-FD and IS-FH groups were higher than in winter, but these differences were not significant (Fig. 3).

Figure 4 shows the relationship between urinary cotinine/creatinine levels of schoolchildren in winter and the number of cigarettes smoked by family members in the same room as obtained by questionnaire.

The correlation coefficients between urinary cotinine levels and the total number of cigarettes smoked by family members per day and the number of cigarettes smoked in same room by family members was calculated for both seasons (Table 1). The correlation coefficients between the urinary cotinine/creatinine levels in schoolchildren and the total familial cigarette consumption per day in winter was 0.494. When only cigarettes smoked in the same room were counted, the correlation coefficient was 0.626. For mothers, high correlations (0.799 and 0.820 respectively) were observed in winter. These were statistically significant ($p < 0.01$). The summer data also showed high correlations, but these were lower than in winter. Correlation coefficients were higher for the number of

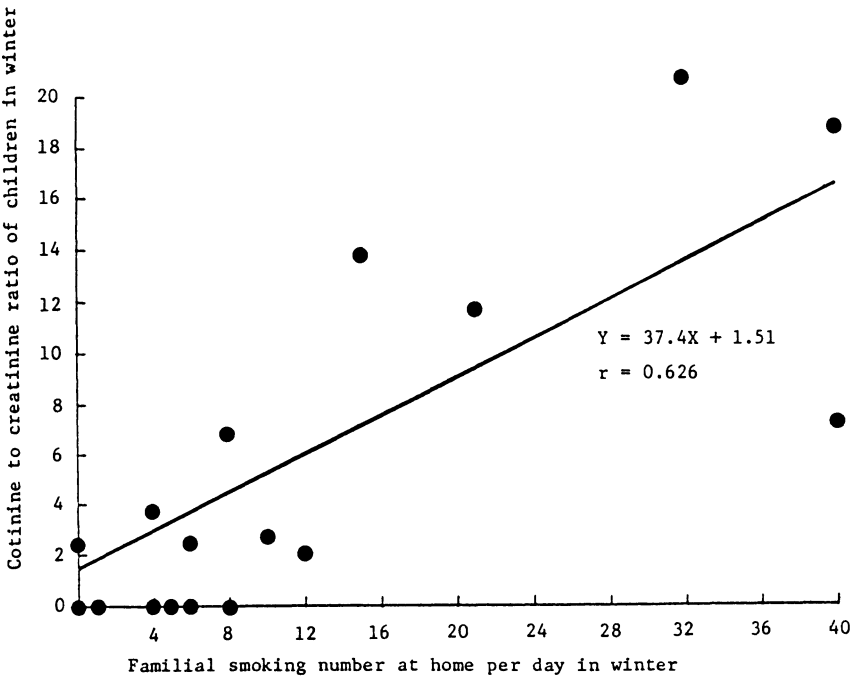

Fig. 4. Correlation between urinary cotinine level and number of cigarettes smoked by parents at home

Table 1. Correlation coefficients among urinary cotinine level and involuntary smoking

	Child Co/CR	Mot. Co/CR	Fam. Cig/day	Fam. Cig house/day
Winter				
Child Co/CR	–	0.396*	0.494**	0.626**
Mot. Co/CR	–	–	0.799**	0.820**
Fam. Cig/day	–	–	–	0.851**
Fam. Cig house/day	–	–	–	–
Summer				
Child Co/CR	–	0.250	0.389*	0.526**
Mot. Co/CR	–	–	0.426*	0.730**
Fam. Cig/day	–	–	–	0.854**
Fam. Cig house/day	–	–	–	–

*$p < 0.05$, **$p < 0.01$.

Remarks: Child Co/CR: Cotinine to creatinine ratio in children: Mot. Co/CR: Cotinine to creatinine ratio in mothers; Fam. Cig/day: Familial smoking per day; Fam. Cig house/day: Familial smoking at home per day

cigarettes smoked by family members in the same room with involuntary smokers as compared to the total number of cigarettes smoked per day in both summer and winter. This relation was observed in mothers as well as in schoolchildren.

Housing structure, i.e. wooden houses, mortared frame houses with aluminium sash and steel reinforced frame houses did not show significant differences in cotinine levels in winter and summer (data not shown). Also no significant correlation was observed between personal nitrogen dioxide exposure levels and the cotinine/creatinine ratios.

Time spent indoor was estimated from the diaries on daily activities. Schoolchildren spent an average of 17.6 h indoors in winter and 13.8 h in summer. The mothers' indoor stay was 18.2 h in winter and 15.8 h in summer. No relation was found between the length of time spent indoors and urinary cotinine/creatinine levels.

Discussion

In epidemiological studies concerning involuntary smoking, questionnaires have been used most frequently for estimating personal exposure levels to ETS [1–10]. Interviews with questionnaires or self-administered questionnaires provide information on the smoking habits of parents, spouses, and other family members. Based on this information, the subjects sometimes are classified into NPS, light passive smokers, moderate passive smokers and heavy passive smokers. The use of questionnaires for classification of involuntary smokers on ETS exposure has some limitations. First, the information acquired by questionnaires is not completely free of bias, i.e., the information contains subjective interpretations of interviewers and/or subjects. Secondly, the information may be grossly inaccurate when smoking habit histories of the subjects are asked. Thirdly, in evaluating ETS exposure of involuntary smokers in the home, usually the total number of cigarettes smoked by household members has been used as an indicator of exposure intensity at home. This variable may not be reliable because not all cigarettes are usually smoked at home. Therefore a simple questionnaire may contain high risks of over or underestimation of personal exposure level and as a result, it may bring upon serious misclassification of involuntary smokers [11].

Estimating exposure to ETS has been considered to be very complicated, but recently, the development of biological markers for personal exposure to ETS has been studied. The marker that at present holds the highest promise is cotinine, the major metabolite of nicotine. Cotinine can be measured in saliva, blood, or urine. Several studies have demonstrated a good correlation between the cotinine levels in body fluids and the estimated exposure to tobacco smoke [21–27]. Cotinine may be the best marker for tobacco smoke intake in smokers and at present for exposure to ETS by involuntary smokers. It is highly sensitive and specific for tobacco smoke and it can be detected not only in active smokers but also in biological fluids of involuntary smokers. This survey also confirmed the usefulness of cotinine as a marker for exposure to ETS. However, this does not necessarily apply for large scale epidemiological studies, because analysis of urine samples for cotinine is time consuming. The results of this study suggest that a minor improvement of questionnaires increases the reliability for ETS exposure estimation. Asking for the number of cigarette smoked by smokers in the same room as the involuntary smokers (in this study children and mothers) provides data which may be as accurate as urinary cotinine measurement. But, additional work is required to further improve questionnaire, since this survey was carried out with a small number of subjects and low levels of ETS exposure may be affected by other confounding factors such as

room size and ventilation rate. In fact, the influence of ventilation rate was suggested from the seasonal differences in ETS exposure in this study.

Urinary cotinine/creatinine ratio is a useful marker for estimating personal ETS exposure levels. But this marker does not reveal health effects caused by involuntary smoking because it is too speculative to conclude that high level urinary or serum cotinine levels directly indicate the possibility of disorders in the human body.

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A Comparison of Plasma and Urinary Nicotine and Cotinine Levels in Smokers and Nonsmokers: Nicotine Excretion Pathways Are Possibly Differential According to the Dosage of Tobacco Smoke Uptake

S. Itani, E. Higashi, and Y. Shimizu

Summary

Nicotine and cotinine levels in plasma (pnic, pcot) and urine (unic, ucot) sampled at a steady state were studied in 83 smokers and 90 nonsmokers.

Although there was considerable interindividual variability in measured levels for any given self-reported number of cigarettes smoked per day (CPD), some regularity was discovered among these four levels in relation to CPD.

Average pnic and pcot increased in proportion to CPD up to 15 CPD and more than 50 CPD, but from 20 to 40 CPD, a discrepancy involving more pcot and less pnic was discovered. Average unic rose more rapidly than average ucot up to 15 CPD, but at above 20 CPD, ucot increased more predominantly than unic. In nonsmokers, these four levels were, if detectable at all, extremely low, particularly as concerns cotinine.

The results indicate that the nicotine excretion mechanism may be differential according to the recent uptaken nicotine dosage. In most nonsmokers, the main pathway for nicotine excretion is the nicotine to nicotine route (NNR). The nicotine to cotinine route (NCR) may act as a backup. Light smokers may acquire the ability to convert a greater amount of nicotine to cotinine in proportion to CPD, with both pathways equally available.

Predominant production and excretion of cotinine is suggested for smokers who smoke more than 20 CPD, with the main route replaced by NCR. In extremely heavy smokers who smoke more than 50 CPD, it is suggested that the transaction limits of the nicotine to cotinine conversion system are exceeded and that both pathways are at maximum availability.

As concerns the indicator of ETS exposure for nonsmokers, all four levels are not always completely measurable. It is suggested that pnic is the most sensitive, but all four markers are equally necessary to estimate the low dosage of tobacco smoke uptake.

Introduction

Our previous statistical comparison of the levels of plasma nicotine (pnic), cotinine (pcot) and thiocyanate, urinary creatinine ratios of nicotine (unic), cotinine (ucot) and thiocyanate as well as COHb and expired carbon monoxide in a cross-sectional study revealed that these tobacco smoke uptake parameters (TSUPs) were more significantly elevated in the smokers than in the nonsmokers. The results suggested that pcot and ucot are the most suitable parameters for discrimination of smokers from nonsmokers [15].

Recently, urinary cotinine determination has frequently been used as an excellent TSUP in the study of ETS effects. Significantly elevated ucot levels have been pointed out for nonsmokers living with smokers as compared with those for nonsmokers living with

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nonsmokers, particularly when determination is made with the radioimmuno assay (RIA) method [14, 20]. In our study population, however, only 2% of the 90 nonsmokers showed detectable amount of ucot by gas chromatographic (GC) method. This is extremely low in frequency compared with the previous reports.

In order to increase the sensitivity and accuracy of the measurement of ETS effect, we have undertaken to reevaluate the determined levels of nicotine related parameters (i.e., pnic, unic, pcot and ucot) in smokers and nonsmokers. Nicotine and its major metabolite-cotinine are considered to be derived from tobacco only [4]. The determined levels of these markers in blood and urine on the same occasion may reflect a dynamic state of nicotine metabolism within the body at the time.

Accordingly, possible nicotine excretion pathways as well as the significance of in vivo nicotine to cotinine conversion in relation to daily cigarette consumption are also discussed.

Materials and Methods

Subjects

Eighty-three smokers aged 23 to 61 and 90 healthy nonsmokers aged 27 to 55 in natural condition were considered in the study. Most were office workers leading ordinary social lives. No particular attention was paid to the grade of ETS exposure to nonsmokers.

Analytical Methods

In most cases, random spot blood and urine samples were taken at almost the same time in the early afternoon. Smoking was prohibited for three hours before sampling. These plasma and urine samples (only cases with acidic urine samples were made available in the study) were stored at -20°C until analysis.

Nicotine and cotinine levels were determined by a modified FTD-GC method as previously described [8, 9, 15]. Urinary levels of these components were expressed by creatinine ratios.

Evaluation of the Four Parameters in Relation to the Number of Cigarettes Consumed Per Day

Eighty-three smokers were divided into seven groups according to the self-reported number of cigarettes smoked per day (CPD) as follows: 1 to 9 (5 CPD), 10 (10 CPD), 11 to 19 (15 CPD), 20 (20 CPD), 30 (30 CPD), 40 (40 CPD) and more than 50 CPD (50 CPD).

In order to estimate the relationship of the four parameters to CPD, the four individual levels were compared in a graphic pattern analysis. The four levels determined for each subject were plotted on the respective axes of XY orthogonal co-ordinates and connected with four lines to form a tetragon-figure, i.e., individual components on the upper, left, right and lower axes represent the levels determined for pnic, unic, pcot and ucot, respectively. Pattern analysis was performed taking notice of size and deviation in the form of the tetragon. Prominent deviations in the upward, left, right and downward direction are expressed by the letters N, n, C and c, respectively. For nonsmokers, all the

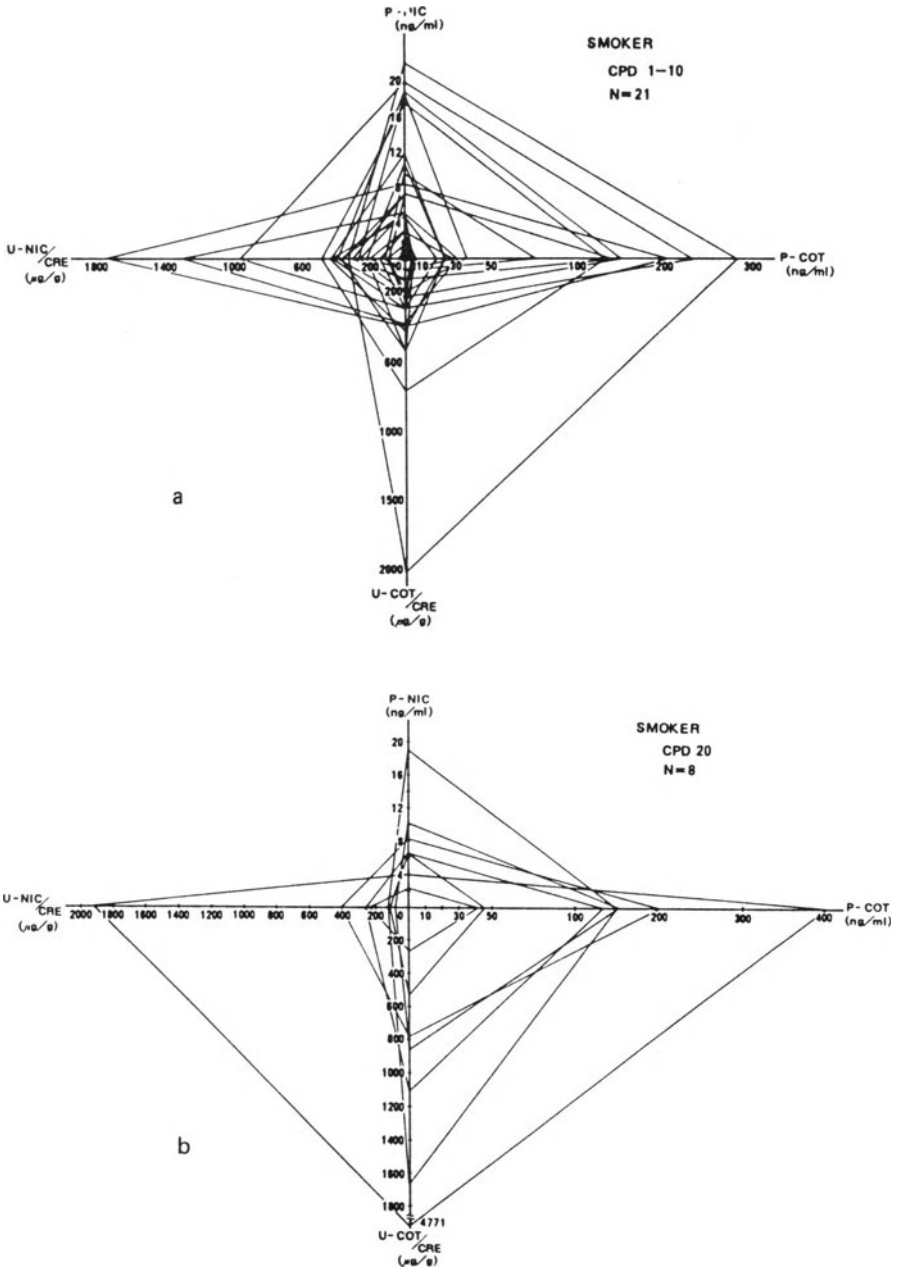

Fig. 1 a, b. Individual pnic, unic, pcot and ucot levels in (**a**) 21 light smokers (≦ 10 CPD) and in (**b**) eight 20 CPD smokers. Notice the tendency toward more pnic with less ucot in the former and, in contrast, toward less pnic and less unic with more ucot in the latter

detectable components, if any, are described by the corresponding primed letters N′, n′, C′ and c′, and no detectable one is expressed by the letter o.

Average nicotine to cotinine ratios in plasma and urine were also compared among smoker-groups in order to detect whether or not a tendency exists in comparative changes of nicotine and cotinine levels.

Results

Graphs of individual levels of all four markers of (a) 21 light smokers (≦ 10 CPD) and (b) eight heavy smokers (= 20 CPD) are shown in Fig. 1a, b, respectively.

It is clear that there was a high variability among the levels determined for different individuals who smoked almost the same number of cigarettes even for light smokers. However, marked differences between these two figures are as follows: Light smokers (a) showed a tendency to show higher levels of pnic with lower levels in ucot. Heavy smokers (b), by contrast, generally showed a tendency to have lower levels of pnic and unic with higher levels of ucot. Thus, most of them could be classified into several patterns based on the size and deviated form of the tetragon using the letters defined above.

Distribution ranges, averages and results of pattern analysis of the levels of the four markers determined in individual smoker-groups and in nonsmokers are summarized in Table 1.

Characteristics of Tetragons Formed by the Four Average Levels in Individual Smoker-groups

The four average levels in each smoker-group are shown in Fig. 2. The area between the axes of pnic and unic is considered as the nicotine-related plane, while the area between the axes of pcot and ucot is defined as the cotinine-related plane.

The smallest tetragon labeled 5 CPD in the nicotine-related plane is that for 5 CPD. It indicates higher pnic and unic levels but lower pcot and ucot levels. The 10 CPD tetragon shows a high level of pnic and a low level of ucot. This tendency is found more markedly in the 15 CPD tetragon. Even higher levels of pnic and unic as well as of pcot are noticed, but the level of ucot remains low. The 20 CPD tetragon, labeled in the cotinine-related plane, is quite different from the previous tetragons. This tetragon is characterized by considerably lower levels of pnic and unic with predominantly higher level of ucot compared with the 10 and 15 CPD tetragons, as shown in Fig. 1 (b).

One of the characteristics of the 30 and 40 CPD tetragons which follow 20 CPD tetragon appears to be another increase in unic level in addition to that of the 20 CPD tetragon. The pnic level remains relatively low, however. The 50 CPD tetragon is also quite different, characterized by extremely high levels of all the components.

Relationship of Average Plasma and Urinary Nicotine and Cotinine Levels to Daily Cigarette Consumption

As shown in Fig. 3 (a), pcot levels seem to have a roughly positive correlation to CPD.

Contrary to our expectations, however, pnic levels appear to have no positive correlation to CPD. The level of pnic was observed to peak first at 15 CPD, then fall

Table 1. Distribution ranges, averages and patterns of plasma and urinary nicotine and cotinine levels in smoker-groups by CPD and in nonsmoker-group

Group (CPD)	No. of subjects	Range (Average)				Patterns
		pnic ng/ml	unic μg/g	pcot ng/ml	ucot μg/g	
5	6	0– 7.4 (3.0)	0–1,280 (254.5)	0– 31 (7.0)	0– 375 (144.5)	o* (2), N (1), nC (3)
10	15	3.4–20.0 (11.1)	102–1,784 (422.4)	6–234 (93.3)	134– 771 (428.7)	N (1), n (4), Nn (1) NC (1), Nc (1), nC (2) nc (1), NnC (3), NnCc (1)
15	8	4.0–22.4 (15.0)	71–4,128 (961.3)	37–392 (208.0)	140–1,068 (513.1)	n (1), Nn (1), Nc (3) Cc (1), NnC (1), Nnc (1)
20	8	2.3–19.0 (8.6)	108–1,917 (409.0)	42–392 (190.0)	266–4,771 (1,459.0)	n (1), c (1), Cc (2) NCc (2), nCc (2)
30	11	2.5–21.4 (9.6)	90–1,860 (843.6)	111–720 (235.9)	818–2,300 (1,572.1)	N (2), Nc (1), Nnc (1) nC (3), Cc (1), c (2) NnCc (1)
40	23	0.6–21.4 (6.4)	49–3,600 (872.6)	65–635 (239.2)	228–3,617 (1,569.2)	Nn (1), NCc (2), nc (3) nCc (3), Cc (1), c (11) NnCc (2)
50 ≦	12	5.9–37.0 (21.1)	137–5,603 (1,866.0)	310–557 (375.0)	1,145–5,182 (2,812.2)	NCc (2), nCc (1), NnCc (9)
Nonsmokers	90	0– 8.6	0– 120	0– 6	0– 28	o* (75), N′ (4), n′ (1) N′n′ (2), N′C′ (6), N′n′C′c′ (2)

* No measurable amount discovered.

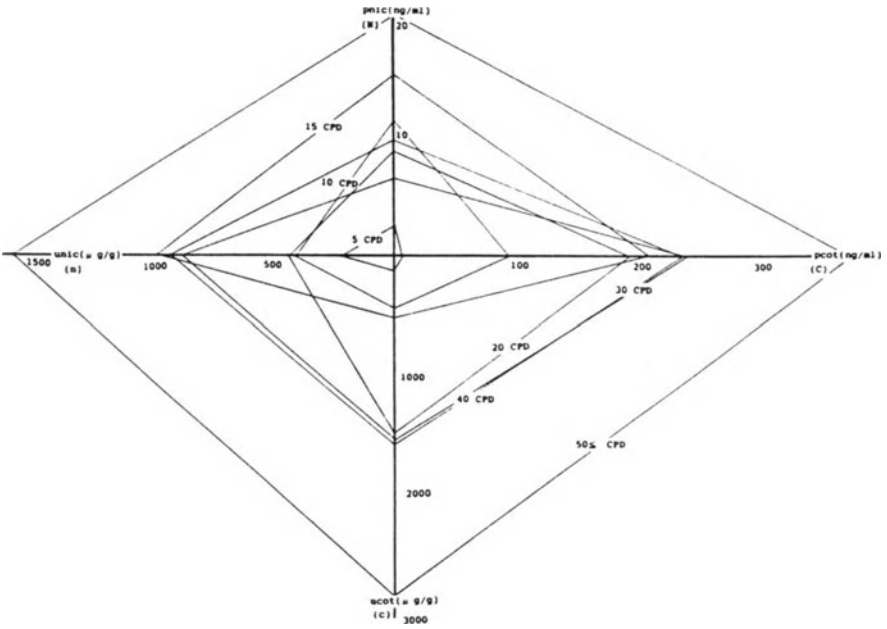

Fig. 2. Graph of average pnic, unic, pcot and ucot levels in smoker-groups divided by CPD. Compare the characteristic size and deviated form of each tetragon among inter-smoker-groups

rapidly at 20 CPD. This was followed by a gradual decrease up to 40 CPD, then a rapid increase at 50 CPD.

Pnic to pcot ratios in individual smoker-groups up to 40 CPD indicate a somewhat inverse correlation to CPD. In addition, significant differences in pnic/pcot ratios were found between 10 and 20 ($p < 0.05$); 10 and 30 ($p < 0.05$); and 10 and 40 CPD ($p < 0.001$), respectively. These results indicate that pnic and pcot levels increase in proportion to the daily cigarette consumption up to 15 CPD and more than 50 CPD, but in the intermediate region from 20 to 40 CPD, a discrepancy of more cotinine but less nicotine in plasma is found.

These relations in urinary components are shown in Fig. 3 (b). The ucot levels increased in proportion to the increase in CPD, but rapid stepped rises were discovered at 20 and 50 CPD. As for unic levels, an initial peak and trough were found at 15 and 20 CPD, respectively. Unlike pnic levels, however, unic levels increased gradually from there up to 40 CPD. This was followed by a final marked increase at 50 CPD.

Unic to ucot ratios in individual smoker-groups were somewhat discrepant from those in plasma. An initial marked peak and trough were observed at 15 and 20 CPD, respectively. Then a gradual increase occurred. Significant differences in unit/ucot ratios were found between 10 and 20 ($p < 0.01$); 10 and 30 ($p < 0.05$); 10 and 40 ($p < 0.001$); and 15 and 20 CPD ($p < 0.01$), respectively.

These results indicate that nicotine levels in urine rise more rapidly than cotinine levels up to 15 CPD, but that at above 20 CPD, the increase in cotinine levels is more predominant than that in nicotine levels.

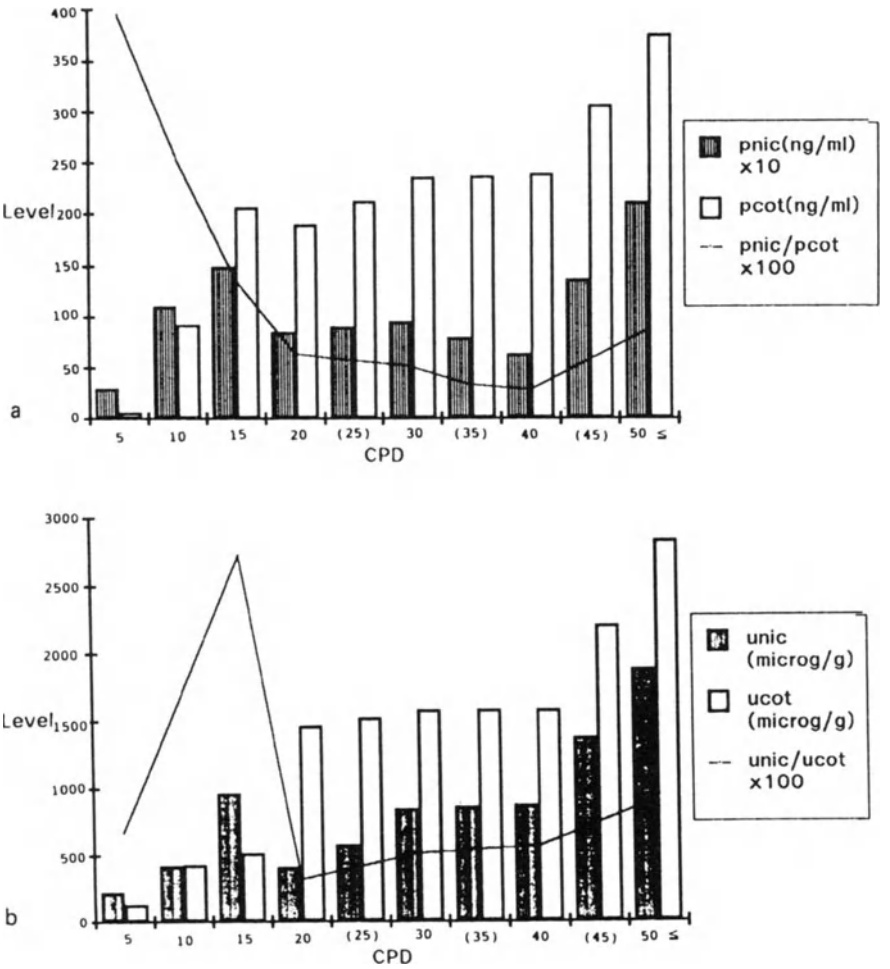

Fig. 3a, b. Relationship of (**a**) average pnic, pcot and pnic/pcot levels to CPD and of (**b**) unic, ucot and unic/ucot levels to CPD. Individual levels indicated by the number in parentheses indicate the estimated values for the corresponding CPD

Plasma and Urinary Nicotine and Cotinine Levels in Nonsmokers (Table 1, Fig. 4)

Out of 90 nonsmokers, at least one of the four parameters could be detected positively in 25 cases (28%). Unlike those for smokers, the amounts were extremely low for nonsmokers with detectable levels of these parameters, particularly as concerns cotinine levels, and all four levels were not always completely measurable. Detectable ucot levels could be measured in only two cases (2.3%).

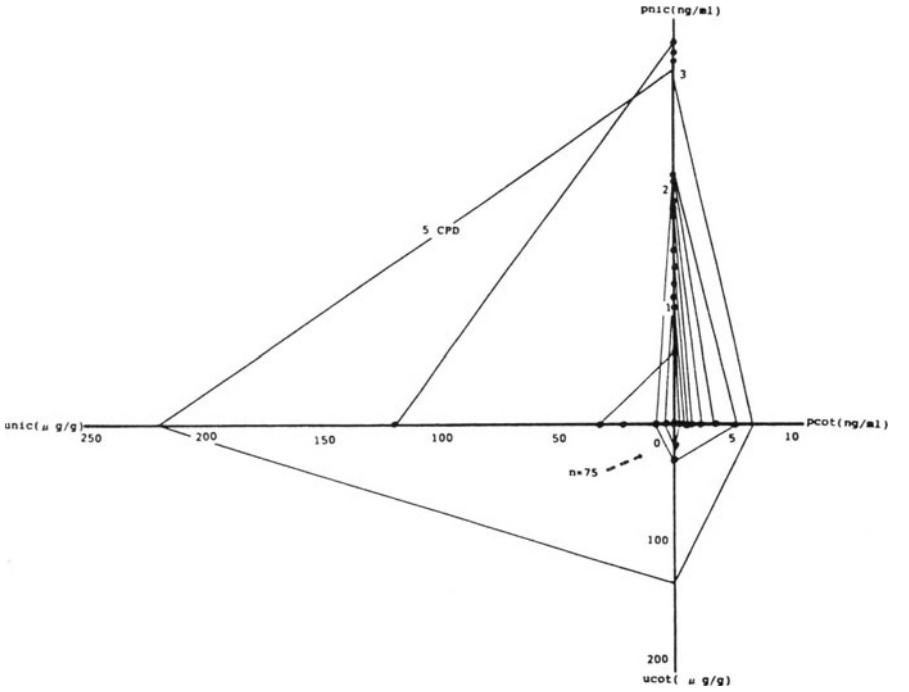

Fig. 4. Graph of pnic, unic, pcot and ucot levels in nonsmokers (n = 90). The outer tetragon represents the averages of these levels in 5 CPD smokers as shown in Fig. 2

Discussion

The nicotine excretion pathways following cigarette smoke inhalation may be considered to be as follows. A large portion of nicotine absorbed will finally be excreted into the urine in unchanged form through the nicotine to nicotine route (NNR) or is excreted in a converted form such as cotinine through the nicotine to cotinine route (NCR) [20]. Cotinine, the primary metabolite of nicotine, is formed in the liver in a two-step process [7, 17]. It has been recognized that at a steady state, as in the early afternoon, the rate of metabolite excretion reflects the rate at which the metabolites are generated [4].

Our findings (Fig. 5) that these four levels increased in proportion to the increase in CPD up to 15 CPD and that unic level rose more rapidly than ucot level indicate that NNR is the main route but that NCR is also made available in light smokers (1 ~ 15 CPD). Similarly, in smokers who smoked 20 to 40 CPD, the findings indicate that the main route is replaced by NCR. In smokers who smoked more than 50 CPD, both pathways are suggested to be fully used in order to excrete the rather large amount of uptaken nicotine.

Our findings that cotinine levels were extremely low or absent as compared with nicotine levels in the nonsmokers in whom any of these markers could be detected indicate that NNR is the main route in nonsmokers. This may be supported by an early finding of Beckett and Triggs [1] who observed that the excretion of nicotine was greater in nonsmokers than in smokers.

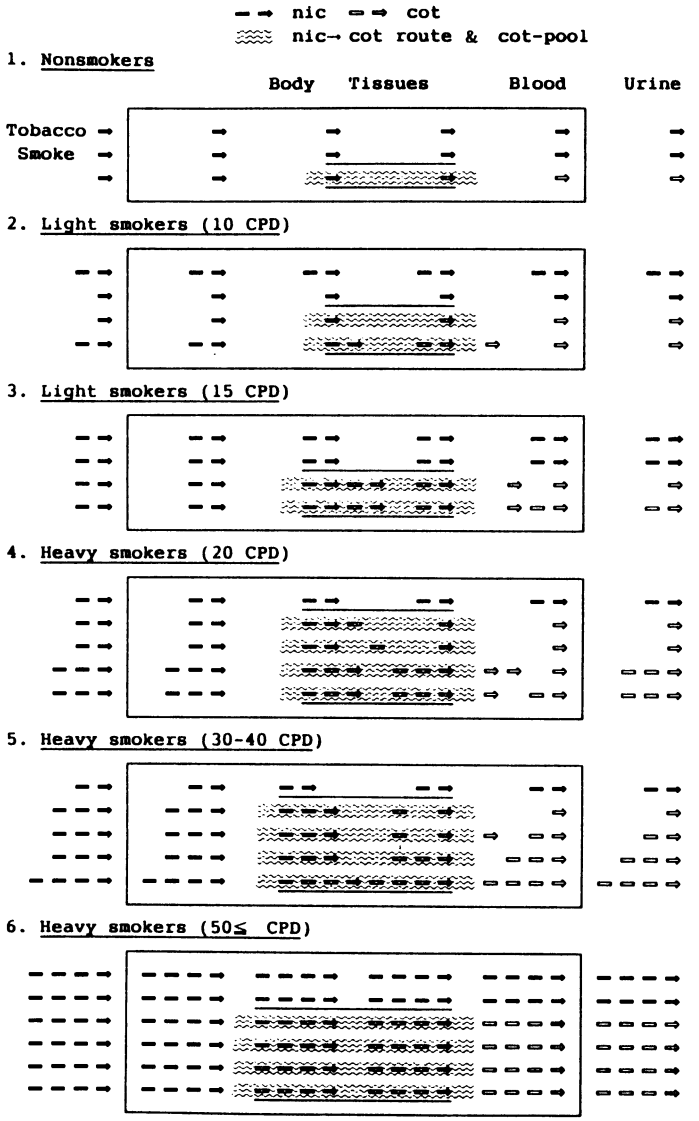

Fig. 5. A tentative schema of nicotine to nicotine (NNR) and nicotine to cotinine (NCR) pathways in relation to CPD based on the present findings. In most nonsmokers, NNR and NCR may be the main and salvage pathways, respectively. Switching of the main pathway from NNR to NCR may be differential in most smokers according to the usual nicotine dosage from tobacco smoke uptake

A time course study on the rise and decline of these four levels after smoking a single cigarette by current nonsmokers is in progress. The preliminary findings show an initial plasma nicotine peak not so inferior to the smoker's peak level at 5 min and of a sudden fall at 15 min followed by a gradual decline until 48 h and a rapid predominant increase in

urinary nicotine level from immediately after smoking to 60 min with a transient appearance of cotinine in plasma and urine. This also supports the theory that NNR is the main route in nonsmokers.

It has been discovered that chronic nicotine administration to rats or mice does not increase the rate of nicotine metabolism [6], but that among humans, the nicotine metabolism is faster in smokers than in nonsmokers [2, 12, 18, 19]. This evidence may be in agreement with our present findings. The induction of hepatic microsomal enzymes as explanation, however, is equivocal since reports of inhibition as well as induction have been made occurred [2, 12, 18].

Our present explanation of the switching from the main pathway from NNR to NCR as a result of an increase in CPD may be coincident with these literature findings for the following reasons.

1. Most smokers, who may regulate nicotine intake by modifying puff and inhalation patterns [5], may acquire an ability to convert a greater amount of nicotine to cotinine rapidly, possibly due to the induction in increasing activity of cytoghrome P 450 in the liver [7, 16, 17, 18] in proportion to CPD up to about 40 CPD. The levels of the markers in most of the 50 $\geqq$ CPD smokers suggest that this enzyme system has a limited capability, and is not able to treat excess nicotine in a short duration. Rapid cotinine formation in smokers may be a defence mechanism in a sense, since cotinine is much less toxic than nicotine in rats [13], and probably in humans as well. High plasma nicotine with the inhibition of cotinine formation as seen in most 50 CPD smokers may be a sign of "true" nicotine toxicity.
2. Interindividual variability at any given CPD as shown in Fig. 1 may result partly from individual differences in enzyme activity. The conversion rate and amount of nicotine to cotinine is suggested to be highly dependent, however, on the recent uptaken quantity of tobacco smoke.

Out of 90 nonsmokers in a natural condition, positive levels of at least one parameter were found out in 28%. The pnic level seems to be the most sensitive indicator of exposure to other people's smoke, and ucot may be a rather insensitive marker in determination of such low levels of the alkaloid as found in nonsmokers.

These findings, however, seem to be contraversial to recent literature in which greater ucot levels in many more nonsmokers have been reported [10, 11, 14, 20], although the study populations and methods employed (RIA) were different from ours.

This discrepancy may partly be due to difference in detection methods. The recent international interlaboratory study on nicotine and cotinine determination has revealed that GC derived values showed reasonable agreement but that cotinine determinations in urine by RIA are less precise than those in serum. It also showed that RIA values were higher than GC values in urine samples and that relative variability is extremely high for both of GC and RIA is samples from nonsmokers [3].

As for the indicator of ETS uptake in nonsmokers, all four levels are not always completely measurable. This may be one of the characteristics of ETS effect on nonsmokers, probably a result of the use of NNR as the main pathway. This indicates that not only cotinine levels in blood and urine but also nicotine levels in blood and urine are equally important in dosage estimates for tobacco smoke uptake.

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The Significance of Urinary Hydroxyproline Excretion in Smokers and Passive Smokers

F. Adlkofer, G. Scherer, W.-D. Heller, X. Sünkeler, and T. Heintz

Summary

The urinary hydroxyproline/creatinine ratio was reported to be increased after smoking, passive smoking and exposure to ambient air polluted with nitrogen dioxide. In two field studies we tried to verify the results obtained in smokers. A weak positive association was found between the hydroxyproline/creatinine ratio and cigarette consumption for male smokers. In contrast, the amount of hydroxyproline excreted in the 24-h urine was not increased in male and female smokers as compared to their non-smoking counterparts. Standardizing the data for body surface led to the same results. From the findings obtained in smokers we conclude that passive smoking does not lead to an elevation of hydroxyproline excretion either.

In addition, we measured lower amounts of creatinine excreted in the 24-h urine of male, but not female smokers and higher 24-h urine volumes in smokers of both sexes as compared with non-smokers. Whereas an inverse correlation was found between the extent of smoking and the excretion of creatinine, the association between the extent of smoking and urinary volume was positive. Both findings acting together may explain the increased hydroxyproline/creatinine ratio as seen in smokers. Therefore the hydroxyproline/creatinine ratio is not a measure of the hydroxyproline excretion in smokers, nor is its determination an appropriate method of detecting lung damaging effects due to smoking and passive smoking.

Introduction

Increased urinary excretion of hydroxyproline is an established diagnostic marker for certain osteopathic destructions, some endocrinological disorders and severe burns [10]. However, only controversial results are available when hydroxyproline excretion is used to indicate degradation of lung collagen and elastin in subjects with lung diseases [9, 16]. Kasuga and co-workers introduced the hydroxyproline/creatinine ratio as a biomarker for exposure to pollutants with lung damaging properties in epidemiological field studies. They reported dose-related increases in the hydroxyproline/creatinine ratio of smokers, passive smokers and subjects exposed to ambient air polluted with automobile exhaust [9]. In an earlier investigation involving male smokers of cigarettes, pipes and cigars and passive smokers [2], we were unable to confirm the results of Kasuga and co-workers. Instead of this, we found an inverse correlation between urinary creatinine concentration and smoke uptake in cigarette, pipe and cigar smokers which could have caused the observed weak association between smoking and the hydroxyproline/creatinine ratio. In order to shed new light on this controversy we extended our study by a group of 120

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subjects consisting of 60 smokers and 60 non-smokers. Hydroxyproline and creatinine in 24-h urine samples were independently measured in the laboratory of Prof. Kasuga and in our Munich laboratory.

Subjects and Methods

Subjects

All subjects were recruited as described elsewhere [2]. The data of cigarette smokers and non-smokers of study 1 in this paper are those of study 1 and 3 of an earlier publication [2]. In study 2, 60 non-smokers (30 males, mean age: 27.8 years; 30 females, 28.1 years) and 60 smokers (31 males, 31.3 years; 29 females, 30.8 years) were investigated. The subjects collected 24-h urines before they came to the laboratory between 4 and 7 p m. On this occasion blood samples were drawn and questionnaires on life style factors were completed.

Analytical Methods

Hydroxyproline and creatinine in the urine samples of study 1 and 2 were analyzed in the laboratory of Prof. Kasuga at Tokai University, School of Medicine, by autoanalyzer techniques [8, 15]. The samples from study 2 were additionally analyzed in our laboratory using the method of Prockop and Udenfriend for hydroxyproline [12] and Jaffe's reagent (Merckotest 3385, Fa. Merck, Darmstadt, W.-Germany) for creatinine. Carboxyhemoglobin (COHb) was measured with a CO-Oximeter (Instrumentation Laboratories Ltd, Model 182) immediately after taking the blood samples. Cotinine in serum was determined by gaschromatography (study 1) [6] and radioimmunoassay (study 2) [5].

Results

The 24-h urine parameters for smokers and non-smokers of both studies are summarized in Table 1. Male smokers of study 1 showed significantly higher hydroxyproline/creatinine ratios than did male non-smokers. In study 2, the same trend is obvious for male and female subjects if Kasuga's data (TDS) are used, but could not be seen with our data (MDS). There was no difference in the amount of hydroxyproline excreted in the 24-h urine either standardized for body surface or unstandardized between male smokers and male non-smokers. In female smokers, the hydroxyproline excretion rate was similar to that in female non-smokers if our data set was used, but was significantly higher with Kasuga's data. In both studies significantly lower amounts of creatinine were measured in the 24-h urine of male smokers as compared to male non-smokers. No such difference was seen for female subjects. Our results are in line with the Japanese data set. In study 2, in both sexes the volume of the 24-h urine of smokers was significantly higher than that of non-smokers.

The relationship between the smoke uptake variables (cigarette consumption, COHb, serum cotinine) and the 24-h urine variables (hydroxyproline, creatinine, volume) are shown in Table 2. Notably, the extent of smoking is positively correlated with the 24-h urine volume and negatively correlated with the amount of creatinine excretion over 24 h. This is also true for female smokers, even if their average amount of creatinine excreted

Table 1. Hydroxyproline (HOP) and creatinine (CREA) excretion in 24-h urine of smokers and non-smokers (mean ± SD) (TDS = Tokyo Data Set; MDS = Munich Data Set)

Smoking status (n)	HOP (mg/24 h)		HOP (mg/24 h/m^2)		HOP/CREA (mg/g)		CREA (mg/24 h)		Volume (ml/24 h)
Study 1 (TDS)									
Males									
Non-smokers (23)	32.3 ± 11.5		16.9 ± 6.2		17.3 ± 4.0		1,863 ± 481		1,416 ± 511
Smokers (88)	34.7 ± 16.5		17.7 ± 6.2		25.5 ± 8.5		1,373 ± 549		1,318 ± 595
p	0.41		0.62		0.0001		0.0001		0.44
Study 2									
Males									
	TDS	MDS	TDS	MDS	TDS	MDS	TDS	MDS	
Non-smokers (30)	41.5 ± 17.6	29.2 ± 10.8	22.8 ± 11.6	16.5 ± 8.2	19.5 ± 11.9	16.3 ± 5.4	2,310 ± 623	1,822 ± 490	1,399 ± 380
Smokers (31)	40.0 ± 14.6	26.2 ± 9.7	20.6 ± 8.2	13.5 ± 5.1	23.2 ± 9.9	17.1 ± 5.5	1,832 ± 508	1,543 ± 385	1,846 ± 710
p	0.73	0.26	0.40	0.09	0.19	0.55	0.01	0.02	0.01
Females									
Non-smokers (30)	29.4 ± 9.4	21.7 ± 9.3	17.5 ± 5.6	12.8 ± 5.1	22.9 ± 8.0	21.2 ± 8.3	1,326 ± 300	1,051 ± 273	1,209 ± 524
Smokers (29)	37.8 ± 17.7	20.8 ± 7.0	22.8 ± 10.9	12.8 ± 5.5	29.9 ± 16.7	19.0 ± 5.1	1,331 ± 293	1,100 ± 233	1,611 ± 846
p	0.03	0.67	0.03	0.98	0.06	0.23	0.95	0.46	0.04

Table 2. Coefficients of correlation (Pearson) between variables of cigarette smoke uptake and 24-h urinary hydroxyproline (HOP) and creatinine (CREA) excretion and urinary volume (TDS = Tokyo Data Set; MDS = Munich Data Set)

Study 1 (TDS), Males (N = 88)

Variables	Consumption (Cig/d)	Serum cotinine (ng/ml)	COHB (%)
HOP (mg/24 h)	0.07	0.19	0.14
CREA (mg/24 h)	-0.08	0.07	-0.07
Volume (ml/24 h)	0.23*	0.19	0.27**

Study 2

Variables	Consumption (Cig/d)		Serum cotinine (ng/ml)	
	TDS	MDS	TDS	MDS
Males ($N = 31$)				
HOP (mg/24 h)	-0.11	-0.38*	0.13	-0.03
CREA (mg/24 h)	-0.44*	-0.40*	-0.24	-0.33
Volume (ml/24 h)	0.34		0.08	
Females ($N = 29$)				
HOP (mg/24 h)	0.05	-0.19	-0.14	-0.29
CREA (mg/24 h)	-0.33	-0.34	-0.62***	-0.69***
Volume (ml/24 h)	0.36		0.14	

* $p < 0.05$. ** $p < 0.01$. *** $p < 0.001$.

was not found to be different from that of non-smokers (Table 1). No stable trend of a correlation between the amount of hydroxyproline excreted and the smoke uptake variables could be observed.

Discussion

This investigation deals with the question of whether urinary hydroxyproline may in fact be regarded as a validated biochemical marker for assessing health hazards due to tobacco smoke exposure. The increase in urinary hydroxyproline caused by degradation of lung collagen and elastin is thought to be very low. This is due to the fact that hydroxyproline containing lung proteins constitute only some 2% of the total collagen present in the entire human organism [1]. Therefore very high turnover rates in the lung would have to be assumed if measurable increases in urinary hydroxyproline excretion were to result. It is thus not surprising that in several studies including our own no increase in hydroxyproline excretion was found after smoking [2, 7, 13] or after exposure to nitrogen dioxide [11]. Similar conclusions must be drawn from investigations of

subjects with lung disease [10, 14]. Our present data again support the view that urinary excretion of hydroxyproline is not sensitive enough to detect a lung damaging effect of cigarette smoking, as we do not find an increase in hydroxyproline excretion in male and female smokers. As far as male smokers are concerned, our data are in line with those of Kasuga. In female smokers, Kasuga's data show a significantly higher hydroxyproline excretion. At present, we have no explanation of this discrepancy.

If there is no measurable difference in urinary hydroxyproline excretion over 24 h between smokers and non-smokers, the question arises whether the increased hydroxyproline/creatinine ratio in smokers as found in several studies might be caused by factors other than an elevation of hydroxyproline. First of all, the interlaboratory comparison shows that the hydroxyproline/creatinine ratio is subject to a high analytical variability. On the average, higher hydroxyproline levels were found in Kasuga's laboratory as compared with our laboratory (regression line is parallel to the ideal line).

The coefficient of correlation was rather low ($r = 0.76$). A better correlation was observed for the creatinine measurements ($r = 0.96$). However, the regression line systematically deviates from the ideal line. Due to this interlaboratory variance, the hydroxyproline/creatinine ratios calculated from the data obtained in both laboratories show a weak correlation only ($r = 0.27$).

Furthermore, our data demonstrate an increase in the 24-h urinary volumes in relation to the extent of smoking. The data of study 1, in which smokers and non-smokers have similar urine volumes, may at first sight not support this finding. However, it has to be considered that in this study the smokers were investigated in winter and the non-smokers in summer which makes a comparison rather meaningless, since people use to drink more in summer than in winter. We must assume that the urinary flow rate influences excretion of hydroxypyroline and creatinine in a different way. Whereas a nearly complete tubular reabsorption is reported for free hydroxyproline which accounts for 80–95% of total hydroxypyroline in the plasma [1], no tubular reabsorption of creatinine takes place at all. According to the principle of forced diuresis, an increased urinary flow rate as found in smokers may cause a reduction in tubular reabsorption of hydroxyproline, thus leading to an increased urinary excretion. This remains to be established by experimental evidence.

Finally, the evaluation of the data sets clearly shows that the urinary creatinine excretion is inversely correlated with the extent of smoking. So far we cannot offer any convincing explanation of this finding. However, our observation is supported by at least two papers. One of them reports lower creatinine concentration in serum of smokers as compared with non-smokers [3]. The other describes lower serum creatinine levels in male but not in female smokers as compared to their non-smoking counterparts [4]. Therefore the increased hydroxyproline/creatinine ratio if found in smokers might, for the most part, be caused by a diminished urinary creatinine excretion.

In conclusion, increases in the hydroxyproline/creatinine ratios in smokers might be falsely interpreted as an elevated excretion of hydroxyproline. This may in fact be caused by smoking-related decreases in creatinine excretion and/or increases in urine volume. Moreover, hydroxyproline excretion is unlikely to be an appropriate biomarker for detecting a lung damaging effect of smoking or passive smoking. Low increases in urinary hydroxyproline after smoking, which cannot be excluded, may remain undetected due to the wide interindividual and methodological variabilities, and in view of the high release of hydroxyproline from organs other than the lung.

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The Effect of Parental Smoking and Industrial Pollution on Birth Weight

P. Rantakallio, A.-L. Hartikainen-Sorri, and T. Leino

Summary

The effect of maternal and paternal smoking on birth weight was studied in a birth cohort of 9478 children born in a geographically defined area in Northern Finland in 1985–1986. Data were collected in a prospective manner and included 99% of all births in the study area during one year. Some 22.3% of the mothers and 36.5% of the fathers smoked, and in 42.8% of the cases at least one parent smoked. The effect of maternal and paternal smoking on birth weight was studied by analysis of covariance employing 43 confounding variables. Maternal smoking had a highly significant effect, but paternal smoking had no significant effect. The effect of environmental pollution was studied by the same method in a subgroup of 2086 cohort families living in the city of Oulu and its surroundings. Environmental pollution did not affect birth weight either alone or in combination with parental smoking. The effect of paternal smoking on low birth weight, less than 2,500 g, rate was studied also separately among the full-term infants, and after adusting 57 confounding factors it had no statistically significant effect.

Introduction

Since the classic work of Simpson 30 years ago on retarding effect of maternal smoking on foetal growth [8], there have been hardly any well-collected sets of data in which it is impossible to show that maternal smoking during pregnancy retards foetal growth [5]. Only lately, however, has attention been focused on the possible effect of indirect exposure to tobacco smoke on the pregnant mothers. Martin and Bracken [3] compared pregnant women who were exposed to passive smoking for at least 2 h per day with women who were not exposed, and found that the relative risk of having low birth weight infants was increased among the term deliveries, althought no statistically significant difference in mean birth weight was found. A clear effect of paternal smoking on birth weight in full term infants was found in a retrospective Danish study [6] contrary to the observations of Hauth et al. [2], in which there was no evidence that passive cigarette smoke exposure resulted in a higher maternal or umbilical cord thiocyanate concentration than in non-smokers. If passive smoking can be a source of adverse effects on the human reproductive system, similar effects can be suspected to be caused by many toxic agents in the general environment [7]. The ratio of low birth weight infants has been found to be increased among women living near a disposal site for various chemicals [9], and a geographical variation in the low birth weight rate has been found in Sweden with a suspected correlation with the degree of industrialization [1].

In the present survey we have studied the effect of paternal and maternal smoking on birth weight in a one-year birth cohort of 9,362 pregnant mothers in a geographically

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defined area of Northern Finland in 1985–1986. In addition to parental smoking, the effect of industrial pollution on birth weight is examined among 2,086 cohort families.

Material and Methods

The birth cohort was collected in a geographically defined area of Northern Finland, the provinces of Oulu and Lapland. The region concerned extends about 250 km on either side of the Artic Circle and the mean temperature in January is −12°C and that in July +15°C. The data collection was of a prospective kind and the cohort was designed to include all pregnancies with expected dates of delivery falling within one year, from 1st July 1985 to 30th June 1986. The 9,362 mothers gave birth to 9,478 children, accounting for 99% of all births in the area in 1985. Data were collected three times during the pregnancy: before the 24th week of pregnancy, at the last visit to the antenatal clinic and in the maternity hospital after delivery. Hospital records of all pregnancies with the expected delivery data falling into the study period were collected by the study group. When visiting the antenatal clinics, the mothers were asked to fill in questionnaires with the help of the health service staff. In 15.1% of the cases the mothers did not participate in this survey, but many of variables included in the questionnaires were later filled in from their records at the antenatal clinics, e.g. variations in maternal smoking during pregnancy. 16 mothers, 0.2%, had not visited antenatal clinics and 8 mothers, 0.1%, had a home delivery. Birth weight was known in all cases, and maternal smoking in 9,404 out of the total series of 9,478 births, 99.2% (Table 1).

In 477 of these cases the mother was unmarried and did not live with the father, while among the remaining 8,927 cases paternal smoking was unknown in 914 (10.3%), leaving 8,490 births in which both maternal and paternal smoking was known. 3,096 of the fathers (36.5%) and 1,891 of the mothers (22.3%) smoked. In 3,847 cases (42.8%) at least one parent smoked and in 1,140 of these (29.6%) both smoked. In 751 cases (19.5%) only the mother smoked, including 237 single mothers and in 1,956 cases (50.8%) only the father.

The city of Oulu possesses about 100,000 inhabitants in all, including 2,086 of the present cohort families. The city has a number of factories with toxic emissions into the air which cause damage to the trees and other vegetation in the vicinity. Damage of this kind was first noted in the city in the 1960s. The air pollution recorded in Oulu differs

Table 1. Parental smoking

Father's smoking	Mother's smoking							
	Non-smoker		Smoker		Not known		Total	
	N	[%]	N	[%]	N	[%]	N	[%]
No father	240	49.5	237	48.9	8	1.6	485	100.0
Non-smoker	4,403	89.5	514	10.4	2	0.1	4,919	100.0
Smoker	1,956	63.1	1,140	36.8	2	0.1	3,098	100.0
Not known	742	76.0	172	17.6	62	6.4	976	100.0
Total	7,341	77.4	2,063	21.8	74	0.8	9,478	100.0

Table 2. Approximate pollution discharges (1,000 kg) in Oulu per year. (From [4])

SO_2	10,000–12,820
CO	10,000
NO	7,000– 8,000
Dust	7,000– 8,000
H_2S	1,200
Pb	20
Hg	0,2

Table 3. Confounding factors controlled in the analysis

Biological factors

Paternal and maternal height and weight, maternal age, sex of the child, chronic diseases of the mother and father

Obstetric history of the mother

Parity, number of children under 15 years, previous preterm and low birth weight infants, abortions, perinatal deaths, other abnormalities in previous pregnancies, deaths during the first year.

Present pregnancy and delivery

Number of visits to antenatal clinics, hospital admissions, sick leave, fever, bleeding during pregnancy, blood pressure at first and second trimester, urinary tract infection, twin pregnancy, induction of labour, breach delivery, placenta praevia, treatment for infertility

Social conditions during pregnancy

Marital status, desirability of the pregnancy, state of mind, week of gestation at first antenatal visit and on stopping work, help in housekeeping, various household amenities, number of people in the household, internal migration, social class according to father's and mother's occupations, years of schooling, gainful employment, strenuousness of work

Place of residence

North-South axis, developmental scores for the community, population density

Living habits

Maternal and paternal smoking and alcohol consumption

from that in many cities of comparable size in involving unusually high concentrations of the oxides of nitrogen, hydrogen sulphide and mercaptans. During the present study period there were five industrial concerns in the area producing air pollution: a nitric acid factory, a sulphide cellulose mill (until July 1985), a sulphate cellulose mill and two heating plants. These are located in a circle round the centre of the city so that exposure depends on the prevailing wind direction. Annual discharges of toxic substances into the air in Oulu are given in Table 2 [4].

Mean sulphur dioxide concentrations vary in the range 13–23 $\mu g/m^3$ from one area to another, thus remaining well below the annual danger level laid down by the National Board of Health (70 $\mu g/m^3$). The hydrogen sulphide emitted by the sulphate cellulose

Table 4. Mean birth weights (corrected by analysis of covariance) by maternal smoking and environmental pollution

Mother	Area			
	Polluted		Clean	
	N	Mean birth weight	N	Mean birth weight
Smoker	198	3,447.4	238	3,416.8
Non-smoker	680	3,574.3	970	3,576.0

Table 5. Analysis of covariance on the effect of maternal smoking and environmental pollution on birth weight with 43 covariates

Variables	F	p
1. Maternal smoking	22.03	0.0000
2. Environmental pollution	0.24	0.6230
3. Interaction between 1. and 2.	0.34	0.5587
4. Twin delivery	48.09	0.0000
5. Height of the mother	18.09	0.0000
6. Sex of the child	28.14	0.0000
7. Breech presentation	21.91	0.0000
8. Admission to hospital during pregnancy	25.14	0.0000
9. Number of visits to antenatal and maternity clinics	31.19	0.0000
10. Systolic blood pressure in 30–36th week of pregnancy	16.95	0.0000
11. Previous preterm deliveries	14.69	0.0001
12. Induction of labour	11.77	0.0006
13. Diastolic blood pressure in 30–36th week of pregnancy	11.54	0.0007
14. Placenta praevia	11.43	0.0007
15. Paternal height	7.81	0.0052
16. Number of children under 15 years	7.29	0.0070
17. Maternal weight before pregnancy	4.89	0.0271
18. Help in housekeeping	4.34	0.0374
19. Parity	4.13	0.0424

mill, on the other hand, causes a pronounced smell and its concentrations (1.1–8.3 $\mu g/m^3$/month) frequently exceed the limits laid down in other countries (3.4). The mean annual concentration of oxides of nitrogen is 15 $\mu g/m^3$, the maximum one-hour level recorded being 160 $\mu g/m^3$.

The city was divided into a polluted area, with 878 births and an area which is relatively free of pollution, with 1,208 births. Thus, only pollution in the place of residence was counted. An analysis of covariance was used to control confounding factors, when birth weight was adjusted in the groups by parental smoking and environmental pollution (Tables 4 and 5), and also parental smoking and the number of

Table 6. Effects of paternal smoking and other factors on low birth weight in full-term deliveries (at least 37th gestational week), according to logistic regression

Variables	Exp (β coefficient)	95% CI	p
1. Maternal smoking	1.5126	1.21–1.90	0.000
2. Twin delivery	4.3501	3.39–5.59	0.000
3. Height of the mother	0.9515	0.92–0.98	0.000
4. Sex of the child	1.3999	1.17–1.67	0.000
5. Diastolic blood pressure in 30–36th week of pregnancy	1.0597	1.04–1.08	0.000
6. Maternal weight at 16th week	0.9719	0.95–0.99	0.001
7. Breech presentation	1.4620	1.12–1.90	0.005
8. Systolic blood pressure in 30–36th week of pregnancy	1.0237	1.01–1.04	0.009
9. Diastolic blood pressure before 20th week of pregnancy	0.9770	0.96–1.00	0.012
10. Parity	0.8437	0.73–0.97	0.016
11. Urinary tract infection	1.3268	1.03–1.71	0.021
12. Place of residence north/south	0.7126	0.54–0.94	0.021
13. Earlier place of residence	0.7854	0.63–0.97	0.022
14. Bleeding during pregnancy	1.2928	1.03–1.63	0.028
15. Maternal schooling	0.8712	0.78–0.97	0.031
16. Previous low birth weight infants	1.7288	1.21–2.47	0.034
17. Maternal employment	0.8259	0.68–1.01	0.049
18. Paternal smoking	1.1767	0.98–1.41	0.076

rooms in the house. Forty-three confounding factors were considered in the former case (Table 3) and five in the latter. The association of passive smoking with low birth weight (<2,500 g) rate was examined by multiple logistic regression analysis according to a stepwise method, adding all the variables which were significant at the 0.10 level to a model which contained the passive smoking variable (paternal smoking, Table 6).

Results

In order to study the combined effect of maternal and paternal smoking and industrial pollution on birth weight, the series was divided into four groups with the families living in the areas with obvious air pollution and those in areas relatively free of pollution divided into cases in which the mother smoked and cases with non-smoking mothers. A covariance analysis was performed for birth weights within these four groups, adjusted for 43 confounding background variables. Birth weight by maternal smoking and air pollution in the place of residence, adjusted by an analysis of covariance, is seen in Table 4. The statistical significance of maternal smoking and environmental pollution is given in Table 5, in which only statistically significant background variables are indicated. Paternal smoking was not significant (p 0.900). Maternal smoking was found to have a statistically highly significant effect on birth weight, but environmental pollution had not, neither was the interaction between maternal smoking and industrial pollution significant. The same was repeated with respect to the father's smoking. Paternal smoking had no significant effect on birth weight (p 0.4847). The rate of low birth weight

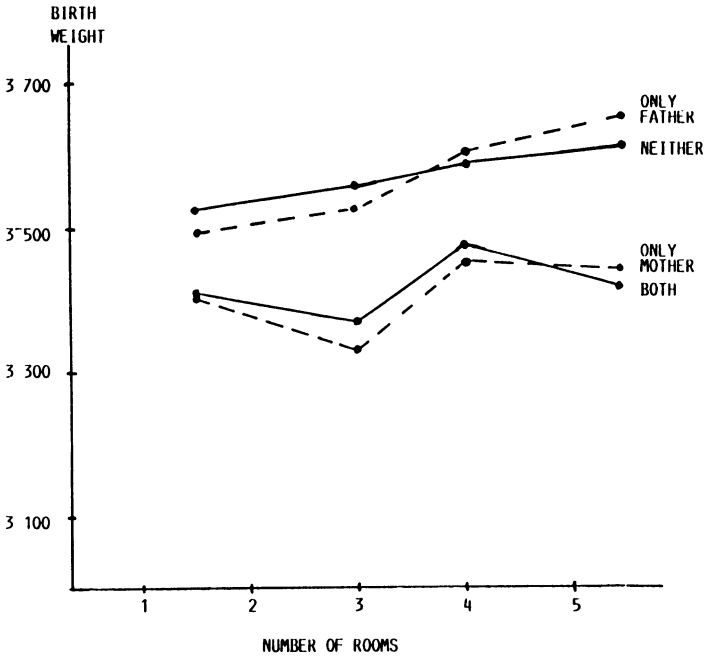

Fig. 1. Birth weight by parental smoking and number of rooms in the house

infants, <2,500 g was 4.0% in the polluted area of the city and 3.5% in the clean area, the difference being not significant (p 0.491).

The effect of maternal and paternal smoking on birth weight was further studied in the total series in relation to the number of rooms in the house, the families being divided into four groups according to the parents' smoking habits: 1) only the mother, 2) only the father 3) both parents, and 4) neither of them. Figure 1 presents birth weight by parental smoking and number of rooms in the house. It is seen that the birth weight curve when only the father smoked is very similar to that found when neither parent smoked, and that birth weights among the children whose parents both smoked are very similar to those for the children whose mother alone smoked. Mean birth weight was slightly lower in the cases of smaller houses in each of these groups, the explanation for this being studied by examining birth weight in groups with different numbers of rooms in the house and different maternal and paternal smoking habits by covariance analysis with maternal age, parity, height, years of schooling and father's social class adjusted. The effect of maternal smoking was highly significant (p 0.000) and the number of rooms significant (p 0.002) but they had no significant interaction (p 0.189). Because of this lack of interaction, the variable number of rooms probably reflects social standing rather than a more polluted atmosphere in the smaller houses. This finding did not alter when paternal smoking was adjusted in the analysis. The opposite was found when the effect of paternal smoking and the number of rooms was studied, paternal smoking being significant only when no adjustment was made for maternal smoking.

The percentage of low birth weight infants <2,500 g was 5.3% among the smoking mothers and 3.6% among the non-smokers, the difference being statistically highly

significant (p 0.000). The corresponding figures for paternal smoking were 4.5% and 3.7%, the difference being without statistical significance (p 0.113). The low birth weight rate among the full-term infants (at least 37 gestational weeks) was 2.0% among the smoking fathers and 1.4% among the non-smokers, the difference being significant (p 0.023). When multiple logistic regression analysis was performed for term low birth weight infants with 57 explanatory variables, paternal smoking had no significant effect on the low birth weight rate (Table 6). The percentage of low birth weight infants was 5.6% when both parents smoked and 3.7% when neither of them smoked, this difference being statistically highly significant (p 0.0004). In cases in which only the mother smoked the low birth weight rate was 4.8%, while if only the father smoked it was 3.8%.

Discussion

The finding that maternal smoking decreases birth weight is similar to those in numerous previous studies [5]. Far less is known of passive smoking among pregnant mothers. In contrast to the retrospective Danish study by Rubin et al. [6], our prospective study could not find any significant effect of paternal smoking on birth weight. For them, paternal smoking had nearly as large an effect as maternal smoking in term deliveries (66%). No statistically significant difference was found in the rate of low birth weight infants either in the total series or among the full-term infants when confounding factors were controlled in our study, the latter finding being different to that of Martin and Bracken [3]. Our study similarly could not show any significant effect of environmental pollution birth weight. It is obvious that more research is needed to find which of these contradictory findings is correct. Unusually many confounding variables were taken into consideration here when analysing the effects of parental smoking and environmental pollution, but even so environmental pollution was assessed only respect to place of residence but not the place where the mother worked, for example. Neither was it recorded how much the father smoked indoors at home. Further studies are thus needed before we understand fully the relationship between exposure to toxic substances and conditions and growth of the foetus.

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Effect of Sidestream Smoke (Passive Smoke) on Cell Viability and Interferon Production*

G. Sonnenfeld

Summary

Several studies have been carried out to evaluate the toxicological effects of sidestream smoke. The work carried out in our laboratory will be reviewed herein. Sidestream (passive) smoke has been generated utilizing the peristaltic pump smoking machine. This machine allows for simultaneous exposure of specimens to sidestream and mainstream smoke. The target cells used were the murine L-929 fibroblast-like cell line. Exposure of these cells to sidestream smoke from the 2R1 reference cigarette resulted in dose-dependent cytotoxicity. Use of the 1R4F reduced yield cigarette also resulted in dose-dependent cytotoxicity. A lower dose of sidestream smoke from the 1R4F cigarette was required to generate 50% cytotoxicity of L-929 cells than when sidestream smoke from the 2R1 cigarette was used. The effects of sidestream smoke exposure on production of interferon-alpha/beta, an antiviral, anticancer, and immunoregulatory substance, was also determined. Production of interferon by L-929 cells was inhibited severely after exposure of the cells to non-cytotoxic doses of sidestream smoke from the 2R1 cigarette. Filtration of the smoke through activated charcoal reduced the inhibition of interferon production. In addition, aging of the smoke also resulted in reduction of the inhibition of interferon induction.

Introduction

Over the past several years, a peristaltic pump smoking machine has been used in our laboratory to study the ability of sidestream (passive) smoke to induce various toxic effects in a cell culture system. These *in vitro* studies will now be reviewed in this paper.

The smoke exposure system used was the peristaltic pump smoking machine especially adapted for exposure of tissue cultures (Griffith 1985; Griffith and Hancock 1985). Cultures of L-929 cells, a murine fibroblast-like line, were grown to confluency and exposed to sidestream smoke. The cytotoxic effects of the sidestream smoke generated from a 2R1 unfiltered reference cigarette were determined (Sonnenfeld et al. 1985). In addition, these effects were compared with the cytotoxic effects of sidestream smoke from the 1R4F filtered, ventilated, reduced yield experimental cigarette (Sonnenfeld and Wilson 1987).

The interferon system was originally described as an antiviral defense system, but may play a role in defenses against respiratory tract infections and cancer (Sonnenfeld and

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Hudgens 1986). Therefore, it was of interest to extend the toxicity studies to the interferon system. The effects of sidestream smoke exposure on production of interferon-alpha/beta by L-929 cells was determined (Sonnenfeld and Hudgens 1986). In addition, the effects of filtration of sidestream smoke through activated charcoal and aging of sidestream smoke on the ability of that smoke to affect interferon production was determined (Sonnenfeld and Hudgens 1987). In this fashion, an attempt was made to begin to establish a toxicological profile for the sidestream smoke generated using the peristaltic pump smoking machine.

Material and Methods

The Peristaltic Pump Smoking Machine

A peristaltic pump smoking machine (Griffith and Hancock 1985) provided by the Kentucky Tobacco and Health Research Institute was utilized for all exposure studies. This machine has been described in detail elsewhere (Griffith and Hancock 1985). Sidestream and mainstream smoke were generated as described previously (Sonnenfeld et al. 1985; Sonnenfeld and Hudgens 1986; Sonnenfeld and Wilson 1987). Smoke was filtered by placing acetate filters with or without activated charcoal between the pump and the dilution chamber (Sonnenfeld and Hudgens 1986). Aging of smoke was carried out by placing 2.5 cm diameter glass chambers of differing lengths between the smoke source and the tissue culture flasks that were to be exposed to smoke (Sonnenfeld and Hudgens 1987).

Cigarettes

The 2R1 cigarette was used in most experiments. This cigarette is the University of Kentucky standard research cigarette with high tar and no filter. It was designed to approximate cigarettes in popular use in the 1950's (Huber and Vaught 1979). In some experiments, the 1R4F cigarette was used. This is a reduced-yield University of Kentucky experimental cigarette with a filter and 30% tip dilution. It has more porous and faster burning paper than the 2R1 cigarette, and it approximates modern cigarette design (Davis et al. 1984). When the effects of smoke from the two cigarettes were compared, similar smoke exposure conditions were used.

Tissue Culture Procedures

Murine L-929 cells were grown to confluency in Falcon 25 cm tissue culture flasks (Falcon Plastics, Oxnard CA). Culture and exposure procedures and parameters have been described elsewhere in detail (Sonnenfeld et al. 1985; Sonnenfeld and Hudgens 1986). Flasks of cells used as controls were subjected to all experimental procedures except smoke exposure and were included in all experiments. Viability of cell cultures was determined 24–48 h after smoke exposure by means of trypan blue dye exclusion. Mortality of all control cultures was less than 20%.

Interferon Procedures

Murine interferon-alpha/beta was induced with polyriboinosinic-polyribocytidylic acid as described previously (Dianzani et al. 1968; Sonnenfeld and Hudgens 1986). Interferon induction was carried out 24 h after smoke exposure, and the highest dose of sidestream smoke that did not induce obvious mortality was used. The mortality as assessed by trypan blue dye viability staining was 9%, and cells that had been exposed to smoke could be cloned to new cultures and would divide and grow (Sonnenfeld and Hudgens 1986). Cultures were incubated for 24 h at 37°C in 5% CO before supernatant fluids were harvested and assayed for interferon activity by means of a plaque reduction assay using the Indiana strain of vesicular stomatitis virus on L-929 cells (Hanna et al. 1966; Sonnenfeld and Hudgens 1986). The interferon titer corresponded to the reciprocal of the greatest dilution of test samples that reduced virus plaquing by 50%. In this assay system, one unit of interferon was equivalent to 0.88 NIH G-002-904-511 reference standard units.

Results

The Cytotoxic Effects of Sidestream Smoke

L-929 cells were exposed to mainstream and sidestream smoke from the 2R1 cigarette. Viability was determined by trypan blue dye exclusion. There was a dose-dependent cytotoxic effect of sidestream smoke that could be diluted by air (Sonnenfeld et al. 1985) (Table 1). It was also possible to obtain non-toxic doses of smoke exposure (Sonnenfeld et al. 1985). In addition, when cytotoxic effects of mainstream smoke from the 2R1 cigarette were compared with those from the 1R4F cigarette, there was a greater cytotoxic effect of mainstream smoke from the 2R1 cigarette (Sonnenfeld and Wilson 1987) (Table 2). When cytotoxic effects of sidestream smoke from the 2R1 cigarette were compared with those from the 1R4F cigarette, there was a greater cytotoxic effect of sidestream smoke from the 1R4F cigarette (Sonnenfeld and Wilson 1987) (Table 2).

Table 1. The cytotoxic effects of smoke from the 2R1 cigarette

Type of smoke	Cytotoxicity generated as smoke dose increases
Mainstream	Cytotoxicity increases
Sidestream	Cytotoxicity increases

Table 2. Comparison of the cytotoxic effects of smoke from the 2R1 and 1R4F cigarettes

Type of smoke	Cigarette yielding smoke with greater cytotoxicity
Mainstream smoke	2R1 > 1R4F
Sidestream smoke	1R4F > 2R1

Table 3. Effect of sidestream smoke from the 2R1 cigarette on interferon-alpha/beta induction in L-929 cells

Exposure of cells	Effect on interferon-alpha/beta induction
Sidestream smoke	Inhibited
Sidestream smoke filtered through 100 mg activated charcoal	Return to near normal
Sidestream smoke aged for 8 s	Return to near normal

The Effects of Sidestream Smoke on Interferon-alpha/beta Production

L-929 cells were exposed to doses of sidestream smoke from the 2R1 cigarette that induced minimal (less than 20%) mortality (Sonnenfeld and Hudgens 1986). Confluent cells were exposed to 4 puffs of 50% of generated sidestream smoke from the 2R1 cigarette. Cells were returned to the incubator, medium replaced, and then allowed to incubate at 37°C in 5% CO for 24 h (Sonnenfeld and Hudgens 1986). The cells were then challenged with polyriboinosinic-polyribocytidylic acid and then alllowed to incubate for an additional 24 h, at which point cell supernatant fluids were removed and assayed for interferon activity (Sonnenfeld and Hudgens 1986). Exposure of the cells to sidestream smoke under these conditions inhibited severely the induction of interferon-alpha/beta in those cells (Sonnenfeld and Hudgens 1986) (Table 3). Filtration of the smoke through 100 mg of activated charcoal or aging of smoke for 8 s prior to reaching the cells resulted in an abrogation of the inhibitory effects of the sidestream smoke on interferon-alpha/beta production (Sonnenfeld and Hudgens 1986)(Table 3).

Discussion

The results reviewed in this paper indicate that sidestream smoke has the potential to be cytotoxic to cells in culture (Sonnenfeld et al. 1985; Sonnenfeld and Wilson 1987). In addition, sidestream smoke exposure can inhibit the induction of interferon-alpha/beta, an important host defense and regulatory substance, in these cells (Sonnenfeld and Hudgens 1986).

Using the peristaltic pump smoke machine, it has been shown that there is a dose-dependent cytotoxic effect of sidestream smoke, and that the smoke can be diluted with air to lessen cytotoxic effects (Sonnenfeld et al. 1985). In addition, aging or filtration of smoke also decreased cytotoxic effects (Sonnenfeld et al. 1985).

When cytotoxic effects of mainstream smoke from the 2R1 cigarette were compared with the cytotoxic effects of mainstream smoke from the 1R4F cigarette, the mainstream smoke from the 2R1 cigarette appeared to have a greater cytotoxic potential (Sonnenfeld and Wilson 1987). This might be due to the tip dilution of smoke in the filter of the 1R4F cigarette (Sonnenfeld and Wilson 1987). However, when the cytotoxic effects of sidestream smoke from the two cigarettes were compared, sidestream smoke from the 1R4F cigarette appeared to have a higher cytotoxic potential (Sonnenfeld and Wilson 1987). This could perhaps be due to an increased level of toxic materials in the gas phase of sidestream smoke generated from the 1R4F cigarette (Leuchtenberger and Leuchtenberger 1971, 1976; Leuchtenberger et al. 1974; Pryor et al. 1984; Sonnenfeld and Wilson 1987).

Interferon-alpha/beta production was inhibited after exposure of cells to non-cytotoxic doses of sidestream smoke (Sonnenfeld and Hudgens 1986). However, when the smoke was either filtered through activated charcoal or aged prior to reaching the cells in the exposure chamber, the effects of sidestream smoke on interferon-alpha/beta production were abrogated (Sonnenfeld and Hudgens 1986). Therefore, the gas phase of sidestream smoke appears to play a major role in generating the effects of the sidestream smoke on interferon production. In addition the inhibitory effects of sidestream smoke on interferon-alpha/beta production appear to be of limited duration after generation of the smoke (Sonnenfeld and Hudgens 1986).

The results reviewed in this paper suggest that sidestream smoke can have toxic effects on cells and can inhibit the induction of interferon. These could be seious deleterious effects for a host. However, the toxic effects of sidestream smoke *in vivo* in an actual environmental tobacco smoke situation remain to be established by further experimentation and modeling.

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Passive Exposure to Nicotine in Daily Environment

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Summary

Passive smoking is a typical example of indoor air pollution occurring in daily living spaces such as offices and homes and is a topic of extensive dispute throughout the world from the viewpoint of health effects on those within these spaces, as shown in the Surgeon General's Report [1] and Weiss et al. [2]. However, there are relatively few quantitative analyses of how ambient spaces are polluted by secondhand smoking and how the residents within these spaces are exposed to secondhand smoke. As a step to clarify the actual situation of passive smoking, we started to measure environmental nicotine concentration in daily life [3].

This study is in two parts. The first consists of measurements of nicotine concentration in the air of various spaces such as offices, restaurants, cars and houses. The second is an analysis of nicotine exposure of individuals who are walking and moving at random in these spaces.

Method

For the quantitative analysis of nicotine, a solid state sampling method was utilized. In the analysis of nicotine in indoor environment, the method utilized was originally developed by our coworkers Matsushita and Mori [4]. The equipment consists of a sampler tube (glass tube, 12 mm i.d., 15 mm long) and a handy sampling pump (2.3 kg in weight, Kimoto HS-A, Japan). The sampling tube contains 0.4 g of acid treated diatomite, Uniport-KA, as a nicotine absorbent. Ambient nicotine was collected on the sampler tube by drawing air through the tube at a constant rate of 1.5 liters/min with the handy sampler. Absorbed nicotine in Uniport-KA is dissolved with alkaline methylalcohol after adding quinoline as an internal standard. After ultrasonic mixing for 10 min, and centrifugation at 3,000 rpm for 10 min, nicotine within the supernatant is measured by a gas chromatograph with a thermionic detector. Nicotine of more than 0.5 microgram per cubic meter is measurable by this method.

In the analysis of personal exposure to ambient nicotine, the sampling system consists of a sampler tube (pyrex glass, 12 cm long, 6 mm i.d.) and a small sampling pump (about 340 g; MDA Scientific Inc., Model 808) [5]. The personal pump can be carried conveniently by subjects throughout a sampling period. The sampler tube contains 0.45 g of acid treated Uniport-S. Ambient nicotine was collected on the sampler by drawing air through the tube at a flow rate of 40 ml per min for a period of 1 to 8 h. The nicotine absorbed on the sampler was treated similarly and measured with the gas chromatograph as described above.

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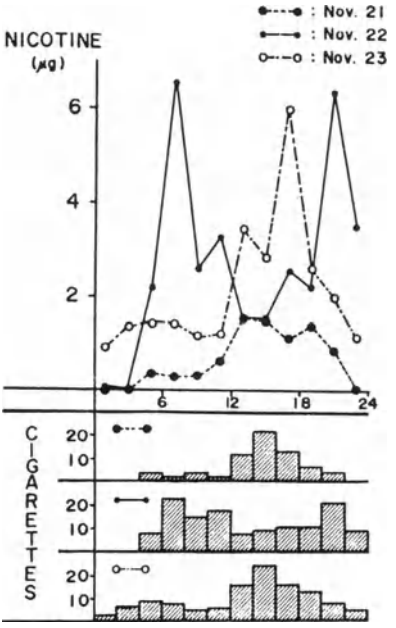

Fig. 1. Variation of nicotine concentration in a lobby attached to the ward in a hospital through 3 consecutive days, which is open to visitors for hospitalized patients. (See details in text)

Results

Analysis of Ambient Nicotine in Daily Environment

Figure 1 shows results obtained in a lobby attached to the ward in a hospital. This room is always open to visitors of hospitalized patients. The nicotine sampler was set at the center of the lobby. Continuous measurements were taken for three whole days from November 21 to 23. The X axis is the time from zero to 24 hours. The Y axis in the upper half is the mean concentration of nicotine for one hour in the room air in micrograms per cubic meter. The lines connecting the small, large and open circles depicted in the upper graph show the variation of nicotine concentration with time. On November 21, the concentration in the afternoon was higher than in the morning. On November 22, there were two peaks in the early morning and late afternoon. The figure in the lower half shows the number of cigarettes consumed during the respective sampling period.

Figure 2 shows the mean concentrations of nicotine measured in 2 office rooms of a private company, in an office room of a hospital and in 3 public houses such as bars during the respective working hours (from 8 a.m. to 5 p.m. in the offices and from 6 p.m. to 12 p.m. in the bars). The difference is very clear between the office rooms and public houses. The concentration is less than ten micrograms per cubic meter, and its variation is quite narrow in the offices. On the other hand, the concentrations in the public houses are more than 30 micrograms per cubic meter in bars A and C and 16.0 micrograms in B. Furthermore, the variation in concentrations is very wide. In the lower half of the figure, the mean of the total measurements and its variation are shown with the sample number.

Figure 3 shows results obtained in domestic airplanes and in the Superexpress, Shinkansen, in Japan. The samples were obtained from smoking and nonsmoking seats

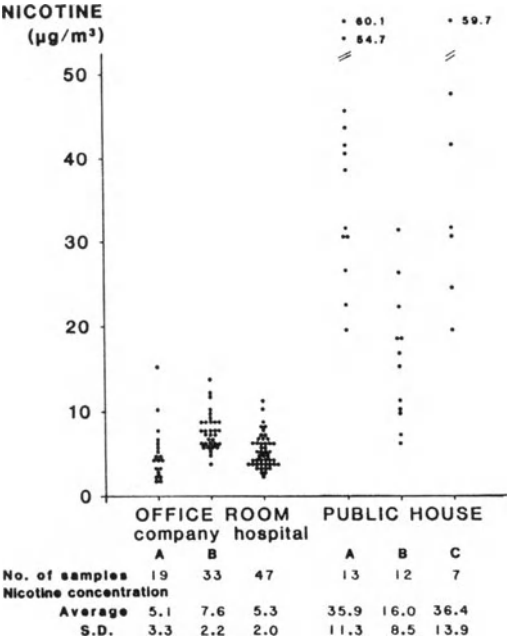

Fig. 2. Concentration of nicotine in 2 office rooms in a private company, a business office in a hospital and 3 public houses. (See details in text)

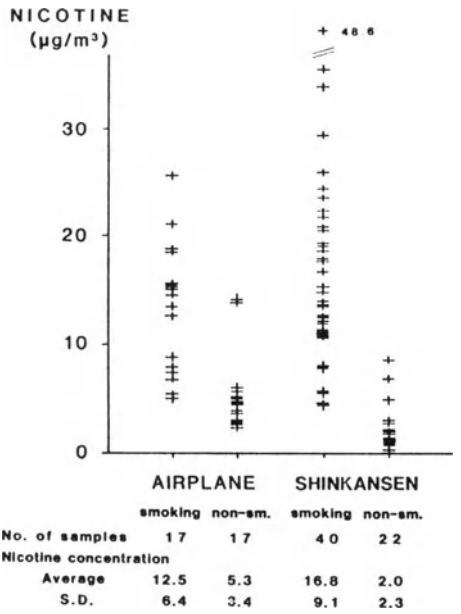

Fig. 3. Concentration of nicotine at smoking permitted and nonsmoking seats in domestic airplanes and Super-express trains, Shinkansen, in Japan. (See details in text)

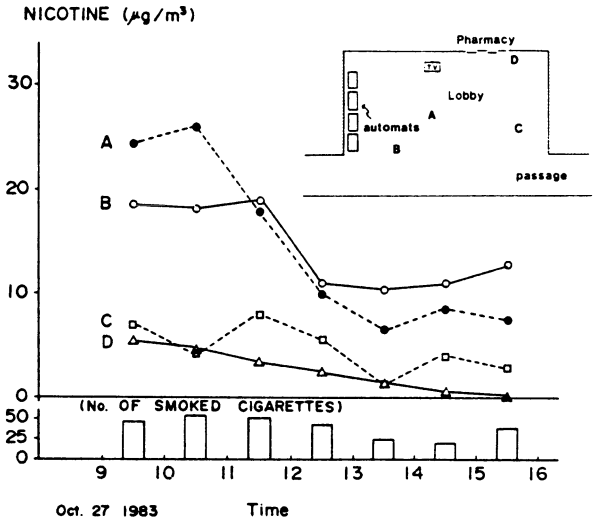

Fig. 4. Variation of nicotine concentration in a waiting lobby at the front of the pharmacist's office in a hospital. (See details in text)

in both types of transportation. In both, the mean concentration is clearly lower and their variations are more narrow in the nonsmoking seats than in the smoking seats, as shown in the lower half of the figure.

Figure 4 shows results obtained in a waiting lobby at the front of the pharmacist's office in Jichi Medical School. The space is 24 m × 12 m × 2.7 m in size and open to a passage of 24 m × 5 m × 2.7 m in size. It has artificial ventilation with a rate of 8.1 times per hour. Within this space, there are 170 seats. An average of 1,500 patients in the outpatient clinic each day wait about 30 minutes for delivery of their prescribed drugs. As shown in the inserted figure, there is a TV set and vending machines for magazines, food and drink. We set four samplers at spots A, B, C and D, and sampled airborne nicotine continuously in these spots from 9 a.m. to 4 p.m. As in the previous figure, the X axis is time in hours, and the Y axis in the upper part is concentration of nicotine while that in the lower part is the number of cigarettes consumed during the sampling period. As shown in the figure, the nicotine concentration is not distributed uniformly in space or in time. In spots A and B which are close to the TV set and to the vending machines, the concentration is higher than in spots C and D. Furthermore, the concentration in each of the four spots is higher in the morning than in the afternoon, in relation to the number of outpatients within the hospital.

Figure 5 gives another example of topographical difference in nicotine concentration within a closed space. This result was obtained at a paty of 20 persons. The size of the room is 6 m × 3.4 m × 2.3 m. The ventilation of the room is not automatically set, and purely dependent on voluntary opening of the windows and doors by party guests. As shown in the figure, nicotine was sampled at two spots, A and B. Spot A is close to a window, and spot B is in front of sliding doors. The mean concentration of nicotine in spot A is 90.3 ± 43.5 micrograms per cubic meter and clearly higher than in spot B where the mean is 15.8 ± 12.1 micrograms per cubic meter. This can be explained by the frequent opening of the door by party guests entering and leaving. A sharp drop observed around hour 20 on the record from A coincided with an opening of the window behind this sampling spot.

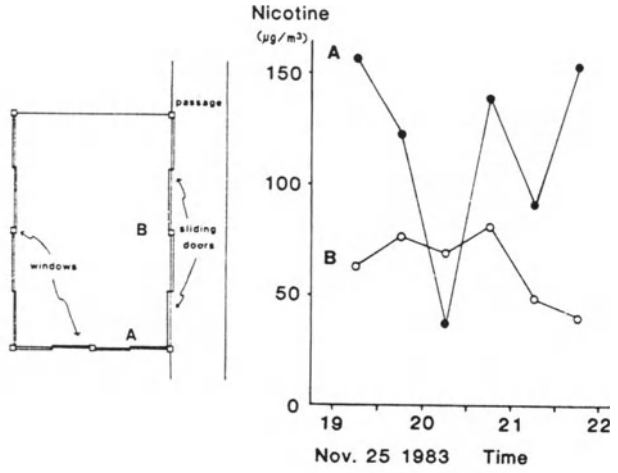

Fig. 5. Variation of nicotine concentration in a party room. A schematic presentation of shape of the room, arrangements of window and sliding doors in the rooms and two sampling sites are shown on left. (See details in text)

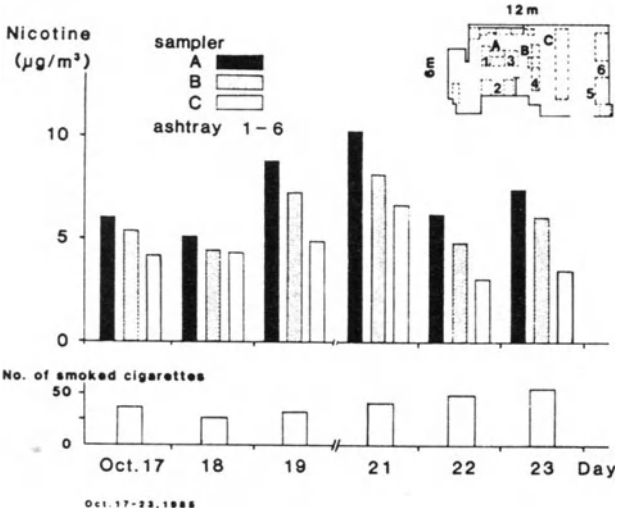

Fig. 6. Variation of personal exposure for nicotine of three office ladies for a period of 6 days in a bank office. (See details in text)

Personal Exposure to Ambient Nicotine in Daily Environment

The sampler is carried by subjects in a pocket or in a handbag. With a sampler it is possible to collect nicotine for 8 h.

Figure 6 represents results obtained in a tiny bank office, 12 m × 6 m × 2.7 m. Three nonsmoking office ladies, A, B and C, assisted in our study. Each carried a personal sampler for 6 days, from 9 a.m. to 4 p.m. They usually sit during their business hours, as shown in the inserted figure. Numbers 1 to 6 denote the locations of ashtrays in the office room. Ashtrays 1 to 4 are for the use of three smoking male staff members, and 5 and 6 are for customers. Regular ventilation, 8 times per hour, is set automatically within this space. The X axis of the figure is the date and the Y axis is the mean concentration of

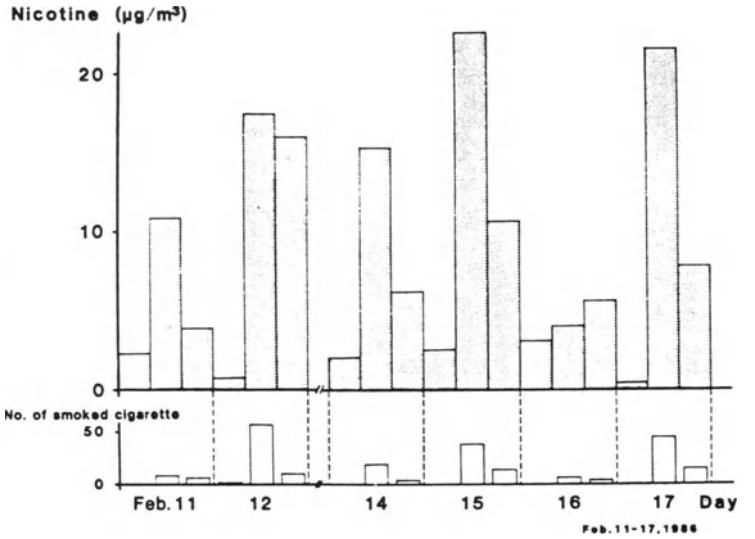

Fig. 7. A record of the personal exposure of a nonsmoking, married office lady through 6 consecutive days. (See details in text)

nicotine per day in micrograms per cubic meter, from October 17 to 23, 1985. As is shown in the upper graph, personal exposure to nicotine is not the same for the three office ladies, even though they work in close proximity throughout their working day. As is shown in the lower half, the number of cigarettes consumed by the smoking staff members and customers ranged from 25 to 50 per study day.

Figure 7 depicts the personal exposure of an office lady, measured for 6 consecutive days as shown on the X axis. She is a nonsmoker, but her husband is a smoker. Smoking is permitted in her office, and there are many smoking visitors each day. In the graph, the results for each day are portrayed in three columns. The first column shows results obtained during the previous night, from 10 p.m. to 6 a.m.; the second, results from 8 a.m. to 4 p.m.; and the third results from 4 p.m. to 10 p.m. February 11 and 16 were a national holiday and Sunday respectively, and the subject stayed at home for the whole day. From these results it is clear that she is exposed to her husband's smoking when she gets back to her house, but her exposure to nicotine is more serious in her office than in her house.

Discussion

From the results obtained in the first part of our study it is clear that the room size and the amount of ventilation as well as the amount of tobacco smoked per unit time strongly influence the concentration of nicotine. Furthermore the nicotine level fluctuates widely from spot to spot and time to time in the respective space (Figs. 1 and 4). Because the room size and the amount of ventilation are fixed in the respective space, the first and most important step for controlling nicotine concentration in room air is to limit smoking. This is clearly shown by the different results obtained between smoking and nonsmoking seats in trains and airplanes (Fig. 3).

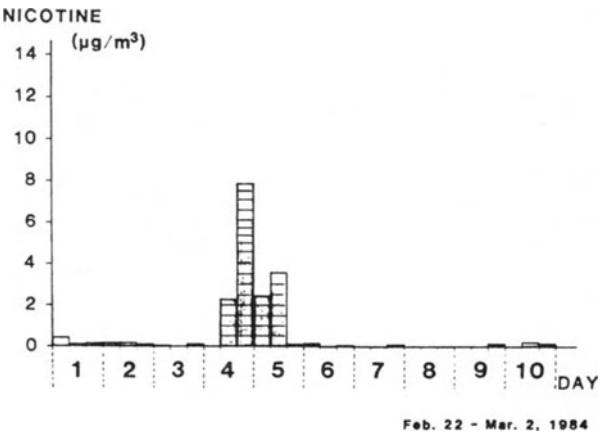

Fig. 8. A record of the personal exposure of a housewife from a non-smoking family through 10 consecutive days. (See details in text)

The concentrations of nicotine obtained in various spaces in our study are consistent with those reported by Hinds and First [6] and by Weber and Fisher [7]. From these results it may be said that the nicotine level in the daily environment will rarely exceed 100 micrograms per cubic meter. The nicotine concentration is not constant in these spaces and fluctuates spatially and with time as we showed clearly. Furthermore, the individual who is in danger from passive smoking moves quite unpredictably and at random within these spaces. Therefore, it is not proper to consider the problem of passive smoking based only on results of average nicotine concentration in environmental air. This is the reason why we carried out the second part of our study: an analysis of personal exposure to nicotine.

Contrary to what we might have expected, personal exposure was not identical for three office ladies who worked in close proximity in a tiny office throughout their business day (Fig. 6). This may be explained by the spatial unevenness of nicotine in environmental air, and the unpredictable and random movement of subjects within the space.

The results are not shown in the text, but personal exposure is clearly heavier for subjects who are living with a smoker in their family than for subjects living without a smoker. However, as shown in Fig. 7, the exposure of a nonsmoking lady was more serious in her office than in her house where she lived with her smoking husband.

As detailed above, analysis of the personal exposure is quite complicated and not easy to carry out. But it is also true that nobody can escape from exposure to nicotine these days because of unexpected sources of nicotine. We have evidence of the unexpected exposure of a nonsmoking housewife during shopping (Fig. 8) and of a 6-year-old girl during her stay with her smoking grandfather.

The problem to be solved in the future is to determine what correlation exists between personal exposure as measured in the present study and the real amount of nicotine absorbed into the body. Along these same lines, analysis of the physical response induced by absorbed nicotine is another important topic to be studied.

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Chapter 3:
Epidemiology of Passive Smoking

Harvard's Indoor Air Pollution Health Study

J. D. Spengler

Introduction

It is well established that indoor sources of air pollutants in homes, offices, public buildings, and transportation vehicles can result in higher indoor concentrations of contaminants. However, in epidemiologic studies it may not be entirely sufficient to characterize subject exposure with a description of sources and source use. Emission rates vary, source use varies, and air exchange rates differ among homes, as well as other structures. Therefore, questionnaires will not be adequate for many contaminants. This point is illustrated by the distribution of annual indoor home concentrations of NO_2 shown in Fig. 1.

One-hundred gas cooking homes in Portage, Wisconsin were monitored using integrating passive samplers. Annual concentrations range from 15 $\mu g/m^3$ to 150 $\mu g/m^3$. While a question about cooking fuel differentiates mean concentrations in gas versus electric homes, descriptive questions cannot predict indoor concentrations within a gas cooking home.

Recognizing the limitation of questionnaires, we designed a more comprehensive indoor air pollution survey to characterize exposures in a multi-city air pollution health study. Several personal exposure studies have demonstrated that indoor (home) concentrations of respiratory particles, nitrogen dioxide, CO etc. are predictive of personal exposures [1–4]. Therefore, a microenvironmental monitoring approach was adapted for characterizing exposures to elementary school-age children. Homes, schools and ambient environments were monitored for respiratory particles (PM 2.5) and nitrogen dioxide (NO_2).

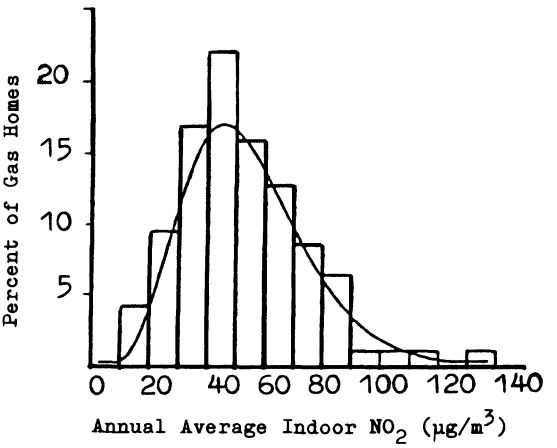

Fig. 1. Distribution of annual mean indoor NO_2 concentrations for approximately 100 gas cooking homes in Portage, WI

H. Kasuga (Ed.) Indoor Air Quality

This paper describes the design and preliminary results of Harvard's Indoor Air Pollution Health Study. This study was conducted in six U.S. cities between 1984 and 1988: Watertown, MA; Kingston, TN; St. Louis, MO; Steubenville, OH; Portage, WI; Topeka, KS. Approximately 1,000 children in the 3rd to 5th grades in each community were administered two annual Health Characterization Questionnaires (HCQ) through the schools. In addition, pulmonary functions were measured. Using the first HCQ, homes were stratified on the presence of sources for NO_2 and particulate matter. The indoor environments of approximately 300 homes were monitored over a year. Children in these homes participated in a diary survey of daily respiratory symptoms.

Design Overview

The first annual HCQ was administered through the school system to children in grades 3 to 5. Parents completed a questionnaire that includes a history of respiratory illnesses, respiratory symptoms over the previous 12 months, and several items on potential home factors. Pulmonary function measurements were made on the children in the schools. Details are presented elsewhere [5, 6]. A second HCQ and exam was administered approximately one year later.

Using the results of the first HCQ, homes were stratified based on the presence or absence of gas cooking and parental smoking. In most of the communities four cells were selected. The homes were randomly selected within these cells to participate in a year-long respiratory health diary study. The cells had unequal weights because concentrations within homes with sources had been shown to have greater variation. In Kingston, Tennessee and Portage, Wisconsin, additional stratification was based on wood and kerosene heating fuels.

Approximately 350 children were recruited to participate in a respiratory symptoms diary study starting in October. Mothers were instructed on how to use a calendar to record symptoms and severity from a set of predefined conditions. Table 1 lists symptoms that were recorded on the calendar. Approximately every two weeks the mother was called to read off symptoms. At the end of each month, calendars were returned to Harvard for entry and for comparison to the data obtained by telephone. Preliminary analysis of symptoms have identified three clusters of symptoms. One set of symptoms appears to reflect upper respiratory tract infection, another reflects lower respiratory tract infection, and a third allergenic conditions. Table 1 lists symptoms and severity of symptoms included in the diary. Only preliminary health analysis has been performed because the study has not been completed for all cities.

The exposure component consisted of a core set of parameters that were measured in all homes. Measurements consisted of integrated week-long NO_2 and particle samples

Table 1. Symptoms included in Harvard's respiratory health diary

Hoarseness	Ear pain or discharge
Sore throat	Runny or stuffed nose
Cough	Burning, aching or red eyes
Phlegm from the chest	Restricted activities
Pain in the chest	Saw doctor or nurse
Wheezing	Hospitalized
Fever	Healthy or none of the above

collected during the winter and summer. School and outdoor measurements were made to the complete assessment of the primary microenvironments for children.

Indoor Air Quality Assessment

A large variety of contaminants have the potential to cause or aggravate respiratory symptoms. However, the primary focus of this Harvard study was two combustion sources: tobacco and cooking fuel. Thus, particulates and nitrogen dioxide were measured in every home to derive an exposure estimate for each child.

It was recognized that other contaminants might be important contributors to respiratory symptoms or might be confounding results. Additional substudies were performed. First, questions about mold, mildew and moisture were included in the follow-up HCQ. Preliminary analysis indicated significant association among these factors and respiratory symptoms. Fungal and bacteria sampling were then performed in a subset of homes, in four cities, to examine the relationship among these categorical descriptions and actual contamination levels.

Substudies were performed to determine the impact of woodburning stoves and kerosene heaters. These sources were more prevalent in two of our communities: Kingston, TN and Portage, WI.

In order to quantify the impact of sources to indoor air pollution, additional investigations were conducted. A subset of homes (approximately 30) were monitored for two weeks in each of the four seasons. Air exchange measurements were made using a tracer gas method. Further, in several hundred homes the particulate samples were analyzed for elemental composition, ionic concentrations of sulfates and nitrates.

The monitoring protocol required two winter weeks (November–March) and two summer weeks (May–August) of monitoring in each home. Previous year-round studies had indicated that between 70 and 90 percent of the pollution concentration variance within a home type was accounted for by capturing the seasonal variations. Nevertheless, a set of 30 homes were monitored in each season. Particulate samplers had pre-separation impactors to collect only particles less than 2.5 μm diameter [7]. The device had 14 day times that were set to operate when the child was expected to be at home. This was approximately 128 hours per week. Filters were changed each week. Thus, most homes had four week-long particle samples. Integrating, passive NO_2 diffusion tubes were placed in the kitchen, living room, bedroom and outdoors [8]. For the first three communities the integration time was one week. Because the week-to-week correlation was very high ($R^2 > 0.75$) the sampling times were changed for the last three communities to two weeks for both winter and summer.

Passive water vapor tubes were also placed in each home. These one-week integration tubes provide a measure of moisture content of the air in a home that can be converted to relative humidity.

In a subset of approximately 100 homes per city, air exchange rates were estimated from the dilution of a conservative tracer gas that was being leaked continuously into the home [9]. Sources of a non-reacting perfluorocarbon molecules were placed in a central region of the home, and up to four passive charcoal collections were placed in various rooms of the home. Whole house air exchange rate was calculated by the average across the interzonal concentrations.

Results

This research is ongoing and only partial results are available at this time. Summarized in this paper are the concentrations of NO_2 and respirable particles sampled in five of the six cities. This paper highlights the findings for several of the substudies conducted.

Nitrogen Dioxide

The ambient sources of nitrogen dioxide are automobiles and fossil fuel combustion from power plants and industries. Auto exhaust is the primary source in our six communities. Ambient concentrations ranged from a city mean of 8 ppb in Portage, Wisconsin to 24 ppb in St. Louis, Missouri. There was a pattern of lower ambient concentrations in the smaller, more rural towns versus larger metropolitan areas. The percent standard deviation of the outdoor measurements were between 15 and 20 percent. The rural communities had greater spatial variation in NO_2 that reflected differences in auto traffic density. Similarly, higher concentrations were noted near intersections and heavily travelled roadways in the larger communities.

Indoor sources of NO_2 included gas cooking fuels, unvented kerosene and gas heaters, and faulty gas furnaces and waterheaters. The influence of gas cooking on indoor concentrations is most notable. In homes with gas cooking, the kitchen concentrations are higher than the activity room and bedroom concentrations. The bedroom and activity

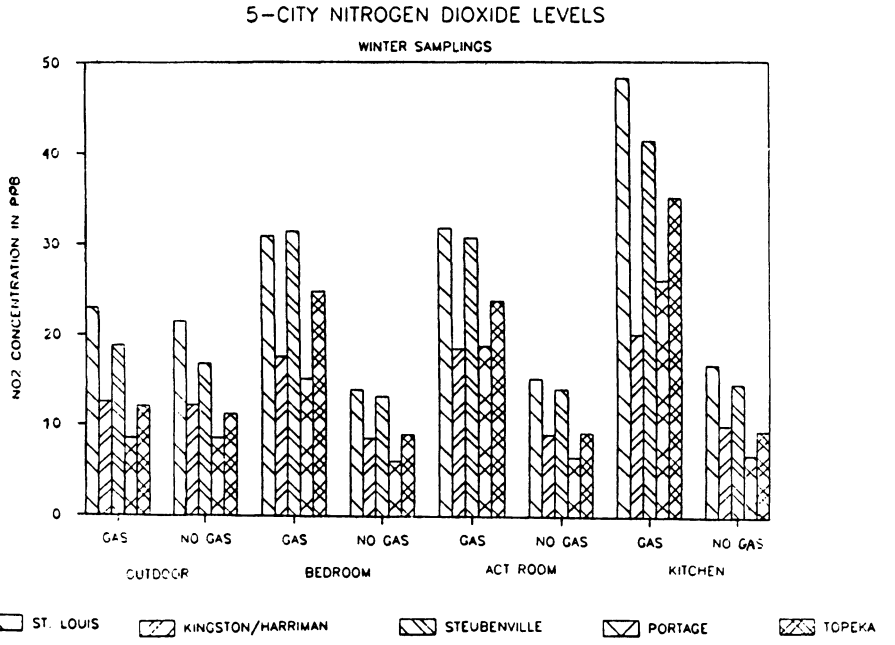

Fig. 2. Mean winter indoor NO_2 (ppb) concentrations inside and outside homes in five communities

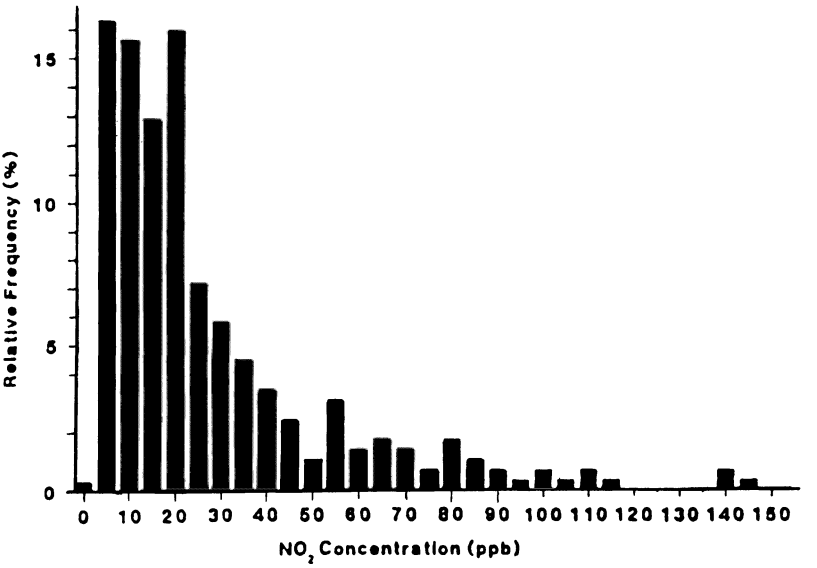

Fig. 3. Distribution of NO_2 levels (ppb) in Kerosene heater substudy homes

room have similar concentrations. In non-source homes the indoor concentrations are determined by outdoor concentrations. Levels are always lower because NO_2 will either react or be absorbed on indoor surfaces. For gas cooking homes, winter indoor concentrations are higher than summer concentrations. The opposite is true for non-source homes. This reflects the differences in the air exchange rate between winter and summer for most homes. Figure 2 presents the overall mean concentrations for NO_2 for the winter sampling period in five cities. Kingston, TN is not shown because there were very few gas cooking homes. This illustrates the differences among cities, differences among rooms within a home, and differences between home types.

Kerosene

Unvented gas and kerosene heaters are a major source of indoor NO_2. Kingston/ Harriman, Tennessee had more kerosene heaters than any of the other communities. They are banned in some states and less likely to be used in urban areas. With the assistance of the Oak Ridge National Laboratories a special study was conducted to assess the indoor NO_2 concentrations associated with kerosene heater use. Residents were given a set of samplers to measure NO_2 over ten consecutive weeks during the winter. In a few homes continuous monitoring equipment was used to document short-term concentrations. Figure 3 displays the frequency distribution of week-long NO_2 concentrations in homes with kerosene heaters. The range of concentrations reflects differences in heater type, actual usage, home and room volumes, and air exchange rate. Note that approximately 21% of the weeks had concentrations exceeding 50 ppb. The short-term concentrations are even higher. It is not uncommon for 1-h NO_2 concentrations to exceed 200 ppb during kerosene burner use. Figure 4 plots the combined NO and NO_2

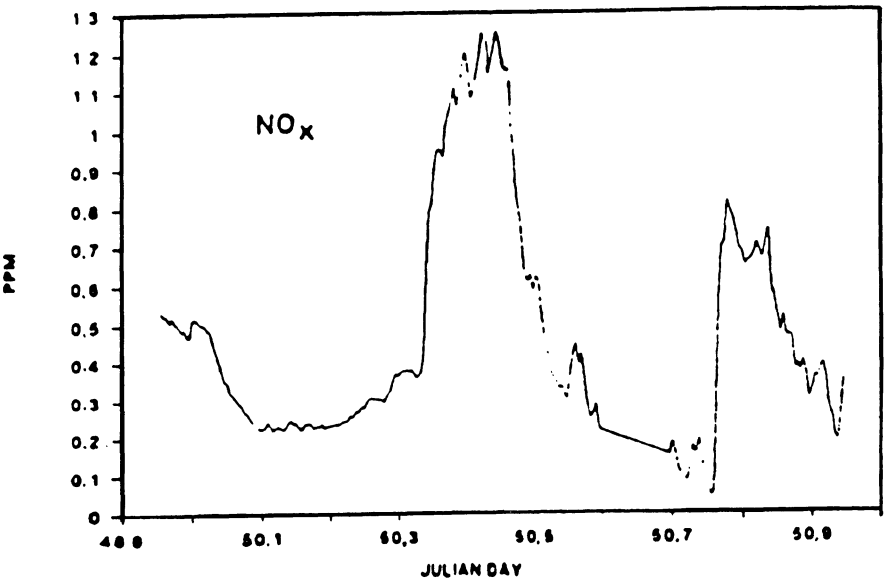

Fig. 4. One day of time-dependent pollutant levels from house 6476 during February

concentrations (ppm) inside one home that had a kerosene heater operating intermittently. Note that concentrations often exceed 500 ppb.

Respirable Particles

There are numerous sources of indoor and outdoor particulates. From previous studies we learned that outdoor fine particles penetrate into homes. The penetration ratio can be estimated by examining the indoor and outdoor concentration of elements and/or compounds that are outdoor contaminants that are introduced into the indoor air once they settle out or react with surfaces. Sulfate particles and elemental lead are good tracers for submicron size particles of outdoor origin. The penetration of outdoor particles varies by season and by home. During the winter the penetration factor is typically 0.4 and during the summer it is typically 0.8. Homes that are airconditioned or are constructed to have low air exchange rates have lower penetration values.

Indoor sources originate from a variety of activities including vacuuming, cooking, aerosol sprays and general human and pet activities. Quantifying the mass contributions of these activities is not possible in our large scale study that collects time integrated concentrations. There are other sources of indoor particle contamination. Tobacco smoke, kerosene heaters, woodburning stoves, cool mist and ultrasonic humidifiers can contribute to indoor particle concentrations. Tobacco smoke is the largest and most consistently identified source of indoor pollution in our study.

The indoor PM 2.5 particle concentrations in nonsmoking homes range between 19 $\mu g/m^3$ for Portage to 32 $\mu g/m^3$ for Kingston during the winter. In the summer, ambient PM 2.5 concentrations are higher because of secondary aerosol formation (sulfates). The indoor concentrations in non-airconditioned homes reflect this increase. However,

Table 2. Particle concentrations indoors

		Winter			Summer		
		N	Mean	SD	N	Mean	SD
Watertown	Nonsmoking	78	21	9	72	19	7
	Smoking	176	53	24	168	33	18
St Louis	Nonsmoking	120	26	18	101	23	8
	Smoking	172	59	27	169	46	21
Steubenville	Nonsmoking	120	21	13	112	28	13
	Smoking	188	47	32	168	46	23
Portage	Nonsmoking	167	19	18	167	14	5
	Smoking	148	47	38	146	29	19
Kingston	Nonsmoking	162	32	28	164	25	14
	Smoking	137	73	44	123	51	30

overall there is only a slight effect. Indoor concentrations in Portage nonsmoking homes are still low, 14 $\mu g/m^3$, but the indoor concentrations in Steubenville increased by 7 $\mu g/m^3$ to 28 $\mu g/m^3$ during the summer (Table 2).

Indoor particulate concentrations in homes with smokers are higher than for homes without smokers. The excess due to tobacco combustion varies by season and by city. Winter concentrations are higher than summer concentrations. During the winter, homes with smokers in St. Louis have 22 $\mu g/m^3$ more particulate mass than homes without smokers. In Kingston the excess is 40 $\mu g/m^3$. Other cities are intermediate. During the summer, tobacco smoke contributes an additional mass concentration of 16 $\mu g/m^3$ in Portage and up to 26 $\mu g/m^3$ in Kingston. The summer difference may reflect the increase in air exchange.

Regression of indoor particulate concentrations on several home factors indicates that only the number of cigarettes smoked and inverse home volume are important. For an over-all impact, a cigarette smoked within a home contributes approximately 1 $\mu g/m^3$ to the integrated respirable particulate concentrations.

Preliminary Health Results

Since the indoor air quality and diary symptom study has just been completed in September 1988, no results are available. However, the symptoms reported in the annual health questionnaire have been examined. The questionnaire included questions about smoking, heating and cooking fuels, heating appliances, and moisture and mildew conditions in the home.

Passive smoke exposure was prevalent in this sample of 6,273 children. Approximately 62% of the children were exposed to passive smoke in the home. The percentage ranged from 41.5% in Portage to 65.1% in St. Louis. The relative odds of respiratory symptoms were calculated for four categories of smoking, controlling for age, sex, parental education, gas cooking, wood stoves, and kerosene heaters. There was a general positive trend of increasing symptoms. When calculating the relative odds normalized to one

pack/day smoking, all symptoms were significantly greater than one, except bronchitis and other non-respiratory illnesses. The increase in reported symptoms range between 15% for chronic cough to 24% for wheeze.

Wood stoves were associated with increased relative odds for respiratory illnesses, 1.32 (95% CI 0.99 to 1.76). Other symptoms were not significantly greater for children in homes with wood stoves. The only positive association of respiratory symptoms and gas cooking fuel was for doctor diagnosed respiratory illness before the age of two-relative odds 1.09 (95% CI 0.89 to 1.33). A similar estimate for the same symptoms is reported for homes with kerosene heaters, 1.13 (95% CI 0.88 to 1.44). However, kerosene heaters are only prevalent in one city, Kingston (33.1%).

The health questionnaire included questions concerning moisture in the home. The presence of molds, mildew and previous water damage were assessed. In five of the six cities at least one of these conditions was reported in more than 50% of the homes. There was a consistent and statistically strong association among respiratory symptoms and "moisture conditions." After adjusting for smoking, age, sex, city and parental education, the relative odds ratio varied from 1.27 to 2.12 for all respiratory symptoms including asthma and hay fever. After removing asthmatic children the relationships were even stronger.

Preliminary Conclusions

Given the prevalence of smoking (approximately 60%) and "moisture" related problems (approximately 45%) in U.S. homes surveyed in this analysis, a large number of children may be at risk of increased respiratory illness. The associations between respiratory symptoms and parental smoking is similar across all cities and consistent with an exposure response function that increases with the number of cigarettes reported. Indoor particulate concentrates also increase in proportion to the number smoked at home per week.

The evidence associating molds, mildew and dampness with increased respiratory illness is consistent across six different communities. Unfortunately, the relationship between questionnaires and actual indoor concentrations of microorganisms (fungal spores) has not been fully characterized. Therefore, while strongly suggestive, we cannot say with certainty if there is an environmental agent responsible.

By comparison, the evidence for effects associated with other combustion sources indoors is not as strong. However, linking actual indoor concentrations (NO_2, particles) to the respiratory illness diaries of each child should increase statistical power.

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Chest Diseases of Elderly Women Due to Domestic Cooking and Passive Smoking: The Cracow Study

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Introduction

Numerous epidemiological studies have demonstrated an association between outdoor air pollution or urban residence and the occurrence of chronic chest symptoms. Comparing the results of the studies on chest problems among children it was suggested that not the polluted nature of urban air is the main and single factor causing the excess in morbidity from chronic bronchitis in population, but indoor air pollution (domestic heating or passive smoking) may play a very important role in the etiology of chronic nonspecific chest diseases.

The objective of this study was to measure the possible effect of indoor air pollution resulting from the use of gas cookers by elderly women, who may be more susceptible to the harmful effects of indoor air pollutants because they tend to spend a great proportion of time in their houses. In this study passive smoking and related confounding variables have been considered. The data were collected in the course of a cross-sectional study on health effects of environment in the elderly.

Material and Methods

A total of 1,158 elderly women took part in the survey in Cracow. The subjects under study came from a random sample of city center residents, 65 years of age and older.

The assessment of the health status of the population sample included standardized interviews and spirometric measurements. The questionnaire was based on a Medical Research Council questionnaire for studies of chronic nonspecific respiratory diseases. The spirometric testing was performed with the Vitalograph nondigital wedge spirometer. On all three occasions examined persons repeated the maximal forced expiration effort five times, and the highest tracing to estimate FEV_1 was chosen, and later corrected to BTPS.

Chronic cough or chronic phlegm was diagnosed in those persons who reported the symptoms usually during day or night at least for three consecutive months. Dyspnea on effort was diagnosed in respondents who reported that they are troubled by shortness of breath when climbing up the stairs so that they had to rest at the first or second floor. Also persons who confirmed that they were short of breath when hurrying on the level or walking up a slight hill were included in this category.

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Table 1. Characteristics of the population under study, never-smokers, using gas cookers (n = 823)

	$\bar{x}$	SD
Age (years)	71.9	5.0
Height (cm)	142.1	21.7
FVC (in ml)	2,993.9	1,760.0
FEV_1 (in ml)	2,469.7	2,064.5
FEV_1 (%)	60.5	32.2

Table 2. Prevalence and odds ratio of chronic chest symptoms due to cooking exposure. Non-smoking elderly women in Cracow study

Chest symptoms	Daily cooking time		Odds ratio and 90% CI
	short (< 2 h)	long (2 h >)	
Chronic cough	1.9%	5.3%	2.959 (1.457–6.004)
Chronic phlegm	1.2%	8.8%	7.730 (4.107–14.550)
Chronic bronchitis (chronic cough + phlegm)	0.9%	3.5%	3.909 (1.509–9.556)
Shortness of breath	16.8%	70.5%	11.890 (8.871–15.937)

Results

In total the final analysis covered 823 elderly never-smoking women who used gas cookers for at least 20 years in preparing the meals. All of them were above 65 years and were not involved in the regular occupational activity. The characteristics of the sample under study are presented in Table 1. The analysis was concerned with self-reported chest symptoms and exposure-effect relationship. The duration of exposure to indoor pollutants associated with domestic cooking was divided in two categories i.e. a) short exposure (less than 2 h daily) and b) long exposure (more than 2 h daily).

The prevalence of chronic cough and phlegm, chronic bronchitis symptoms and dyspnea on effort was much higher among those women who usually spent longer time in cooking the meals on the gas oven (Table 2). Odds ratio of chest symptoms due to duration of cooking time was 11.9 for shortness of breath and 3.0 for chronic cough. Comparing the prevalence of chest symptoms by duration of cooking and passive smoking one can see rather clear excess of dyspnea on effort among those women who were "passive smokers" in both groups of cooking exposure (Table 3). As the duration of cooking appeared to have very clear effect on the prevalence of shortness of breath, it was necessary to treat this variable as the strong confounder when dealing with dyspnea on effort in the context of passive smoking. In order to remove the confounder, the odds ratio standardized to duration of cooking was calculated (Table 4). The results of this analysis showed that the relative risk of shortness of breath due to passive smoking is about 2 times higher than in women not exposed to passive smoking.

Table 3. Chronic chest symptoms by cooking exposure and passive smoking (PS)

	Short cooking (< 2 h)		Long cooking (> 2 h)	
	PS (−)	PS (+)	PS (−)	PS (+)
Chronic cough	1.6%	2.8%	4.7%	7.3%
Chronic phlegm	1.3%	0.0%	9.3%	7.3%
Shortness of breath	13.7%*	34.3%	59.0%	63.4%

* Significant at 0.01 level.

Table 4. Shortness of breath by cooking exposure and passive smoking (PS)

Cooking exposure		Passive smoking	
		(−)	(+)
Short (- 2 h)	Cases	96	13
	Controls	518	22
Medium (2–3 h)	Cases	27	9
	Controls	15	7
Long (3 h >)	Cases	63	21
	Controls	24	4

$X_{M\text{-}H} = 2.535$ $X^2_{HET} = 6.207$

DF = 2 $\bar{R}\bar{R} = 1.963$

90% confidence interval (1.267–3.04)

Table 5. Regression of FVC, FEV_1 on age and height by exposure to gas cooking (exposed to passive smoking excluded)

	Short cooking (n = 525) (< 2 h)		Long cooking (n = 108) (> 2 h)	
	FVC	FEV_1	FVC	FEV_1
Age	-0.018*	-0.019*	-0.042*	-0.040*
Height	3.369*	2.537*	2.193*	1.869*
Constant	-1.993	-1.042	1.595	1.519
R^2	20.3%	19.9%	14.4%	17.5%

* Significant at 0.05 level.

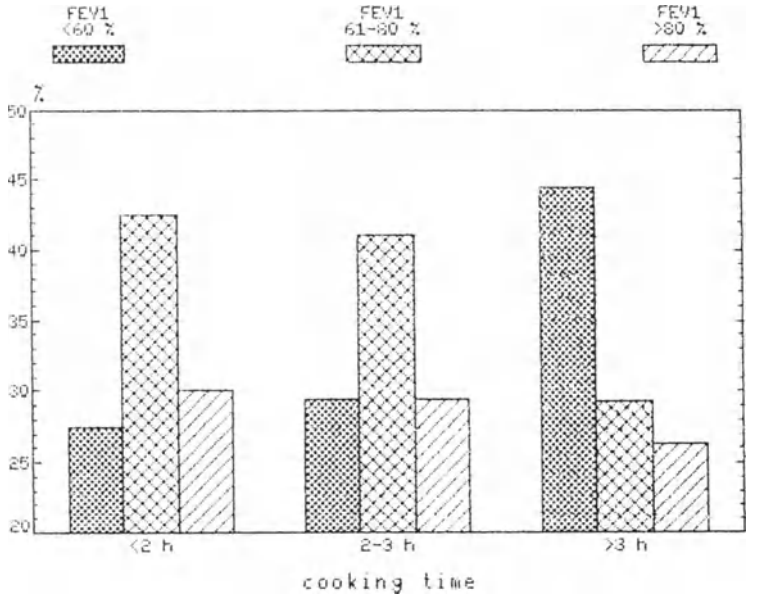

Fig. 1. FEV_1% level by exposure to gas cooking in non-smoking elderly women (in %)

Table 6. Regression of FVC, FEV_1 on age and height by exposure to gas cooking in those elderly women who were exposed to passive smoking

	Short cooking (n = 28) (< 2 h)		Long cooking (n = 38) (> 2 h)	
	FVC	FEV_1	FVC	FEV_1
Age	0.015	-0.004	-0.053*	-0.049*
Height	5.070*	3.753*	1.128	0.997
Constant	-6.660	-3.847	4.022	3.511
R^2	18.6%	18.3%	29.3%	29.7%

* Significant at 0.05 level.

Lung function level (FVC, FEV_1) was about in the same range among persons who cooked shorter or longer. However, those who cooked longer showed a higher regression slope coefficient with age (Table 5). The prevalence of obstructive symptom (FEV_1% 60%) increased with the duration of cooking time (Fig. 1). In those who cooked daily very long (more than 3 h) the prevalence of lung obstructive syndrome reached 44.4%. Those persons who were exposed to passive smoking and cooked daily over longer period of time showed slightly higher regression slope of FVC and FEV_1 with age than those women who did not confirm exposure to passive smoke (Table 6). The effect of exposure to cooking and passive smoking could not have been caused by the differences in the age

Table 7. Correlation matrix between self-evaluation of health status of elderly women and variables under study

	Self-evaluation	Age	Passive smoking	Gas cooking
Self-evaluation	-			
Age	-0.103	-		
PS	-0.141	-0.091	-	
GC	-0.486	0.037	0.141	-

structure of the compared groups as the exposure categories had the same age. However, those who cooked longer declared that they were generally in worse health status than the women who cooked daily for a shorter time (Table 7).

Discussion

The significant associations found in this analysis were between duration of cooking meals on the gas stove and self-reported chronic chest symptoms. Contrary to expectation there was no association between the exposure to NO_2 and ventilatory lung function level. The evidence that homes with gas cooking stoves have high levels of NO_2 has been demonstrated by Melia et al. (1978), Wade et al. (1975) and it was found that peak levels over gas stoves may reach occasionally even 1 ppm and concentration of NO_2 correlated with stove use. Other factors affecting the observed association between "cooking time" and chest symptoms, like smoking habit have been excluded. Others like socio-economic status, heating system of the household and passive smoking could not have had any impact on the results, as these confounding variables were rather evenly distributed over exposure categories.

The results of our study differ from the data obtained in children in whom lung function deterioration has been also disclosed (Melia et al. 1977, 1978). Studies in adults on health effects induced by the use of unvented gas appliances indoors are scarce and give conflicting results. Keller et al. (1979a, 1979b) were not able to demonstrate an association between the use of gas for cooking, NO_2, and respiratory illness. Helsing et al. (1982) showed that in non-smoking white adults the use of gas for cooking was associated with significantly increased frequency of cough and with a significantly greater percentage of people with impaired ventilatory function. Jones et al. (1983) found a small but significant association between low FEV_1 and the use of gas for cooking in a population of non-smoking women. Fischer et al., (1985) measuring exposure to NO_2 and tobacco smoke in the home, found statistically significant negative associations between pulmonary function level and exposure to NO_2 in non-smoking, but not in smoking women.

In our study on the health consequences of exposure to gas combustion products the exposure was simply classified as short versus long gas cooking. One may have some doubts on the discriminating power of such an exposure classification in health effect studies of indoor NO_2 levels, as "gas cooking homes" have a wide range of NO_2 concentrations. This is supported also by the data by Remijn et al. (1985) who found that estimation of historical exposure to indoor NO_2 on the basis of the house characteristics only is inaccurate. The authors showed that residents of houses in which high NO_2

concentrations were measured in the kitchen tended to spend less time in the kitchen. Therefore kitchen concentrations might not be a good measure for general NO_2 exposure.

A clear dose-response relationship in our study between chronic chest symptoms and the time spent in the kitchen for cooking meals shows that this variable has a good discriminatory power and probably classifies the respondents correctly with respect to the exposure level. The most striking differences between the exposure groups have been found for chronic phlegm, and this is quite reasonable as nitrogen oxides and other combustion gases develop an irritant action on the bronchial tree. Less of contrast between groups was found with respect to chronic cough and dyspnea on effort. The latter symptom is of major interest as it is the most important symptom causing disability of pulmonary origin. Having this in mind one might have expected consistent lung function changes in the group studies as well. However, ventilatory lung function levels were not different between groups with the shorter and longer cooking exposure. In fact, we could not confirm any substantial impairment of lung ventilatory function as measured by FEV_1, but this may occur if the pathological changes are more pronounced in the small bronchial tree. In the interpretation of lung function level in the cross-sectional approach one has to keep in mind that the level of given variable is the consequence of different individual initial values and decline rate with age. Despite the lack of difference in FEV_1 levels between exposure groups, we found that supposed decline rate of FEV_1 with age is faster in those non-smoking women who spent more time at cooking daily. This finding, suggesting that stronger lung function loss with age is present in more exposed persons could have been confirmed only if the initial baseline level of FEV_1 in prospective observation had been taken into account. However, there is much evidence to show that poor lung function is highly predictive of mortality, so that persons with a low FEV_1 will tend not to survive to the older ages. A survival effect therefore plays an important part in cross-sectional data, and the figures here must not be read as representative of longitudinal changes within individuals.

There maybe also some doubt that the observed clear excess in dyspnea symptoms in those who are exposed longer to cooking should be attributed entirely to lung impairment, as the symptoms may be caused also by secondary factors like cardiovascular diseases. To what extent the dyspnea on effort is to be attributed to lung damage or to cardiac failure in elderly is very difficult to ascertain and the clear answer cannot be given here. As our data show no statistically significant higher prevalence of cardiovascular diseases diagnosed by physicians in the longer exposed group, one is tempted, however, to conclude that the observed excess in dyspnea on effort is attributable to respiratory impairment due to gas cooking.

The results of our study regarding the passive smoking confirmed only a very weak hazardous effect of this factor on chronic chest symptoms and lung function deterioration in elderly women. This was greatly confounded by other indoor pollutants, especially those associated with cooking the meals on gas ovens. Since the hazards attributed to cooking on the gas cookers appeared to be stronger than that of passive smoking, the effect of passive smoking is difficult to prove as women are usually engaged in this kind of daily activity. In our study we took into consideration only the current passive smoking experience at home and took no account of the history of passive smoking that might have been present in the work place. This could evidently bias the results of the study with respect to passive smoking.

In the study performed, there was a clear excess of dyspnea symptoms among those exposed to passive smoking, and this did not appear to be confounded with age or cooking on gas ovens. We expected primarily to find an excess of cough or phlegm but the

reaction of respiratory airways to cigarette smoke and development of particular symptoms may differ in various age groups. At older ages we may observe the cumulative effect of the exposure that occurred in the past, and this cumulative effect may result not in cough or phlegm but predominantly in shortness of breath.

Abstract

The purpose of the study was to assess the effect of indoor air pollution resulting from the use of gas cookers by the elderly women (above 65 years) who may be more susceptible to the harmful effects of indoor air pollutants because they tend to spend a great proportion of their time at home. A total of 1,158 elderly women living in the city center were included in the survey. The survey data were collected by standardized interviews dealing with coughing, phlegm production, dyspnea on effort, past chest diseases diagnosed by a doctor, smoking habit, education, socio-economic conditions, heating system in the household, passive smoking, type of cooking oven, average time needed daily for coking the meals, proportion of time spent daily in the kitchen and other rooms of the household, place in which the meals are consumed etc. In all respondents lung function was tested with Vitalograph spirometer. The relative risk of chronic cough and chronic phlegm was strongly related to the exposure duration due to cooking time. As regards the dyspnea on effort, there was also an increased risk among those with longer exposure. The mean FEV_1 level was not related to domestic cooking exposure time. The results of the study regarding passive smoking confirmed only very weak hazardous effect of this factor on chronic chest symptoms and lung function deterioration.

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Model Specification Effects in ETS/Nutrition Research

S. J. Kilpatrick

Summary

In Hirayama's study the average annual death rate for wives aged 60–69 from lung cancer is 18 per 100,000 as compared with 39 for all Japanese women (Exhibit 9). Also, wives aged 50–59 have the same lung cancer death rate as wives aged 60–69 (i.e., no age trend). These results may arise from the 23% of the cohort which is missing.

These anomalies are obscured in Hirayama (1984) by the use, in all but one table (Table 2), of husband's age rather than the wife's age.

Using wife's age to analyze wife's mortality leads to an additive model for lung cancer. The use of the relative risk is thus contra-indicated.

The weak association of husband's smoking status with wife's lung cancer mortality is probably a consequence of incomplete age adjustment when coarse age groups of 10 years are used over a 16-year period. Suggestions are made for further analyses using ungrouped information.

The effect of daily intake of green and yellow vegetables on lung cancer is also reanalyzed. A standard analysis of these data leads to different results than those given by Hirayama (1984).

Public examination of these data is called for to yield independent answers to the questions raised here.

Introduction

Hirayama (1984) reports on a longitudinal record linkage study of married women who, in 1965, were reported to be non-smokers. Interviews using form 1 (see Exhibit 1) were carried out October through December 1965 of persons 40 years and above in 49 districts in 29 health center districts in Japan. In 1971, a 3% sample of those subjects were re-interviewed (Hirayama 1982) using form 2 (Exhibit 2). Form 2 is form 1 with additional questions on current health status and illnesses in the past five years. A second follow up was apparently done between 1971 and 1983 since Hirayama (1984) refers to a recent study of 410 males and 158 females in Aichi province. Apart from these, no monitoring of the population was carried out apart from linking deaths in the period 1966 to 1981 to the original questionnaire (Exhibit 1).

The cause of death in those women who had died by 1981 was linked to the initial interview in 1965 of both husband and wife. In the sequel it is important to note that date of birth, age of first marriage, age started smoking and date of death are recorded. Linkage of a married couple's original responses to the wife's death certificate can therefore yield the woman's precise age at entry. Likewise, for a non-smoking wife, the

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Exhibit 1

Form 1 **Initial survey**

Health Questionnaire Name of Prefecture Health Center

District code		Household code		Individual code
Name		M F	Date of birth (year month day) 1. Single 2. Married 3. Divorced 4. Widowed	
Address				
Place of birth	Prefecture	City	Occupation (in detail)	
For women	Number of children	Length of breast feeding after last delivery month(s)		Age at first marriage

Anamnesis

Eating Habits	Rice/Wheat	Amount/day Frequency
	Meat	1. Daily 2. Occas 3. Rare 4. None 5. Obscure
	Fish and shell fish	1. Daily 2. Occas 3. Rare 4. None 5. Obscure
	Milk and goat milk	1. Daily(amount) 2. Occas 3. Rare 4. None 5. Obscure
	Green-yellow vegetables	1. Daily 2. Occas 3. Rare 4. None 5. Obscure
	Pickles	1. Every meal 2. Daily 3. Occas 4. Rare 5. None 6. Obscure
	Soybean paste soup	1. Daily 2. Occas 3. Rare 4. None 5. Obscure
Favorites	Smoking	1. Smoking daily (a) Cigarette No./day (b) Kizami (c) Others 2. Occas 3. Ex. 4. None 5. Obscure Age started ( )
	Alcohol	1. Daily 2. Occas 3. Rare 4. None 5. Obscure Type (1) Sake (2) Shochu (3) Beer (4) Whisky (5) Others (6) Obscure
	Green tea	1. Very hot 2. Moderate 3. None 4. Obscure

age at which the husband started smoking and the date of the marriage can yield the duration of exposure to husband's cigarette smoke at the first interview.

The data from this study as presented by Hirayama (1984) has been summarized in 10 tables for non-smoking wives. Exhibit 3 lists these tables and shows by table number the cause of death and the factors by which the cause of specific death rates are classified. The levels of a given factor are given in parentheses. Note that Table 5 is a collapsed form of Table 6 or of Table 10 and Table 7(1) of Table 7(2). Note that Table 9 is Table 8 omitting non-smoking husbands. Only one Table, Table 2, gives wife's age group. The relationship of wife's age group to her daily intake of green/yellow vegetables is not given, nor of wife's age group to husband's age group, husband's drinking habit or husband's occupational group.

Poisson Regression

The following gives the standard analysis of the tables published in Hirayama (1984). Since Tables 5, 7(1) and 9 are all collapsed versions of other Tables, they are omitted from

Exhibit 2

Form 2 **Second survey**

Health Questionnaire Name of Prefecture Health Center

District code	Household code	Individual code
Name	M / F	Date of birth (year month day) 1. Single 2. Married 3. Divorced 4. Widowed
Address		
Place of birth: Prefecture	City	Occupation (in detail)
For women: Number of children	Length of breast feeding after last delivery month(s)	Age at first marriage

Anamnesis		
Eating Habits	Rice/Wheat	Amount/day Frequency
	Meat	1. Daily 2. Occas 3. Rare 4. None 5. Obscure
	Fish and shell fish	1. Daily 2. Occas 3. Rare 4. None 5. Obscure
	Milk and goat milk	1. Daily(amount) 2. Occas 3. Rare 4. None 5. Obscure
	Green-yellow vegetables	1. Daily 2. Occas 3. Rare 4. None 5. Obscure
	Pickles	1. Every meal 2. Daily 3. Occas 4. Rare 5. None 6. Obscure
	Soybean paste soup	1. Daily 2. Occas 3. Rare 4. None 5. Obscure
Favorites	Smoking	1. Smoking daily (a) Cigarette No./day (b) Kizami (c) Others 2. Occas 3. Ex. 4. None 5. Obscure Age started ( )
	Alcohol	1. Daily 2 Occas 3. Rare 4. None 5. Obscure Type (1) Sake (2) Shochu (3) Beer (4) Whisky (5) Others (6) Obscure
	Green tea	1. Very hot 2. Moderate 3. None 4. Obscure Others (1. Tea 2. Coffee 3. Cola 4. Cider)
Current Health Status (danger signals)		1. Stomach trouble, indigestion, no appetite, change in food choice. 2. Vaginal discharge, irregular bleeding. 3. Lump in the breast 4. Difficulty in swallowing. 5. Blood or mucos in stool. 6. Continued cough, bloody sputum, hoarseness. 7. Chronic ulcer in the mouth/skin. 8. Difficulty in urination, blood in urin. 9. Irritation/uneasiness 10. Difficulty in sleeping. 11. Heart trouble.
Currently		1. Healthy 2 In bed (by) from when.
Major illness during past 5 years		name of illness time duration. 1) 2)
Health Check		1 none 2 yes (stomach X ray chest X ray blood pression, others)

analysis. Note that, because of different groupings of husband's occupational group, Table 3 cannot be derived from Table 8, nor Table 6 from Table 10. Indeed, since person years are not given, the study appears to call for a Proportional Mortality Analysis of lung cancer, other cancer and ischemic heart disease mortality in non-smoking wives, cross-classified by wife's age group (4) × husband's age group (4) × husband's smoking classification (5) × husband's drinking habit (4) × husband's occupational group (10) ×

Exhibit 3

Tables as presented in Hirayama(1984)

TABLE	OUTCOME	FACTORS*
1	LCD	HAGE(4) x HCIG(5)
2	LCD[1]	WAGE(4) x HCIG(3)
3	LCD	HAGE(4) x HCIG(3) x HOCC(10)
4	LCD	HAGE(4) x HALC(4)
5	IHD[2]	HAGE(4) x HCIG(3)
6	IHD	HAGE(4) x HCIG(3) x HOCC(10)
7(1)	OTHCA[3]	HAGE(4) x HCIG(3)
7(2)	OTHCA	HAGE(4) x HCIG(3) x HOCC(10)
8	LCD	HAGE(4) x HCIG(3) x HOCC(2) x GYV(2)
9	LCD	HAGE(4) x HCIG(2) x HOCC(2) x GYV(2)
10	IHD	HAGE(4) x HCIG(3) x HOCC(2) x GYV(2)

1 LCD.....lung cancer deaths

2 heart disease deaths

3 cancer deaths

*Factors:

HAGE husband's age group

WAGE wife's age group

HCIG husband's daily smoking habit

HALC husband's daily alcohol intake

HOCC husband's occupational group

GYV wife's daily intake of green & yellow vegetables

Levels: In a factor XXX(n), n is the number of levels of factor XXX in the specified table

wife's daily intake of green/yellow vegetables (2). Parenthetically there is no reason today why, with modern computing techniques this basic tabulation should not have been analysed directly, instead of piecemeal as reported. Unfortunately the basic data is not available to the author (Hirayama, personal communication).

The analysis which follows is that recommended by Breslow & Day (1986) for cohort studies. In the absence of person years, the cumulative mortality rate over the period 1966–1981 is used as the response variate. (This assumes no "competing" causes of death and no loss to follow-up. This rate is not strictly a risk estimate since it depends on the duration of the study, the period of the study and on the choice of study population). A Poisson error structure is specified with a logarithmic link function which is the default for a Poisson error structure in GLIM (Payne 1985). The regressions are weighted according to the number of non-smoking wives in each cell.

Following Breslow (1987), nuisance variables, irrespective of their technical significance, are fitted before the factor of interest, i.e. either husband's smoking status or green and yellow vegetable intake. A factor is considered to have a significant association with the specified mortality rate only if the deviance reduction in the model, for the degrees of freedom associated with fitting that factor, is significant at the 5% level. (Note that Dr. Hirayama here uses a one-sided 10% level of significance which is equivalent to a two sided test at 20% significance). Analysis of residuals and regression diagnostics are not given here. Rather the model fit is evaluated using the approximation of the residual deviance and its degrees of freedom to the χ^2 distribution which "may overstate the degree of departure from the fitted model when many cells contain small counts" (Breslow & Day 1986, p. 137).

Husband's Age Group, Husband's Drinking Habit and Lung Cancer Mortality

Age at interview is clearly a powerful factor which must be fitted first. In some tables age exhibits a powerful linear trend and can be fitted as a single numeric variable. Where this is possible it is done to achieve the most parsimonious model.

Table 4 gives a cross classification of husband's age group × husband's drinking habit for lung cancer mortality in non-smoking wives. It is surprising that other "nuisance factors" are not included. Nevertheless, this table is analysed first, largely to investigate the association of lung cancer mortality with husband's age group.

Standard Poisson regression of Table 4 confirms that husband's age group is an important factor in lung cancer mortality (see Exhibit 4). Husband's age group exhibits a strong linear trend with lung cancer mortality. A log-log plot of lung cancer mortality rate vs husband's age group however gives a slope less than 3 whereas a slope of 4 has been reported for non-smokers using attained age (Seidman 1985). Husband's drinking habit shows no significant association in this table with lung cancer mortality but no adjustment has been made for other nuisance variables. Thus one would expect an association between husband's drinking and smoking habits.

ETS and Lung Cancer Mortality (Tables 1, 2, 3)

The only measure of ETS exposure given is husband's smoking classification, the number of cigarettes reported in 1965 as smoked daily by the husband. The standard practice of demonstrating that a factor is significant before looking for a trend is followed here. As for husband's age group in Table 4 above, husband's smoking classification shows a strong linear trend in certain tables and is entered as a single numeric variable in the interests of parsimony where possible.

"Typical practice is to consider 5 year intervals of age and time so as to be able to study variation in rates" (Breslow & Day 1980, p. 47–48). Hirayama (1984) uses 10 year age groups and does not divide the 16 year period. In general, an age classification of 10 years at entry in a study lasting 16 years with no time dependent factors may mean that the age effect has been incompletely adjusted (Mantel 1983). Thus, for a lung cancer mortality rate which rises exponentially with age, it is plausible that the significance of husband's smoking classification is an indication of incomplete age adjustment, given the rapidly changing habits of cigarette smoking in the period before 1966 (Kristen 1986).

Note also that duration of ETS exposure is confounded to an unknown extent with age at first interview. Thus, in the absence of other information, assume a constant age at

Exhibit 4

Summary of the fit of the best† multiplicative model

OUTCOME TABLE	PREDICTIVE MODEL	DEVIANCE(d.f.)
LCD 1	A	13.0 (18)
	A+HCIG	3.7 (14)
LCD 2	WAGE	16.8 (8)
	WAGE+HCIG	10.7 (6)
LCD 3	A+HOCC+C	71.9 (108)
LCD 4	A	15.3 (14)
IHD 6	HAGE+HOCC	115.1 (106)
	HAGE+HOCC+HCIG	109.6 (104)
OTHCA 7(2)	HAGE+HOCC	134.7 (106)
LCD 8	A+HOCC+C	50.8 (44)
IHD 10	HAGE+HOCC+HCIG	50.7 (41)

Key:

A is husband's age fitted as a linear trend

C is husband's daily smoking habit fitted as a linear trend

other factors, outcomes as defined in Exhibit 3

†Best in the sense of minimum residual deviance after fitting all 'nuisance' parameters as factors or (if warranted) as trends and then fitting the explanatory variables, HCIG [Tables 1, 2, 3, 4, 7(1)] or GYV [Tables 8, 10].

marriage and at starting smoking. In 1965. older non-smoking wives of smoking husbands will have been exposed to ETS for a longer period than younger wives. (This expectation of an increased relative risk for older wives is not evident from an analysis of Table 2 (see Exhibit 7)). Form 1 (Exhibit 1) records the age at which the husband started smoking. Given this and the date of the marriage from a linked wedding certificate, it should be possible to estimate the duration of ETS exposure by the non-smoking wife of a smoking husband prior to 1966 as well as the wife's age at first exposure.

Table 1, like Table 4, gives the cross-classification of husband's age group × husband's smoking status. As shown in Exhibit 4, only husband's age group is significant and exhibits a strong trend, as in Table 4. Although husband's smoking classification is not significant, it approaches significance ($\chi^2 = 9.3$ on 4 degrees of freedom, P just greater than 5%).

The effect of re-classifying husband's smoking classification from 5 levels to 3 levels can be seen in Table 3 which also gives a breakdown by 10 occupational groups, HOCC (10). Although husband's occupational group with 9 degrees of freedom is not significant, husband's smoking classification with 3 levels now is. Indeed husband's smoking classification with three levels now exhibits a strong trend (Exhibit 4).

Table 2 is unique in this publication in that lung cancer mortality is adjusted for wife's age group. Indeed this appears to be the only occasion on which Hirayama has included wife's age group in an analysis in any of his many publications from this study. (We shall see that husband's age group is not a surrogate for wife's age group.)

Standard Poisson regression of Table 2 as presented shows (Exhibit 4) that wife's age group, while a significant factor, does not exhibit a trend against lung cancer mortality. Again husband's smoking classification is on the borderline of statistical significance as judged by the change in the deviance ($\chi^2 = 6.1$ on 2 degrees of freedom). Clearly the evidence for a significant relationship between lung cancer mortality and husband's smoking classification is ambivalent even without considering the influence of non-sampling errors and confounding factors.

ETS and Ischemic Heart Disease (Tables 5, 6)

The consideration of multiple outcomes for associations with ETS indicates the multivariate nature of the analysis and the lack of prior hypotheses in this study. One should allow for multiple or repeated tests of significance in the evaluation of these results.

Table 6 gives a tabulation of ischemic heart disease mortality by husband's age group, husband's smoking classification and husband's occupational group. After adjustments for both husband's age group and husband's occupational group are made (Exhibit 4), husband's smoking classification is just non-significant by the established criteria ($\chi^2 = 5.6$ on 2 degrees of freedom). This is in contrast to Table 5 (not shown) which is Table 6 collapsed over husband's occupational group, showing some confounding between husband's occupational group and husband's smoking classification for ischemic heart disease.

ETS and Other Cancers

Table 7(2) classifies other cancer against husband's age group, husband's smoking classification and husband's occupational group, the same classification as for lung cancer mortality (Table 3) and for ischemic heart disease (Table 6). This again points out that a Proportional Mortality Analysis is the preferred method of analysis here. A univariate log linear analysis confirms that husband's occupational group is significantly associated with other cancer mortality. This association is almost entirely due to husband's occupational group 5, "farmers, laborers and fishermen" which has an estimated relative risk of 1.45 with 95% confidence limits of (1.04–2.03). No significant association with husband's smoking classification is detected with other cancer.

Green/Yellow Vegetables and Lung Cancer Mortality (Table 8)

Switching the focus now from husband's smoking classification to daily intake of green/yellow vegetables, we first fit all factors other than daily intake of green/yellow vegetables in Table 8 as nuisance parameters. The analysis of deviance reduction establishes that daily intake of green/yellow vegetables has a non-significant association (Exhibit 4).

Green/Yellow Vegetables and Ischemic Heart Disease (Table 10)

Table 10 gives ischemic heart disease mortality by husband's age group, husband's smoking classification, husband's occupational group and daily intake of green/yellow vegetables.

No significant association is found (Exhibit 4) with daily intake of green/yellow vegetables, after adjustment for these other factors ($\chi^2 = 0.6$ on 1 degrees of freedom).

In summary, standard Poisson regression, using the conventional 5% level of significance indicate, on the basis of these published tables,

- husband's smoking classification is marginally associated with wife's lung cancer mortality, the size of the effect being of borderline significance and dependent on the presence or absence of other factors in the model and the number and grouping of classes used in the husband's smoking factor.
- that husband's drinking habit shows no significant association with lung cancer mortality in the limited data published here.
- that daily intake of green/yellow vegetables shows no significant association with lung cancer mortality or with ischemic heart disease mortality.
- that husband's smoking classification is of borderline significance with wife's ischemic heart disease mortality.
- that husband's smoking classification shows no significant association with other cancer mortality.

These findings may be compared against those of the original report. There Hirayama (1984) claims "a significantly increased risk of" lung cancer mortality "in relation to the extent of the husband's smoking... The association was significant when observed by age of husbands... and also by age of wives." "Similar significant risk elevation of lung cancer with the increase in the extent of husband's smoking was observed with ischemic heart disease when observed by husband's age group and husband's occupational group."

"The risk-reducing effect of daily intake of green-yellow vegetables on lung cancer was observed for passive smoking... Those women eating green-yellow vegetables daily showed a significantly lower risk of lung cancer from the passive influence of their husbands' smoking."

Power Fit

Exhibit 4 which summarizes the best fitting multiplicative model indicates that in some instances this fit may not be too good (or that interaction terms are necessary). Thus, the residual deviance considered as an approximate χ^2 indicates that for both models fitted toTable 2, the fit is of borderline significance. This is true also of Table 7 (2), Table 8 and

Exhibit 5

Deviances (df) for additive, multiplicative and best fitting power models

OUTCOME TABLE	MODEL ADDITIVE	POWER	MULTIPLICATIVE
LCD Table 1	3.79 (12)	2.76 (12)	3.24 (12)
LCD Table 2	7.91 (6)	7.85 (6)	10.72 (6)
LCD Table 3	2.57 (6)	1.50 (6)	1.95 (6)
IHD Table 5	2.32 (6)	2.17 (6)	2.72 (6)
OTHER CA Table 7(1)	3.28 (6)	2.46 (6)	3.68 (6)

Model is 1+HAGE(4)+HCIG(5) for Table 1
..... 1+WAGE(4)+HCIG(3) for Table 2 and
..... 1+HAGE(4)+HCIG(3) for Tables 3, 5 and 7(1)

Rates are DTHS/POP (1966-1981)
for LCD (Tables 1,2,3), OTHER CA (Table 7(1)), IHD (Table 5)

Table 3 has been collapsed over HOCC

Table 10. This test is approximate. Nevertheless, it was decided to investigate the best fitting power model (Breslow 1986) to these tables. The goodness of fit of the additive, multiplicative and best fitting power model to these data are compared in Exhibit 5 in terms of residual deviance. Note that the additive and multiplicative models are special cases of the power model with exponents equivalent to one and zero respectively.

In Exhibit 5, an attempt has been made to fit the same predictive equation, adjusting for age and ETS exposure across the different sets given in Hirayama (1984). Overall, husband's age in 1965 classified by 10 year age groups, gives very satisfactory fits, irrespective of which Poisson model is used. In contrast, Exhibit 5 shows that poor fits result from the use of wife's age in 1965, classified in 10 year age groups, the multiplicative model giving the worst fit.

Exhibit 5 also reveals that the power-deviance curve is generally quite flat. Apart from Table 2, for which the additive model is the model of choice, the data, as presented in Hirayama (1984), do not discriminate well between additive and multiplicative models.

Exhibit 6

POWER VALUE FOR BEST MODEL

OUTCOME	ρ	POWER $\hat{\rho}$	ρ
Table			
LCD	1	0.40	0
Table 1			
LCD	1	1.14	0
Table 2			
LCD	1	0.39	0
Table 3			
IHD	1	0.61	0
Table 5			
OTHER CA	1	-	0
Table 7(1)			

predictive equations as in Exhibit 5

- $\hat{\rho}$ meaningless since HCIG has zero estimates

The power value in the best fitting model is given in Exhibit 6. This lies between $\rho = 1$, the additive model and $\rho = 0$ (which is equivalent to the multiplicative model) for all but Table 2. The best fitting power model for Table 2 is larger than 1.00, indicating that the multiplicative model as fitted above, is contra-indicated. An additive model, then, is clearly preferred over the multiplicative model for Table 2, which, alone, uses wife's age group. However, the flatness of the deviance curve against ρ may indicate that the assumption of a Poisson error term is incorrect.

This finding may be interpreted in biological terms and in terms of information content. Although this study is considered to be one of the largest on ETS and lung cancer and contributes heavily to any meta-analysis estimate of passive-smoking effect (NRC report. 1986) it contains little information because of the absence of specific exposure, person year and time dependent data.

Wife's Age (Table 2)

Having shown that the additive model is the model of choice for Table 2, we now consider this analysis more fully. Unfortunately we are restricted to this one simple cross classification of wife's age group by husband's smoking classification using coarse intervals and omitting others factors. Under the additive model, wife's age group and husband's smoking classification are significant factors ($\chi^2 = 32.6$ on 3 degrees of

Exhibit 7

Table 2 Lung Cancer Relative Risk (1966–1981)

		HUSBAND'S SMOKING		
		Non	Ex or 1 – 19/*d*	20 + /*d*
WIFE'S AGE	40–49	1.0	2.4	3.3
	50–59	1.0	1.6	1.9
	60–69	1.0	1.2	1.0
	70–79	1.0	0.1	0.5

freedom for wife's age group and 8.84 on 2 degrees of freedom for husband's smoking classification, $0.05 > P > 0.01$).

Although this is an improvement over the multiplicative model, the residual deviance is 7.91 on 6 degrees of freedom, indicating that this model may still not be good fit. Likewise the best fitting power model had residual deviance of 7.85 on 6 degrees of freedom – not a great improvement.

This is paradoxical. As we move from husband's age group to wife's age group (which should give a more direct relationship between age and lung cancer mortality) we, in fact, find continued evidence of an interaction between wife's age group and husband's smoking classification, irrespective of which model we use. It must be concluded that Table 2 contains insufficient detail in wife's age group and exposure to ETS or that other factors, not shown, are associated with lung cancer mortality in the non-smoker.

An alternative way of explaining why the multiplicative model is not the model of choice when wife's age is used is to examine the relative risks. The use of the multiplicative model assumes that the relative risk is constant with age. Exhibit 7 however demonstrates a clear trend in the relative risk which falls from values above 1 at young ages to values below 1 over 70. These trends arise because of the different effects of age in the three smoking status categories. Clearly (as may be seen from Exhibit 8 (figure)) the rates for the three smoking status categories are approximately equal at wife's age 60–69 but differ (in different directions) at other ages. Exhibit 9 compares average annual rate by wife's age (Table 2) with the same rate when classified by husband's age (Table 1) and both are compared with estimated Japanese rates for females. The rates for Table 1 and Table 2 are both uniformly lower than Japanese rates for women. Either wives have a much more favorable experience than all women or Hirayama's study subjects are unrepresentative of Japanese wives or both. In addition Exhibit 9 reveals an anomaly in Table 2 in that, unlike Japan or Table 1, the lung cancer death rates when classified by wife's age show no age trend from age group 50–59 to 60–69!

This suggests a serious misclassification of wife's age, wives who were 50–59 being recorded as 60–69 at the initial interview. Alternatively, and more likely, lung cancer deaths for wives aged 60–69 at initial interview are seriously under reported, giving a spuriously low average annual year lung cancer death rate of 18 per 100,000 as compared with a Japanese rate for all women of 39.

Turning now to an examination of the selected cohort, we look at the percentage distribution of husband's smoking status by wife's age. Exhibit 10 gives a 1965 cross-

Exhibit 8

Table 2 Wife's Lung Cancer Death Rate (logarithm) (1966–1981) by Husband's Smoking Status (1965)

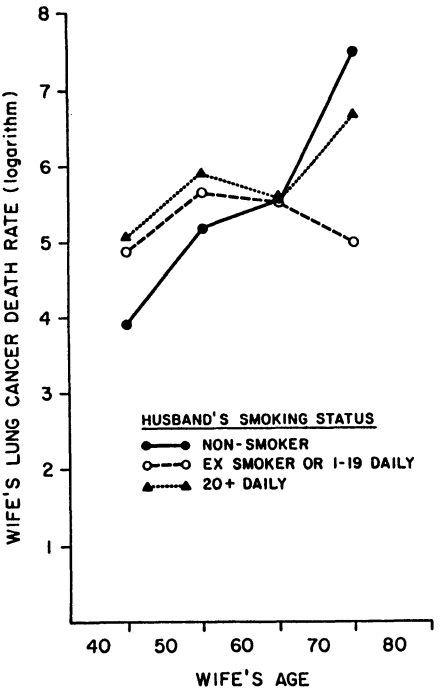

Exhibit 9

COMPARISON OF RATES BY AGE

Annual Average Lung Cancer Death Rate /100,000

1966–1981

AGE	JAPAN†	TABLE 1*	TABLE 2
40–49	12	7	8
50–59	20	12	18
60–69	39	23	18
70–79	46	36	35

† based on Japanese rates for women. (Segi et al., 1981)

* husband's age.

Exhibit 10

Table 2 Distribution of Husband's smoking status by Wife's age

		HUSBAND'S SMOKING			
		Non	Ex or 1 – 19/*d*	20 + /*d*	Total
WIFE'S AGE	40–49	21%	46%	33%	38,025(100%)
	50–59	24%	49%	27%	32,089(100%)
	60–69	30%	51%	19%	20,344(100%)
	70–79	16%	62%	22%	1,082(100%)

Exhibit 11

Table 1 Distribution of husband's smoking status by his age

		HUSBAND'S SMOKING					
		Non	Ex	1 – 14/*d*	15 – 19/*d*	20 + /*d*	TOTAL
HIS AGE	40–49	19%	4%	27%	16%	34%	32,027(100%)
	50–59	23%	6%	29%	12%	30%	33,253(100%)
	60–69	29%	11%	30%	10%	19%	24,214(100%)
	70–79	37%	17%	30%	5%	11%	2,046(100%)

sectional view of cohort changes in husband's smoking habits. A number of points arise. Although Dr. Hirayama has published no information from his 3% re-interview survey on changes in smoking status between 1965 and 1971, such changes in smoking status occurred and may be of the order demonstrated in Exhibit 10 for husbands. (We have no information on wife's changes in smoking habits. Dr. Hirayama claims that 1.96% of the women polled in his 3% re-interview survey were misclassified as to smoking status. It is difficult to understand how he can discriminate between conversion from non-smoking to smoking status given the nature of the smoking question revealed in Exhibits 1 and 2. If 1.96% of wives were misclassified, what is the conversion rate from non-smokers to smokers in the period 1965–1971 among these wives?)

Secondly, the intermediate smoking classification (Ex or 1–19/d) is the most numerous of the three smoking status classifications for the husband and is a composite of ex-smokers and light and intermediate smokers (1–14/d and 15–19/d). It could be argued that as the most numerous the intermediate group should be used as the baseline for testing the significance above and below these rates for non-smokers and heavy smokers (20+/d) respectively. However, this group of wives has an unknown mixture of exposures to passive smoking. As indicated above, form 1 (see Exhibit 1) records

information on duration of exposure of a wife to her husband's smoking but this has never been used in Dr. Hirayama's many publications.

Finally, a husband's smoking status is clearly dependent on his age (Exhibit 11). Thus, as a surviving husband ages he is less likely to be classified as a 20+/d smoker and most likely to be classified as a non-smoker or ex-smoker. Dr. Hirayama groups ex-smokers with light smokers (what happens to "occasional smokers"? (see form 1 (Exhibit 1)). In terms of exposure before 1966 this is correct but it may be argued that ex-smokers should be grouped with non-smokers since wife's exposure is zero after 1965 and lung cancer latency is of the order of 10 years.

Better still, fine detail should be preserved in order to allow for the true expression of factors and covariates. Thus it is likely that the association of husband's smoking status with wife's lung cancer mortality is simply an example of incomplete age adjustment, using 10 year age groups with a 16 year cumulative mortality. In other words, husband's smoking status is confounded with wife's age. Again this can be remedied by using modern analytical techniques to analyse the data in detail.

Discussion

Dr. Hirayama's publications, over the years, have analyzed this longitudinal record linkage study from many aspects. Given the nature of the study and the absence of specific details, it is clear that these data can not be used to confirm hypotheses or to strengthen the evidence for or against a causal mechanism between causes of death (his outcomes) and his factors, since "we can be easily misled by variables not represented or recognized in a study" (Tukey & Mosteller 1977, p. 119) and since "tests of significance and confidence intervals that fail to account for the lack of fit of a given model may be seriously misleading " (Breslow 1987, p. 37).

The absence of relevant factors and specific details is shown here in the inability of these published data to discriminate between additive and multiplicative Poisson regression models. It is unfortunate that the Committee on Passive Smoking (NRC 1986) gave so much weight to Dr. Hirayama's conclusions in their review of the evidence for and against passive smoking as a cause of lung cancer.

This standard re-analysis of Hirayama (1984) points to husband's smoking status being a surrogate for some other factor or factors. Thus, an unadjusted analysis of husband's alcohol intake showed no association with lung cancer mortality. If husband's smoking status were a causal factor in the formation of lung cancer, one would expect alcohol intake also to be associated with this risk because of the association of smoking and drinking habits.

Comparison with other cohort studies shows how approximate the evaluation of ETS exposure is in this study. Thus, for example, Smith & Doll (1982), investigating the effect of irradiation on leukemia mortality use both age at first exposure and duration since first exposure as factors. Dr. Hirayama has linked his initial interview file with death certificates for selected causes of death. It should be possible to link wedding, divorce and death certificates (for all causes) to the original file in order to estimate the duration of the marriage. Further, since the age at which the husband started smoking was recorded, the duration of the wife's exposure to passive smoking could be estimated. This assumes that no non-smoking wife started smoking in the interval 1966–1981. Figure 1 of Hirayama (1984) and Kristen (1986) show a rapid rise in per capita cigarette consumption in this period in Japan. In the light of this increase, it is plausible to assume that a number of these wives became smokers after 1965. More non-smoking wives of smoking husbands

would be expected to become smokers than among those married to non-smokers because of the husband's example. Likewise, more wives of smokers are likely to have been misclassified as non-smokers in 1965 than wives of non-smokers (Lee, in press).

In the absence of information on duration of exposure, we know only the reported smoking status of husband and wife at initial interview. Assuming stability throughout, older wives in 1965 have been exposed for longer than younger wives. If so, relative risks should increase but the opposite is true (Exhibit 7). Indeed, as has been indicated, wife's age in 1965, is a less effective explanatory variable for cumulative lung cancer mortality than husband's age. Dr. Hirayama's analyses which use the spouse's age for age standardization are of questionable value. Theories of carcinogenesis relate the incidence of cancer to the age of the experimental animal or the individual. The analytical comparisons given here indicate that husband's age *cannot* be used as a surrogate for wife's age if the age at entry of the decedent is used. The importance of this conclusion may be seen in the observation that, if Dr. Hirayama's study is excluded from a global estimate of passive smoking effects on lung cancer, the resultant meta-analysis gives a value which is not significantly greater than 1!

Dr. Hirayama's study ascertained 142,857 women 40 years or over in 1965. Figures 7 and 8 of Hirayama (1984) document the smoking history or exposure of 108,906 females, leaving 33,951 women unaccounted for. It might be assumed that 24% of the female cohort were widows in 1965 except for Dr. Hirayama's statement "information on the smoking history of the husbands of non-smoking women with lung cancer was available – in 77.3% of cases (174 out of 240)" (Hirayama 1981). This means that the 91,540 wives analysed here and in Hirayama (1984) represent 77.3% of a total of 118,422 wives in 1965. Clearly it is impossible to re-construct the total female cohort from the information given. If, as stated by Dr. Hirayama, 23% of his study group are missing, then his confidence limits are too narrow in that they do not allow for the effect of these non-sampling errors. Inclusion of non-sampling errors for the 23% missing wives totally negate his claims of significance for the association between passive smoking and lung cancer and between green and yellow vegetable intake and lung cancer.

This investigation prompts the author to call for an international panel of scientists to be given access to Dr. Hirayama's files. An independent evaluation is needed of the contribution which this unique study can make to the role of passive smoking and dietary habits in the etiology of lung cancer and heart disease.

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Effect of Paternal Smoking on Fetuses

S. Kikuchi and T. Takahashi

Summary

A total of 830 Japanese women who had had babies were interviewed and asked about their and their husbands' smoking habits during various stages of pregnancy.

Maternal indirect or passive exposure to smoking by the father was found to deteriorate the neonatal condition as assessed by Apgar Score at 1 min after birth, but not to reduce the neonatal birth weight or cause preterm labor.

Introduction

There is ample evidence that maternal cigarette smoking during pregnancy is associated with delivering low birth weight infants, but it remains unknown whether paternal smoking during pregnancy has a deteriorating effect on the fetus or not.

In the present retrospective study, we assessed the effects of paternal smoking on rates of preterm labor, intrauterine growth retardation and fetal asphyxia.

Material and Methods

All the mothers who had babies in Dai-Ni hospital, Nippon Medical School and its affiliated hospitals between July 1 and October 15, 1987, were asked about their and their husbands' smoking habits, and their habits were analysed in connection with the baby's weight, Apgar Score and duration of pregnancy, etc.

The mothers had no stillbirths and twin pregnancies were excluded. 830 couples were eligible for this study.

The husbands and wives were categorized into 6 groups according to their smoking habit – not smoking at all, smoked only before marriage, smoked after marriage but stopped when the wife's pregnancy was determined, and other smoking habit at the various stages of pregnancy. The No. of cigarettes consumed per day was not taken into consideration.

However, for the statistical convenience, the couples were recategorized into 4 groups. In Group 1, both parents were nonsmokers, but in this group, the wives and husbands who smoked until the initial stage of pregnancy were included.

Group 2 parents were those of whom husbands were persistent smokers. However, wives who smoked only before pregnancy were also included in this group.

In Group 3, both husbands and wives were persistent smokers, and in Group 4, only wives smoked, while husbands were nonsmokers. Group 2 was the largest group. It

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Table 1. No. of couples divided by smoking habit

Group	Paternal	Maternal	Total (%)
G-1	−	−	246 (29.6)
G-2	+	−	532 (64.1)
G-3	+	+	46 (5.6)
G-4	−	+	6 (0.7)
			830 (100.0)

Table 2. Age distribution of parents according to smoking habit: m ± sd (in years)

	Nonsmoker	Occasional smoker	Persistent smoker
Father	31.8 ± 4.8	32.0 ± 4.6	30.7 ± 4.9
Mother	27.9 ± 4.0	26.7 ± 3.9	26.6 ± 4.5

Table 3. Distribution of maternal smoking habit according to parity (%)

Parity	Nonsmoker	Occasional smoker	Persistent smoker
0	281 (42.3)	62 (53.9)	20 (39.2)
1	269 (40.5)	36 (31.3)	22 (43.1)
2	114 (17.2)	17 (14.8)	9 (17.7)
Total	664	115	51

comprised about two thirds of the couples and Group 1 was the 2nd largest group, accounting for most of the rest (Table 1).

Results

1) Age distribution of parents (Table 2): As for the age distribution of nonsmokers, occasional smokers and persistent smokers, there was no statistical difference.

2) Parity (Table 3): As for parity, that is the No. of children already born to nonsmoking or smoking mothers, there was no big difference.

3) Neonatal sex: As shown in Table 4, the distribution of neonatal sex was not biased.

Table 4. Distribution of neonatal sex

♂	417	(50.2%)
♀	413	(49.8%)
Total	830	

Table 5. Smoking habit in parents (n = 830)

	Paternal [%]	Maternal [%]
None	171 (20.6)	664 (80.0)
Only before marriage	60 (7.2)	57 (6.9)
Stop before gestation	8 (1.0)	44 (5.3)
Stop in 1st trimester	6 (0.7)	11 (1.3)
Occasional	2 (0.2)	3 (0.4)
Persistent	583 (70.3)	51 (6.1)

Table 6. Parents' smoking attitude to gestation

	Paternal [%]	Maternal [%]
Only before marriage	60 (9.1)	57 (34.4)
Stop before gestation	8 (1.2)	44 (26.5)
Stop in 1st trimester	6 (0.9)	11 (6.6)
Occasional	2 (0.3)	3 (1.8)
Persistent	583 (88.5)	51 (30.7)
Total	659	166

4) Smoking habit in parents: Tables 5 and 6 show the smoking habit in parents. Roughly speaking, fathers continue to smoke throughout pregnancy, while about one third of the smoking females continue to smoke during pregnancy.

5) Effect of smoking: As for the effect of paternal smoking on the weight of newborn babies, it can be concluded that it does not increase the incidence of premature babies, that is, babies with a birth weight of less than 2.5 kg (Table 7).

However, if the line is drawn at 2.75 kg, instead of 2.5 kg, it can be concluded that the incidence of the birth of low weight babies is increased when the parents are persistent smokers, but paternal smoking has no deteriorating effect (Table 8).

As for the duration of gestation, paternal smoking does not shorten the duration, but when both parents are persistent smokers, preterm labors are liable to occur (Table 9).

As for the Apgar Score, that is, the assessment system of neonatal condition directly after birth, the condition of the neonate is jeopardized when its father keeps smoking before and throughout the time the mother is pregnant.

Table 7. Parental smoking and newborn weight (n = 830)

Group	Smoking		Newborn weight		Total	
	Pat.	Mat.	< 2.5 kg (%)	2.5 kg ≦		
G-1	−	−	8 (3.3)	238	246	
G-2	+	−	24 (4.5)	508	532	insig. (p = 0.2697)
G-3	+	+	4 (8.7)	42	46	insig. (p = 0.1021)
G-4	−	+	1 (16.7)	5	6	insig. (p = 0.1753)

Table 8. Parental smoking and newborn weight (n = 830)

Group	Smoking		Newborn weight		Total	
	Pat.	Mat.	< 2.75 kg (%)	2.75 kg ≦		
G-1	−	−	22 (8.9)	224	246	
G-2	+	−	56 (10.5)	476	532	insig. (p = 0.2925)
G-3	+	+	11 (23.9)	35	46	sig. (p = 0.0062)
G-4	−	+	2 (33.3)	4	6	sig. (p = 0.0108)

Table 9. Parental smoking and fetal gestational age

Group	Smoking		Gestation week		Total	
	Pat.	Mat.	< 37 (%)	37 ≦ (%)		
G-1	−	−	7 (2.8)	239 (97.2)	246	
G-2	+	−	14 (2.6)	518 (97.4)	532	sig. (p = 0.0262)
G-3	+	+	5 (10.9)	41 (89.1)	46	sig. (p = 0.0129)
G-4	−	+	0 (0.0)	6 (100.0)	6	

When the parents are nonsmokers, the baby is deteriorated in 2.4% of cases, and when the husband is a persistent smoker, the incidence is 6.0%. This difference is significant.

No statistically significant difference was found when both parents were persistent smokers, but this may be because the sample number was too small (Table 10).

Table 10. Paternal smoking and neonatal jeopardy (Apgar Score ≦ 7)

Group	Smoking		Neo. jeopardy		Total	
	Pat.	Mat.	+ (%)	−		
G-1	−	−	6 (2.4)	240	246	sig. (p = 0.0223)
G-2	+	−	32 (6.0)	500	532	
G-3	+	+	1 (2.2)	45	46	insig. (P = 0.5565)
G-4	−	+	0 (0)	6	6	

Table 11. Maternal smoking during pregnancy and preterm labor

Smoking before pregnancy	Smoking during pregnancy	No	No. Preterm labor (%: fid. lim.)	
−	−	1,126	47 (4.2: 5.8 ~ 3.4)	
+	−	117	7 (6.0: 10.9 ~ 3.4)	P = 0.017
	±	66	4 (6.1: 13.1 ~ 3.0)	
	+	75	8 (10.7: 18.4 ~ 6.3)	

Discussion

Table 11 shows the result of our previous study on the rate of preterm birth in expecting mothers who smoke. It is clearly shown that maternal smoking increases the incidence of preterm labor, in other words, a labor taking place more than 3 weeks before the expected date of confinement. When the mothers are not smokers at all, the incidence of preterm labor was 4.2%, and when they have always smoked, the incidence was 10.7% and the difference is significant.

In the present study, we investigated the effect of paternal smoking on fetuses, that is, babies still in the mother's uterus, and obtained the result that the paternal smoking during pregnancy is not without hazard to fetuses, though it may not be so serious as maternal smoking.

Paternal smoking deteriorates the neonatal condition at birth, evaluated by Apgar Score.

The Apgar Score system is a method of assessing neonatal condition directly after birth, based on five factors, which are the neonate's heart rate, respiratory condition, muscle tone, reflex irritability and skin color. A score from 0 to 2 is allocated to each factor and the total sum of points is taken as the assessment of the neonate's condition. When the baby is given 10 points, it is deemed to be in the best possible condition, and when it gets no points, it means the baby is dead. The lower the baby's score, the more deteriorated is the baby's condition, and in Japan, a score of 7 or less usually indicates that the baby's condition is bad.

Conclusion

Paternal smoking does not reduce the baby's weight, it does not shorten the gestational duration, but it does deteriorate the neonatal condition at birth.

The fetus can be a victim of double passive smoking: its mother is a victim and through its mother, the fetus itself is a victim.

It is better for neither of the parents to smoke even before their baby is born.

Passive Smoking as a Low Level Carcinogen: Epidemiologic Risk Assessment

D. Trichopoulos and K. Katsouyanni

To the extent that mainstream smoke (MS) is a potent carcinogen and sidestream smoke (SS) only quantitatively different from MS, an excess lung cancer risk from exposure to environmental tobacco smoke (ETS) should be expected. Nevertheless, two important questions remain. First, is the excess risk expected from long-term exposure to ETS large enough to be empirically demonstrable with existing epidemiologic techniques? Second, are the epidemiologic data supportive of, rather than compatible with, an etiologic role of passive smoking in lung carcinogenesis [1–6]?

On the basis of the dose-response curves linking active smoking to lung cancer risk, and the extrapolations of these curves to low levels of smoking exposures, several authors have attempted to predict the excess cancer risk that could be generated from exposure to ETS. Their predictions were based on nicotine absorption (and cotinine excretion), on urinary mutagenicity, and on tar or "cigarette equivalents" exposure of individuals involuntarily exposed to ETS. The predicted relative risk figures fell short of the actually observed ones. However, body nicotine and therefore cotinine are variably related to the 3000 compounds in ETS and, furthermore, nicotine exists as particulate in MS and as gas in SS. Therefore the fact that nicotine absorption in nonsmokers corresponds to about 1%–2% of the average nicotine absorption in smokers may not be relevant for estimating, by calibration, ETS exposure. In this context it should be noted that the increase of urine mutagenicity after passive exposure to cigarette smoke is about 4% of the increase observed in active smokers. Furthermore, model-derived estimates use a referent group that includes all nonsmokers (including those passively exposed), whereas empirically derived estimates use a referent group of nonsmokers that exclude those "heavily exposed" to passive smoking. The baseline risk in the first instance is clearly higher than the corresponding risk in the second instance. When the necessary adjustments are made the predicted figures closely agree with the observed ones. In addition, exposure to passive smoking may start soon after birth whereas exposure to active smoking does not start until the late teens or later; since lung cancer risk is a power function of the duration of exposure, the early exposure to ETS may have disproportionally large risk implications. Lately, the delayed clearance of nicotine among the passive smokers (in comparison to the corresponding clearance among active smokers) may lead to increased formation of endogenous, tobacco-specific, nitrosamines with carcinogenic potential [2–16].

There are no biologic markers for past (rather than recent) ETS exposure, and validated questionnaires probing past passive smoke exposure are not yet available. Therefore, most of the studies concerning diseases of long latency (including cancer of the lung) have focused on comparisons between nonsmoking women married to husbands who were, or were not, regular cigarette smokers.

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The underlying assumptions are:

1) that a smoking husband is the main source of passive smoking for a relatively older woman – this appears to be true in general, since housewives spend more than 80% of their time in their homes;
2) that information concerning the smoking behaviour of a husband is much more reliable than information concerning other sources of passive smoking – there is a substantial empirical evidence in support of this assumption;
3) that nonsmokers married to smokers are likely to be more tolerant towards other sources of passive smoking – there are already studies with results that support this assumption; and
4) that smokers tend to cluster, thus amplifying the exposure differentials of nonsmoking women married to smokers rather than to nonsmokers – there are many studies with converging results supporting this assumption [1, 9, 17–20].

In January 1981 Trichopoulos et al. reported the results of a case-control study in Athens, specifically undertaken to explore the lung cancer-passive smoking association [21]. It was found that nonsmoking women married to smoking husbands had 2.3 times the lung cancer risk of nonsmoking women married to nonsmoking husbands [22, 23]. Simultaneously, Hirayama reported very similar results from a methodologically different multipurpose cohort study in Japan [24, 25]. The results of Garfinkel based on the cohort data of the American Cancer Society and published also at about the same time were equivocal but not incompatible [26]. Since then, 17 other epidemiologic studies have examined the question of involuntary smoking's relationship with lung cancer [18, 27–45] and 12 of them found a positive association which, however, failed to reach statistical significance in four studies. Given these low dose levels and the limited range of ETS exposure differentials it should be expected that in a few studies no association would be found and that in others the association would lack statistical significance.

Furthermore, it should be noted that:

1) When all studies (including the "negative" ones) are combined in order to examine the consistency of the evidence, there is no indication of heterogeneity among the various relative risk estimators (or the corresponding sample regression coefficients), and the weighted common relative risk estimator is significantly higher than the null value of 1 [1, 19, 44].
2) Larger studies, with better validation of disease status and ETS exposure, are usually more supportive of the passive smoking-lung cancer association than smaller studies with less satisfactory methodological designs [1].
3) Misclassification of smokers or ex-smokers (who are in an increased lung cancer risk and tend also to live with smokers) as nonsmokers does not explain more than about 15% of the excess lung cancer risk associated with passive smoking. Lee believes that the effect of this bias is substantially larger, but the empirical data, as summarized in four necessary and sufficient parameters (the proportion of misclassified current and ex-smokers, the risk of lung cancer among those misclassified, the aggregation of smokers, and the proportion of ever smokers), are more supportive of the arguments and estimates adopted by Wald et al. [19].
4) Relative risk figures generated from empirical studies should be adjusted upwards, since few, if any, subjects are actually completely unexposed to passive smoking [1].
5) Random misclassification of ETS exposure and misspecification of latency lead to systematic underestimation of effect parameters (relative risk, regression coefficient) and to substantial reduction of study power [1].

The results of any epidemiologic study, or any set of such studies, may be interpreted in terms of chance, bias, confounding and causality (direct or indirect). Chance is a highly unlikely explanation of the collective evidence generated by the 20, until now, epidemiologic studies exploring the role of passive smoking in the etiology of lung cancer. Several sources of bias have been examined, and several authors have tried to quantify their postulated effects. Misclassification of smoking status does not appear to explain more than about 15% of the excess lung cancer risk associated with passive smoking; there is no evidence of selective publication of studies with "positive", rather than "negative", results; and interviewer bias could not exist in the original studies, could not account for the results of prospective cohort studies, and could not generate differential associations between passive smoking on the one hand and squamous or other histological types of lung cancer on the other [1, 18, 19, 39]. Finally, established or suspected confounding factors have been controlled with extreme care in many of the published epidemiologic studies. Therefore it appears that causality is the most likely explanation of the agregate empirical evidence. However, given the extensive exposure to ETS of many population segments, and the substantial ethical, social and legal aspects of the problem, the passive smoking-lung cancer association should be studied further, with more refined methodology and with more attention to potential hidden confounders and modifiers.

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Passive Smoking and Lung Cancer: An American Cancer Society Study

S. D. Stellman and L. Garfinkel

Summary

The American Cancer Society conducted a case-control study of lung cancer in 134 non-smoking women in four hospitals. Controls were 402 women with colon-rectum cancer, matched to the cases on age and hospital. The odds ratio (OR) for lung cancer in women whose husbands smoked 20 or more cigarettes at home was 2.11 (95% CI: 1.13–3.95). Odds ratios (OR) increased with increasing number of cigarettes smoked by the husband, particularly for cigarettes smoked at home. Special care was taken to "purify" the cases by eliminating smokers, and unusually rigorous scrutiny was given to histological verification of lung cancer. Six types of methodological problems which can affect studies of epidemiologically "weak associations" and their potential effects upon these results are discussed.

Introduction

It has long been known that cigarette smoking may be hazardous to the health of persons other than the smoker. Even before the wealth of data linking lung cancer with passive smoking was available, it was observed that women who smoked were more likely to experience higher rates of neonatal and perinatal loss, or to give birth to lower weight babies, than were non-smoking mothers (USDHEW 1979; USDSSH 1980). Children of smoking parents have higher rates of pneumonia, bronchitis, and other respiratory symptoms (Lebowitz and Burrows 1976; Ware et al. 1984; Schenker et al. 1983; Charlton 1984). Non-smoking adults exposed passively to cigarette smoke experience eye, nose, and throat irritation (Weber 1984), headaches, dizziness, and nausea (Shephard et al. 1979), aggravation of allergies and asthma (Knight and Breslin 1985), and impaired lung function (Kauffmann et al. 1983).

There is little doubt that the non-neoplastic conditions cited above result from exposure to numerous chemical constituents present in the smoke. Many of these substances are carcinogens, such as benzene, benz(a)anthracene, and a group of nicotine-derived nitrosamines (Brunnemann and Hoffmann 1978). Furthermore, both nicotine and its metabolite cotinine can be detected in the saliva and urine of non-smokers exposed to sidestream smoke (Hoffmann et al. 1984), so that systemic exposure has clearly been established.

During the past eight years evidence has been accumulating which strongly suggests that passive or involuntary inhalation is related to lung cancer as well. The literature has been adequately reviewed in a recent report by a committee of the National Research Council, which concluded that "the risk of lung cancer is roughly 30% higher for nonsmoking spouses of smokers than it is for nonsmoking spouses of nonsmokers"

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(Committee on Passive Smoking 1986). The Council report noted, however, that a considerable potential for misclassification and other biases exists in many published studies, which needs further exploration, quantification, and resolution. Furthermore, Lee and colleagues (1986) criticized many of the published studies on methodological grounds.

The American Cancer Society's case-control study (Garfinkel et al. 1985) contains many features which directly address or circumvent some of the serious problems which often affect such studies. In this paper we review the main findings of the ACS study, placing special emphasis on those methodological features which reduce misclassification and bias.

Material and Methods

All cases of lung cancer in women which were diagnosed during 1971–1981 were identified in three New Jersey hospitals and one Ohio hospital. Women with colon-rectum cancer, a type of cancer which has not been associated with cigarette smoking, were identified as controls. Great pains were taken to "purify" the sample with respect to both exposure and outcome, to satisfy the requirement that the cases truly were non-smokers, and truly had lung cancer.

The Tumor Registry, surgical index, or pathology reports from which potential cases were initially identified served only as screening devices. A woman was accepted as a lung cancer case only after a blinded review of all available slides (15 per subject on average) by a single reviewer, Dr. Oscar Auerbach. The reviewer was constantly challenged with repeat slides, and with lung cancer slides from smokers and from sites other than lung or colon-rectum, in order to check the consistency of his findings. If slides were missing or of poor quality, blocks for the case were located and new slides were prepared. In no circumstance was a subject admitted as a case solely on the basis of clinical or cytological findings.

Hospital chart information on smoking, when available, was also used as a screen, so that only subjects stated by the chart to be non-smokers, or for whom smoking history was not indicated, were investigated further. This information, however, did not serve as a source for classifying exposure. All subjects or next-of-kin were given a detailed face-to-face interview with a standard questionnaire, to obtain information on smoking habit of subject, spouse, other family members, and various other details germane to evaluation of exposure to cigarette smoke of others. Women found to be current or former smokers upon interview were immediately eliminated from further consideration as study subjects.

Table 1 shows the process by which the 1,175 women initially identified as possible cases were eventually reduced to a group of 134 validated non-smoking women with histologically proved lung cancer. Of these 1,175 women, all of whose charts indicated microscopically proved lung cancer, 283 were listed as non-smokers (68%), or else had no smoking history listed in the chart (32%). But out of these 283 promising subjects, 113 (39.5%) turned out on questioning to be smokers, and lung cancer could not be positively verified for another 36 (12.7%), leaving 134 (47.3%) confirmed cases of lung cancer in non-smokers.

The age distribution of subjects is shown in Table 2. Three controls were obtained for each case, matched on age (within 5 years) and hospital. Approximately half of the cases and controls were over the age of 70, and more than one-fifth were 80 years or older. The distribution of histological diagnoses was: 65% adenocarcinoma, 16% large cell, 8%

Table 1. Initial selection of subjects

Subject status	No.	[%]
Microscopic proof of lung cancer stated on hospital record	1,175	
Smoker on hospital record	892	
Non-smoker (68%) or no smoking habit stated (32%) on hospital record	283	100.0
Interview revealed smoker	113	39.9
Histopathologic scrutiny failed to confirm primary lung cancer	36	12.7
Interview revealed non-smoker	134	47.3

Table 2. Age distribution of lung cancer cases and controls

Age [years]	Cases		Controls	
	No.	[%]	No.	[%]
40–49	5	3.7	17	4.2
50–59	28	20.9	86	21.4
60–69	28	20.9	88	21.9
70–79	44	32.9	121	30.1
80+	29	21.6	90	22.4
Total	134	100.0	402	100.0

Table 3. Odds Ratios (OR) for matched groups of women for risk of lung cancer from passive exposure to cigarette smoke, classified in four different ways

Classification	OR	95% confidence interval
Exposed to smoke over last 5 years	1.28	0.96–1.70
Exposed to smoke over last 25 years	1.13	0.60–2.14
Husband smoked	1.22	0.97–1.71
Husband smoked at home	1.31	0.94–1.83

squamous cell, 4% oat cell, 3% alveolar cell, 3% mixed, and 1% too undifferentiated for classification by cell type.

The principal findings are summarized in Tables 3–5. The odds ratio (OR) for lung cancer was computed for four different categories of exposure: exposure to smoke over the last 5 years, exposure to smoke over the last 25 years, marriage to a husband who smoked, and marriage to a husband who smoked at home. The ORs ranged from 1.13 to 1.31, several of which were marginally significant ($p = 0.06$). Classification by the

Table 4. Odds Ratios (OR) for exposure to husband's total smoking habits

No. cigarettes smoked per day	No. cases	No. controls	OR	95% confidence interval
None	43	148	1.00	
<20	11	45	0.84	
20–39	32	102	1.08	
40+	30	52	1.99*	
Pipe/cigar	18	55	1.13	
All smokers	91	254	1.23	(0.94–1.60)

* p (trend) < 0.05

Table 5. Odds Ratios (OR) for exposure to husband's smoking habits at home

No. cigarettes smoked per day	No. cases	No. controls	OR	95% confidence interval
None	44	157	1.00	
<10	29	90	1.15	
10–19	17	56	1.08	
20+	26	44	2.11*	
Pipe/cigar	18	55	1.17	
All smokers	90	245	1.31	(0.99–1.73)

* p (trend) < 0.05

estimated number of hours per day during the past 5 or 25 years also failed to yield statistically significant ORs.

Significant ORs were found, however, for women whose husbands smoked at least 40 cigarettes a day in total (OR = 1.99, 95% CI = 1.13–3.50), or at least 20 per day at home (OR = 2.11, 95% CI = 1.13–3.95); both analyses showed significant dose-responses as well (Tables 4 and 5). A logistic regression analysis showed a significant positive trend of increasing risk with increased exposure to the husband's smoking at home, controlled for age, hospital, socioeconomic status, and year of diagnosis.

Discussion

Dr. Wynder, in his keynote address at the beginning of this conference, pointed out that the evaluation of the cancer risk due to involuntary smoking belongs to a larger class of perplexing but important public health problems which involve epidemiologically "weak associations," and has been a leading advocate of development of guidelines for the conduct of such studies (Wynder 1987). The issues of bias (Feinleib 1987), misclassification, and confounding are of paramount importance, and have been studiously considered in all stages of our study. Of these sources of possible error, misclassification

is probably the most serious. In their original presentation of this data, Garfinkel et al. (1985) computed hypothetical ORs which would have resulted from a less rigorous classification of non-smokers. They showed that, had they included women originally identified as non-smokers but who were really smokers, the ORs would have been greatly increased, from about 1.3 to about 1.6 (or a doubling of excess risk).

In yet another keynote address, Dr. Peter Lee raised six specific criticisms of both case-control and cohort studies, suggesting that failure to account for some of these problems might have led erroneously to findings in some studies of increased lung cancer risk in passively exposed non-smoking women. We can address all six of these problems in the context of the present study.

Lack of Representativeness

The criticism that cases selected for study are not representative of the population from which they come is often raised with respect to case-control studies (Winkelstein and Levin 1981), but it is really a non-issue. We agree with Cole (1975), who states that it is sufficient that cases and controls should be comparable with respect to selection.

Choice of Controls

There has been considerable debate about whether or not it is appropriate to exclude as controls subjects with tobacco-related illnesses. We believe it is essential to do so, and have used women with colon-rectum cancer. Since cigarette smoking is responsible for a variety of serious illnesses in addition to lung cancer, smokers are over-represented among hospital patients; therefore, randomly selected hospital patients are more likely to be smokers than those chosen with specific diagnoses like colon cancer. Absent such selection, controls would have too high a proportion of smokers, and ORs would be too low.

Sample Size and Statistical Power

A major problem with this and all related studies is that lung cancer in non-smokers is in all events rare, and smokers tend to be married to smokers. Therefore, the number of exposed cases available for study in any population is small, and the time and expense required to accumulate sufficient cases to warrant a statistically useful analysis is long. This dilemma is basic to all "weak association" problems, and can be overcome only by diligence of investigators and concordance of results of a multitude of studies, conducted in different populations, by different investigators, using different methodologies.

Accuracy of Diagnosis

Not all studies have involved diagnostic verification as elaborate as that conducted here. We believe that the effort invested by Dr. Auerbach in the reading and re-reading of thousands of slides for this study have paid handsome dividends in terms of quality of data.

Misclassification of Exposure

This problem is by far the most worrisome of this and most other studies. Correct classification of exposure involves two factors: reliance on the memory of a study subject (who may be extremely ill) or a close relative, and construction of a well designed questionnaire suitable for eliciting the desired information in a clear, unambiguous way.

One can obviously never hope to achieve perfect classification of historical exposures remembered by study subjects, but the internal consistency of the data, the care with which the questionnaire was constructed and tested, and the mutual comparability of the results with those of many other studies all increase our confidence in the assertion that misclassification has played at most a minor role. This is particularly reinforced by the similarity between our results (Table 3) and the estimate of 1.25 given by the National Research Council for the relative risk after allowance for misclassification bias (Committee on Passive Smoking 1986). Furthermore, Wald (1986) has suggested that misclassification of the type encountered here most likely results in *underestimation* of true ORs.

Confounding Variables

The results obtained by traditional Mantel-Haenszel analysis were confirmed by a more elaborate logistic regression analysis in which numerous additional variables not already accounted for through matching were controlled. Stellman (1987) has previously demonstrated that for many "weak association" problems the influence of confounding is usually of far less consequence than initially feared. This proved to be true here, and we do not believe confounding is a source of misleading results in this study.

Conclusions

No single analytic study can resolve a difficult and complex epidemiologic problem where associations are "weak" (e.g., OR < 2.0). The best one can hope to achieve is consistency among studies of varying designs conducted in different populations. Numerous studies of passive smoking in relation to lung cancer have been reported in the literature but they do not all uniformly confirm this association.

It may in fact never prove possible to assert that passive inhalation of cigarette smoke causes lung cancer with the same degree of certainty as for active smoking, because of the multitude of methodological uncertainties catalogued herein. In matters of public health, however, to wait for perfect data is not always appropriate or necessary. The accumulated data on lung cancer and the other conditions related to passive exposure, which were described in the introductory section, are more than sufficient justification to continue expansion of legislative restrictions on smoking in public places.

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Is There a Threshold Effect for ETS? Results of Data from Chinese Females Who Had Never Smoked

L. C. Koo and J. H-C. Ho

Summary

Although environmental tobacco smoke (ETS) contains compounds which are known to be carcinogenic to humans, does exposure to it in sufficient amounts cause lung cancer or other respiratory diseases in adult women with no history of active smoking? Data from studies in Hong Kong show that the association between ETS and lung cancer is extremely weak, if apparent at all. Furthermore, although symptoms of chronic bronchitis are associated with increased risk for lung cancer in never- and ever-smokers, this symptom was not found to be associated with increasing doses of ETS.

The independent role of diet as being more important than ETS in lung cancer etiology among never-smoked subjects is suggested. More frequent consumption of vegetables and fruit have been consistently found to reduce lung cancer risk in various international studies. Data from Hong Kong indicate that increasing amounts of fresh fruit and decreasing amounts of smoked/cured meats/fish decreased risk for squamous or small cell lung tumors. These same dietary habits were found to be more prevalent among wives with non-smoking versus smoking husbands. Since most studies linking ETS with lung cancer have found the relationship to be specific to squamous or small cell tumors, these findings are consistent with the diet and lung cancer association. Therefore, the lifestyles of wives with smoking husbands are correlated with habits that could independently exert a deleterious effect on health and help explain the controversial worldwide epidemiological findings linking ETS with lung cancer.

Introduction

Although the carcinogenicity of substances in sidestream and mainstream tobacco smoke is well documented [5 ,6], the question in recent epidemiological studies is whether exposure to it is in sufficient amounts to cause respiratory diseases. Another words, although environmental tobacco smoke (ETS) is a known human carcinogen, is there a threshold effect before its detrimental effects on human health can be measured? As stated by Hoffmann and Hoffmann [3] "The significance of exposure to ETS must be evaluated on the basis of severity of the pollution, the duration of exposure and personal variations in uptake" (p. 8). Such factors have been taken into account in assessing the role of ETS in lung cancer and symptoms of chronic bronchitis among Hong Kong Chinese females.

H. Kasuga (Ed.) Indoor Air Quality

ETS and Lung Cancer Among Hong Kong Chinese Women

Because Hong Kong's world age-adjusted female lung cancer incidence rate of 27.1/100,000 in 1982 [4] placed it to be among the highest in the world, and only 36% of the cases could be attributed to a history of active smoking [9], intensive study has focused on the possible role of ETS as an etiological factor [7–10].

From 1981–1983 200 female lung cancer patients and 200 district and age (± 5 years) matched controls were interviewed in a retrospective study to study the factors associated with the high female lung cancer rates in Hong Kong. The data collected on ETS exposure attempted to be as comprehensive as possible by specifically asking about the various sources of it over the lifetime of the subject. The interviews were structured to take into account major regular sources of ETS by asking who smoked, what type of tobacco was smoked, when the exposure occurred, and where it took place. As a result, more than 30 separate variables on ETS sources were collected. From these data, four measurements which combined the sources of ETS exposures from different persons, places (home or work), times, and types of tobacco were identified as reasonable indicators of lifetime exposure levels: total years, total hours, mean hours/day, and average cigarettes/day weighted by the years of exposure.

Analysis of such data did not indicate dose-response relationships [10]. At the highest levels of ETS exposure, the relative risks (RR) were approximately 1.00 for all four measurements. Even when the data were adjusted for possible confounders such as age, number of births, schooling, and years since exposure to cigarette smoke had ceased in the home or workplace, similar results were obtained. Analyses were also done to see whether increasing the intensity of the exposure or earlier age of initial exposure would lead to increases in RR. Again, those at the highest exposure levels had among the lowest RR, and none of the findings were statistically significant. Only when the cases were segregated by histological type and location of the primary tumor, those with tumors in the middle or lower lobes that were peripherally situated or of the squamous/small cell type had RR that weakly exhibited dose-response results [10].

If we had been studying active smoking, these types of analyses would have produced statistically significant results. On the other hand, the biochemical data indicate that the actual amounts inhaled by a passive smoker is only a small fraction of that inhaled by an active smoker. Measurements of urinary cotinine levels in exposed subjects have revealed that the levels in passive smokers average 1% of those in active smokers, and those exposed to heavy levels of ETS may absorb the equivalent of actively smoking 1/2 cigarette per day [1]. Therefore, evaluation of the effects of ETS on health is difficult because sidestream smoke is diluted by ambient air and affected by ventilation conditions.

Other results from our studies in Hong Kong seem to corroborate the weak effects of ETS on lung cancer. Firstly, the risk for lung cancer among active smokers was not increased by their inhalation of the sidestream smoke of cigarettes from other smokers [8]. Secondly, the lifetime cumulative duration of ETS exposure among never-smoked lung cancer cases or controls was about the same. It was estimated that cases averaged 13,400 h and 19.8 years versus 14,200 h and 18.6 years for the controls [8]. And finally, although it may be argued that a sample size of 88 cases and 137 controls would provide insufficient statistical power to find significant results [18], it should be noted however, that an analysis of the effects of diet and lung cancer risk among the same group of subjects did find highly significant RR. Unlike the ETS data, the protective effects of fresh vegetables and fruit were clearly apparent in dose and trend [11].

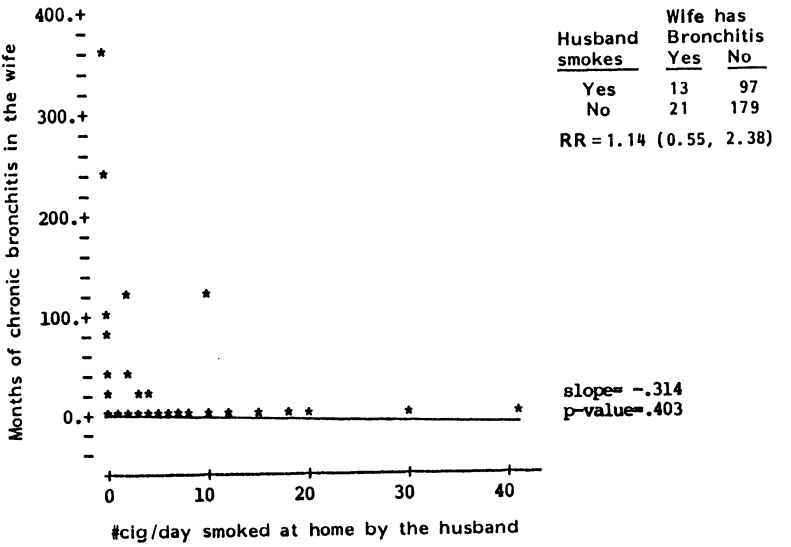

Fig. 1. Husband's cigarette consumption levels at home and duration of chronic bronchitis among their never-smoked wives (n = 310)

ETS and Symptoms of Chronic Bronchitis

Since the effects of ETS on lung cancer risk were unclear, the possibility that ETS might be associated with other respiratory symptoms indicative of bronchial irritation were studied. It was already noted in the Hong Kong study [9] that increasing duration of chronic phlegm expectoration was associated with increased risk for lung cancer among ever- and never-smoked female subjects.

As part of a community survey on the prevalence of respiratory symptoms among mothers and children in Kwun Tong, a manufacturing district in Hong Kong, 351 mothers and their children filled out a questionnaire in May 1985 as part of a larger study on air pollution and respiratory symptoms [12]. From the initial sample, 310 were identified as never-smoked wives. Figure 1 plots the relationship between the duration of chronic bronchitis (chronic phlegm or cough for $\geq$ 3 months) in the wife and the number of cigarettes smoked by her husband *at home* only. As can be seen, there was no relationship between the cigarette consumption levels of the husband at home, and the duration or appearance of chronic bronchitis in his wife. If the husband smoked at home, the RR for chronic bronchitis in his wife was a non-significant 1.14 (95%CI = 0.55, 2.38).

A similar analysis was done among the never-smoked district-matched controls from the lung cancer study [10]. Figure 2 shows the correlation between the duration of chronic bronchitis in the wife and the number of cigarettes smoked by her husband throughout the day. In contrast to the previous finding, the slope was statistically significant (p = 0.02) in showing a positive correlation, although the RR was a nonsignificant 0.78 (95%CI = 0.36, 1.67). More detailed analysis on the relationship between our ETS measurements like total years, total hours, and mean hours per day,

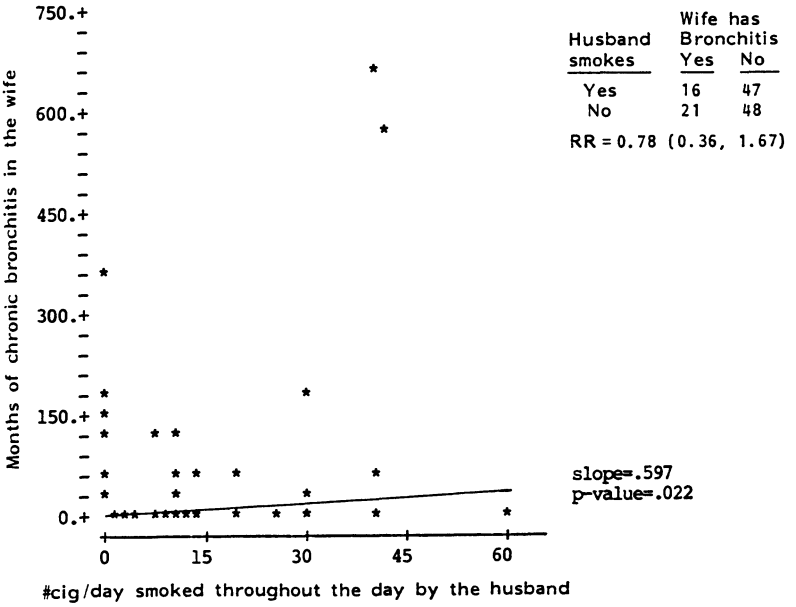

Fig. 2. Husband's daily cigarette consumption levels and duration of chronic bronchitis among their never-smoked wives (n = 132)

and the appearance of chronic phlegm in the never-smoked controls did not indicate any dose-response effects (Table 1).

The different findings of these two figures suggest some problems in evaluating ETS exposure on health. On the one hand it has been estimated from a previous study [13] that about 90% of the wife's total ETS exposure comes from the husband. On the other hand, the question that arises from the above figures is why the husband's *daily* cigarette consumption levels correlates with the wife's duration of chronic bronchitis, and not the levels he actually smokes at home. The latter data would seem to be a more accurate estimation of the actual exposure of the wife to her husband's cigarettes. Is it possible that the husband's daily cigarette consumption levels acts as a surrogate measure of some other lifestyle factor(s) that affects risk for respiratory and other diseases associated with ETS?

Confounders of ETS Exposure

In order to study possible lifestyle correlates of passive smoking, the lifehistory profiles of the 136 never-smoked wives who acted as district controls in the lung cancer study were compared. The wives were defined by the smoking status of their husbands, and classified into three groups: husband never smoked, husband was a light smoker ($\leq$ 20 cigarettes/day), and husband was a heavy smoker ($>$ 20 cigarettes/day). These categories were used since most epidemiological studies use the cigarette consumption levels of the husband as an index of the wife's ETS exposure.

Table 1. Lifetime doses of environmental tobacco smoke (ETS) and relative risk (RR) for chronic phlegm symptoms in never-smoked women

	# Subjects chronic phlegm		RR* (95%CI)
	Yes	No	
Total years of exposure to tobacco smoke			
0 years	6	34	1.00
1–20	14	21	3.95 (0.14, 115.00)
21+	13	49	1.71 (0.42, 7.01)
Total hours of exposure to tobacco smoke			
0 hours	6	34	1.00
1–10,000	14	24	3.60 (0.16, 81.23)
> 10,000	13	46	1.68 (0.43, 6.50)
Mean hours per day exposed to tobacco smoke			
0 hours/day	6	34	1.00
≤ 1.5	19	33	3.61 (0.79, 16.38)
> 1.5	8	37	1.43 (0.30, 6.67)

* Odds ratio adjusted for age, number of live births, schooling (+/−), and years since exposure to cigarette smoke had ceased in the home or workplace by a conditional logistic regression package based on N:M matching by strata defined by district (n = 34) and housing type (public or private).

The subjects were all never-smoked women who were the district controls used in the lung cancer case-control study of Koo et al. 1987.

Although the full report can be found in Koo et al. [13], Table 2 summarizes some of the significant findings. As can be seen, wives with never-smoked husbands had "healthier" lifestyles than wives with smoking husbands. The former generally were more likely to own their own home and a car, spent more years in cooking and house-cleaning, and were more frequent consumers of fresh vegetables, and milk. By comparison, wives with smoking husbands had poorer levels of socio-economic status, were less conscientious housewives, and were more frequent consumers of salted/dried fish, pickled vegetables, chilis, and alcohol. The implications of these dietary differences was that wives of smoking husbands generally consumed higher levels of cholesterol, sodium, alcohol and N-nitroso compounds than wives of non-smoking husbands. According to the U.S. National Research Council's 1982 report on *Diet, Nutrition and Cancer* [15], the dietary habits of wives with non-smoking husbands would be protective of cancer, whereas those with smoking husbands would be associated with higher risk for cancer. Moreover, these differences were usually greatest when comparing wives of non-smoking versus heavy smoking husbands.

Although most of the consistent data on the effects of ETS on health have been on the correlation between ETS and respiratory illnesses in children [14], it is also possible that these findings may not be directly due to ETS inhalation by the child. Studies among

Table 2. Lifestyle correlates of passive smoking: a comparison of non-smoking wives with non-smoking vs. smoking husbands

	Mean values[a] for wives					
	Non-smoking husband	Smoking husband				Non-smoking vs. smoking husband
	N = 70	Light smoker 1–20 cig/day N = 49	Heavy smoker > 20 cig/day N = 17	Trend p-value[b]	All smokers N = 66	t-test or chi-square test p-value[c]
Lifestyle variable:						
% family own car & home	13%	4%	6%	–	5%	0.088
Years cooking	36.13	36.16	30.06	0.41	34.59	0.03
Years house-cleaning	35.11	35.08	31.41	0.78	34.14	0.02
Dietary habits:						
Fresh vegetables[d] per month	9.17	6.55	5.88	0.06	6.38	0.0001
Dried/salted fish, seafood per month	4.73	6.26	8.41	0.24	6.82	0.09
Pickled/salted vegetables per month	7.01	9.94	7.76	0.78	9.38	0.0001
Chili, fresh or sauces, per month	1.94	4.61	5.65	0.17	4.88	0.0001
Milk totaling 1 cup per month	7.21	2.88	2.71	0.07	2.83	0.0001
Years of alcohol consumption	3.23	8.63[e]	3.53	0.22	7.29	0.0001

[a] Mean value for all subjects.
[b] p-value for trend by linear test on regression coefficient.
[c] p-value by chi-square or t-test of exact values of wives with non-smoking vs smoking husbands.
[d] Times per month consume cruciferous vegetables, carrots, beans, or legumes.
[e] N = 48. Data for one subject was missing.

primary school children in Hong Kong and Japan [12] show a highly significant correlation between the frequency of respiratory illnesses in a mother and her child with a Pearson's correlation coefficient of 0.2 and $p \leq 0.009$. Since it is known that smokers tend to succumb to respiratory diseases more often than non-smokers, the role of cross-infection between smoking parents and their children should be assessed. This is especially so when many of the infectious upper respiratory diseases are contracted by close physical contact or air-borne agents, which would be highly likely in the family environment.

Conclusion

Data have been presented from the Hong Kong studies which show that studying the role of ETS on respiratory diseases and lung cancer cannot be simply based on the assumption that the husband's cigarette consumption levels is an index of ETS exposure in the wife. As pointed out by Wynder and Goodman [19] in their review of unresolved issues in smoking and lung cancer, the question of whether "a practical threshold for carcinogenicity exists for cigarette smoking" should be examined, and data should be evaluated by Koch's postulates, i.e. "consistency, strength, specificity, temporal relationship, and coherence of the association" (p. 178). These issues seem even more pertinent when evaluating ETS, since exposure levels are a minute fraction of the levels of exposure among active smokers.

Overall, the data from Hong Kong on the relationship between lifetime measurements of ETS and lung cancer risk did not show dose-response results. Only when the lung cancer cases were statistically analyzed by histological type and location of the primary tumor, those with tumors in the middle or lower lobes that were peripherally situated or of the squamous/small cell type, had RR patterns that weakly suggested increasing dose with increasing risk. However, less than a quarter of the lung cancer cases among never-smoked women had lung tumors with these characteristics.

Analyses were also done to see whether ETS was associated with other respiratory symptoms indicative of bronchial irritation. No correlation was found between the presence or duration of chronic bronchitis among never-smoked wives and the number of cigarettes their husbands smoked *at home* per day in a community survey. Yet the results of another study on the never-smoked district controls used in the lung cancer study did find a correlation between the number of cigarettes smoked by the husband *throughout the day* and the duration of chronic bronchitis in his wife. Unfortunately the same questions were not asked in both studies so that the implications of the difference between the number of cigarettes the husband smokes at home only versus throughout the day cannot be ascertained. It is also possible that the differing mean age of 38 in the community survey and 59 among the lung cancer district controls contributed to the differing results.

However, we feel that these data corroborate the highly diluted effects of ETS exposure found in the biochemical assessments of exposure. The inconsistent worldwide epidemiological findings [6, 14, 18] linking ETS with lung cancer suggest a threshold effect, which is not apparent in the studies of active smoking and lung cancer. Since everyone ingests, inhales, or comes in contact with thousands of carcinogens or pro-carcinogens in everyday life, ETS may have such a weak efffect that it is easily overshadowed by other risk factors.

In addition, we have been able to show that among never-smoked wives, having a smoking husband is correlated with other lifestyle factors that could independently exert

a deleterious effect on health. Wives with husbands who did not smoke led healthier lifestyles than those with husbands who did. These differences were especially apparent in their dietary habits. Wives with non-smoking husbands more frequently consumed those foods that have been linked with reduced risk for cancer, whereas those with smoking husbands more frequently consumed foods associated with increased risk for cancer.

The independent role of diet as being more important than ETS in lung cancer etiology among never-smoked Hong Kong Chinese women is suggested by these results. Unlike the inconclusive analysis of ETS exposure and lung cancer risk, the analysis of dietary patterns among the same group of never-smoked cases and controls found statistically significant RR and clear dose-response effects. Higher consumption of leafy green vegetables, carrots, tofu, fresh fruit and fresh fish were found to be protective, especially among those with adenocarcinoma or large cell histological types of lung tumors. On the other hand, for squamous or small cell tumors, higher consumption of fresh fruit led to reduced RR and smoked meats to increased RR. To further support the role of ingestants in risk for lung cancer among non-smokers, never-smoked wives of smoking husbands were found to less frequently consume the same foods which conferred protection, and more frequently the foods that increased risk for lung cancer.

In fact, the histological findings in epidemiological studies linking ETS with lung cancer are consistent with these data. Most studies have found the association of ETS with lung cancer to be specific to lung tumors of the squamous or small cell type [2, 10, 16, 17]. In our Hong Kong studies, wives of husbands who were heavy smokers (i.e. more than 20 cigarettes per day) consumed fresh fruit the least often, and smoked/cured/salted meats, poultry, or fish the most often [13] and these were the same significant dietary factors affecting risk for squamous or small cell lung cancers in the same population. These results are supported by the worldwide epidemiological data which, unlike the studies on ETS and lung cancer, have been consistent in showing the protective effects of fresh vegetables or vitamin A compounds in lung cancer risk. Thus, as emphasized by Rylander in this same conference, it may be too simplistic to only look at the role of inhalants in lung cancer etiology. The role of ingestants needs further research and may actually overshadow the effects of ETS in lung cancer risk among the never-smoked population.

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Passive Smoking and Cancer: The Association Between Husbands Smoking and Cancer in the Lung of Non-smoking Wives

T. Hirayama

Summary

There is sufficient evidence that tobacco smoke is carcinogenic to humans (IARC Monographs vol 38, p 314, 1986). Epidemiological evidence supporting this statement was reviewed with special reference to lung cancer. An elevated risk for lung cancer, mostly dose-dependent, was observed in non-smoking women whose husbands smoke in 10 or more epidemiological, both cohort and case-control, studies in Japan, Greece, Sweden, the USA, and in other countries. The results are compatible with the existence of various kinds of carcinogens in much higher concentrations in sidestream smoke than in mainstream smoke and other laboratory evidence such as impaired lung function, demonstration of mutagens in urine, and higher frequency of chromosome abnormalities such as sister chromatid exchange (SCE) in lymphocytes in persons passively exposed to tobacco smoke. A significant association was also found with nasal sinus cancer and brain tumors in a large scale cohort study in Japan, probably reflecting the carcinogenic hazards of continued inhalation of sidestream smoke through the nose. Analysis by age of wives revealed a significantly elevated risk of breast cancer between the age of 50–59 with an increase in the amount of cigarettes smoked by the husbands. In addition to these, passive smoking is likely to promote risks for ischemic heart disease, to damage the health and growth of fetuses, and to increase the risk of selected childhood cancers and childhood respiratory diseases. Decisive action to minimize this danger is urgently required.

Introduction

Most constituents in tobacco smoke, including carcinogens of many kinds, occur in markedly higher concentration in sidestream smoke than in mainstream smoke (Table 1) [4, 5, 35]. If inhaled at a close distance (direct passive smoking), or when ventilation of space is poor or there are many smokers in the room, inhalation of polluted air (indirect passive smoking) could create a carcinogenic potentials and cause adverse health effects such as pulmonary dysfunction in people exposed to such air [41], Bos et al. [3] demonstrated excretion of mutagens in human urine after passive smoking. If such conditions last for a long time it is possible that the risk of cancer of lung and other selected sites could go up. Such speculation was supported by reports of epidemiological studies from Japan, Greece, Sweden, the U.S.A. and from other countries which demonstrated an elevated risk of lung cancer in non-smoking women with smoking husbands.

H. Kasuga (Ed.) Indoor Air Quality

Table 1. Distribution of selected components in the sidestream smoke (SS) and the ratio of SS to mainstream smoke (MS) of U.S. cigarettes (Source: Adams et al. (1985))

	SS			SS/MS		
	Nonfilter cigarette	Filter cigarette	Perforated filter tip cigarette	Nonfilter cigarette	Filter cigarette	Perforated filter tip cigarette
Tar [mg/g]	22.6	20.0	14.1	1.1	2.9	15.6
Nicotine [mg/g]	4.6	3.4	3.0	2.2	4.2	20.0
Carbon monoxide [mg/g]	28.3	33.2	26.8	2.1	3.5	14.9
Benzo[a]pyrene [ng/g]	67	51.7	44.8	2.6	4.2	20.4
N-Nitrosodimethy-amine [ng/g]	735	611	685	23.6	50.4	167

Passive Smoking and Cancer: Epidemiologic Evidence

Prospective Studies

Study in Japan

A prospective study was conducted on the mortality of 91,540 non-smoking wives in Japan in relation to the husbands' smoking habit [13–18].

A total of 265,118 adults, 122,261 men and 142,857 women, aged 40 years and above, 95% of the census population in 29 Health Center Districts in Japan, were interviewed from October 1 to December 31, 1965 and were followed up by establishing a record linkage system between the risk factor records and death certificates.

Lung Cancer: A total of 429 deaths from lung cancer in women was recorded during the 16 year follow-up (1966–81). Samples of these showed that 74% of them were adenocarcinomas. Out of these 429 lung cancers, 303 were non-smokers and 200 occurred among 91,450 non-smoking married women whose husband's smoking habits were known. The standardized mortality ratio of lung cancer in non-smoking women was 1.00, 1.36, 1.42, 1.58, and 1.91 when husbands were non-smokers, ex-smokers, daily smokers of 1–14, 15–19, and 20 or more cigarettes per day, respectively (p for trend: 0.00178). A similar significant dose-response relationship was observed by age and by occupation of husbands, by age of wives, and in each time period of observation (internal consistency of association) (Fig. 1) [14]. The relationship was unclear, however, in older ages (husband's age over 70 or wife's age over 60) probably because of possible disappearance of exposure to passive smoking by the death of husbands plus higher smoking cessation rate and lesser proximity between husbands and wives in such old age group (Fig. 2). No characteristics of husbands other than cigarette smoking nor any characteristic of wives themselves were found to elevate risk of lung cancer in their non-smoking partners (specificity of association) (Fig. 3) [14]. A nested case-control study revealed the association between husbands smoking and lung cancer is independent to each of other

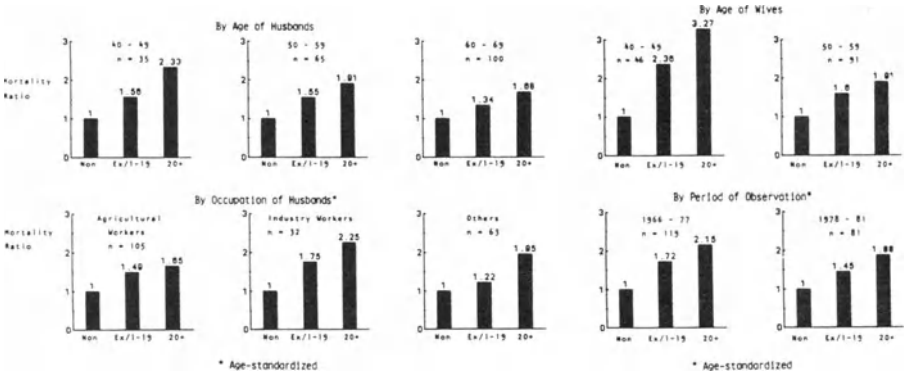


Fig. 1. Mortality ratio of lung cancer in non-smoking wives by husband's smoking habit (prospective study, 1966–81, Japan)

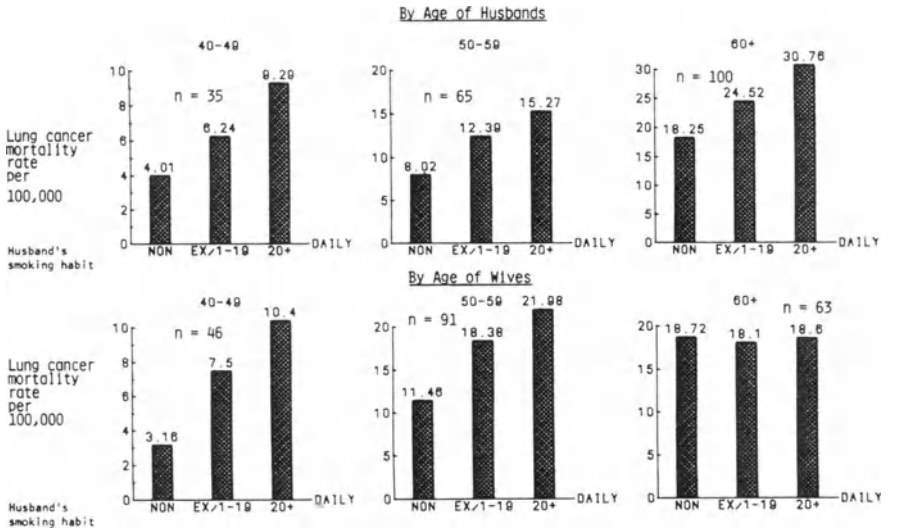


Fig. 2. Mortality rate for lung cancer (per 100,000) in non-smoking wives by smoking habit of husband (prospective study, 1966–81, Japan)

risk factors such as diet, prefecture of residence and density of population (Fig. 4). Further, non-smoking husbands with smoking wives also showed an elevated risk of lung cancer, standardized mortality ratio being 1.00, 2.14, and 2.31 in non-smoking husbands with non-smoking wives, with wives smoking 1–19, and with wives smoking 20 or more cigarettes daily, respectively (p for trend: 0.0177) [16]. Based on this large scale cohort study it was estimated 1,189 non-smoking women annually die from lung cancer in Japan due to their husband's smoking (63 out of 429 female lung cancer or 14.7% were due to husband's smoking. Female lung cancer death in Japan in 1986 was 8,088. $8{,}088 \times 0.147 = 1{,}189$).

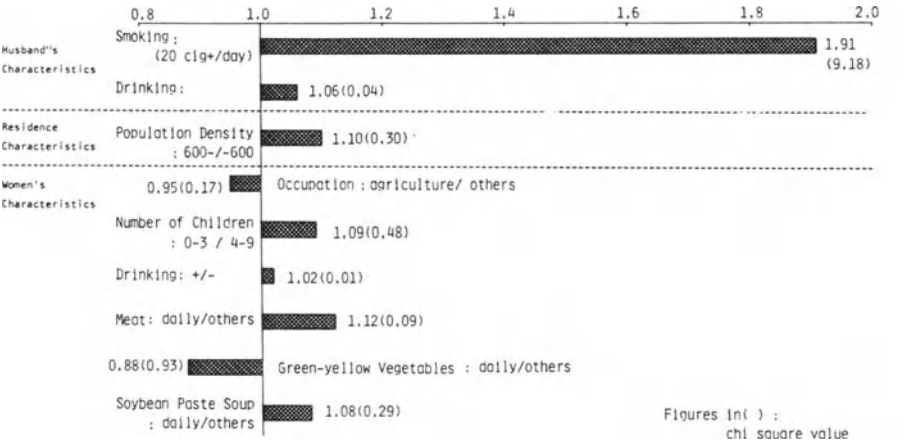


Fig. 3. Lung cancer mortality in non-smoking women ratio by selected risk factors (prospective study, 1966–81, Japan)

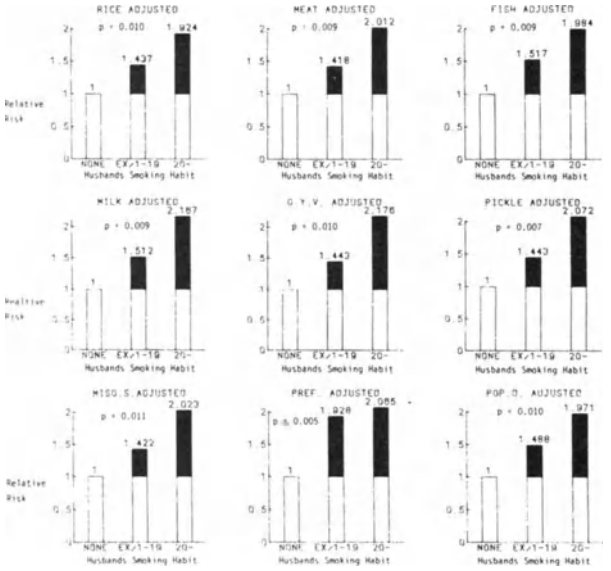


Fig. 4. Relative risk for lung cancer in non-smoking wives by smoking habit of husbands; comparison of 200 lung cancer cases and age-occupation matched controls; observation by selected life style and demographic variables (Prospective Study, 1966–81, Japan)

Nasal Sinus Cancer and Brain Tumor: No significant association was observed between husbands smoking and most other cancers such as stomach cancer. However a significant risk elevation of cancer of paranasal sinuses and brain tumor in non-smoking wives was detected according to the amount of a husband's smoking, relative risk for nasal sinus cancer being 1.00, 1.57, 2.02, 2.55 and relative risk for brain tumor being 1.00, 3.05, 6.25, 4.32 when husbands were non-smokers, smokers of 1–14, 15–19 and 20 or more cigarettes daily [16] (Table 2). No other risk factors studied were identified to significantly alter the

Table 2. Spouse smoking and cancer. Dose-response relationship

	(Number of death)	Mantel-extension chi	One-tail p value
Cancer of all sites	(2,705)	2.659	0.00392*
Ca. mouth & pharynx	(22)	-0.829	0.20355
Ca. esophagus	(58)	0.246	0.40284
Ca. stomach	(854)	-0.270	0.39358
Ca. colon	(142)	0.463	0.32168
Ca. rectum	(112)	-0.007	0.49721
Ca. bile duct & gall bladder	(91)	0.972	0.16553
Ca. liver	(226)	0.696	0.24321
Ca. pancreas	(127)	-0.860	0.12500
Ca. nasal sinus	(28)	1.963	0.02482*
Ca. lung	(200)	2.915	0.00178*
Ca. breast	(115)	1.320	0.09342
Ca. cervix	(273)	1.156	0.12384
Ca. ovary	(54)	0.394	0.34679
Ca. urinary organs	(49)	0.125	0.45026
Ca. skin	(23)	1.445	0.07423
Bone tumor	(17)	0.358	0.36017
Brain tumor	(34)	2.673	0.00376*
Malignant lymphoma	(85)	1.134	0.12840
Leukemia	(51)	1.389	0.08242

Husbands smoking		non	ex-	1–14	15–19	20–
Rate ratio in non-smoking wives	Ca. all sites	1.00	1.16	1.13	1.04	1.20
	Ca. lung	1.00	1.36	1.42	1.58	1.91
	Ca. nasal sinus	1.00	-	1.57	2.02	2.55
	Brain tumor	1.00	-	3.05	6.25	4.32

risk of these cancers in women. The finding strengthens the plausibility of carcinogenic hazards of sidestream smoke inhalation through the nose. For brain tumor, a significant risk elevation by passive smoking was reported for childhood brain tumor [31]. It is of importance that a similar risk elevation by passive smoking was observed also for adult brain tumor.

Breast Cancer: Although association was not significant for all age groups, analysis by age groups of wives, standardized by occupation of husbands, revealed a significant dose-response relationship between amount of cigarettes smoked by the husbands and mortality from breast cancer in non-smoking wives of age 50–59, relative risk being 1.0 (breast ca./population; 6/7,635, 1.3 (16/15,640) and 2.68 (18/8,814) respectively when husbands were non-smokers, smoked 1–19 and smoked 20 or more cigarettes daily (p for trend: 0.00969). Existence of highly susceptible "window age" is strongly suspected for this cancer.

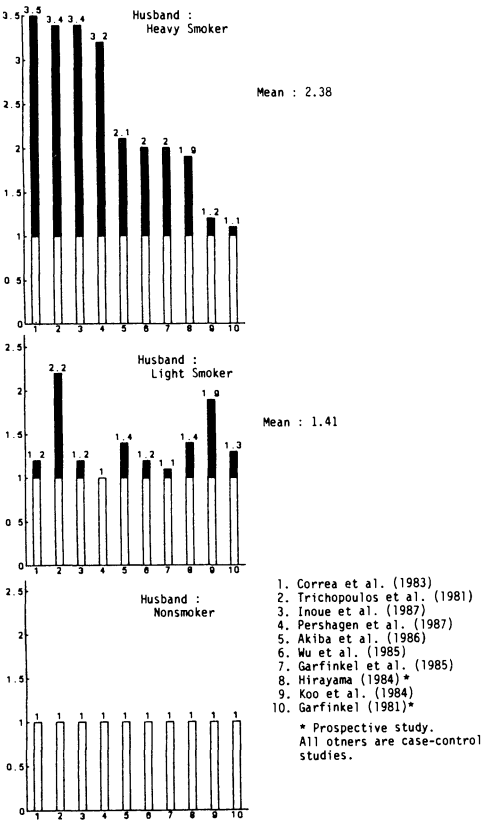


Fig. 5. RRs of lung cancer among non-smoking women by husbands smoking habits

When cancers of lung, nasal sinus, breast and brain tumors were excluded, the significant association observed between husbands smoking and cancer of all sites was noted to become non significant.

Epidemiologic Studies Conducted in Other Countries: Since the reports of initial studies by us in Japan [13] and in Greece [37], a large number of epidemiological studies have been conducted on the subject [1, 6–9, 18, 22, 30, 36, 43]. Results of main studies on lung cancer are summarized in Fig. 5 and Table 3. In most studies, dose-response relationship is clearly seen (Table 4). It must be reasonable to consider therefore that spouse smoking does raise the risk of lung cancer in their partners, although the extent of risk elevation in heavily exposed case is at most in the order of 2–3 fold.

In addition husbands smoking habit were observed to be significantly associated with the risk for ischemic heart disease, suicide and all causes of death in a cohort study in Japan [18].

Table 3. Summary of the epidemiological studies of risk of lung cancer in non-smokers associated with exposure to environmental tobacco smoke

	Exposed to environmental smoke		Unexposed to environmental smoke		Relative risk	95% Confidence limits	
	Lung cancer	No Lung cancer	Lung cancer	No Lung cancer			
Values overall for							
case-control studies*	425	1,200	286	1,126	1.27	1.05	1.53
prospective studies**	251	193,148	163	91,538	1.44	1.20	1.72
all studies	676	194,348	449	92,664	1.35	1.19	1.54

* Chan and Fung (Hong Kong), Correa et al. (US), Trichopoulos et al. (Greece), Buffler et al. (US), Kabat and Wynder (US), Garfinkel et al. (US), Akiba et al. (Japan), Lee et al. (England), Koo et al. (Hong Kong), Pershagen et al. (Sweden).
** Garfinkel (US), Gillis et al. (Scotland), Hirayama (Japan).
Abbreviated from Wald et al.: Br M J, 293, 8 Nov. 1986.

Table 4. RRs of lung cancer among non-smoking women, according to number of cigarettes smoked per day by their husbands

	Husband's smoking status		
	Non-smoker	Light	Heavy
Correa et al.	1.0	1.2	3.5
Trichopoulos et al.	1.0	2.4	3.4
Inoue et al.	1.0	1.2	3.4
Pershagen et al.	1.0	1.0	3.2
Akiba et al.	1.0	1.4	2.1
Wu et al.	1.0	1.2	2.0
Garfinkel et al.	1.0	1.1	2.0
Hirayama*	1.0	1.4	1.9
Koo et al.	1.0	1.9	1.2
Garfinkel*	1.0	1.3	1.1

* Prospective study. All others are case-control studies.

Evaluation of Currently Available Data

Lung Cancer

As shown in Table 4 and Fig. 5, there are several reports showing mostly consistent dose-dependent elevated risk of lung cancer in non-smokers whose spouses have a smoking habit, and no essential statistical difference exists among the major reported results [2].

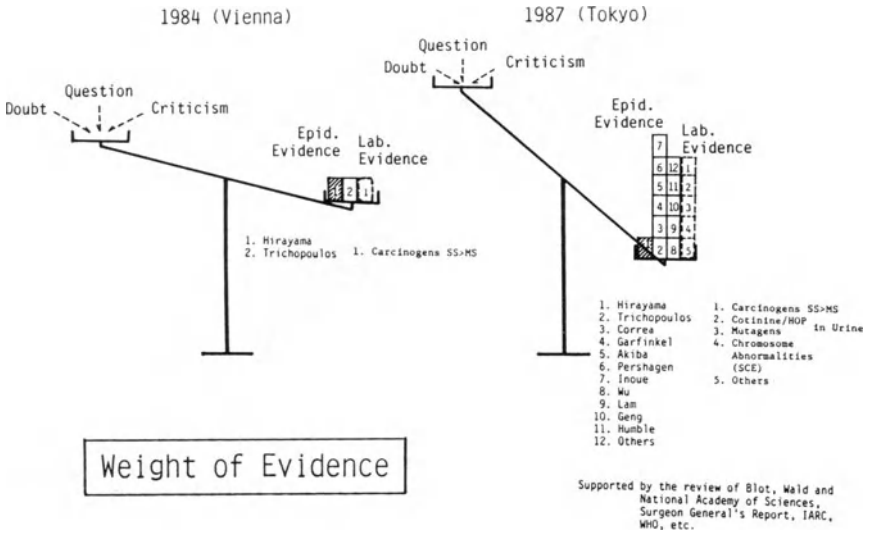


Fig. 6. Passive smoking and lung cancer

Weight of evidence for causative association of spouse smoking on lung cancer must have become much heavier in recent years (Fig. 6) by many epidemiological studies conducted since our report in 1981 including the reports in 1987 [10, 19, 20, 23] and also by laboratory studies such as further demonstration of higher toxicity and carcinogenicity of sidestream smoke than mainstream smoke, demonstration of elevated levels of cotinine, HOP and mutagens in urines, and finding of significantly higher SCE levels in chromosomes in lymphocytes obtained from persons passively exposed to tobacco smoke than those from non-smokers [29].

Three questions often asked regarding the issue are (1) possibility of misclassification of smoking status (2) extent of association by age of spouses and (3) possibility of confounding with other risk factors (e.g. diet).

Misclassification of Smoking Status: Misclassification of smoking status of wives such as classifying former smokers as non-smokers was found to be less than 2% in the large scale cohort study in Japan, only 62 being either smokers or ex-smokers in 1965 out of 3,163 women randomly selected who stated as non-smokers in 1971.

Extent of Association by Age of Spouses: The effect of husband's smoking habit on the risk of lung cancer in non-smoking women could not be observed when husband's age was over 70 years. It could neither be observed when the age of wives themselves was over 60. The most probable reason would be the disappearance of source of passive smoking due to the death of smoking husbands. Since these are the age at enrollment, most husbands in such old age group must expire during the long follow-up period of 16 years. In addition increased cessation rate of smoking and lesser proximity between couples in old age husbands must also be responsible for such diminished association.

The age adjustment to total female population in 1965, Japan as was attempted by Dr. Üherla [38] is clearly inappropriate. If adjustment be made it should be to the population

of married women with alive husbands. Since it is apparent that the passive smoking effect is not clear in women over 60 years of age at enrollment, adjustment to the population overrepresented older women are naturally diminish the effect of passive smoking. Therefore such trial of age adjustment is neither of scientific significance nor of creative value.

Confounding with Other Risk Factors: Although possibilities of confounding with other risk factors have frequently been discussed in the literature, the study in Japan almost wiped out such possibility as association between lung cancer in non-smoking wives and the husband smoking habit was found to be independent to any of risk factors cross tabulated.

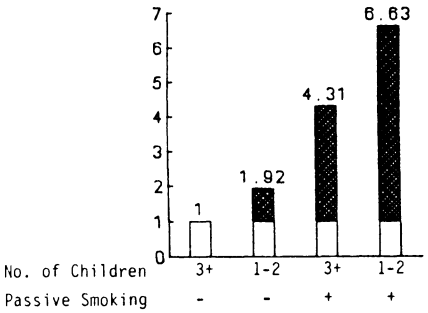
Obviously, exposure to spouse smoking is only a part of the total exposure to passive smoking. Walds et al. [40] estimated relative risk to completely unexposed group was 1.53 based on urinary cotinine levels among non-smokers married to non-smokers. These results thus strongly indicate the carcinogenic potential of continued inhalation of sidestream smoke. It is likely that passive smoking is more closely related to adenocarcinoma of the lung, common in women, than active smoking, reflecting the different histological responses to the two different routes of inhalation; sidestream smoke mainly through the nose while mainstream smoke solely through the mouth. Different size of particles must also influence on the site of their deposit.

Nasal Sinus Cancer and Brain Tumor

Since sidestream smoke is usually inhaled through the nose, it is of importance to study the influence of passive smoking on cancers of nose, nasal sinus and brain tumor. A large scale prospective study in Japan showed a statistically significant elevated risk of cancer of the nasal sinus and brain tumor in non-smoking women with smoking husbands. Association of childhood brain tumors with passive smoking was shown in a case-control study conducted in California [31]. These results confirm the carcinogenic potential of inhaled sidestream smoke over a long time. Thus cancers observed to be significantly influenced by household passive smoking (lung cancer, nasal sinus cancer, and brain tumor) mostly statisfy each of the neccessary postulates of causality: the consistency, the strength, the specificity, the temporal relationship of the association and, above all, the biological plausibility.

Breast Cancer

It must be of importance a significant dose-response relationship was observed between husband's smoking habit and risks of breast cancer of age 50–59. Since such association was not observed in other age groups extreme caution must be required before accepting causal role of passive smoking for breast cancer of this particular age group. But similar relationship was also observed for breast cancer in other risk factors such as daily meat consumption, of which risk promoting effect was observed only in post-menopausal age and not in pre-menopausal age. Thus in case of breast cancer existence of highly susceptible "window" age is suspected in relation to various risk factors. Passive smoking may also be one of them. For breast cancer a nested case-control study showed the association with husbands smoking was mostly independent to other risk factors such as diet and reproductive histories. An additive effect was detected with parity, risk being



No. of children	Others	Husband smoke 20 or more/daily
1 - 2	1.92(0.61-6.04)	6.63(2.19-20.01)
3 or more	1.00	4.31(2.07-8.96)

Fig. 7. Relative risk for breast cancer (age 50–59) in non-smoking women by number of children and by husbands smoking habit

highest when husbands smoke 20 or more cigarettes daily and number of children of non-smoking women is less than 3 (Fig. 7). Sandler et al. [32] reported a statistically significant association between smoking by spouse and pre-menopausal breast cancer. In our large-scale cohort study and selected case-control studies such as conducted in Canada [34] showed significantly elevated risk of breast cancer in active smokers, although there are many studies which showed negative results probably reflecting inadequate adjustment of socio-economic conditions or educational histories. An elevated risk of breast cancer in alcohol drinkers has been identified by case-control studies conducted in various countries such as U.S. [12], Italy [24] and France [25]. Since alcohol drinkers have generally much higher chances of getting exposure to passive smoking such results of positive association with alcohol drinking could be in favor of passive smoking-breast cancer hypothesis. A significantly higher frequency of lung cancer in breast cancer relatives reported by Lynch et al. [27] also support the hypothesis. A positive geographical correlation is observed between mortality rate for breast cancer and for lung cancer in females (e.g. in China, $r = 0.831$). Considering available evidence for possible association such as these the likelihood must be high that the relationship of passive smoking and breast cancer of "window age" will be confirmed by carefully planned epidemiological studies in near future.

Urinary Cotinine in Passive Smokers

Urinary cotinine, a metabolite of nicotine with a longer half-life, was demonstrated in persons exposed to passive smoking [28, 39]. The cotinine levels among heavy passive smokers in Japan [28] were about one-seventh the levels in average smokers, in contrast to about one-fiftieth in Britain [39], possibly reflecting higher exposure to passive smoking due to the closer physical proximity of spouses at home in Japan. In both studies, the urinary cotinine levels increased in proportion to estimated passive smoking exposure. The cotinine concentrations among Japanese non-smokers living with heavy smokers were roughly eqivalent to the cotinine levels of smokers of 3 cigarettes per day.

Parental Smoking

The effect of parental smoking on the risk of lung cancer in family members must also be seriously considered as shown in the Louisiana [6] and North Carolina studies [33], and as suggested by studies which demonstrated elevated levels of cotinine in saliva, serum and urine from infants exposed to passive smoking [11, 26, 42].

Passive Smoking at the Workplace

As shown in Kabat and Wynder's study [21] and the Hiroshima-Nagasaki study [1] some suggestive evidence exists for the carcinogenic influence of passive smoking at the workplace. The issue must also be an important item for future epidemiological research.

Chromosome Abnormalities in Passive Smokers

An elevated levels of SCE (Sister Chromatid Exchanges) frequency was detected in lymphocytes from persons occupationally exposed heavily to ETS (Environmental Tobacco Smoke).

Lymphocytes from passive smokers showed significantly higher SCE induction (27.6 $\pm$ 0.20 per cell) than those from non-smokers (24.7 $\pm$ 0.98) ($p < 0.05$) when cells were exposed to 3×10^{-8} M Mitomycin C for the entire culture period of 72 h.

The results suggest that SCE-leading DNA damage might be produced more in lymphocytes from passive smokers. This must strengthen the carcinogenetic likelihood of passive smoking together with reports of the detection of mutagens in urines of passive smokers (e.g. Bos et al. [3].

Health Consequences of Passive Smoking

Health consequences of passive smoking are summarized in Fig. 8. Smokers should be regarded as moving sources of environmental pollution. Smoking at home,

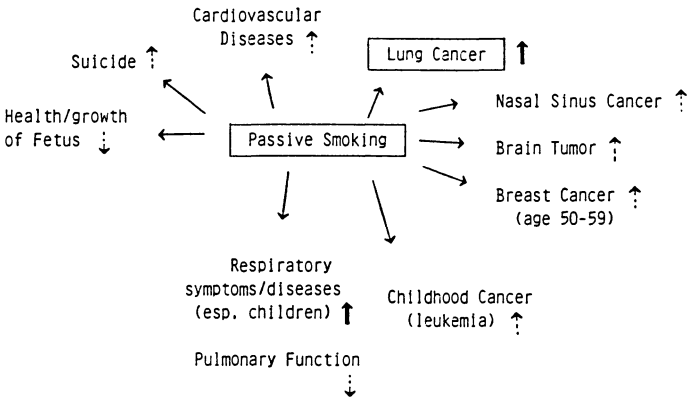


Fig. 8

workplace and other public places should therefore strictly be restricted in order to prevent such undesirable health consequences due to exposure to air polluted by sidestream smoke.

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Air Pollution and Lung Cancer

D. G. Xian, Y. W. Qing, and X. Z. Yi

Shenyang is situated in the province of Liaoning, in the north-eastern part of China. It is a heavily industrialized city and air pollution is a serious problem. In order to determine the relationship between air pollution and lung cancer, we studied the effect of air pollution on the development of lung cancer in an epidemiological survey.

The standardized mortality ratio of lung cancer in Shenyang (standardized mortality ratio in China, CSMR) from 1976 to 1978 is $17.65/10^5$. CSMR from 1979 to 1981 is $21.7/10^5$. The ratio increased by 22.9%. CSMR for men is a little higher than for women (see Table 1).

The concentration of air pollution in Shenyang is high. All of the sites measured exceeded the national standardized concentration. The concentration in January is especially high (see Table 2).

The mortality ratio from 1976 to 1978 and the airborne dust concentration for 20 years in the same district in Shenyang are linearly correlated. The regression equation is $\hat{y} = 6.977 + 0.0195x$. Correlation coefficient (r): $r = 0.81$, $p < 0.01$ (Table 3).

The mortality of residents in areas of high suspended particulate concentrations, such as districts with industrial pollution, is high. Suspended particulate concentrations and the mortality of residents are linearly correlated: $r = 0.79$, $p < 0.05$ (see Table 4).

Table 1. CSMR of lung cancer ($1/10^5$)

Year	Population	Death	CSMR of lung cancer			Sex ratio
			Total	Men	Women	
1976–1978	6,259,846	1,265	17.65	21.83	13.54	1.59
1979–1981	7,438,775	1,982	21.70	26.29	16.96	1.54

CSMR, standardized mortality ratio in China

Table 2. Concentration of TSP, SO_2 and B(a)P in Shenyang (1980–1982)

	January	Mean/year	Max/day
TSP (mg/m^3)	0.58	0.43	1.13
SO_2 (mg/m^3)		0.19	1.16
B(a)P (ng/m^3)	49.1	28.6	140.6

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Table 3. Relation between concentration of falling dust in Shenyang and CSMR of lung cancer ($1/10^5$)

Street name	Falling dust ($T/km^2 \cdot year$) (1955–1957)	CSMR of lung cancer (1976–1978)
Guang ming	1,328.3	24.96
Du gong	1,207.9	37.78
Sheng Li	967.8	29.56
Ji hong	804.8	23.11
Tai yuan	780.1	20.87
Xing gong	743.8	15.74
Nan zhan	660.4	24.48
Gui hi	608.7	19.70
Ya ming	428.7	19.15
Yuan Lu	412.7	16.14
Malu Wan	361.5	9.82
Hua Shan	358.7	11.70

$r = 0.8109$; $P < 0.01$; $\hat{y} = 6.9774 + 0.0195x$

Table 4. Relation between concentration of suspended particulate in Shenyang and CSMR of lung cancer

Street name	TSP (mg/m^3) (1972–1973)	CSMR of lung cancer ($1/10^5$) (1976–1978)
1	1.08	30.66
2	0.89	24.96
3	0.54	20.28
4	0.58	17.11
5	0.61	16.80
6	0.38	17.61
7	0.77	15.87

$r = 0.79$; $P < 0.05$; $\hat{y} = 7.8972 + 18.4961x$

Table 5. Smoking rate of population in Shenyang (over 15 years of age)

	Subjects	Smoking rate (%)	CSMR of lung cancer (1/10)
Heavily polluted area (1)	13,958	29.83 ($u = 1.29$*)	24.97
Heavily polluted area (2)	7,596	29.87 ($u = 1.08$*)	37.78
Slightly polluted area	2,016	26.14	18.21
Total	23,560	28.28	

* $P < 0.05$

Table 6. Multiplication analysis with conditional logistic regression model

Type	Sex	Factor	R . C(B)	SE(B)	STD(B)	RR	$\bar{X}^2$
Squamous cancer (including undifferentiated cancer)	Men	x_1 Smoking	0.8775	0.4558	1.8373	2.3165	3.3757
		x_3 Living in air polluted areas	0.8105	0.3708	2.1860	2.2491	4.7786*
		x_6 Chronic bronchitis	1.3832	0.6060	2.2824	3.9875	5.2093*
		x_9 Less intake of vegetables	1.2637	0.6431	1.9727	3.6561	3.8915*
	Women	x_1 Smoking	0.6094	0.7764	2.0779	5.0000	4.3177*
Adenocancer	Men	x_5 Passing through air polluted areas on way to work	1.2528	0.5669	2.2097	3.5000	4.48837*

* $P < 0.05$

Smoking is an important factor in lung cancer. The rate of smoking is almost equal among persons over 15 years of age who live in districts of Shenyang with different levels of air pollution. The mortality in severely polluted districts is higher than in slightly polluted districts. The difference is highly significant and cannot be attributed to smoking (see Table 5).

A case-control study of 139 persons with lung cancer in Shenyang by Guan Baipen et al. [1] also showed that residents of districts with polluted air and/or men who pass through such districts on their way to work have a significantly increased risk of suffering from lung cancer (squamous cell carcinoma, undifferentiated, adenocarcinoma) RR = 2.25, 3.50; $P < 0.05$ (see Table 6).

In summary, morbidity (mortality) from lung cancer and airborne dust or air suspended particulate concentration in Shenyang are linearly correlated.

Discussion

The CSMR for lung cancer is positively associated with the content of air suspended particulate matter and airborne dust. The smoking rate among residents of slightly and heavily polluted areas is nearly the same, yet the CSMR for lung cancer is significantly different and is thought to be related to the concentration of air pollution. Air pollution in Shenyang city mainly originates from industrial dust, industrial waste gas, and solid fuel combustion.

Reference

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Meta-Analyses on Passive Smoking and Lung Cancer

H. Letzel and K. Überla

Summary

Up to now, meta-analysis has rarely been used in epidemiology and no generally accepted standards are available. Combining risk estimates from biased or confounded studies by meta-analysis cannot provide correct answers.

In our paper two cohort and ten case-control studies were analyzed using several statistical techniques (Fisher, Mantel-Haenszel, Yusuf). Only data from women were included and a quality indicator (histology exposure, methodology) was used to analyze different study combinations, i.e. an analysis of sensitivity was performed. For the Hirayama study two different risk estimates were used. In addition, all 1,023 logically possible combinations of the 10 case-control studies were analyzed.

Of all possible meta-analyses of the 10 case-control studies, 670 (65.5%) were not significant at $P \leqq 0.05$ (Yusuf technique). The Trichopoulos study is involved in 330 of the 353 significant study combinations, indicating that this is the dominating case-control study, although the methodological quality is unacceptable.

Combining case-control and cohort studies, the relative risk estimates range from 1.013 to 1.118, depending on the specific subset of studies analyzed. These relative risk estimates include unity. The quality of the individual studies is highly variable and sometimes poor. We conclude that as long as no better studies are available, meta-analyses cannot and do not add much new evidence to the question of whether passive smoking is related to lung cancer.

Up to now, meta-analyses have mainly been used with randomized clinical trials. The technique has been criticized [6, 10, 23] for various reasons. Standards for meta-analyses in epidemiology are not yet available. Bias by non-reporting of studies, by selecting certain subgroups or by redefining sample sizes can create additional difficulties for a statistical evaluation. How different study designs – e.g. case-control versus cohort studies – should be weighted is left to the investigator. It is not surprising that the application of such methods in a controversial field like passive smoking and lung cancer does not come up with uniform results.

The inclusion of studies in meta-analyses is justified as long as there are no major methodological shortcomings in the individual studies. Combining biased or confounded results by meta-analysis cannot provide correct answers. There is a strong case for an analysis of sensitivity [23]. It investigates the effect of different study selections as well as the impact of different statistical methods on the results.

When the first papers on passive smoking and lung cancer were published a serious hypothesis was created [11, 27]. This hypothesis is serious because – if it is right – thousands of non-smokers are being killed worldwide by smokers. But the hypothesis is also serious because – if it is wrong – smokers are being accused of killing other people without actually doing so.

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Last year Wald [31] published the first meta-analysis of the available studies on passive smoking and lung cancer. In his paper the results obtained in men were included, and in two studies the subgroup of women married to ex-smokers was excluded. The quality of the individual studies was not taken into account and no analysis of sensitivity was performed.

Every meta-analysis has to state its goals, criteria and methods before it starts. In our analysis we planned

1) to include only studies which fulfil minimal methodological requirements. We wanted to eliminate statistical noise.
2) to select carefully the "best" relative risk estimate from every study, not just the one which was reported by the authors or the highest one.
3) to classify the quality of the studies regarding determination of histology, estimation of exposure and overall study methodology.
4) to use different statistical techniques, namely the Fisher method and the method used by Yusuf [32] or Wald [31].
5) to study the sensitivity of the results with regard to including different subsets of studies depending on their qualities.

Selection of Studies

We did not include the studies by Gillis [9], Knoth [16], Miller [22] and Sandler [24–26]. These studies do not fulfil minimal methodological criteria and they do not contain relevant information. Only insufficient data are available from them. Wald [31] had included the Gillis study [9], which only has 14 non-smoking lung cancer cases and correspondingly wide confidence intervals contributing nothing to the available evidence.

We also excluded men because the majority of evidence comes from studies in women. Only about 11% of the reported cases are men. Their results vary widely. There is not a single significant result in men. The situation regarding biology, exposure and reporting habits is considerably different in men as compared to women.

We included two cohort studies [7, 12–14] and 10 case-control studies [1–5, 8, 15, 17, 19–21, 27, 28]. These studies had also been included by Wald [31]. The only difference is that we didn't include the Gillis study [9] and that we restricted our analysis to women. The availability of histology, the quality of the exposure indicator and an overall quality rating of the study were judged by K. Überla. Three study groups resulted: cohort studies, case-control studies with reasonable quality (quality +) and case-control studies with poor quality (quality −) (Table 1).

The 2×2 tables and RR estimates for the 12 studies used are presented in Table 2. Generally, these numbers are the same as used by Wald [31] with the exception that we did not exclude the wives of ex-smokers in the studies by Hirayama [14], Trichopoulos [27, 28] and Koo [17].

Regarding the Hirayama study we did not use a relative risk estimate of 1.63 as did Wald [31]. In a subsequent paper by Überla and Ahlborn [30], which will be presented in this session of the conference, it is shown that, when one adjusts the Hirayama cohort to the age of the female population in Japan, the relative risk is 0.90. We alternatively used a risk estimate of 1.45 for the Hirayama study. This was calculated from Table 2 of the 1984 publication by Hirayama [13] and was standardized by the age of women only.

Table 1. Quality rating of studies selected for meta-analyses

Author	Histology	Exposure	Quality rating**	Resulting group
Hirayama	−*	−	3	Cohort
Garfinkel	−	−	2	Cohort
Chan et al.	+	+	4	CC quality +
Correa et al.	−	−	5	CC quality −
Trichopoulos et al.	−	−	6	CC quality −
Buffler et al.	+	−	4	CC quality +
Kabat et al.	+	+	4	CC quality +
Garfinkel et al.	+	+	4	CC quality +
Akiba et al.	−	−	5	CC quality −
Lee et al.	−	+	5	CC quality −
Koo et al.	+	+	4	CC quality +
Pershagen et al.	+	+	4	CC quality +

The included studies are the same as in the paper by Wald et al. (1986). We included women only.
** 2 = acceptable; 3 = possibly flawed; 4 = bias and confounding suspected; 5 = major bias and confounding suspected; 6 = unacceptable

Table 2. 2 × 2 Tables and relative risk estimates for studies selected for meta-analyses

Author	Exposed lung cancer		Unexposed lung cancer		Relative risk
	+	−	+	−	
Hirayama	163	69,428	37	21,858	1.45 (1) 0.90 (2)
Garfinkel	88	127,164	65	49,422	1.18
Chan et al.	34	66	50	73	0.75
Correa et al.	14	61	8	72	2.03
Trichopoulos et al.	53	116	24	109	2.01
Buffler et al.	33	164	8	32	0.80
Kabath et al.	13	15	11	10	0.79
Garfinkel et al.	91	254	43	148	1.23
Akiba et al.	73	188	21	82	1.48
Lee et al.	22	45	10	21	1.03
Koo et al.	66	97	22	40	
Pershagen et al.	33	150	34	197	1.27

The underlined numbers are different from those assumed by Wald. We did not exclude the wives of ex-smokers.

(1) Hirayama standardized by age of women only (from Table 2, Hirayama 1984)
(2) Hirayama with age selection bias removed (Überla and Ahlborn, 1987)

Results

Meta-Analyses for All Possible Case-Control Study Combinations

In order to get a feeling for the consequences of random selection of studies, we first considered all possible combinations of case-control studies. With 10 case-control studies there are 1,023 possible study combinations or subsets for which a meta-analysis can be performed. We calculated them all. The results can be summarized as follows:

34.5% of all possible meta-analyses – using the Yusuf technique – are technically significant at $p \leqq 0.05$. That means that a random selection of studies leads to a probability of 65.5% for a negative result of the meta-analysis.

The Trichopoulos study is involved in 330 of the 353 significant study combinations, that is in 93.5%. This study is the dominant study in the significant combinations. Without the Trichopoulos study only 23 out of the 511 then possible study combinations are "significant", that is 4.5%. One has a probability of 95.5% for a negative result selecting a subset of studies for a meta-analysis randomly.

The Trichopoulos study was judged as methodologically unacceptable. It is a textbook example of how a case-control study should not be performed [29]. If it were included, however, the impact of this study on the results would prove to be heavy.

Table 3. Results of meta-analyses I

Author		Cohort only	Case-control quality +	Case-control quality −	Cohort plus CC quality +	All
Hirayama*		×			×	×
Garfinkel		×			×	×
Chan			×		×	×
Correa				×		×
Trichopoulos				×		×
Buffler			×		×	×
Kabath			×		×	×
Garfinkel			×		×	×
Akiba				×		×
Lee				×		×
Koo			×		×	×
Pershagen			×		×	×
Fisher:	p	0.017	0.604	0.007	0.137	0.009
Yusuf:	$\widehat{RR}$	1.271	1.074	1.652	1.178	1.260
	IL 95	1.025	0.848	1.201	1.005	1.093
	IU 95	1.575	1.361	2.272	1.381	1.453
	p**	0.014	0.277	0.001	0.022	0.001

* Hirayama standardized by age of women only, RR = 1.45 as calculated from Table 2, Hirayama, 1984

** one-tailed

Table 4. Results of meta-analyses II

Author		Cohort only	Cohort plus CC quality +	All without Trichopoulos	All
Hirayama adjusted*		×	×	×	×
Garfinkel		×	×	×	×
Chan			×	×	×
Correa			–	×	×
Trichopoulos			–	–	×
Buffler			×	×	×
Kabath			×	×	×
Garfinkel			×	×	×
Akiba			–	×	×
Lee			–	×	×
Koo			×	×	×
Pershagen			×	×	×
Fisher:	p	0.105	0.336	0.158	0.028
Yusuf:	$\widehat{RR}$	1.013	1.035	1.076	1.118
	IL 95	0.848	0.941	0.941	1.273
	IU 95	1.210	1.193	1.230	1.299
	p**	0.443	0.317	0.142	0.046

* With age selection bias removed. RR = 0.902 (Überla and Ahlborn 1987)
** one-tailed

Meta-Analyses for Selected Study Groups

Meta-analyses for various combinations of cohort and case-control studies were calculated. The results are given in Table 3. For the Hirayama study a relative risk of 1.45 for the exposed versus non-exposed persons is used in all these combinations as one of the starting points. The results show that the probability using the Fisher method is always higher than the probability using the procedure as applied by Yusuf [32] or Wald [31]. This had to be expected. The other methods – Mantel-Haenzsel or for the cohort studies risk ratios – do not differ much from the Yusuf method. All the study combinations on Table 3 are significant with the exception of the reasonable quality case-control studies. These six studies have a common risk estimate of 1.07, being not statistically different from unity.

The meta-analyses for these study combinations were repeated using a relative risk of 0.90 for the Hirayama study as was calculated by Überla and Ahlborn [30]. The pooled risk estimates are very close to unity and are not statistically significant (Table 4). When one includes the Trichopoulos study, the pooled estimate for the relative risk is 1.118, approaching but not reaching statistical significance.

Discussion

To summarize, the expected overall risk of dying of lung cancer for non-smoking women married to smoking men is:

- 1.074 out of six case-control studies of reasonable quality,
- 1.013 out of two prospective studies, using the Hirayama study with the age selection bias removed as shown by Überla and Ahlborn,
- 1.035 out of two prospective studies and six case-control studies of reasonable quality,
- 1.076 out of eleven studies, with the Trichopoulos study excluded, and
- 1.118 out of all twelve studies including the Trichopoulos study.

These risk estimates are not statistically different from unity.

Thus, the overall result of various meta-analyses can be summarized as follows: Meta-analysis of 12 relevant studies (using women only and adjusting the relative risk of Hirayama for age selection bias) gives an overall estimate of relative risk of dying of lung cancer for non-smoking women married to smoking men of $\widehat{RR} = 1.076$ (Trichopoulos excluded) or $\widehat{RR} = 1.118$ (Trichopoulos included). These risk increases of about 8% or 12% are not significantly different from unity.

Our results differ widely from the results given by Wald [31]. The main reasons are different relative risk estimates for the individual studies. The papers by Hirayama and Trichopoulos were the first studies to be published on this issue. All later studies give less indicative results. Whether wives of ex-smokers should be included or not, whether the Hirayama study has to be adjusted for age selection bias and whether the Trichopoulos study is methodologically as stringent as a case-control study should be is open for discussion and will be answered differently by individual scientists. We have shown a variety of possible outcomes of meta-analyses and demonstrated the sensitivity of the results with varying assumptions.

The whole question of meta-analyses comes down to the question of the quality of the individual study. As long as there are no better studies available, meta-analyses cannot and do not add much new evidence to the question whether passive smoking is related to lung cancer.

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Epidemiological Issues on Involuntary Smoking and Lung Cancer

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Summary

Both case-control and cohort studies of passive smoking and lung cancer published since 1981 were reviewed with the intent to make recommendations for future epidemiologic study of this controversial topic. The relative risk of lung cancer among non-smoking women married to smoking men compared to non-smoking women married to non-smoking men varied considerably over a range from 0.75 to 3.4 dependent on sample size, histological type studied, type of questionnaire administered, case ascertainment method, country or nationality of the study population, and age of the study population [28]. Major possible sources of bias and misclassification have been considered by other investigators and committees [22, 28]. Some new observations are made on these already carefully scrutinized data and an attempt is made to give concrete solutions for solving the problems of low-level risk assessment of this indoor environmental air pollutant and its potential carcinogenic effect.

Introduction

Since the disclosure of the 1964 Surgeon General's report [29], cigarette smoking has been labeled one of the most insidious health hazards encountered by humans in the twentieth century. With the establishment of tobacco smoke as a carcinogen, the question arises: If tobacco smoke is hazardous to those who directly inhale it, then what are the possible health consequences to an individual who breathes this potential carcinogen on a second hand basis by sharing the same air space as an active smoker?

This issue has ignited a conflagration of public debate, beginning in 1981 [11], due to the involuntary nature of exposure to environmental tobacco smoke (ETS) in the workplace and at home. Scientific debate is ongoing, involving careful scrutiny of the dozen or so reports of the effects of ETS on lung cancer incidence.

An epidemiological review of the relevant papers was conducted to improve future studies of passive smoking and lung cancer and the following general observations were made:

1) The age range of subjects in some studies was inappropriate to allow for latency of the outcome of interest (lung cancer) to occur;
2) Adequate statistical power was not obtained in many studies due to small numbers of cases and controls;
3) Misclassification of the disease variable (lung cancer), of case or control eligibility (non-smokers), and of the exposure variable (smoking spouse) is not only possible but probable to some degree in all of the studies reviewed;

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4) Only qualitative measurement of a surrogate for actual exposure (marriage of a non-smoker to a smoker) was used in all studies reviewed;
5) The histology of lung cancer cases is not presented in all studies and when available it seems to exhibit an interesting pattern which is not entirely consistent between studies; and
6) Finally, almost without exception, each author herein reviewed pointed to the drawbacks of his or her study and cited the need for more and larger studies. These conclusions are drawn in part because of small sample sizes, difficulties in measurement of exposure and disease variables, and the general findings of associations greater than one without statistical significance. Given that these problems were almost universal, each study is equally likely of finding a result somewhere within the confidence interval cited when presented by the author.

Results

Latency and Age Range of Subjects

Just as the incubation period must be taken into account in tracing the epidemic spread of an infectious disease, so with cancer the latency period must also be considered in determining the relevant exposure. Theoretically the induction period begins at the time of first exposure, and for many cancers the time interval between exposure and subsequent disease development can be quite lengthy. In the case of primary carcinoma of the bronchus related to active smoking the mean latent period is several decades between initiation of malignant change and growth of the tumor to a diagnosable size [27].

To examine the effects of a low level environmental exposure such as air pollution or passive smoking, it is logical to assess the risk of lung cancer in individuals with at least 20 years or more of continuous exposure. The information presented in Tables 1 and 2 represent the relationship between age range of subjects and relative risk (odds ratio) found in the reviewed studies. The range of risk is 1.2 to 3.4 in studies using subjects aged 40 and above (Table 1). A lower range of risk, 0.75 to 1.5, was found in studies including subjects under the age of 40 (Table 2). These findings suggest a possible dilution of the effect of passive smoking on risk when subjects under the age of 40 are included.

Because of the relatively low exposure levels of ETS, it is natural to assume a longer latency period would be required than for active smoking. Thus it is essential to have accurate information on length of the non-smoker's marriage to a smoker. If lung cancer appeared before 20–30 years of marriage had elapsed, other possible causes could be involved.

Additional information needs to be collected or its absence corrected for in future studies of causality of lung cancer in non-smokers. In the Hirayama study [11] a relative risk of 2.06 is obtained when "other workers" are compared to the "agricultural workers" category. The increased risk among the "other workers" suggests that an underlying factor other than smoking could cause an excess of lung cancer cases in one locale over another. Three of the studies reviewed were conducted in areas of reported high incident lung cancer rates, Scotland [9] and Hong Kong [4, 16]. These studies would need a reference population of the same ethnic group in a different locale to correct for potential environmental or ethnic factors which could be in effect [3, 10, 20].

To draw conclusions concerning the effect of age on lung cancer risk and ETS exposure, age-stratified odds ratios need to be calculated. Even though matching was

Table 1. Age range of subjects 40 and above

Study	Passive smokers age	EXP	RR	Confidence intervals
Hirayama et al. (1984)	40 + @ Enrollment	1–19:	1.45	(1.04, 2.02)[a]
		20 +:	1.91	(1.34, 2.71)[a]
Trichopoulos et al. (1981)	Mean age of Cases = 61.7	1–20:	2.4	(no CI)
	Mean age of Controls = 62.1	21 +:	3.4	(no CI)
			Ever vs. never exposed	
			OR	Confidence intervals
Koo et al. (1984)	Range = 50–70		1.24	(not significant)
Garfinkel et al. (1985)	Range = 40–90 +		2.11	(1.13, 3.95)[b]
Pershagen et al. (1987)	Range = 40–91		1.2	(0.7, 2.1)[b]

Range of Risk 1.2 to 3.4

[a] 90% Confidence interval
[b] 95% Confidence interval

Table 2. Age range of subjects 35 to 39 and above

Study	Passive smokers age	EXP	Mortality ratio	Confidence intervals
Garfinkel (1981)	Range = 35–89	<20:	1.27	(0.85, 1.89)[a]
		20+:	1.10	(0.77, 1.61)[b]
			Ever vs. never exposed	
			OR	Confidence intervals
Chan & Fung (1982)	Range = 39–70 +		0.75	(no CI)
Lee et al. (1986)	Range = 35–74		1.00	(0.37, 2.71)[b]
Akiba et al. (1986)	Range = 35–95		1.5	(1.0, 2.5)[a]

Range of Risk 0.75 to 1.5

[a] 90% Confidence interval
[b] 95% Confidence interval

done on age in many of the reviewed papers, this procedure does not effectively correct the potential problem.

Based on a study of non-lung cancer in families of lung cancer patients [25] an underlying genetic susceptibility to malignancy is seen to exist, perhaps the result of multiple genetic factors, or in conjunction with passive smoking (which was not

measured). In cases with an earlier onset than expected from a low level exposure (under the age of 40) a genetic form of the disease could be involved. Thus collection of additional information on lung cancer and other cancer incidence among first and second degree relatives would be helpful in future studies especially if patients in the younger age range are included.

These three variables, length of marriage, environmental locale, and genetic susceptibility, could all help to explain the differences seen in the risk ratio range between the data in Table 1 and the data in Table 2.

Statistical Power of Case-Control Studies

In Table 3 only one-sided p-values are included as the parameter under study (lung cancer) under the alternative hypothesis (exposure to ETS) is only expected to be greater than the null hypothesis, 1.0, non-exposure to ETS [24]. Of the eight studies included, two, [5, 26], had the potential statistical power (greater than 60%) to detect the relative risk (odds ratio) observed. However, all of the cited studies in Table 3 had greater than 50% power to detect a RR = 2. It is clear that to investigate low level risk associations such as those found in passive smoking and lung cancer a larger number of cases and an increase in the number of controls per case must be obtained to achieve statistical significance.

This goal of increased numbers might be approached by combining scientific researchers' efforts into a multi-national collaborative study to collect cases of lung cancer among non-smokers. Such an approach has been agreed upon in principle by several authors [18]. Also, if cases are limited and collaboration not possible, the number of controls per case can be increased to achieve statistical significance. Power calculations need to be made at the inception of a study and numbers of cases and controls set accordingly.

Another strategy [6] is to improve the reliability of measurement techniques in "apparently negative studies of the early health effects of environmental factors." This

Table 3. Study power for case-control study based on an unmatched analysis. (From [28])

Study	Number of cases	Control case ratio	Observed relative risk for ever vs. never exposed to spouses' smoking	Power for one-sided test based on observed RR	Power for one-sided test based on RR = 2 for ever vs. never exposed
Trichopoulos et al. (1983)	77	2.92	2.11	0.87	0.88
Correa et al. (1983)	30	10.43	2.97	0.88	0.55
Chan and Fung (1982)	84	1.66	0.75	0.26	0.80
Koo et al. (1984)	88	1.56	1.23	0.17	0.64
Garfinkel et al. (1985)	134	3.00	1.23	0.36	0.94
Lee et al. (1986)	47	2.04	1.11	0.08	0.52
Akiba et al. (1986)	84	2.96	1.47	0.38	0.75
Pershagen et al. (1987)	67	5.18	1.23	0.19	0.83

can be done by conducting a pilot study in which the factor in question (exposure) is measured multiple times and the results compared for reliability. In this manner, random error (misclassification and underestimation) can be reduced and a study of manageable size which accounts for these sources of error by increasing sample size accordingly can be conducted.

Misclassification

Table 4 presents results of three studies in which disease misclassification was quantified and the percentage of overreporting was found to range from 11.8 to 16.3 percent. Histology and medical records were used to confirm cases originally identified by death certificates. In most cases the primary site of cancer was found to be other than the lung. This verification is essential for any study of lung cancer in women as a higher percentage of secondaries are reported as primaries among women. A large number of these secondaries were found to be primarily breast cancer as evidenced in a large cohort study [7]. The problem of misclassification was reversed among males in the same study as lung cancer deaths, ascertained by death certificates and later verified in hospital records, were underreported by ten percent [7].

Case status misclassification is quantified in only two of the 12 studies reviewed. In a study working from hospital records [8], 40% (113/283) of subjects reported as non-smokers or status not known were found upon interview to be smokers. Cross checking interview reports with hospital summaries in another study revealed a 14.3% (N = 28)

Table 4. Disease misclassification

Study	Percent overreported females
Garfinkel (1981)	11.8%
Garfinkel et al. (1985)	12.7%
Pershagen et al. (1987)	16.3%

Table 5. OR for smoke exposure categories by identity of respondent. (From [8])

Specification	No. of Cases	Smoke exposure			
		Last 5 Yr OR	Last 5 Yr OR	Husband's smoking habits	
				Total OR	At home OR
Respondent					
Self	16	1.96	0.91	0.83	1.00
Husband	34	1.00	0.46	0.77	0.92
Daughter or Son	48	0.92	1.41	3.57	3.19
Other	36	2.23	2.23	1.58	0.77

misclassification error of non-smokers who were actually smokers [13]. Therefore some method of smoking status verification is necessary to reduce such a large degree of observed misclassification, especially if quantitative measurements are not going to be administered. An alternative methodology for correction of misclassification error in a low level risk assessment study is to estimate the amount of misclassification likely to occur and then correct for it by an appropriate increase in sample size [6].

The most disturbing source of potential error is variability of relative risk by respondent and question category [8]. In Table 5, odds ratios can be seen to vary according to respondent category; self, husband, daughter or son, or other, and they also vary simultaneously by smoke exposure category according to response to differently worded questions posed in the interview. The total range of odds ratios thus observed is 0.46 to 3.57. Therefore, it is recommended that respondent category be limited to one type, dependent on study design and, failing this, to match cases and controls on respondent category for analysis purposes.

Exposure Measurement

Considerable work needs to be done to standardize questionnaires used to assess qualitative exposure to ETS. Using marriage to a smoking spouse as an ETS exposure indicator is at best a crude system of measurement. Using Fleiss' guidelines [6] of repeatedly administered questionnaires in a pilot study to increase reliability along with the questionnaire composition guidelines of Johnson and Letzel [15] to quantify time exposed (perhaps modified for easier administration) could increase the precision with which exposure is measured.

Carbon monoxide testing is an inexpensive and simple method to *quantify* non-smoking status. Cotinine level is the method of choice but in a study to detect smoking status, carbon monoxide tests accurately revealed *ten percent* of the non-smokers to be "deceivers", active smokers denying their habit [14]. None of the papers reviewed used any quantitative methods of verification for cases or controls and this technology is severely underutilized given the effect of misclassification when measuring low level exposures.

Histology

In Table 6 the trend in percentage of squamous and small cell carcinoma reverses that of adenocarcinoma and large cell carcinoma from non-smokers, to non-smokers exposed to ETS, to active smokers in female Chinese. The figures of 42% squamous and small cell carcinoma and 58% adenocarcinoma and large cell type can support the trend seen worldwide of squamous and small cell carcinoma more highly associated with cigarette smoke exposure.

Table 6. Smoking history and histology. (From [16])

Smoking history	Squamous + small cell	Adenocarcinoma + large cell
Ever smoked	64% (61/95)	36% (34/95)
Passive smoking	42% (23/59)	58% (34/59)
None	37% (7/19)	63% (12/19)

Table 7. Lung cancer histology of non-smoking women

Study	% Histology	N	Type	[%]
Chan & Fung (1982)	70.0	84	squamous	25.4
			small cell	6.8
			adenocarcinoma	64.4
			large cell	3.4
Pershagen et al. (1987)	99.0	76	squamous	15.6
	(100.0)	(77)	small cell	15.6
			adenocarcinoma	57.1
			large cell	6.5
			other	5.2

Table 8. Lung cancer histology of non-smoking women married to smokers

Study	% Histology	N	Type	[%]
Correa et al. (1983)	97.0	22	adenocarcinoma	54.0
Koo et al. (1984)	97.0	59	squamous and small cell	42.0
			adenocarcinoma and large cell	58.0
Akiba et al. (1986)	57.0	73	squamous and small cell	16.0
			adenocarcinoma and large cell	84.0
Garfinkel et al. (1985)	100.0	134	squamous	8.2
			adenocarcinoma	64.7
			large cell	15.7
			mixed and other	11.2
Humble et al. (1987)	100.0	16	squamous	12.5
			small cell	12.5
			adenocarcinoma	50.0
			large cell	25.0

A study of U.S. Veterans done in the 1960's [29] found male cigarette smokers had a mortality ratio of 15.4 for Kreyberg Group I (epidermoid and small cell) carcinomas and ratio of 5.1 for Group II (adenocarcinoma, bronchiolo-alveolar, carcinoid, and tumors of the mucous glands) compared to non-smokers. Thus active cigarette smoking carries an increased risk of causing all forms of lung cancer including the Kreyberg Group II and therefore no histological type should be excluded as a matter of course from any epidemiologic study of passive smoking. On the contrary, active smoking present and past is a significant risk factor for adenocarcinoma in males and females [2], increasing the need for both histologic typing and confirmation of all cases and inclusion of all types in epidemiologic studies of lung cancer.

Tables 7 and 8 provide information on the number of subjects per study and the percent with histology obtained on them. Of these subjects (non-smoking women and non-smoking women married to smokers) the percentage of different histological cell types was reported in 7 out of the 12 studies reviewed. Adenocarcinoma among passive smoking women ranges from 50.0–64.7% [5, 7, 13]. Kreyberg Type II (adeno and large cell carcinoma) range from 58.0–84.0% [1, 7, 13, 16]. Therefore, the range of Kreyberg Type I is from 8.2–42.0% [1, 8, 13, 16].

In a study conducted in Western Europe of lung cancer histological types that included non-smokers, the percent of adenocarcinoma was 48% in non-smokers, 52% Kreyberg Type I, with adenocarcinoma reducing steadily to 16% in the highest smoking category [19]. A study conducted in Los Angeles found 93% adenocarcinoma, 7% small cell carcinoma in non-smokers; 72.4% adenocarcinoma, 27.5% small cell carcinoma in ex-smokers; and 62% adenocarcinoma, 38% small cell carcinoma in active smokers [30] further supporting a shift from Kreyberg Type I to Kreyberg Type II dependent on case smoking status and ETS exposure. With all the data presented and reviewed it is unclear what sorts of percentages and figures would be expected in a passive smoking population.

What could account for the variability seen in Tables 7 and 8 and in the other data presented? Histological type is dependent on how soon case ascertainment follows after diagnosis because if both living and deceased cases are not included, a differential survival rate accompanies each histological type dependent on stage at diagnosis and treatment and therefore different percentages will result. Histological type also depends on whether biopsies are done differentially on certain groups of patients or universally on all patients. It also depends on sex of study subjects as adenocarcinoma occurs more frequently in smoking and non-smoking females. Histological determinations are dependent upon a pathologists judgement of cell type and this can vary with criteria used and background of the individual. If agreement is sought from a panel of pathologists, reliability is increased through standardization of criteria although these differing techniques introduce variability between studies. The total percentage histological type in passive smokers is also dependent on the percentage potentially misclassified as non-smokers who are actually smokers.

Discussion

In conclusion, histology may hold one of the keys to unraveling the risk of passive smoking and lung cancer. If large enough numbers of lung cancer cases are obtained to achieve statistical significance, a test for trend of percentage change in histological type can be conducted on smokers, non-smokers married to smokers, and non-smokers married to non-smokers as stratified in Table 6. To achieve adequate sample size a large national or perhaps multi-national study could be conducted with a central pathology committee where all slides are double or triple read until a consensus is reached. A significant difference between Kreyberg types in the three categories would indicate a positive association of lung cancer and passive smoking, as Kreyberg Type I is more highly associated with cigarette smoke carcinogenesis [29]. However, it would be of utmost importance that other factors such as case status be as accurate as possible.

Non-smoking females married to smoking males and age stratified in accordance with latency issues are suitable study subjects, surrogates though they are for measured ETS exposure. In a study of exposure to measured ambient nicotine in the daily environment, a housewife with a smoking husband had the highest exposure of all non-smokers, an equivalent to smoking 0.31 cigarettes in the day measured [21]. This result raises the

question of biological plausibility based on dosimetry as it has been calculated by other researchers [22]. Is it plausible that a low dose exposure of an ambient air contaminant can cause carcinogenesis? Only a larger, accurate and controlled quantitative study of ambient air ETS exposure than has been conducted in the past will answer this question.

After careful scrutiny and repeated discussion of former studies' shortcomings, the path is clear for construction and implementation of epidemiologically, pathologically, and statistically correct studies that include pilot studies to correct for inherent misclassification error and questionnaire weaknesses. Modern technology (personal monitoring and biological markers) available must be utilized to add a much needed quantitative element that could possibly bring this important public health issue out of the haze of speculation and into the light of scientific reality.

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Passive Smoking and Lung Cancer: A Reanalysis of Hirayama's Data

K. Überla and W. Ahlborn

The statistical association between environmental tobacco smoke and lung cancer is controversial. The Hirayama Study seems to provide sound epidemiological evidence supporting this hypothesis. In a recent paper [6] I have analyzed the published studies. Regarding the Hirayama study the following facts have to be kept in mind:

- The study was not designed to test the hypothesis, whether passive smoking is associated with lung cancer or not. It can therefore only generate this hypothesis, not prove it.
- The cohort was not representative for the population of Japan. A selection bias is possible.
- The exposure indicator – the fact of being married to a man who smokes – is not reliable, not valid and not specific.
- The event indicator – dying on lung cancer as noted on death certificates – is neither reliable nor valid.
- Various confounding factors – for instance exposure at the working place, indoor air pollution, overall air pollution, type of medical care – were not accounted for.
- Bias in registering the fact, that a woman is a nonsmoker, was not controlled. Resulting differential misclassifications of the cases, who were smokers and had to be excluded, have not been considered.
- Almost nothing is known about the 200 cases. No case reports are available, autopsy and histology are available in only 11.5%.

The core of the information, on which the results of this study rely, is

1) that during 1965 200 women in Japan told an interviewer on a single occasion that they were – during that time – nonsmokers and their husbands told that they were smokers, which might have been different before and afterwards and
2) that their death certificates subsequently contained the diagnosis lung cancer, which might have been erroneous.

Such sparse information does not seem to be convincing.

In our paper we consider three questions:

1) What is the relative risk when one removes the selection bias regarding age of women in the Hirayama cohort?
2) What is the relative risk for women married to men with different occupations, when one removes the selection bias regarding age of men?
3) What is the relative risk when additionally some differential misclassification is assumed?

H. Kasuga (Ed.) Indoor Air Quality

Material and Methods

We start from Tables 1, 2, and 3 of Hirayama 1984 [4]. These tables contain the most detailed published data. In order to check our program, we reproduced some of the reported relative risk estimates with good accuracy.

There are marked differences between the Hirayama cohort and the female age distribution over 40 in the population of Japan 1965. Women 50–59 are overrepresented, women older than 70 are severely underrepresented. In this age group only a single case from 12 was observed. The investigated cohort certainly has a severe selection bias by age, which needs no statistical test. This is likely due to the fact, that the smoking behaviour was not known in the elderly or that the husbands of older women have died. Since it takes 20 years and more from exposure to lung cancer, older women surely are relevant and should not be excluded. The majority of lung cancer cases occur in older age groups, in Germany more than 67% in women over 65 years.

In order to answer the question what the relative risk is when the age selection bias is removed, we adjusted the data to the age distribution of the female population of Japan.

Table 1. Differences between Hirayama cohort and the female age distribution over 40 in the population of Japan 1965*

Age group	Percent female	
	Japan population	Hirayama cohort
40–49	39	42
50–59	30	35 ↑
60–69	19	22
70 +	*12*	*1* ↓
	100	100

* Population Census 1965. Statistical survey of economy of Japan; 1967. Ministry of Foreign Affairs of Japan.

Table 2. Smoking habit of husband by age of wife.* Original data

Wives age	Husbands smoking habit							
	Non		1–19		20 +		Total	
40–49	4	7,918	21	17,492	21	12,615	46	38,025
50–59	14	7,635	46	15,640	31	8,814	91	32,089
60–69	16	6,170	31	10,381	10	3,793	57	20,344
70 +	3	172	1	671	2	239	6	1,082
Total	37	*21,895*	99	*44,184*	64	*25,461*	200	*91,540*

* Table 2 of Hirayama 1984.

Table 3. Smoking habit of husband by age of wife*. Removed selection bias: Data adjusted to the age distribution of women in the population

Wives age	Husbands smoking habit							
	Non		1–19		20 +		Total	
40–49	3.91	7,748.8	19.12	15,927.8	20.02	12,024.0	43.05	35,700.6
50–59	12.49	6,813.7	38.20	12,987.1	26.95	7,661.2	77.64	27,462.0
60–69	14.25	5,496.6	25.70	8,604.9	8.68	3,291.1	48.63	17,392.6
70 +	32.02	1,835.9	9.93	6,664.2	20.79	2,484.7	62.74	10,984.8
Total	62.67	*21,895*	92.95	*44,184*	76.44	*25,461*	232.06	*91,540*

* Table 2 of Hirayama 1984.

The technique of iterative proportional fitting of a contingency table to given marginals as described by Bishop et al. [1] or by Hartung et al. [3] was used. This technique keeps the risks constant as observed in every cell and changes the marginals and the cell counts according to the given age distribution of the population. Iterative proportional fitting of contingency tables to given marginals is a well known technique in multivariate statistics and can be applied here without changing the observed interrelations between smoking habit, occupation, and lung cancer. From the fitted or adjusted tables the risk ratios are calculated in the usual way. Such risk ratios based on data with removed age selection bias are the correct ones and should be used.

One has to require that there should be no selection bias by age and the cases should be included as they would have occured in the population. Otherwise statistical tests and p-values are not very meaningful.

Table 2 shows the original data by age of wife. The cells contain the number of lung cancer cases and those under risk as published by Hirayama. The 1–19 group includes ex-smokers in this and the following tables. 200 cases out of 91,540 women were observed. Iterative proportional fitting to the female age distribution of the population leaves the hatched numbers constant. The others are adjusted using a right hand marginal which is made proportional to the age distribution of the population.

Results

Table 3 gives the results of iterative proportional fitting to the female age distribution of the population. It contains the numbers of those under risk and of lung cancer deaths as they would have been observed, if Hirayama had not excluded or preferred certain age groups. The age selection bias is removed. The risks in the individual cells are still the same as those observed by Hirayama. Also the structure of the common distribution regarding age, smoking habit and lung cancer is unchanged. Hirayama would have totally observed 232 cases instead of 200, with the corresponding numbers in the individual cells, had he included all women as they live in the population. This table is the best available starting point for age-standardized risk ratio calculations. It was not used so far.

Table 4. Relative risk by age of women*

	Husbands smoking habit		
	Non	1–19	20 +
$\widehat{RR}$	1.00	*1.37*	*1.56*
IL_{90}		1.00	1.11
MH-CHI		1.51	2.27
$P_{\text{one tailed}}$		0.065	0.012**
$\widehat{RR}$	1.00	*0.77*	*1.06*
IL_{90}		0.59	0.80
MH-CHI		2.19	0.27
$P_{\text{one tailed}}$		0.014***	0.395

Upper part: standardized by age of women only.
Lower part: age selection bias removed and standardized by age of women.
$\widehat{RR}$: Weighted point estimate of rate ratio.
IL_{90}: Lower 90-percent confidence interval.
* Calculated from Table 2 of Hirayama 1984.
** "Significant" in positive direction.
*** "Significant" in negative direction.

In the upper part of Table 4 you find the risk ratios standardized by age only, as done by Hirayama. The lower part are the risk ratios after removing the age selection bias. In the upper part the weighted point estimate of the rate ratio is 1.56 in the 20+-group and is technically "significant". IL_{90} designates the lower point of the 90-percent confidence interval in this and the following tables, as it was used by Hirayama.

This risk increase disappears completely when one removes the selection bias by age. In the 20+-group the rate ratio is 1.06, hardly a relevant risk increase. In the group of 1–19 cigarettes per day it is 0.77 which is a technically significant risk decrease. The adjusted rate ratio, considering all those exposed in one group versus those not exposed is 0.901 with a confidence interval including unity. If Hirayama had observed the cases as they occur in the female population without selection bias by age, he would have observed no risk increase, but a risk decrease. This is the main result of our reanalysis, which corresponds well with the result of the prospective American cohort study as published by Garfinkel [2].

We now consider two occupations, farmers and industry workers. From the upper part of Table 5 one can see that the relative risk for wives of farmers seems substantial, when one standardizes by age of men only. The point estimates of the rate ratios are 1.48 and 1.63 respectively. This was observed earlier and had no adequate explanation. If one removes the selection bias by age and adjusts to the male age distribution of Japan – the numbers in the lower part of Table 5 – the rate ratios are 0.85 and 0.82, not different from unity. This seems more plausible.

Considering the wives of industry workers only, in the upper part of Table 6, the point estimates of the rate ratios are 1.77 and 2.27, standardized by age of men, being not significant. Removing the age selection bias – in the lower part of Table 6 – there is a remarkable risk increase to 4.60 and 6.90, which is significant. However, there are only

Table 5. Relative risk: wives of farmers only*

	Husbands smoking habit		
	Non	1–19	20 +
$\widehat{RR}$	1.00	*1.48*	*1.63*
IL_{90}		0.97	1.01
MH-CHI		1.48	1.92
$P_{\text{one tailed}}$		0.069	0.027
$\widehat{RR}$	1.00	*0.85*	*0.82*
IL_{90}		0.59	0.53
MH-CHI		0.42	0.53
$P_{\text{one tailed}}$		0.337	0.296

Upper part: standardized by age of men only.
Lower part: age selection bias removed and standardized by age of men.
$\widehat{RR}$: Weighted point estimate of rate ratio.
IL_{90}: Lower 90-percent confidence interval.
* Calculated from Table 3 of Hirayama 1984.

Table 6. Relative risk: wives of industry workers only*

	Husbands smoking habit		
	Non	1–19	20 +
$\widehat{RR}$	1.00	*1.77*	*2.27*
IL_{90}		0.70	0.84
MH-CHI		0.73	0.81
$P_{\text{one tailed}}$		0.232	0.208
$\widehat{RR}$	1.00	*4.60*	*6.90*
IL_{90}		1.71	2.45
MH-CHI		2.50	2.78
$P_{\text{one tailed}}$		0.006	0.003

Upper part: standardized by age of men only.
Lower part: age selection bias removed and standardized by age of men.
$\widehat{RR}$: Weighted point estimate of rate ratio.
IL_{90}: Lower 90-percent confidence interval.
* Calculated from Table 3 of Hirayama 1984.

9 lung cancer deaths in the 20+-group and only 3 in women 70 years and older, which are small numbers, but these are numbers observed and used by Hirayama and his risk structure is unchanged. Thus only in the subgroup of women married to industry workers there is a risk increase, in all other occupations there is no risk increase. Omitting industry

Table 7. Relative risk: assumed differential misclassifications*

Number of cases assumed misclassified and removed from exposed groups		Husbands smoking habit		
		Non	1–19	20 +
n = 10 = 5%	$\widehat{RR}$	1.00	*0.74*	*1.00*
	$P_{\text{one tailed}}$		0.006	0.469
n = 20 = 10%	$\widehat{RR}$	1.00	*0.70*	*0.93*
	$P_{\text{one tailed}}$		0.003	0.383
n = 30 = 15%	$\widehat{RR}$	1.00	*0.66*	*0.85*
	$P_{\text{one tailed}}$		0.001	0.238

Age selection bias removed and standardized by age of women.
$\widehat{RR}$: Weighted point estimate of rate ratio.
* Calculated from Table 2 of Hirayama 1984.

workers, the point estimates of the rate ratios are 0.90 and 0.89, not significantly different from unity. These findings are consistent with the assumption of confounding factors in women married to industry workers, who might be exposed to other environmental hazards. Our calculations show that by removing selection bias by age, one can explain hitherto implausible results.

Active smoking is correlated among married couples. In a society in which female smokers were very rare in 1965, more women married to smokers will declare themselves nonsmokers than the other way round. One has therefore to considerr biased or differential misclassification. There are likely more women with lung cancer, who have been misclassified as nonsmokers and have to be removed from the cohort, than the other way round.

We made some moderate assumptions regarding differential misclassification, as shown in Table 7. In order to examine how sensitive the relative risk is we removed 10, 20, and 30 cases from the exposed groups – corresponding to 5, 10, and 15 percent.

Assuming 30 misclassified cases – 15 percent, a percentage which has been observed in the literature [5] – the rate ratios are 0.66 and 0.85. In the group 1–19 cigarettes per day all the risk estimators are significantly smaller than unity. Our personal opinion is that 10 differential misclassified cases from 200, who have to be omitted, are a fair number. The corresponding weighted point estimates of the rate ratio are 0.74 and 1.00. These risk estimates are as reasonable as other risk estimates calculated from the Hirayama data. They indicate – if anything – a risk decrease, not a risk increase.

Discussion

Reanalyses of data, which have been collected by others are not easy. This is because information is not completely available, because information might be misinterpreted or because one has to take another view in order to come closer to the acceptable truth. Our calculations do not diminish the great value and impact the Hirayama study had on the epidemiology of passive smoking. They show however, that reasonable alternative views

Table 8. Reanalysis of Hirayama's data: summary of relative risk

		Husbands smoking habit		
		Non	1–19	20 +
Age selection bias removed and age-standardized (women)	$\widehat{RR}$	1.00	*0.77*	*1.06*
	$P_{\text{one tailed}}$		0.014	0.395
Without industry workers, age selection bias removed and age-standardized (men)	$\widehat{RR}$	1.00	*0.90*	*0.89*
	$P_{\text{one tailed}}$		0.394	0.179
10 cases assumed misclassified, age selection bias removed and age-standardized (women)	$\widehat{RR}$	1.00	*0.74*	*1.00*
	$P_{\text{one tailed}}$		0.006	0.469

$\widehat{RR}$: Weighted point estimate of rate ratio.

on the same data are possible, which lead to opposite conclusions. Our findings are in contrast to Hirayama's thesis that – based on his data – there is a substantial statistical association between passive smoking and lung cancer.

As long as there is no other independent and sound epidemiological evidence, it should be left to the individual scientist which analysis of the same data he thinks is more appropriate. We do not hold that our view is the only correct one. We do hold however, that the risk ratios calculated by us, removing age selection bias, are as valid as other risk estimates. To our opinion they are more appropriate, since they go back to the population and not to a selected sample. Even when one would take another marginal, for instance the age distribution of wives still married to living men – which was not available – the effect would be considerable. Our risk estimates are a consequence of the data published by Hirayama and cannot be rejected from the study data, as they are published so far.

To summarize (Table 8): Removing the age selection bias in the Hirayama study one gets a relative risk of 1.06 in the group of women married to men with more than 20 cigarettes per day. In the group of women married to men with 1–19 cigarettes per day the relative risk is 0.77, a technically "significant" risk decrease. If Hirayama could have observed the lung cancer cases as they occur in the female population, he would have observed no risk increase, but a risk decrease to around 0.90, considering those exposed versus those not exposed. This fact deserves attention.

If one omits the wives married to industry workers because of possible confounding factors in this group, the relative risk is 0.90 and 0.89 respectively. This is of the same size order and smaller than unity. Here we could adjust and standardize by occupation and age of men only, which is not as appropriate as by the age of women.

If one assumes that 10 cases are differentially misclassified and removes them from the exposed groups, the risk estimates are 0.74 and 1.00, respectively. Our findings demonstrate how sensitive the data of this study are and how weak the evidence for a statistical association between passive smoking and lung cancer might be. In view of these and other facts some of which we mentioned in the introduction, the null hypothesis might be true as well and seems to be consistent with the Hirayama data in the same way as the alternative hypothesis.

We would be glad to apply our technique to more detailed data if we can get them from Hirayama, for instance in order to adjust by occupation of men and age of women, or by occupation of men and by age of women married to a husband who is still alive. We are ready to modify our view if such data can support the alternative hypothesis better than the published data. We do hope, that our calculations give rise to a fruitful discussion. The methods we used here might be of interest to the analysis of other cohort and case control studies.

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What Is the Epidemiologic Evidence for a Passive Smoking-Lung Cancer Association?

N. Mantel

Summary

Two survey articles of reports on the association of passive smoking with lung cancer have recently appeared, and also a comprehensive report on the subject of environmental tobacco smoke by a committee of the National Research Council of the United States. The observed excess over a relative risk of unity cannot be explained by chance. Nor can it be fully accounted for by a particular source of bias, the false claims of being non-smokers by individuals who were active or ex-smokers. That possible source of bias leads, in one summary survey, to reducing a relative risk of 1.35 to 1.30, but from 1.34 to 1.15 in the National Research Council report. The latter report suggests that statistical significance would no longer obtain, perhaps, particularly, because of other possible biases. However, to get an estimate of the correct relative risk due to passive smoking, allowance has to be made for actual exposure to passive smoking of those not exposed at home. Thus, the 1.30 is adjusted upwards, by 18 in one survey, to 1.53, but by only 8% in the National Research Council report to 1.24. The National Research Council report had given an anticipated relative risk of 1.1 based on dosimetric considerations. But it is suggested here that that could be as low as 1.05, too low to be detected in an epidemiologic investigation – in any case it would be based on hypothetical assumptions.

In November of 1986 there were two near-simultaneous review articles addressing the subject of passive smoking and lung cancer. One was an invited guest editorial by Blot and Fraumeni in the Journal of the National Cancer Institute, the other a contemporary theme discussion by Wald et al. in the British Medical Journal [1, 2].

There was substantial overlapping in the two articles of the various publications on the subject, and on the basis of which the conclusion of a significant positive association was made. The article by Wald et al. gave, perhaps, more statistical detail about the results of the several studies covered. But, to my mind, there was uncritical acceptance of the results of all the studies. Blot and Fraumeni did suggest that there were some flaws in a particular study, that by Hirayama [3], but decided that any inherent biases in that investigation could not have given rise to the observed elevated risk.

From their overall evaluation of 10 case-control studies (all 10 gave results for females, five separately for males as well) and three prospective studies (two of these covered males separately), which provided 20 separate relative risk (actually odds ratio) values, Wald et al. came up with a summary relative risk of lung cancer due to passive smoking of 1.35 (95% limits 1.19 to 1.54). They trim this down to 1.30 on the basis that some of the presumed non-smokers exposed to passive smoking were actually smokers. Then, on the added basis that even those unexposed to passive smoking at home may still have been exposed when away from home, they raise their estimate of relative risk to 1.53. But note that this last modification presupposes the answer, that passive smoking does

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elevate the risk. For if it did not, there would be no basis for adjusting the 1.30 or 1.35 upwards to 1.53.

Blot and Fraumeni come up with a similar summary measure of relative risk for passive smoking of 1.3 (95% limits of 1.1–1.5), but elevated to 1.7 (95% limits of 1.4–2.1) for heavy passive smoking. These authors suggest that heavy passive smoking is equivalent, at least in terms of nicotine received, to smoking between 1/2 and 3 cigarettes daily, and estimate that smoking a few cigarettes daily would give rise to a relative risk of about 1.5-fold to twofold.

While Blot and Fraumeni do not address the question of correct reporting of non-smoking status, Wald et al. do, having used this as a basis for lowering the relative risk estimate from 1.35 to 1.30. Based on reports and communications from others, Wald et al. estimate that persons reporting themselves as never having smoked (lifelong non-smokers) comprise 2.1% active smokers plus 4.9% former smokers, for a total of 7% ever smokers among the self-claimed never smokers. Wald et al. estimate that these 7% have a combined relative risk of 2, making the assumption in doing this that the active smokers among the 7% smoked on average only a quarter as much as active smokers generally. The relative risk of 2 for the 7% is computed as a weighted average of 3 for active smokers, 1.5 for former smokers, among the 7%.

If 7% of reported never-smokers were actually ex-smokers or active smokers, which were they – the spouses, say, of smokers or the spouses of non-smokers? In my own critique of Hirayama, I had suggested that this false reporting of non-smoking status would preferentially be among those with smoking spouses [4]. If, for example, the 7% overall misreporting of non-smoking status concentrated among spouses of smokers, it would be somewhat higher among persons with smoking spouses who, nevertheless, claimed to be never smokers. Suppose we take it at 20%, in which case the reported lifelong non-smokers relative risk would be 1.20. It could be substantially higher but for the assumption by Wald et al. that the active smokers among the reported never smokers had sharply reduced levels of smoking. However, Wald et al. were ready to make only a small reduction in relative risk for this factor, from 1.35 to 1.30. Their speculative increase, which might have no basis at all, was much greater, from 1.30 to 1.53.

The effect of false reporting of smoking status, specifically of non-smoking, could be much sharper than what Wald et al. have suggested. In a study of biochemical markers of smoke absorption, Jarvis et al. branded as "deceivers" 21 individuals who claimed to be non-smokers [5]. These 21 displayed biochemical patterns very similar to those of actual smokers, not at all like those of accepted non-smokers. The 100 accepted non-smokers comprised 46 without passive smoking, 54 with. Those 21 would constitute 21/121 or about 17% of the total, and these would be active smokers, not just former smokers, or eightfold greater than the 2.1% Wald et al. postulated. Perhaps in the epidemiologic investigations made, false reporting of non-smoking status is at a much lower level, but it would not take much false reporting to account fully for the seeming association between passive smoking and lung cancer.

Recently, a colleague expressed to me the thought that if passive smoking played no role in lung cancer, why are we not finding many negative associations, nor any significantly negative associations? Actually, six of the 20 relative risks reported in Wald et al. are at 1.00 or smaller. And some of those reported as in excess of 1.00 conceal rates of under 1.00. Thus, relative to the rate shown of 1.23 for the study reported by Garfinkel et al., I have brought out in my own critique that that represented a composite of data for various classes of respondents [6, 7]. Where the woman with lung cancer was herself the respondent (as to her husband's level of smoking) the relative risk was 0.83. Using the husbands' responses, the relative risk was 0.77. It was only on the basis of responses by

the sons and daughters, at a time long past when they would have left home, that a relative risk of 3.57 emerged, sufficiently high to raise the overall estimate of relative risk to 1.23. As I indicated in my critique, the replies by the children were more accusatory in nature than revealing of any true relationship.

But even so, it would take 40 large studies to get on average a single seemingly significant negative association of lung cancer with passive smoking, assuming statistical testing at the 5%, two-tailed, level. But we have only 20 evaluations, with many so small that they could not possibly yield any apparently significant protective effect, not even in the unrealistic situation that passive smoking was 100% protective. Suppose a study had a null expectation of only 2 or 3 passive smokers with lung cancer – then there would be some observed number, 5 or 6 or 7 or 8 or more which would be significantly in excess of expectation. But there would be no number, however small or even zero, which would be significantly below expectation. Yet just such low expectations characterize several of the studies reported on by Wald et al. In one study, a relative risk of 2.29 is shown based on only 2 actual cases of lung cancer in passive smokers, expectation 1.20. Another relative risk of 2.45 is based on 3 observed, 1.77 expected. For one prospective study, 4 observed cases have given rise to an estimated relative risk of 3.25, and in another 7 observed cases gave rise to a relative risk of 2.25, suggestive of an expectation little in excess of 3. On the other hand, the four reported risks of under 1.00 had expectations variously of 37.67, 34.08, 6.64 and 13.77.

Of concern to Wald et al. was whether the various relative risks were homogeneous. On this point they cite a chi-square test for heterogeneity of 20.0 on 19 degrees of freedom, $p > 0.2$. However, this is not so much evidence of homogeneity of relative risks as it is reflective of the high unreliability of the individual relative risks. For 8 of the 20 relative risks shown, the upper limit on the relative risk exceeds the lower limit by a factor of about 10 or more, that factor attaining a value of 57 in one instance.

Blot and Fraumeni express concern about other long term consequences of passive smoking, particularly in connection with coronary artery disease. They cite a report by Garland et al. [8] who initially reported a relative risk due to passive smoking of death from ischemic heart disease of 14.9, but seem unaware that the estimate of 14.9 has been revised downward to 2.7. In the report of the National Research Council [9], which I will be discussing below, there is awareness of the downward revision, but not of the fact that the suggestive significance of $p < 0.10$ is lost and becomes $p < 0.20$.

That lung cancer may aggregate in families is also of concern to Blot and Fraumeni, who cite Ooi et al. on the subject [10]. Elsewhere, and yet to appear, I have suggested that apparent familial aggregation, in the instance breast cancer, may be a reflection of an awareness bias rather than of true familial aggregation [11]. If information about relatives is not collected more directly, the apparent aggregation based on reports from the Index case may only reflect heightened knowledge by such cases of similar illnesses about relatives. But the report by Ooi et al. is another instance, like that of Garland et al., in which there has been unreliable statistical evaluation. Thus, Ooi et al. initially reported that the lung cancer risk increased eighteen-fold per 10-year age increase. By letter in the October 1986 issue of the Journal of the National Cancer Institute they have revised that factor downwards, giving separate factors for each 10-year age interval. From age 50 to age 60, the factor is now reported at only 2.9.

The Report of the Committee on Passive Smoking, Board on Environmental Studies and Toxicology, National Research Council [9]

I have chosen to discuss the epidemiologic aspects of this Report separately, since it is essentially the definitive work on current knowledge on environmental tobacco smoke. A member of the committee was Nicholas Wald, senior author of one of the articles discussed above. The report contains a technical appendix which largely duplicates the appendix in the article by Wald et al. and also repeats, with minor variations, the data of Wald et al. The body of the report itself contains those same data, but recast differently, and it is the same 13 studies, with 20 relative risk values, which underlie the epidemiologic aspects of the Committee Report.

There are a great variety of issues which the Committee Report goes into, whether physiochemistry, toxicology, assessment of exposures, use of questionnaires, exposure-dose relationships, etc. But my concern at this time is the epidemiology. There could be a point to estimating the annual number of lung cancer deaths in the United States due to passive smoking, but that would have to be on the presumption that passive smoking does play a causative role.

However, the Committee Report is quite restrained in its findings and leaves open the question of whether anything has been established. If the apparent relative risk is significantly greater than unity, the excess cannot be fully explained away by certain biases considered. However, whether there is statistical significance in view of those biases is not addressed.

From dosimetric considerations, the Report suggests that the excess risk of lung cancer due to environmental tobacco smoke should be 1% of the excess risk due to active smoking. This leads to a relative risk of 1.14 for men, perhaps less for women. From the epidemiologic data, the summary relative risk is 1.34, but it is brought out that for United States studies only the relative risk would be only 1.14. If only large studies are considered, the overall relative risk would be 1.32.

Next addressed by the Report is the effect of biases, particularly the bias associated with the false reporting of individuals that they were not (or never have been) smokers. This leads to a lowering of the estimated relative risk of 1.34 (or 1.30 to 1.34) to 1.15. But note that on this same basis, Wald et al. were willing to reduce an apparent relative risk of 1.35 only slightly, to 1.30.

Yet another adjustment is made. If non-smokers are not exposed to environmental tobacco smoke at home, they might still be exposed to it away from home. An upward adjustment of 8% on account of this yields $1.15 \times 1.08 = 1.24$. This contrasts with the upward adjustment of 18% made by Wald et al., who calculated $1.30 \times 1.18 = 1.53$. The Committee Report differs markedly from the separate report made by one of its own members.

In discussing Wald et al. I suggested that the upward modification they have presupposed a positive role for passive smoking. This same thing is true for the 8% upward adjustment in the Committee Report. For purposes of evaluating the statistical significance of the findings, the relative risk should be taken as 1.15, though the value of 1.24 might be appropriate for assessing the toll in excess lung cancer due to passive smoking assuming that there is causality. With the United States studies indicating an unadjusted relative risk of only 1.14 rather than 1.34, both the 1.15 and the 1.24 might be sharply lowered if intended to apply only to the United States.

But let me stay with the relative risk of 1.15 prior to the 8% upward adjustment. Is that relative risk significantly in excess of 1.00? I suspect not. And even the question of bias remains open. Both in the Committee Report and in the article by Wald et al., the only

biases factored in were just those that would fit into neat mathematical formulas. More subtle biases or ones that had not been thought of did not get in. I gave an example above of the use by Garfinkel et al. of the responses by sons and daughters of the level of smoking by the fathers.

I might even speculate about publishing bias. If an investigator got a weakly or insignificantly negative result for the role of passive smoking in lung cancer, would he bother submitting it for publication? And if he did, would it be accepted for publication? Postulating this kind of bias is not necessary for establishing that the 1.15 relative risk is likely not significant. But I bring it up in connection with a tendency I see towards accepting uncritically or less critically manuscripts which are on the right side of the fence on the issue of passive smoking. A particular example was the publication of the article by Garland et al. on passive smoking and ischemic heart disease mortality, the claims of which fell apart on scrutiny.

Let me bring up now another thought. Some time ago the possibility of subtle or not-so-subtle biases in case-control or other epidemiologic investigations was so much a matter of concern that it was suggested that unless the relative risk were at least 2.0, any increase in risk should not be accepted. Perhaps we can do better now and might employ a less restrictive criterion.

But I can see no relaxation to the point of accepting the relative risks now observed for passive smoking in lung cancer. What we must accept is that it is unlikely that any epidemiologic investigation has been on can be mounted which would establish a causal role for passive smoking in lung cancer. Those who believe such a role exists should continue to believe as much, and might even hazard estimates as to the resulting toll in deaths and disease, with other allowed to hold contrary beliefs. What would be incorrect would be to claim that epidemiologic studies have established the correctness of the belief.

If epidemiologic investigations cannot establish a role for passive smoking, the best we can do is to make suppositions estimates of how great that role may be – and such suppositions estimates can be too high if any of the underlying supposals are false. One supposal would be that the dosage response curve is linear through the origin, another that some particular biochemical measure, say level of cotinine, is a proper measure of the equivalent exposure to cigarettes of passive smoking. And, I point out, there could be the assumption that the temperature at which tobacco smoke is inhaled is not relevant, though I would think that fresh hot smoke would be more active than stale smoke.

With this thought in mind, we can pick up some clues from the report of Jarvis et al. who, after excluding "deceivers", report average cotinine levels in plasma, saliva, and urine of 100 non-smokers to be at 0.55%, 0.55% and 0.364 respectively of those levels from 94 smokers. Let us take it at 0.5%. If the average cigarette smoker has a relative risk for lung cancer of 10.0 (enhancement of 900%, though the enhancement may be 1,400% for very active smokers), this would put the enhanced risk due to environmental tobacco smoke at 4.5%, for a relative risk of 1.045 (it would be 1.07 using the 1,400% enhancement for very active smokers). That relative risk, 1.045, would encompass both passive smoking at home and away from home, including individuals not exposed to passive smoking at home.

What matters, however, relative to the conduct of epidemiologic studies on the subject, is the differential in relative risk between those knowingly exposed to passive smoking and those who believe themselves unexposed. From data available in Jarvis et al., it would appear that those seemingly not exposed to passive smoke (46 in number) nevertheless have a relative risk of about 1.02. For the 54 non-smokers claimed to be actually exposed to passive smoking, the relative risk based on cotinine levels would, in

similar manner, be 1.07. Compared then to seemingly non-exposed to passive smoking, the calculated relative risk for the known exposed to passive smoking would be 1.05. That small increase in relative risk just would not show up on any epidemiologic investigation and would be submerged, in any case, by other very likely biases. The National Research Council report had suggested a relative risk, based on dosimetric considerations, of 1.14, but on the assumption that enhancement in risk due to an active smoking was 1,400%. An enhancement of 900% would have led them to anticipated relative risk of 1.09. But whether we use 1.05, 1.09, or 1.14, the effect would still be undetectable.

As a last point, I raise the issue of passive smoking effects on children. If parents can be shamed into not exposing their children to passive smoking, this is all well and good, even if the supporting basis is unsound. I note that the ill effects arise mostly in early childhood, and have two questions. Have the passive smoking effects been isolated from effects due to mother's smoking prior to the child's birth? To what extent has account been taken that cigarette smoking concentrates in families with lower socio-economic status, as evidenced by lower educational level and more unemployment etc. Rona et al. also brought in the factor of overcrowding at home in their report that passive smoking resulted in some small reduction in the stature of children [12]. But even Rona et al. failed to take properly into account, as I have suggested, the role of some of these important factors on smoking rates in their evaluation [13].

What with subtle biases, not so subtle biases, and even extravagant errors, one should not accept too readily claimed demonstrations of ill effects of passive smoking. Passive smoking has been the favorite whipping boy of epidemiologists for too long already. The public is entitled not to be unnecessarily exposed to environmental tobacco smoke but any panic is unjustified.

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Chapter 4:
General Indoor Air Pollution

Comparison of Personal NO_2 Exposures Among the USA and Asian Countries

Y. Yanagisawa

Summary

The levels of personal exposures to nitrogen dioxide, and NO_2 concentrations indoors and outdoors were compared among the USA, Japan, Korea, Taiwan, Thailand, and the Philippines. The measurements were carried out mainly in winter and in some cases in summer. The personal exposures as well as environmental NO_2 concentrations were higher and their variations were wider in winter than in summer in northern countries where space heating was required. The distribution pattern of the personal exposures in winter in southern countries were similar to that found in the summer in northern countries. NO_2 emission from space heaters and air exchange rates were found to be determinant factors of indoor concentrations. The personal exposures ranged between outdoor and indoor NO_2 concentrations. The unvented space heater, particularly unvented kerosine heater elevated indoor NO_2 concentrations and, in consequence, personal exposures.

Introduction

Amenity of indoor environment can be evaluated from various aspects; quietness, brightness, odor, temperature, relative humidity and air quality. These factors are detectable through the five senses of human being except for certain kinds of air pollutants which are odorless and colorless. Carbon monoxide (CO), nitrogen dioxide (NO_2), sulfur dioxide (SO_2) oxidants (Ox), respirable particulate matter (RSP) and volatile organic carbons (VOCs) are examples of the pollutants. Careful attention should be paid to the pollutants which are odorless and colorless, and which have acute and/or chronic adverse health effects because people can not recognize the presence of such pollutants in their environments. These adverse health effects are evaluated in accordance with dose or exposure to the pollutants. How can we estimate the dose or exposure? This is the primary concern of the air pollution study. Air quality inside residential houses and offices, where people spend most of their time, is a function of emission source strength, ventilation rate and outdoor ambient air quality, whereas the dose or the personal exposure is a function not only indoor and outdoor air quality but also his/her daily activities. Therefore the prediction of the personal exposure is not an easy matter and requires not small number of prediction variables which usually have internal correlation. The direct measurements of personal exposures are desirable to reveal the adverse health effects.

Nitrogen dioxide has been the most characterized pollutants in terms of the personal exposure due to the development of reliable and handy personal monitors. In this paper the characteristics of personal NO_2 exposures and indoor NO_2 pollution will be

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Table 1. Summary of survey protocol

Name of city	Season of measurement	Duration of measurement	Reference
Tokyo Kanagawa Hokkaido	winter and summer	one day	[4]
Tokyo Manila Bangkok	winter	one week	[6]
Seoul	winter	one day for personal one week for indoor	[2]
Seoul	winter	one day	[3]
Taipei Central Taiwan	winter	two days	[1]
Boston	winter and summer	one day	[9]

compared among several countries. Nitrogen dioxide is discharged from industrial processes, automobiles and combustion appliances such as cooking ranges, space heaters and hot water heaters. Therefore levels of personal exposures and indoor NO_2 pollution are thought to depend on the extent of industrialization, usage of automobiles, types of appliances and fuel, and climate.

Procedures

Personal NO_2 exposures, indoor and outdoor NO_2 concentrations were measured by Filter Badge [11] and Palmes tube [7]. The periods of measurements varied from 1 day to 1 week depending on each survey design. The detailed procedures of the measurements were summarized in Table 1.

Results and Discussion

Seasonal and regional variation of personal NO_2 exposure levels in Japan are shown in Fig. 1 [4]. Suginami is a residential area located in central Tokyo and Aikawa is a suburban area about 50 km away from Tokyo. Esashi is placed in Hokkaido, northern island, where temperature is lower than that in Tokyo. The subjects of this study were schoolchildren and their mothers. In winter period, users of unvented space heaters were exposed significantly higher NO_2 concentrations than those of vented space heaters did, while in summer time such a difference was not found. Unvented space heaters are one of the major contributors to personal NO_2 exposures. In Japan it is common to open windows in summer time, so that personal NO_2 exposures in summer period were influenced not by indoor NO_2 pollution but by outdoor NO_2 concentrations which were about 38 ppb, 10 ppb and less than 10 ppb in Suginami, Aikawa and Esashi respectively. The average exposures of mothers were always higher than those of children. This

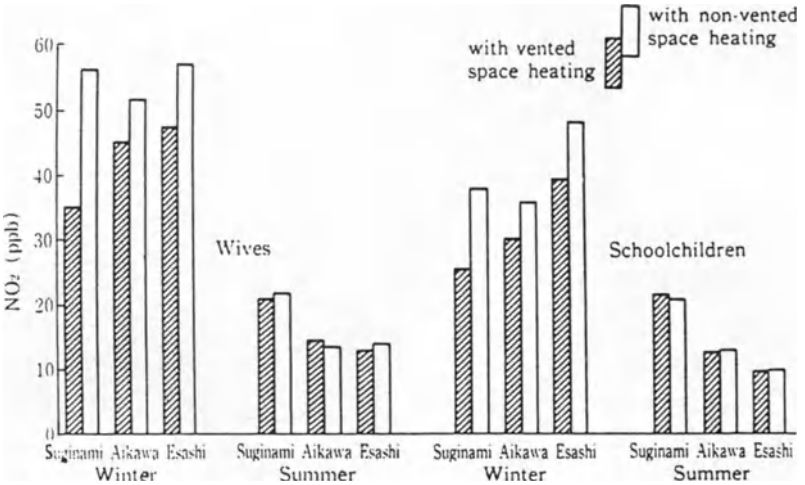

Fig. 1. Seasonal and regional variation of personal NO_2 exposure levels by the type of space heating. (From [4])

suggested that mothers were bared to NO_2 during cooking because gas ranges are the most prevalent appliances for cooking.

The frequency distributions of personal NO_2 exposures of mothers and schoolchildren as shown in Fig. 2a and 2b [4] indicated that higher averages of mother's and children's exposures in winter time resulted from the heavier tails on the high concentration sides. The subjects whose exposures were plotted in the tails were users of the unvented space heaters in almost all cases. Ten mothers in Suginami area were selected for the more detailed exposure study. They were asked to cooperate the personal exposure measurements over 12 consecutive months. Five of them were users of unvented space heater and the rest used vented space heaters or central heating system. In each month daily averages of personal NO_2 exposures for 7 consecutive days were measured. As shown in Fig. 3a and 3b [10], remarkable seasonal change of the personal exposures were observed for the users of the unvented space heaters, while the exposure levels of vented space heater users were steady for entire year. The space heaters seemed to be operated when the minimum temperature of the day became below 10°C (Fig. 4). When the relations of the exposures and health effects are sought, the seasonal differences of the exposure pattern due to the type of space heating method should be taken into account. Yearly average of the personal exposures could be estimated from the equation; Yearly average = (Exposure level in winter) (Exposure level in summer), where α stands for the fraction of heating days in a year [10]. Wide winter variation of personal NO_2 exposures depending on types of space heaters and lower exposures in summer were also found and reported by Mori et al. [5].

As the summary of these studies, characteristics of the personal NO_2 exposures in Japan were;

1) usage of the unvented space heater increased the personal NO_2 exposure levels in winter period,
2) heating season was defined as days of the minimum temperature below 10°C,

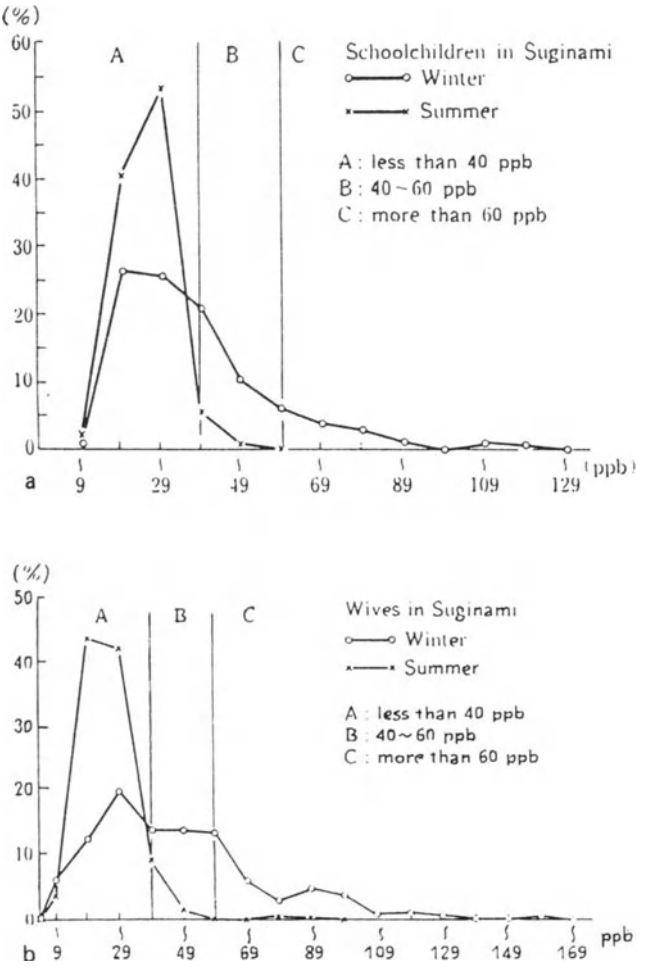

Fig. 2. a Distribution of personal NO_2 exposure levels of schoolchildren. **b** Distribution of personal NO_2 exposure levels of mothers. (From [4])

3) NO_2 exposures were elevated by cooking using gas ranges, and
4) the personal exposures were function of outdoor NO_2 concentration in summer time, while no correlation of the personal exposures and outdoor NO_2 concentrations was found in winter.

The systematic approach to characterize the personal NO_2 exposures has not been conducted in Asian countries except for Japan. However small scale pilot studies in Korea, Taiwan, Thailand and Philippines could suggest the characteristics of the NO_2 exposures. Mori et al. compared the personal exposures as well as indoor and outdoor NO_2 concentrations in Tokyo, Bangkok and Manila [6]. The personal exposures in Bangkok and Manila in winter, although temperature in both cities was around 30°C, ranged 3 ppb to 20 ppb as shown in Fig. 5. The subjects of these three cities were researchers and their family members, so the comparable daily activities were expected. The number of subjects were 44, 17 and 26 in Tokyo, Bangkok and Manila respectively. The standard deviations of the personal exposures in Bangkok and Manila were small,

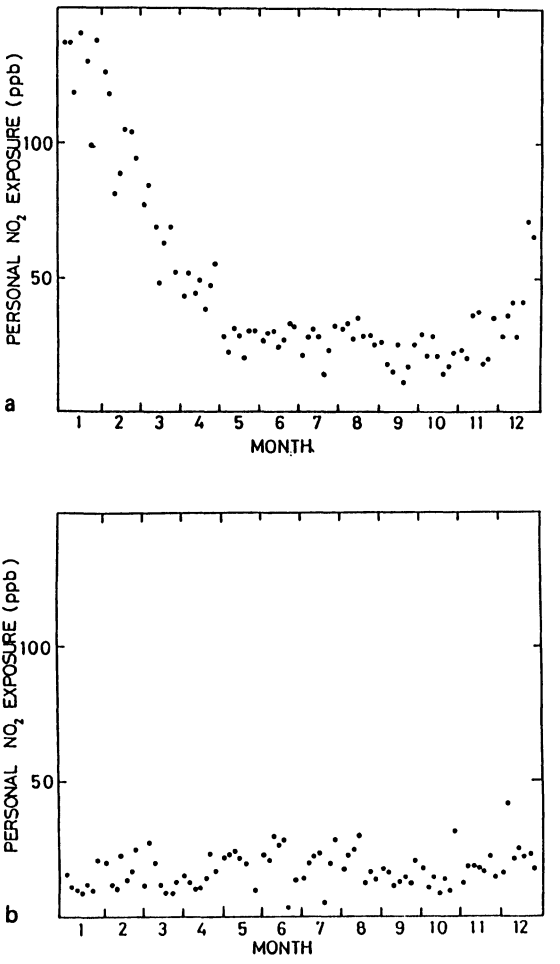

Fig. 3. a Typical seasonal change of personal NO_2 exposures of the unvented space heater user. (From [10]). b Typical seasonal change of personal NO_2 exposures of the vented space heater user

4.1 ppb and 2.9 ppb, whereas in Tokyo it was 25.1 ppb. As shown in Table 2 the indoor and outdoor NO_2 concentrations in the two southern cities were low around 10 ppb and their standard deviations were about 5 ppb which was similar to the standard deviation of outdoor NO_2 concentration in Tokyo. This suggested that air exchange in Bangkok and Manila was high enough to make the indoor NO_2 concentration corresponding to the outdoor concentrations. It is usually found in summer time in Japan. The winter patterns of the personal exposures and indoor NO_2 concentrations in Bangkok and Manila were alike the characteristics found in Japanese summer.

In Taiwan where the winter temperature is 20's°C, 11 homes in Taipei city and 12 homes in rural area of central Taiwan were selected for the pilot study [1]. Measurements of two day averages of the personal NO_2 exposures and indoor and outdoor NO_2 concentrations were conducted in late December of 1987. Fuel for cooking is either piped city gas or tank gas as shown in Table 3 along with the summary of home characteristics. When comparing NO_2 levels between two subject areas, the personal exposures and

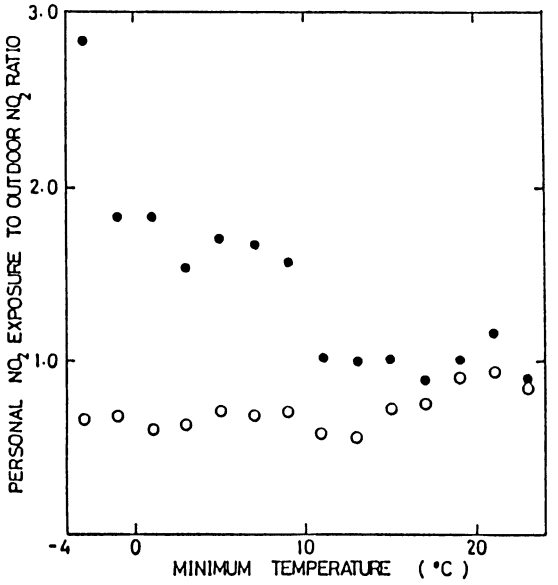

Fig. 4. Dependence of the ratio of personal exposures to outdoor NO_2 concentrations on the minimum temperature of the day. (From [10]). (● = unvented space heater user, ○ = vented space heater user)

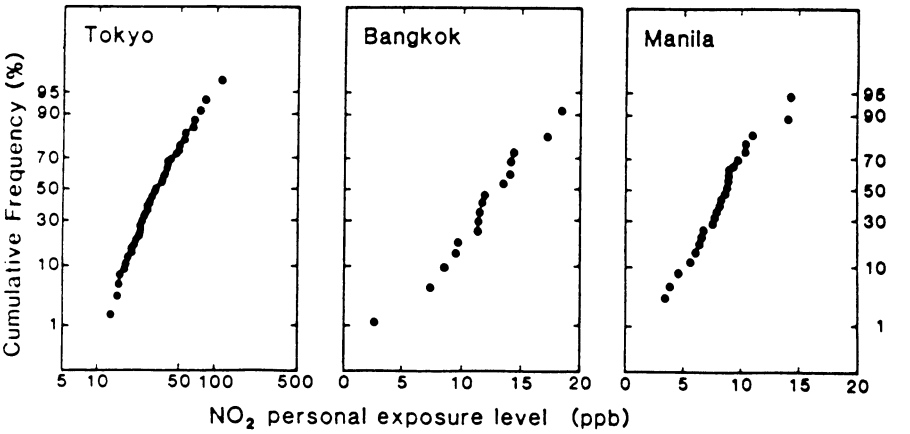

Fig. 5. Cumulative frequency distribution of NO_2 personal exposure levels. (From [6])

bedroom concentrations were significantly higher in Taipei than in central Taiwan as shown in Fig. 6. Average outdoor NO_2 concentrations both in Taipei and central Taiwan were higher than personal exposures and indoor NO_2 concentrations in each area except for kitchen NO_2 concentrations in central Taiwan. It might result from the longer gas range usage for cooking in central Taiwan than Taipei city. The distribution pattern of the NO_2 levels was similar to the summer pattern in Japan. The significant difference of NO_2 levels was found in Taipei when the NO_2 levels were classified according to the fuel type. The NO_2 levels of indoors and personal exposures were higher for the piped city gas

Table 2. Indoor and outdoor NO_2 levels in the home in 3 cities. (From [6])

	Home Indoor*				Home Outdoor*			
	n	Range	Mean	S.D.	n	Range	Mean	S.D.
Tokyo	44	8.0–129	47.6	35.0	44	6.7–32.2	21.0	5.4
Bangkok	20	2.6– 21.9	10.4	5.3	20	2.1–25.6	12.5	6.2
Manila	26	6.6– 27.4	12.6	4.4	26	7.2–23.7	14.0	4.0

*ppb

Table 3. Characteristics of subject houses in Taiwan. (From [1])

House type	conventional	4		apartment = 9
	apartment	9	Taipei:	single = 2
	single	10		conventional = 4
			Central:	single = 8
House vol. (m^3)		mean SE	Taipei:	300.1 (28.5)
	Total:	390.4 (42.3)	Central:	472.7 (70.1)
Kitchen vol. (m^3)		mean SE	Taipei:	19.1 (1.4)
	Total:	29.1 (3.0)	Central:	36.6 (3.8)
Fuel type	pipe gas:	5		pipe gas: 5
	tank gas:	18	Taipei:	tank gas: 6
				pipe gas: 0
			Central:	tank gas: 12
Stove use		mean SE	Taipei:	17.7 (3.2)
(stove hour)	Total:	19.7 (2.2)	Central:	21.4 (3.2)
Fan use	non:	16		non: 9
	fan:	7	Taipei:	fan: 2
				non: 7
			Central:	fan: 5

users than the tank gas users. In central Taiwan the single house residents were exposed to lower levels of NO_2 than the conventional house resident did.

Space heating is required in winter in Korea where coal briquettes (Yeontan) have been widely used as a domestic fuel since 1960's, whereas use of the bottled liquid propane gas and natural gas for cooking and heating has rapidly increased in urban area since early 1970s. In January and February of 1984, the pilot personal NO_2 exposure as well as indoor NO_2 study was conducted on the randomly selected 48 homes in two residential areas 5 to 10 km away from the center of Seoul [2]. The weekly averages of indoor NO_2 concentrations were measured by Palmes tube and daily averages of the personal exposures were monitored by Filter Badge. The cumulative distribution of indoor NO_2 concentration indicated that indoor NO_2 concentrations of homes where the bottled propane gas used as cooking fuel were higher than those of natural city gas user's

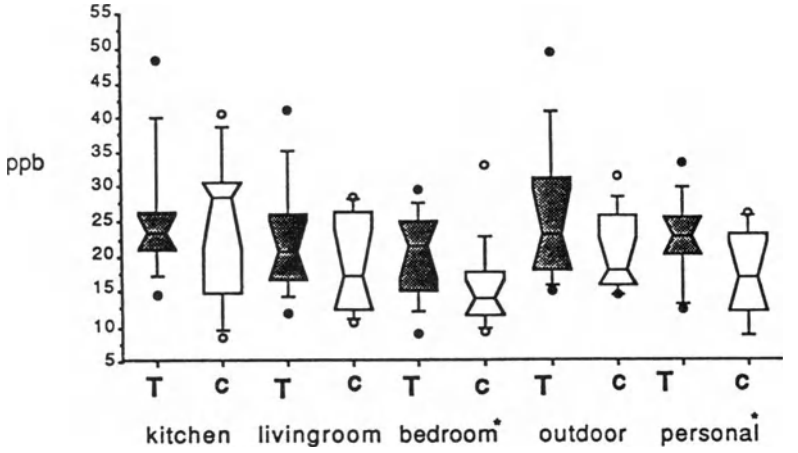

Fig. 6. Comparison of NO_2 concentrations between Taipei (T) and central Taiwan (C). (From [1])
*Differences between means are significant at $p = 0.08$

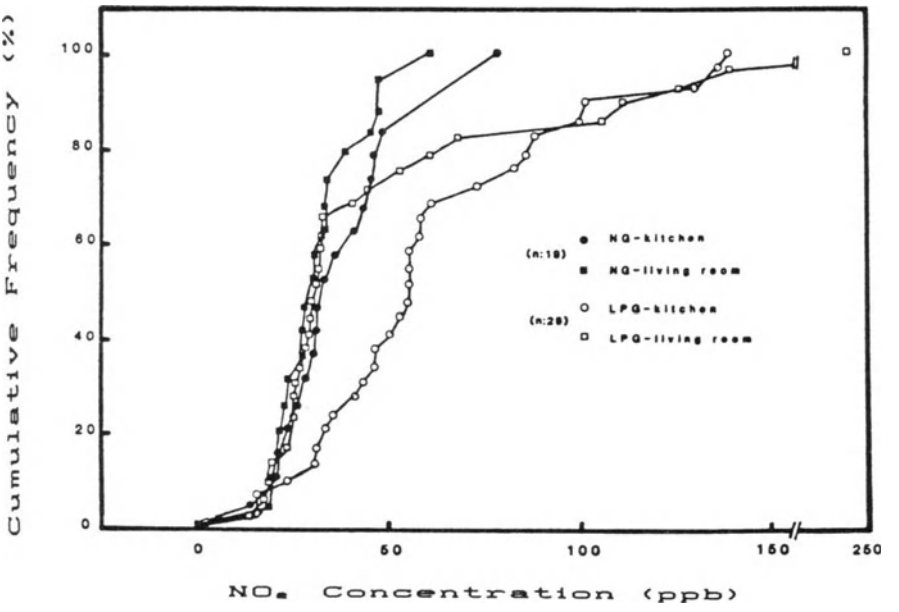

Fig. 7. Cumulative distribution of NO_2 concentrations by location and type of cooking fuel. (From [2])

(Fig. 7). This is contrary to the findings in Taiwan. Confounding factors with the type of fuel must be investigated further. When the subjects houses were divided by kinds of space heating, the houses where unvented kerosine heater and Yeontan stove used for

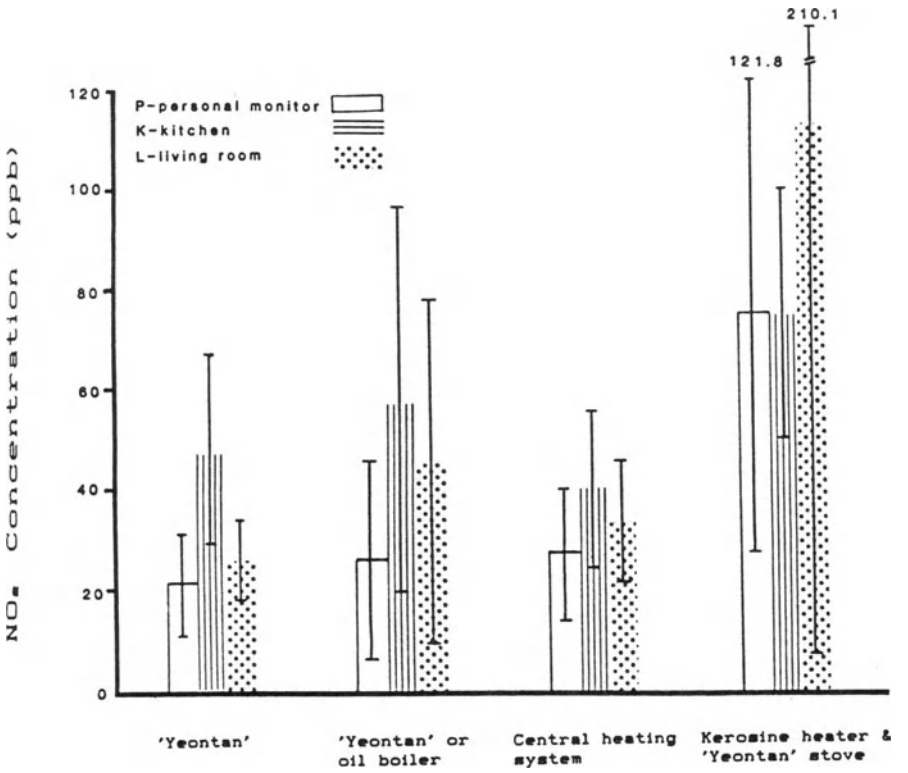

Fig. 8. Mean NO_2 concentrations in homes by type of heating fuel (bars denote 1 standard deviation). (From [2])

Table 4. Average NO_2 concentrations (ppb) by type of space heaters in living room. (From [3])

	Vented heater (20)*	Unvented heater (28)	p**
Personal	26.2	39.6	0.103
Living room	24.6	53.2	0.002
Outdoor	33.5	38.7	0.185

* (Number of data).
** Level of significance.

heating were highly polluted by NO_2 as shown in Fig. 8. Indoor NO_2 pollution in the houses using Yeontan alone seemed not to be serious but careful attention should be paid for carbon monoxide poisoning. The follow-up study focusing on the users of the bottles propane gas for cooking was conducted in winter of 1986 [3]. Twenty vented space heater users and 28 unvented space heater users were chosen for the NO_2 measurements of the personal exposures, and in living room and outdoors. Statistically significant

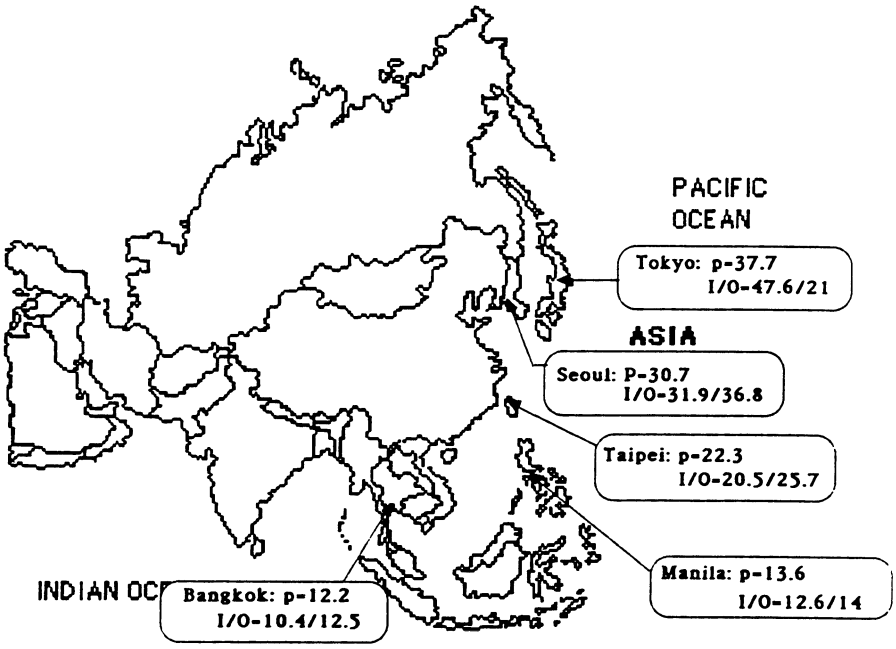

Fig. 9. Personal exposures and indoor/outdoor NO_2 concentrations in Asian cities. (From [1])

difference was observed between the living room NO_2 concentrations of both types of space heater (Table 4) [3]. Usage of the unvented space heater could bring on indoor NO_2 pollution. Further studies are required to characterize indoor NO_2 and CO pollution.

According to the NO_2 measurements performed in Asian countries [1–6], the personal exposures and indoor and outdoor NO_2 concentrations in winter period were summarized in Fig. 9.

Although the detailed survey protocols were different each other, the general tendencies could be extracted;

1) averages of personal exposures ranged between indoor and outdoor NO_2 concentrations,
2) differences of indoor and outdoor NO_2 concentrations in southern cities were diminutive,
3) in northern cities where space heating in winter were indispensable, elevation of indoor NO_2 concentration by unvented space heaters made the personal exposures higher than outdoor NO_2 concentrations, and
4) outdoor NO_2 concentrations might reflect the extent of industrialization and the counter measures of ambient NO_2 pollution.

In USA the population-based indoor NO_2 study was conducted to represent the total population of greater Boston area [9]. Folllowing the residential NO_2 characterization study, the personal NO_2 exposure study for the selected participants has been carried out targeting high-exposure group and the population as a whole [8]. The criteria to chose the

Table 5. Comparison of personal exposure levels by class. (From [11])

Class	Cases	Mean	Std Dev
a) Winter			
1	62	29.2	18.1
2	54	23.5	16.7
3	47	20.5	23.6
4	73	12.9	9.0
9	18	23.4	11.3
All	254	21.3	17.6
ANOVA F	8.5789		
Significance	0.000		
b) Summer			
1	54	24.6	20.1
2	37	17.5	13.3
3	40	16.3	19.2
4	64	17.0	27.1
9	23	20.3	31.6
All	218	19.2	22.8
ANOVA F	0.4377		
Significance	0.7263		

subjects among the participants of the residential NO_2 characterization study were NO_2 concentration in the home and potential out-of-home exposure due to the occupation, commuting and cooking. The classes of 1, 2, 3, 4 and 9 in Table 5a and 5b stand for high out-of-home exposure and high in home NO_2, low out-of-home exposure and high in home NO_2, high out-of-home exposure and low in home NO_2, low out-of-home exposure and low in home NO_2 and unknown respectively. The winter results (Table 5a) suggested a strong separation of individuals by the category. On the other hand such a stratification could not be observed in the summer survey (Table 5b). It may be due to wide variation in activity patterns during summer months and to selecting method of subjects according to their home NO_2 concentrations in winter.

Conclusion

The personal exposures to nitrogen dioxide were compared among USA and Asian countries. The common feature of the personal NO_2 exposures is that it is higher in winter than in summer. It may be due to high NO_2 emission and low air exchange rates. Developing the combustion appliances of low NO_2 emission and maintaining adequate air exchange rate for an entire year are important to prevent the potential adverse health effects.

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The Relationship Between Respiratory Illness in Children and Gas Cookers and Paraffin Heaters in the UK

R. J. W. Melia, R. J. Rona, and S. Chinn

In England, a series of studies have been conducted to investigate the relationship between the prevalence of respiratory illness in children and gas cookers and paraffin heaters. The early studies concentrated on the effects of gas cookers on health. The prevalence of respiratory illness in primary school children from both a national representative sample and a group living in Middlesbrough in the north of England was associated with the use of gas for cooking in the home ($P < 0.05$), independent of other social and environmental factors. It is possible that this association is caused by indoor air pollution, in particular nitrogen dioxide (NO_2) which arises in the emissions of gas combustion. However, in two further studies no consistent relationship was found between the prevalence of respiratory illness and weekly average levels of NO_2 measured in the home. Most recently an association has been found between the prevalence of respiratory illness in Afro-Caribbean and Caucasian primary school children living in inner cities and the combined use of a gas cooker and paraffin heaters in the home ($P < 0.05$). It is possible that the levels of NO_2 in these children's homes are much higher than those previously reported. This is now being investigated.

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Indoor Nitrogen Dioxide Pollution Associated with Gas Stoves and Unvented Heaters in Japan*

H. Nitta, S. Nakai, and K. Maeda

Summary

We have conducted a study of nitrogen dioxide (NO_2) concentrations in nearly 200 houses, including newly built homes supplied by electricity in Tokyo. NO_2 levels were measured in the kitchen and living room of each house for 1 week simultaneously using a Yanagisawa badge and some houses were measured outside in the winter and fall. In both of the kitchen and living room, NO_2 concentrations for homes supplied by gas were higher during both the fall and winter than those supplied by electricity. The mean NO_2 concentrations in the kitchen and the living room for homes with electricity was 6 ppb in the winter. Unvented heaters were used in the approximately 20% of gas homes. Average NO_2 concentration in the living room for homes with gas with vented and unvented heaters was 22 ppb and 72 ppb, respectively. In the fall, the mean NO_2 concentrations in the living room for homes supplied by electricity and gas was 9 ppb and 14 ppb, respectively. The mean levels of NO_2 measured outside homes were 29 ppb in the winter and 20 ppb in the fall, respectively. Mean indoor NO_2 concentrations in homes supplied by gas with unvented heaters were two times higher than those outdoors in the winter. The health consequences of the differences among the three types of households should be investigated. NO_2 levels in this study are likely to be different from those of a lot of studies in Europe and North America. It might depend on the characteristics of houses, e.g., house structure, ventilation, type of cooking facility, and type of heater, in Japan.

Introduction

The effects of indoor NO_2 pollution on prevalence of respiratory symptoms and lung function have been studied mainly in epidemiological studies. In most of these studies, the association between respiratory illness and the usage of gas stove for cooking have been investigated (Melia et al. 1977; Florey et al. 1979; Keller et al. 1979; Speizer et al. 1980; Comstock et al. 1981; Ware et al. 1984). Nevertheless, consistent evidence has not been found. NO_2 exposures were directly measured in only few of the studies. On the other hand, Yanagisawa et al. (1986) found that the hydroxyproline/creatinine (HOP/C) ratios in urine had a significant correspondence to personal NO_2 exposure. This study suggests that hydroxyproline, a metabolite of body collagen degradation, is associated with NO_2. However, Verplanke et al. (1987) showed that the urinary HOP/C ratios were not found to have a close correlation of exposure to NO_2, although the presence of major

* Parts of the study were supported by grants from the Housing Research & Advancement Foundation of Japan.

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NO_2-sources in the kitchen was significantly associated with elevated HOP/C ratios. Thus, the findings regarding the effects of NO_2 even in terms of biological markers, such as HOP/C ratios are inconsistent.

Surrogate measures of NO_2 exposures, such as stove type and heater type, may not accurately classify the exposure of individual subjects. The evaluation of indoor NO_2 levels would provide useful information for epidemiological studies.

Exposures to NO_2 in indoor microenvironments have been obtained from indoor air quality studies and personal exposure studies. All studies show that indoor NO_2 levels are lower than those measured outside when there are no indoor sources (U.S. Environmental Protection Agency 1987). Our earlier study (Nitta and Maeda 1982) had shown elevated NO_2 exposures for individuals from homes with gas and kerosene heaters.

As a part of an epidemiological study on the health effects of indoor air pollution, we conducted a study to assess indoor NO_2 levels, comparing between homes with electric and gas stoves. Almost all of households in Japan have been using natural gas or liquid propane gas for cooking. So far, it was difficult to evaluate directly the contribution of gas cooking to indoor air quality because of the absence of the comparison group. Some houses with electric stoves have been recently developing in the Tokyo Metropolitan, so that we can finally conduct a study of indoor NO_2 levels and its health effects concerning with gas cooking.

Material and Methods

Nearly 200 homes were randomly selected from a row of apartment complexes built in Edogawa, a coastal region in Tokyo to obtain approximately an equal number of houses with gas and electric stoves. NO_2 concentrations were measured in the kitchen and the living room for each house for one week simultaneously using diffusion NO_2 dosimeters (Yanagisawa and Nishimura 1982). Integrated one-week measurements were provided. Kitchen monitors were placed on the top of the refrigerator away from fan or hood, and top burners. Living room monitors were placed on TV set, or hung from the ceiling. For nearly ten percent of the subjects, NO_2 concentrations outdoors were also measured. Outdoor monitor were located near the exterior wall shielded from rain. Samples were collected for each house during two seasons: the winter, the fourth week of February 1985, and the fall, the fourth week of September 1985.

Each household was asked to complete a questionnaire for the brief description of home characteristics and the usage of combustion appliances, such as unvented space heaters, which were in widespread use for heating in Japan. Home characteristics were basically similar to each other due to a standardized planning of the apartments.

In order to estimate the year-long averaged concentration, we roughly calculated the weighted means of measurements for two seasons from the equation below. We have got it by modifying the equation Yanagisawa et al. (1984) showed.

"annual" average concentration
= [concentration in the winter] * 17/52
+ [concentration in the fall] * (35/52)

The coefficient of "17" means a number of weeks being below 10°C in the minimum air temperature of the day out of 52 weeks in a year.

All statistical analyses were performed with SAS (SAS Institute Inc. 1982) using Mann-Whitney U test and Pearson correlation.

Table 1. Summary statistics of indoor NO_2 concentrations (ppb) by types of stove and heater

Phase	Stove	Heater	Location	Quantiles					
				Mean	S.D.	25	50	75	N
Winter	Electric		Kitchen	6	2	4	5	7	87
			Living	6	3	4	6	7	87
	Gas	All	Kitchen	36	36	18	25	34	78
			Living	33	39	15	20	25	78
		Vented	Kitchen	28	25	18	23	30	62
			Living	22	23	15	18	23	62
		Unvented	Kitchen	69	55	23	56	114	16
			Living	72	60	24	51	113	
Fall	Electric		Kitchen	9	3	7	9	11	85
			Living	9	3	7	9	11	85
	Gas		Kitchen	17	5	14	16	19	73
			Living	14	4	12	14	16	73

Results

A total of 169 households participated in the winter phase: 91 were electric homes; 78 were gas homes. During the fall phase 162 households participated: 87 were electric homes; 75 were gas homes. Among them, a pair of NO_2 measurements of both the winter and the fall phase were available for 158 households. So we were able to calculate the weighted "annual" averages of these houses. NO_2 concentrations outside 16 homes were measured in both of the seasons.

Mean NO_2 concentrations are summarized in Table 1. Indoor NO_2 concentrations in homes with gas stoves were higher during both the winter and fall seasons than those measured inside homes with electric stoves ($p < 0.0001$). During the winter, the mean values of indoor NO_2 concentrations for gas homes were 36 ppb in the kitchen, 33 ppb in the living room, respectively. For electric homes the mean values were 6 ppb in both the kitchen and the living room. Indoor NO_2 concentration for homes with gas stoves for cooking were five or six times higher than those for electric homes. Indoor NO_2 concentration varied widely up to nearly 200 ppb and standard deviations were greater for gas homes in the winter phase.

Unvented kerosene/gas heaters were used in the approximately 20% of gas homes. To permit investigations of the effects of unvented heaters, gas homes were classified into those without unvented heaters and with unvented heaters. Mean NO_2 concentrations for gas homes with unvented heaters were 69 ppb in the kitchen, 72 ppb in the living room, respectively. Mean differences between unvented-heating and vented-heating homes were considerable greater than those between electric and gas homes without unvented heaters. During the fall phase, indoor NO_2 concentrations for electric homes were low in the same pattern as the winter. Indoor NO_2 concentrations in home using gas stove were higher than those inside homes with electric stoves ($p < 0.0001$). The mean for gas homes was 17 ppb in the kitchen, 14 ppb in the living room, respectively. For electric homes the mean was 9 ppb in both the kitchen and the living room. Absolute mean differences

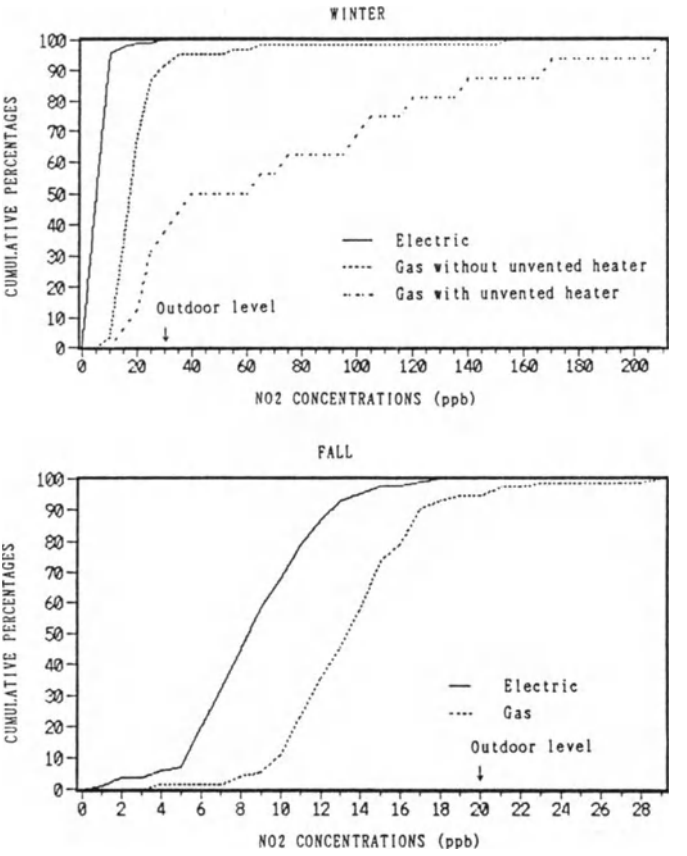

Fig. 1. Cumulative frequency distributions of NO_2 levels in the living room during the winter (above) and fall (below)

between electric and gas homes were smaller in the fall than in the winter phase, even compared with gas homes without unvented heaters. Average levels of NO_2 measured outside homes were 29 ppb in the winter, 20 ppb in the fall respectively. Standard errors of mean were nearly 1 ppb (s.e. = 1.1 ppb in the winter, 0.7 ppb in the fall), so that the variations of outdoor NO_2 concentrations for samples in this study could be negligible.

Cumulative frequency distributions of NO_2 concentration in the living room were illustrated in Fig. 1, comparing with outdoor NO_2 levels. In the winter phase, indoor NO_2 concentrations for electric homes were consistently lower than those outside. For approximately 90% of gas homes without unvented space heater and only one-third of gas homes with unvented space heater, indoor NO_2 levels were lower than outdoor NO_2 levels. In the fall phase, indoor NO_2 concentrations for all electric homes and over 95% of gas homes were below those measured outside homes.

Cumulative frequency distribution of the predicted "annual" mean concentrations in the living room are illustrated in Fig. 2.

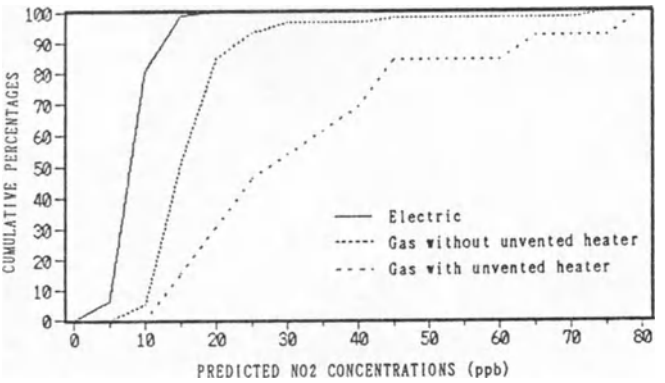

Fig. 2. Cumulative frequency distributions of predicted "annual" mean of NO_2 levels in the living room

Table 2. Correlation coefficients between NO_2 levels in the kitchen and in the living room

	Winter		Fall	
	r	p	r	p
Electric homes	0.916	0.0001	0.866	0.0001
Gas homes with vented heater	0.969	0.0001	0.665	0.0001
Gas homes with unvented heater	0.975	0.0001	0.756	0.0028

Median of the predicted mean for each stove-heater type were 8 ppb for electric-cooking homes, 15 ppb for gas-cooking and vented-heating homes, 30 ppb for gas-cooking and unvented-heating homes, respectively. The shape of the distribution for gas-cooking and vented-heating homes are similar to that for electric-cooking homes, although their absolute values were different. The distribution for gas-cooking and unvented-heating homes are not similar to others in terms of both the shape and the location. There were some household exposed to high NO_2 over 50 ppb in annual averages for gas homes with unvented heaters.

Correlation coefficients between NO_2 levels in the kitchen and levels in the living room for the samples as broken down by stove and heater type are shown in Table 2. These were $r = 0.916$ ($p = 0.000$) for electric homes, $r = 0.969$ ($p = 0.000$) for gas homes without unvented heaters and $r = 0.975$ ($p = 0.000$) for gas homes with unvented heaters in the winter, while in the fall the corresponding correlations were $r = 0.866$ ($p = 0.000$), $r = 0.665$ ($p = 0.000$) and $r = 0.756$ ($p = 0.003$). These strong correlations indicate that air flow rate between kitchen and living room would be large. Correlation coefficients in the fall were slightly smaller than in the winter. It might depend on the increased air exchange rate in the fall.

Discussion

Mean NO_2 levels in the gas cooking homes were substantially higher than those in the electric cooking homes as previously reported in many studies. Mean differences were, however, considerably small compared with the results in the U.K. and U.S.A. studies. Higher levels of NO_2 in dwellings with gas vs. electric were reported by Palmes, et al. (1977). Kitchen NO_2 levels ranges from 20 to 129 ppb in 10 homes with gas stoves and from 2 to 19 ppb in 9 homes with electric stoves. Goldstein et al. (1979) also showed that mean kitchen levels were 112 ppb in 428 homes with gas stoves and 18 ppb in 87 homes with electric stoves. Spengler et al. (1979) reported that the indoor difference between homes using gas and electricity is greater than the differences between homes with the same fuel, and ranges from 3 to 7 times larger for gas by analysis of variance.

There are several possible reasons why NO_2 concentration in gas homes we measured were lower than those recorded in studies of other countries. It has been reported that the presence of pilot lights of gas stoves did significantly influence NO_2 levels (Goldstein et al. 1979; Spengler et al. 1986). Gas stove which are now in widespread use in Japan have electronic ignitions, not pilot lights. Therefore, the effects of pilot lights can be ignored in Japan.

Another important factor influencing indoor NO_2 concentrations is kitchen ventilation. Almost all of kitchens of Japanese houses have fans or hoods which are venting to the outside. In addition, people in Japan make it a habit to use a fan in kitchen while cooking. The ventilation habits such as use of exhaust fan are likely to have contributed to the lower NO_2 levels compared with those in other studies. In general, the natural ventilation rate of traditional Japanese wooden houses seem to be high, although systematic data are unfortunately unavailable. However the houses in this study are reinforced-concreted and ventilation rate has been probably reduced. The incomplete partition between the kitchen and living room is likely to reflect strong correlations between kitchen and living room NO_2 levels. The partitions among rooms of traditional Japanese houses are not complete, but in most cases Japanese houses are less spacious. Accordingly the air inside the houses could be well-mixed and NO_2 emitted from gas stove might be diluted.

An interesting house characteristic relating to indoor NO_2 is a typical flooring of Japanese houses, what is called "tatami" made from rice straw and rush stem. Nishimura et al. (1986) showed that rush carpets had the capacity to adsorb NO_2 and to convert up to 70% of absorbed NO_2 to NO. Although the extent of reduction of NO_2 in homes we investigated in the present study could not be estimated, rush carpets would be potential factor influencing indoor NO_2 levels in Japanese houses.

The generation of NO_2 from unvented kerosene heaters might be the most critical factor influencing indoor NO_2 levels and NO_2 exposure in Japan. Indoor use of unvented heaters is known to cause an increase in indoor air pollutants including NO_2 (Yamanaka et al. 1979; Traynor et al. 1983). So far we were unable to conduct the study comparing between electric and gas homes because there were very few homes with electric stoves. The findings of elevated indoor NO_2 levels in Japanese homes with unvented gas and kerosene heaters we previously reported were not based on the comparison with electric homes (Nitta and Maeda 1982). In the present study we could reveal a larger contribution of unvented heaters to indoor NO_2 levels. Appliances for heating are needed for only one-third of a year on an average in Tokyo. Nevertheless high NO_2 concentration in winter resulted in elevated NO_2 levels in a year-long average.

Therefore indoor NO_2 pollution in Japan is regarded as being the problems of heating rather than cooking. Nearly 90% of the households in general populations of Japan are

using unvented kerosene heaters. Thus we should pay attention to people exposed to high NO_2 concentrations due to unvented heaters. In an epidemiological study on health effects on indoor NO_2, we have to consider three types of subjects: households in electric homes; households in gas homes without unvented heaters; households in gas homes with unvented heaters.

Acknowledgement: The cooperation of the participating families is greatly appreciated.

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Highly Sensitive Methods for the Evaluation of Carcinogens and Mutagens Indoor

H. Matsushita, K. Tanabe, and S. Goto

Summary

This paper deals with low noise samplers for collecting particulates indoors, and analytical and biological methods sensitive enough to determine carcinogens and mutagens indoors. Two types of low noise samplers were devised. One can collect airborne particulates on a filter at a flow rate of up to 25 l/min. The other is a 12 stage Andersen low-pressure impactor sampler for particle size distribution studies operated at a flow rate of 20 l/min. Noise level of these samplers was less than 50 dB. Polynuclear aromatic hydrocarbons (PAH) and nitroarenes in the particulate samples collected by these samplers were determined by the following highly sensitive analytical methods:

1) PAH analysis which consists of ultrasonic extraction and high performance liquid chromatography (HPLC) with spectrofluorometric detector, and
2) nitroarene analysis which consists of ultrasonic extraction, fractionation of nitroarenes by absorption HPLC, chemical reduction of nitroarenes to the corresponding aminoarenes, and separation analysis by HPLC/fluorometry.

Concentration of PAH and nitroarenes in a smoking room were usually higher than those in a non-smoking room, and most of these chemicals were found in particulates smaller than 1 μm in particle size. We confirmed that the micro-forward mutation assay using *Salmonella typhimurium* strain TM677 was 10 times or more sensitive than the Ames method. This bioassay was useful for the measurement of mutagenic activity of particulates indoors and revealed that mutagenic activity in a smoking room was usually higher than that in a non-smoking room. Furthermore, we developed a highly sensitive method for analyzing PAH in particulates, collected by a personal sampler. This method consists of ultrasonic extraction, liquid-liquid partition, and separation analysis by column concentration/HPLC/fluorometry. This method is suitable for analysis of benzo(a)pyrene, benzo(k)fluoranthene and benzo(ghi)perylene in a particulate sample collected by only 300 l-air sampling. Some results on personal exposure to these PAH are also presented.

Introduction

Recently, carcinogens and mutagens indoors have attracted much attention for the following reasons:

1) We spend 80 percent or more of our time indoors [1].
2) Indoor air is polluted not only by pollutants in the outdoor air penetrating the indoor space but also by pollutants from indoor emission sources such as smoking, cooking, heating etc.

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3) All these pollutants contain various kinds of carcinogens and mutagens.
4) Recently, indoor ventilation rates have become lower than in the past due to advances in construction techniques and growing concern with energy saving. Thus, pollutants from indoor emission sources are increasing in their weights in indoor pollution. In fact, several studies show that concentrations of carcinogens, mutagens and related pollutants in a room, where there is being heated, cooked and/or smoked, are higher than those outdoors [2–7].
5) The lung cancer mortality rate is increasing in major countries of the world.
6) There is growing concensus that the indoor air quality is very important for a healthy and comfortable life, and that this is basically controlable because indoor space is generally small and many kinds of techniques for air quality control have been developed during the past years.

However, little information has been published about carcinogens and mutagens indoors. This is mainly due to the fact that the techniques, for the survey of carcinogens and mutagens indoors have not been fully developed through sampling, bioassay and chemical analyses.

Carcinogens and mutagens indoors are divided into gaseous/vaporous ones and particulate ones. We developed several techniques for measuring carcinogens and mutagens in particulates suspended in indoor space. That is, two kinds of low noise air samplers for collecting particulates indoors, a microforward mutation assay which can measure mutagenicity of particulates collected by the low noise samplers, and highly sensitive chemical analyses for polynuclear aromatic hydrocarbons (PAH) and nitroarenes have been developed, and these techniques have been applied to evaluate indoor pollution. This paper describes the outline of these technique and gives some examples of the application of these techniques to measure carcinogens and mutagens indoors.

Development of Low Noise Samplers

Prior to the measurement of carcinogens and mutagens in particulates indoors, the particulates should be collected by a sampler which should meet the following requirements; i) low noise, ii) large sampling flow rate in the range which does not affect the pollution level indoors, and iii) small in size and portable. These requirements are necessary to survey indoor pollution without disturbing the inhabitants of the studied buildings. We developed two types of low noise samplers which satisfied these requirements. The first one is a size-dependent sampler which can collect particulates in 12 stages according to their particle sizes. The deposition rate of particulates into the lung is largely affected by the particle size. Therefore, this sampler will offer useful information about the particle size distribution of carcinogens and mutagens indoors. The other sampler is a low noise sampler which is small in size and can collect particulates without differentiation for size. This sampler is useful for survey of indoor pollution.

The Size-Dependent Sampler

Concentrations of carcinogens and mutagens in indoor air are generally very low. Therefore, the flow rate of the sampler should be as large as possible without disturbance of the indoor pollution level. In Japan, living rooms usually have an 8-mat area. The air volume of an 8-mat room is about 32 m^3. Supposing that the natural ventilation rate in a

living room is 0.5 times per hour and that the permissible extent of disturbance of the indoor by sampling is 10 percent or less of the natural ventilation rate, the maximum sampling flow rate is calculated to be about 27 l/min. Hence, we decided to develop an impactor type size-dependent sampler with a flow rate of 20 l/min, which can collect particulates separately in 12 stages according to the following 50% cut-off particle diameters; 12.1 μm or more, 8.5 μm, 5.7 μm, 3.9 μm, 2.5 μm, 1.25 μm, 0.76 μm, 0.52 μm, 0.33 μm, 0.22 μm, 0.13 μm, and less than 0.13 μm.

A powerful suction pump was needed to operate this sampler, because the pressure loss of the sampler was −377 mmHg. Various kinds of pumps and various sound insulation methods were studied in order to develop a small, low noise size-dependent sampler. As a result, we found that with the Gast DAA-103GB pump housed in a soundproof, anti-vibration case (465 (H) × 400 (W) × 660 (D), made of steel, double structure) with castors, the noise level can be reduced to 50 dB or less even when airborne particulates indoors were collected in the 12 stages at a flow rate of 20 l/min. The sampler can be operated continuously for as long as two weeks or more.

Low Noise Sampler

Pressure loss in the sampler is not large when it is used for the collection of particulates without differentiating for size. Therefore, size reduction of the sampler is feasible. We devised the following sampler by putting the Nittoh Koki VP-0935 Pump with a suction flow rate of 60 l/min under no load in a vinyl chloride case (320 (H) × 300 (W) × 420 (D)) with castors, and packing sound absorbing materials around the pump. This sampler can collect airborne particulates in the flow rate of 5–25 l/min. Noise level was less than 50 dB even when sampling was carried out at the flow rate of 25 l/min. This sampler can operate continuously without any trouble for two weeks or more.

We also devised pocket low noise samplers with the flow rate of 2 l/min and 0.1 l/min, respectively. The latter sampler is about 400 g in weight and can be used as a personal sampler.

Development of a Highly Sensitive Mutation Assay and Its Application to Indoor Pollution Survey

Mutagenicity of particulates in the environmental air has been extensively surveyed by the Ames methods [8–21]. This method can be used only for the measurement of the mutagenicity of particulates collected from 500 m^3 or more of environmental air. Thus this method has no adequate sensitivity to measure the mutagenicity of indoor particulates which are hard to collect in large quantities. We made efforts with Dr. Lewtas, from the U.S.EPA, to develop a highly sensitive and relatively simple mutation assay which permits to measure mutagenicity of particulates indoors [2, 22]. Figure 1 shows the scheme of this micro-forward mutation assay.

The low noise sampler described before was operated at a flow rate of 20 l/min for 24 h each time, and airborne particulates were collected indoors on a quartz fiber filter (Pallfex, QAST2500). The organic compounds in the particulates were extracted by the ultrasonic extraction methods using benzene-ethanol (3:1, v/v) as an extracting solvent [23]. The extracted solution was dried under reduced pressure at 32–35 °C and the residue was disolved in 2 ml of benzene. Aliquots of the benzene solution (1,000, 500, 250 and 100 μl) were transfered in small test tubes, 2 μl of DMSO was added to each tube, and the

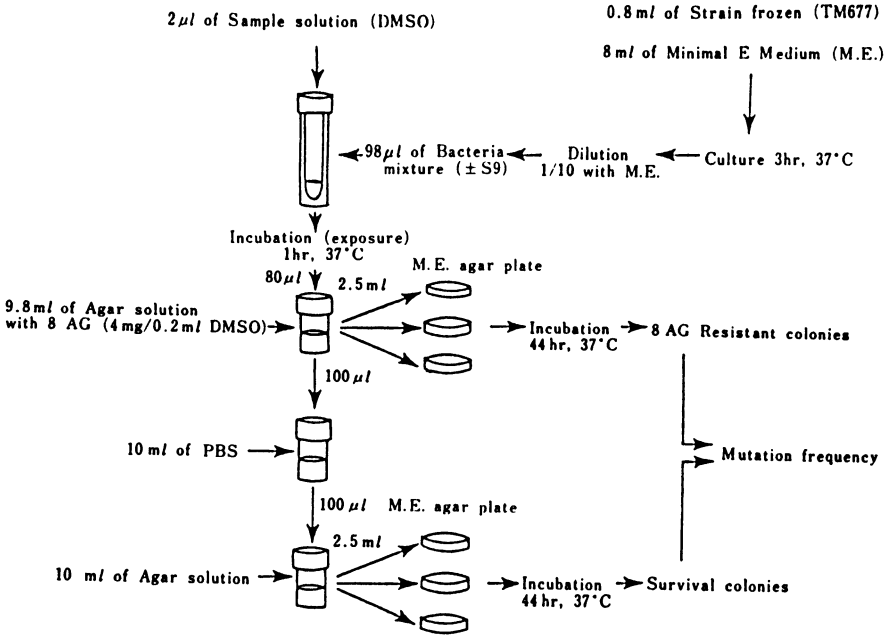

Fig. 1. Scheme of the micro-forward mutation assay

benzene was evaporated under a gentle flow of nitrogen gas at room temperature. Then 98 μl of a solution containing Salmonella typhimurium TM677, which was prepared by the 10 times dilution of the fluid cultured for 3 h at 37°C, with Minimal E medium, was added to the test tubes, and the solutions were preincubated for one hour at 37°C. After that, 80 μl of the incubated solution was added to 10 ml of soft agar containing 4 mg of 8-azaquanine (8-AG), mixed well, and 2.5 ml portions of the agar were poured into each of three M.E. agar plates, and spread uniformly. The plates were incubated for 44 h at 37°C, and the number of 8-AG resistant colonies induced was counted.

On the other hand, survival colonies were measured by the following procedures. 100 μl of the remaining soft agar was diluted 10,000 times in two steps, and 2.5 ml portions of the diluent were poured into each of three M.E. agar plates, and spread uniformly. The plates were incubated for 44 h at 37°C and the number of survival colonies were counted. The mutation frequency was calculated from the number of 8-AG resistant colonies and the number of survival colonies.

Figure 2 shows the dose-response curves for mutagenicity of an airborne particulate extract by the micro-forward mutation assay described above. The extract was prepared from outdoor airborne particulates collected by a high volume sampler. Figure 2 also shows the results of analysis using the Ames method with Salmonella typhimurium TA98 and TA100 with and without S9 mix. This figure demonstrates clearly that the micro-forward mutation assay has a far higher sensitivity than the Ames method. Furthermore, the forward mutation assay needs only one tester strain of Salmonella typhimurium TM677, whereas the Ames method needs several kinds of tester strains in the mutagenicity assay of chemicals, airborne particulates and so on. It was estimated

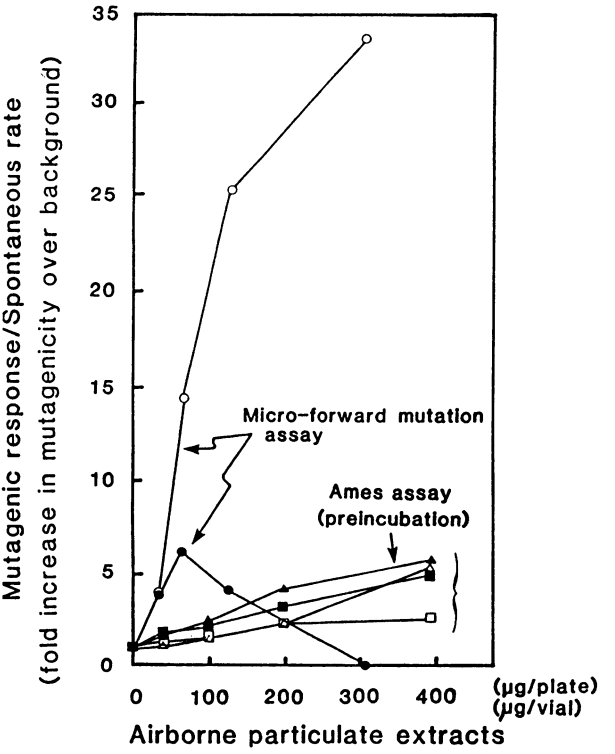

Fig. 2. Comparison of mutagenic responses for airborne particulate extracts by the micro-forward mutation assay and the Ames Method.
Micro-forward mutation assay
○: +S9 mix ●: −S9 mix
Ames method
(Pre-incubation assay)
□: +S9 mix
■: −S9 mix for TA100
△: +S9 mix
▲: −S9 mix for TA98

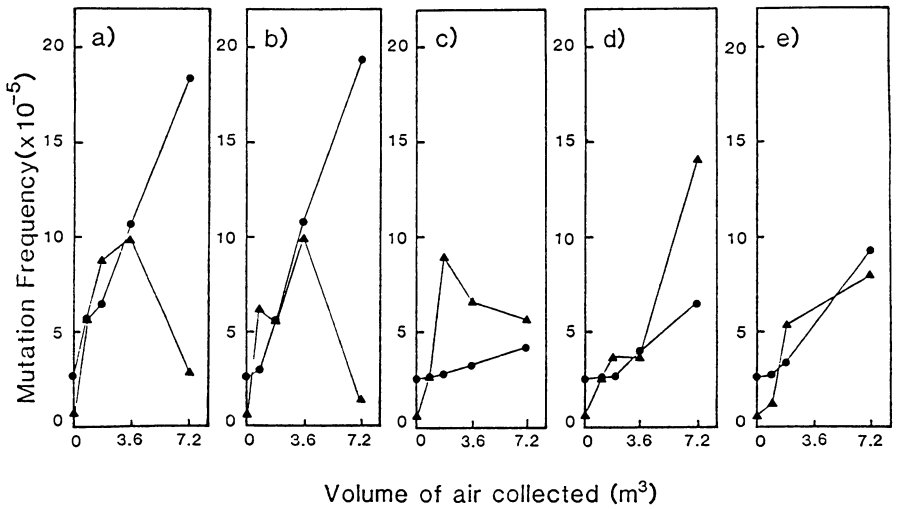

Fig. 3a–e. Dose-mutagenic frequency relationship for indoor and outdoor airborne particulate extracts. a–d: Indoor samples from the room with a smoking, b smoking and boiling water on a portable gas stove, c non-smoking and d non-smoking and handling a gas burner. e Outdoor sample. ●: +S9 mix ▲: −S9 mix

from these facts that the effective sensitivity of the micro-forward mutation assay was 10 to 20 times higher than the Ames method. Relative standard deviation of the mutagenic activity of airborne particulate extracts in the micro-forward mutation assay was less than 12%, showing that the repeatability of this assay was equivalent to that of Ames method.

Figure 3 shows an example of a dose-mutagenic frequency relationship for indoor and outdoor airborne particulate extracts. All airborne particulates were collected by the low noise samplers at a flow rate of 20 l/min for 24 h on the same day in our Institute (air sampling volume: 28.8 m^3). It can be seen from Fig. 3 that the air in a smoking room is apparently more mutagenic than the air in a non-smoking room. The mutagenicity of the air in a non-smoking room where no gas burner is used shows the same pattern as the mutagenicity of outdoor air.

Airborne particulates in a smoking room were collected by the size-dependent sampler at a flow rate of 20 l/min for 3 days, and the mutagenic activity of the extracts from the particulates collected in each stage has been measured by the micro-forward mutation assay. Table 1 shows the results. Mutation frequency per cubic meter of air was 34×10^{-5} under the test condition with S9 mix, and 51×10^{-5} under the test condition without S9 mix. Mutagenic activity of the particulates of 5.7 μm or less accounted for 91% of the total activity under the test condition with S9 mix, and for 94% of the total activity under the condition without S9 mix. Particulates of 1.25 μm or less in particle diameter have a fairly high-deposition rate into the deep part of the lung. Mutagenic activity of these fine particulates accounted for 76% and 83% of the total mutagenic activity in the test conditions with and without S9 mix, respectively. These results demonstrate clearly that the majority of mutagens in indoor particulates are in the small particulates that have a high lung deposition rate.

Table 1 shows also the mutation frequency per μg of particulates. The values were generally high in the particulates less than 1 μm in size. This was remarkable for the

Table 1. Particle size dependency of specific mutagenic activity of airborne particulate indoors

Particle size (μm)*	Particle concentration (μg/m^3, air)	Mutation frequency ($\times 10^{-5}$) per m^3, air		Mutation frequency ($\times 10^{-5}$) per particle amount (μg)	
		+S9 mix	−S9 mix	+S9 mix	−S9 mix
> 12.1	8.0	1.7	1.1	0.21	0.14
8.5	8.3	1.4	2.1	0.17	0.25
5.7	8.0	2.5	4.3	0.31	0.54
3.9	7.2	0.6	0.8	0.08	0.11
2.5	6.4	2.1	0.6	0.33	0.09
1.25	9.1	2.0	5.3	0.22	0.58
0.76	11.0	2.8	5.5	0.25	0.50
0.52	19.0	6.9	9.0	0.36	0.47
0.33	7.8	4.4	12.5	0.56	1.60
0.22	6.7	1.5	2.5	0.22	0.37
0.13	3.1	1.1	1.1	0.35	0.35
< 0.13	4.6	7.4	6.2	1.61	1.35

*50% Cut off size.

Table 2. Detection wavelengths and detection limits for PAH and their recoveries from airborne particulates

Compounds	Detector wavelengths (nm)		Detection limit (ng)*	Recovery from airborne particulates	
	Excitation	Fluorescence		Recovery (%)**	C.V. (%)***
Fluoranthene	360	463	0.04	103	4.9
Pyrene	340	395	0.05	102	3.9
Chrysene	272	364	0.04	101	4.0
Benzo(e)pyrene	335	379	0.2	107	3.7
Perylene	413	474	0.008	103	2.9
Benzo(k)fluoranthene	370	406	0.03	102	5.9
Benzo(a)pyrene	370	406	0.01	99.2	5.0
Benzo(ghi)perylene	385	419	0.05	103	3.9
Indeno(1,2,3-cd)pyrene	388	508	0.1	102	2.0
Coronene	305	428	0.06	100	5.0

*S/N = 2; **Average of 10 runs; ***C.V.: Coefficient of variation.

mutagenicity obtained in the test condition without S9 mix. These results suggest that small particulates that have a high lung deposition rate are more mutagenic than large particulates in the indoor environment.

Development of Highly Sensitive Chemical Analyses and Their Application to Indoor Pollution Survey

A large part of carcinogens and mutagens are contained in the neutral fraction of the extract from airborne particulates [11, 17, 18]. Major carcinogens and mutagens in the neutral fraction are polynuclear aromatic hydrocarbons (PAH) and nitroarenes [20, 24–28]. We have developed several analytical methods for these compounds.

The first one is the major PAH analysis which can analyze easily about 10 PAH indoors [29]. This method consists of the following procedures; collection of indoor particulates by a low noise sampler, ultrasonic extraction of PAH using benzene-ethanol (3:1, v/v) as an extracting solvent, liquid-liquid partition between the extract solution and 5% sodium hydroxide aqueous solution, and separation analysis of PAH by a high performance liquid chromatography (HPLC) with spectrofluorometric detection. HPLC was carried out in the following conditions: Column; ODS column (Number of theoretical plates for benzo(a)pyrene: 8700), Mobile phase; acetonitrile-water (65:35 (v/v) for the first 10 min, 65:35–90:10 (v/v) for the 2nd 10 min, and 90:10 (v/v) for the last 10 min), Column temperature; 30°C, Flow rate of mobile phase; 1.0 ml, Detector; spectrofluorometer.

Table 2 shows the spectrofluorometric conditions for detecting the 10 PAH and their detection limits in this method. Among these PAH, chrysene, benzo(k)fluoranthene, benzo(a)pyrene and indeno(1, 2, 3-cd)pyrene are carcinogenic, and fluoranthene, pyrene, benzo(e)pyrene and benzo(ghi)perylene are cocarcinogenic in experimental animals. The detection limits indicate that even a trace amount of PAH can be detected easily. Table 2

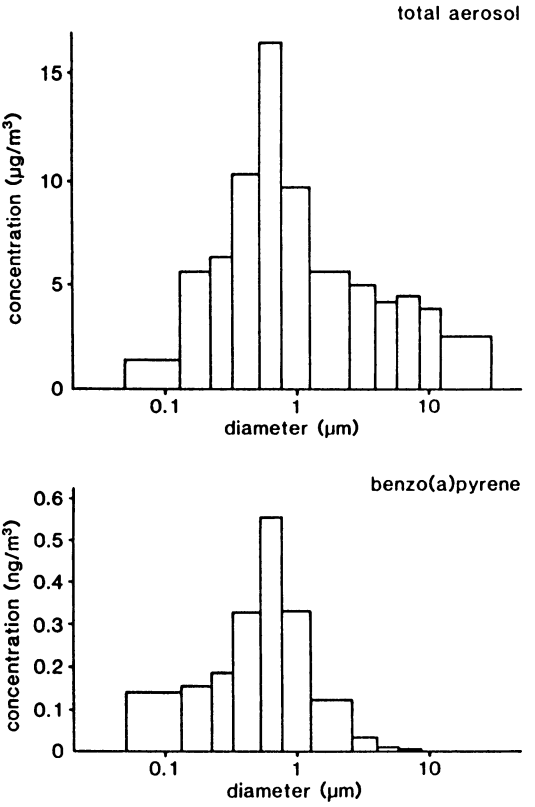

Fig. 4. Size distribution of airborne particulates (total aerosol) and benzo(a)pyrene (BaP) concentrations in indoor air

also shows recovery of PAH from airborne particulates in this method. The recovery for the 10 PAH ranged from 99.2 to 107% and the coefficient of variation from 2.0 to 5.9%. These results indicate clearly that this method is useful for the PAH analysis indoors.

This method was applied to the measurement of particle size distribution of PAH indoors. Figure 4 shows the distribution pattens for particulates and benzo(a)pyrene. Almost all of the benzo(a)pyrene is located in the particulates less than 1 μm in size, in contrast with the distribution of particulates as shown in Fig. 4. The distribution patterns for the other PAH were nearly the same as that for benzo(a)pyrene. This result shows that carcinogenic and mutagenic PAH indoors are present in the small particulates which have a high deposition rate into the deep parts of the lung.

The second method developed is for nitroarene analysis. This method consists of collection of particulates by a low noise sampler, ultrasonic extraction, separation of the neutral fraction by liquid-liquid partitions, isolation of the nitroarene fraction by a normal phase HPLC, chemical reduction of the nitroarenes to corresponding aminoarenes by sodium hydrosulfide, and separation analysis by reverse phase HPLC/fluorometry [30]. By this method, 6 carcinogenic nitroarenes can be analyzed with the following detection limits; 1 pg for 1,6-dinitropyrene, 2 pg for 1-nitropyrene, 1,3- and 1,8-dinitropyrenes, respectively, 4 pg for 2-nitrofluorene, and 40 pg for 3-nitrofluoranthene.

Table 3 shows concentration of some of the PAH and nitroarenes in smoking and non-smoking rooms. Sampling was carried out in 4 different days with low noise samplers at a

Table 3. Concentration of PAH and nitroarenes in non-smoking and smoking rooms

Compound	Concentration in indoor air ($\mu g/m^3$)						
	1	2	3	4	Min.	Max.	Average
(1) Non-smoking room							
1-Nitropyrene	0.069	0.006	0.094	0.111	0.006	0.111	0.070
1-Nitrofluorene	0.011	0.005	0.007	0.004	0.004	0.011	0.007
Benzo(k)fluoranthene	0.91	0.55	0.56	1.88	0.55	1.88	0.98
Benzo(a)pyrene	1.47	1.07	1.33	4.35	1.07	4.35	2.06
Benzo(ghi)perylene	2.42	1.36	1.51	4.89	1.36	4.89	2.55
Airborne particulates*	31.3	26.6	35.6	46.9	26.6	46.9	35.1
(2) Smoking room							
1-Nitropyrene	0.106	0.215	0.238	0.124	0.106	0.238	0.171
2-Nitrofluorene	0.020	0.032	0.029	0.023	0.020	0.032	0.026
Benzo(k)fluoranthene	1.29	3.36	0.87	2.24	0.87	3.36	1.96
Benzo(a)pyrene	2.82	7.41	2.59	4.99	2.59	7.41	4.45
Benzo(ghi)perylene	3.34	7.90	2.22	5.17	2.22	7.90	4.66
Airborne particulates*	92.6	202	105	99.5	92.6	202	125

* unit = $\mu g/m^3$

Sampling of airborne particulates was carried out with low noise samplers at a flow rate of 20 l/min for 24 h in each 4 different days.

flow rate of 20 l/min, respectively. It can be seen from this Table that concentrations of particulates, PAH and nitroarenes in smoking room were 3.5 times, ca. 2 and ca. 3 times higher than those in non-smoking room, respectively.

Measurement of the personal exposure level to carcinogens and mutagens is important in the study of health effects from air pollution. However, determination of carcinogens and mutagens in particulates collected by a personal sampler was extremely difficult, because the amounts of particulates collected by a personal sampler is as low as several tens μg, even if the sampler is operated for 24 h. Thus, no report has been published on the personal exposure levels of carcinogens and mutagens as far as we know.

We developed a highly sensitive method for analyzing three kinds of PAH in particulates collected by a personal sampler [31]. This method consists of the following procedures; ultrasonic extraction, liquid-liquid partition between the benzene-ethanol (3:1, v/v) extract solution and 5 percent sodium hydroxide solution, drying the benzene layer fraction by gentle flushing with nitrogen gas at room temperature, disolution of the residue into 1 ml of acetonitrile, and separation analysis by a precolumn condensation/HPLC/fluorometry. This separation technique permits the introduction of several hundreds of μl of a sample solution, and thus increases the actual analytical sensitivity about 100 times as compared with a conventional HPLC. PAH that can be analyzed by this method are benzo(a)pyrene, benzo(k)fluoranthene and benzo(ghi)perylene.

Figure 5 shows a block diagram of the device used for the separation analysis. The sample solution is introduced into the sample loop D (see Fig. 5), and then the PAH in it are transferred to the concentration column F for condensation. This condensation is done by flowing acetonitrile-water (48:52, v/v) through the column for 5 min. The

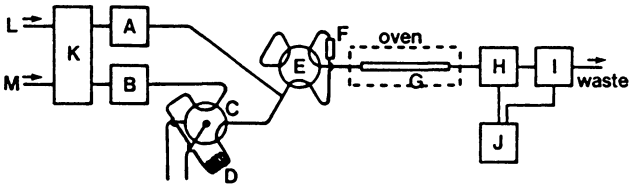

Fig. 5. Schematic diagram of the column concentration-HPLC system. *A, B:* HPLC pump, *C:* injection valve, *D:* Sample loop (0.5 ml), *E:* 6-way valve, *F:* concentration column (4.6 mm i.d. × 30 mm, ODS), *G:* separation column (4.6 mm i.d. × 250 mm, ODS), *H:* spectrofluorometer, *I:* UV monitor, *J:* chart recorder, *K:* degasser, *L:* water, *M:* acetonitrile:water (8:2, v/v)

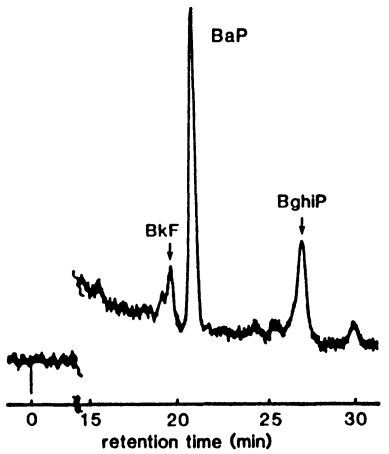

Fig. 6. HPLC chromatogram of PAH in airborne particulates collected by a personal sampler. Sampling: 200 ml/min × 24 h

composition of the mobile phase is prepared by mixing water from pump A with acetonitrile-water (8:2, v/v) from pump B in the ratio of 4:6, respectively, immediately before the inlet of the column. After the condensation procedure is finished, pump A is stopped, and the valve E is turned in order to transfer the PAH from the column F to the column G for separation analysis.

Figure 6 illustrates a HPLC chromatogram of PAH of the extract from particulates collected by a personal sampler. Particulate samples were collected at a flow rate of 0.2 l/min for 24 hours. In this case, samples corresponding to 50 l of air were introduced into the HPLC. It can be seen from this Figure that three PAH in the personal particulate samples can be easily analyzed quantitatively by this method. The repeatability of the retention time and peak height in this method proved to be fairly good. For example, the coefficient of variation for peak height was 1.8% for benzo(a)pyrene, 2.5% for benzo(k)fluoranthene and 2.7% for benzo(ghi)perylene.

We are now surveying the personal exposure level to these PAH by the method described above. Figure 7 presents the daily variation of the exposure level to benzo(a)pyrene for four volunteers. Volunteer A and B were smokers, and C and D were non-smokers. Exposure levels to benzo(a)pyrene were generally higher in smokers than non-smokers. Furthermore, the levels changed day by day and generally decreased on holiday. The same variation pattern was seen for benzo(k)fluoranthene and benzo(ghi)-perylene.

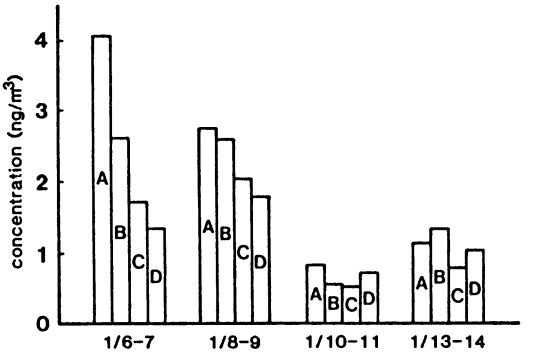

Fig. 7. Personal exposure level to benzo(a)pyrene. A and B: smoker, C and D: non-smoker. Sampling was done January 6–14, 1987. Each sampling time was 24 h (January/10–11 was a holiday)

The methods described here are effective for the measurement of mutagenicity, PAH and nitroarenes in airborne particulates indoors as well as the measurement of personal exposure levels to some PAH. Application of these methods to our living environment will produce many kinds of useful information for the evaluation of air quality indoors and also for the study on the health effects of environmental carcinogens and mutagens.

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Health Effects of 50 Selected Constituents of Environmental Tobacco Smoke

D. M. Aviado

Summary

Recent monographs from IARC, NAS-NRC, and USPHS Surgeon General include a common list of 27 particulates and 23 vapors allegedly responsible for health effects of environmental tobacco smoke (ETS). More than half of listed constituents have workplace standards. It takes from less than one to eight cigarettes for total sidestream emission (in an enclosed unventilated space of 10 m^3) to exceed threshold limit values (TLV) for nicotine, acrolein, formaldehyde, carbon monoxide, and ammonia. For each of 21 constituents, 50 to 29,600 cigarettes would have to be consumed in 10 m^3 to exceed respective TLVs. In all, 11 ETS constituents are suspected tumorigens based entirely on oral, dermal, subcutaneous, and/or tracheal injection in experimental animals. There are six ETS constituents that are in vitro mutagens and seven constituents with no known mutagenicity. The sidestream emission for each constituent is so low that any health consequence is inconceivable. In summary, there are no published animal experiments or human studies indicating that repeated exposure to any one of 50 ETS selected constituents can cause pulmonary tumors.

Introduction

During the past year, biomedical literature on environmental tobacco smoke has been reviewed by three agencies, namely, the Office of the United States Surgeon General, USPHS, [1], the National Academy of Sciences – National Research Council, NAS-NRC [2], and the International Agency for Research on Cancer, IARC [3]. For the first time, the three supposedly independent groups have agreed on a selection of fifty biologically active constituents in environmental tobacco smoke (ETS). The selection was derived from over 150 constituents of sidestream smoke (SSS) analyzed chemically by Elliott and Rowe [4], Hoffmann et al. [5], Klus and Kuhn [6], Schmeltz et al. [7] and Sakuma et al. [8–10]. In reality, only 14 of the 50 selected constituents of cigarette smoke have been detected in environmental tobacco smoke. The other constituents have not been examined because of technical difficulties in analyzing microgram (10 to minus 6) and nanogram (10 to minus 9) concentrations. The 50 constituents comprise 1.3% of over 38,000 chemical substances identified in mainstream smoke (MSS). According to Duke and Green [11], the detection of 3,800+ constituents of cigarette smoke is largely due to recent refinements in collection, separation and analysis introduced by tobacco chemists. Whereas in 1964, there were only 500+ known smoke constituents and 16+ biologically active constituents [12], in 1987 there are 3,800+ MSS constituents, including 50 that are biologically active. This presentation focuses on these 50 constituents highlighted in recent monographs released by USPHS, NAS-NRC and IARC.

H. Kasuga (Ed.) Indoor Air Quality

Table 1. Carbon monoxide (CAS 630-08-0)

Environmental Tobacco Smoke (ETS)	
Experimental chambers and semi-ventilated rooms	45.0–38.0 ppm
Offices and conference rooms	32.5– 2.5 ppm
Restaurants, bars, taverns and night clubs	30.0– 0.5 ppm
Work places	29.4– 2.8 ppm
Moving vehicles	30.0– 2.0 ppm
Treshold Limit Value (TLV)	50 ppm
	55 mg/cubic m
	550 mg/10 cubic m
Main-Stream Smoke (MSS)	23–10 mg
Side-Stream Smoke (SSS)	108–25 mg
Ratio SSS/MSS	4.7– 2.5
Calculation of maximal cigarette equivalent:	
550 mg divided by 108 = 5 cigarettes in 10 cubic meters	

Threshold Limit Value

The most widely used estimate of air quality in the workplace is the Threshold Limit Value (TLV). The TLV is determined by toxicologists, epidemiologists, and hygienists for the American Conference of Governmental Industrial Hygienists [13]. The recommended concentration of a substance, expressed in mg/cubic meter, or in parts per million (ppm), is the maximal level that should not be exceeded to prevent occupational disease. The TLV is arrived at by interpretation of the literature relating to human exposure level, human accidental deaths, if any, and animal lethality; lowest toxic concentration and highest nontoxic concentration derived from case reports and animal experiments; absorption, excretion and kinetics; toxic effects on skin, mucosa, muscles, nervous system, liver, kidneys, blood, reproductive organs, heart and lungs; and experimental induction of neoplasm.

Carbon monoxide is the most widely investigated constituent of environmental tobacco smoke (Table 1). The reported concentrations in public places rarely exceed the TLV of 50 ppm [14]. An essential step in the following discussion of biologically active constituents of cigarette smoke is calculation of "cigarette equivalent" defined as the number of cigarettes generating sidestream smoke (SSS) collected in a sealed enclosure of 10 cubic meters. For carbon monoxide, the maximal amount of SSS is 108 mg which is more than 4 times higher than MSS, representing the SSS/MSS ratio of 4.7. The TLV is defined as the safe level not to be exceeded to prevent occupational disease. For carbon monoxide, the TLV of 50 ppm is equivalent to 55 mg/cubic meter, or 550 mg/10 cubic meters. The TLV of 550 mg is divided by 108 mg SSS, which equals 5 cigarettes consumed in 10 cubic meters. In other words, it takes ignition of 5 cigarettes to maintain the TLV for carbon monoxide in a sealed enclosure of 10 cubic meters.

Milligram, Microgram, and Nanogram Quantities

The fifty selected cigarette smoke constituents that are biologically active (1–3) are listed in Table 2. Half of the chemicals are noted as "V" in the first column to mean vapors and gases, such as line 1V (carbon dioxide) and Line 2V (carbon monoxide); the remaining

Table 2. Fifty selected ETS constituents

Line	CAS	Chemical name	SSS mg	MSS mg	SSS/MSS
1V	124–38–9	Carbon dioxide	440–16	40–20	11.0–8.0
2V	630–08–0	Carbon monoxide	108–25	23–10	4.7–2.5
3P		Particulates	76–20	40–15	1.9–1.3
4V	7664–41–7	Ammonia	22–10	1.3–0.5	170–40
5P	54–11–5	Nicotine	8.2–2.6	2.5–1.0	3.3–2.6
6V	108–88–3	Toluene	8.0–0.6	0.2–0.1	8.3–5.6
7V	10024–97–2	Nitrogen oxide	6.0–0.4	0.6–0.1	10.0–4.0
8V	50–00–0	Formaldehyde	5.0–0.7	0.10–0.07	50.0–0.1
9V	64–19–7	Acetic acid	2.9–06	0.81–0.33	3.6–1.9
10V	74–87–3	Methyl chloride	1.98–0.25	0.60–015	3.3–1.7
11V	107–02–8	Acrolein	1.50–0.48	0.10–0.06	15.0–8.0
12V	67–64–1	Acetone	1.25–0.20	0.25–0.10	5.0–2.0
13V	1121–55–7	3-Vinylpyridine	1.20–0.22	0.03–0.01	40.0–20
14V	110–86–1	Pyridine	0.80–0.10	0.04–0.02	20.0–6.5
15V	64–18–6	Formic acid	0.78–0.29	0.49–0.21	1.6–1.4
16V	71–43–2	Benzene	0.48–0.12	0.05–0.01	10.0
17V	108–99–6	3-Methylpyridine	0.47–0.04	0.04–0.01	13.0–3.0
18P	108–95–2	Phenol	0.42–0.08	0.14–0.06	3.0–1.6
19V	154–23–4	Catechol	0.32–0.06	0.36–0.10	0.9–0.6
20P	123–31–9	Hydroquinone	0.27–0.08	0.30–0.11	0.9–0.7
21V	74–89–5	Methylamine	0.18–0.05	0.03–0.01	6.4–4.2
22V	74–90–8	Hydrogen cyanide	0.12–0.04	0.50–0.40	0.2–0.1
23P	50–21–5	Lactic acid	0.12–0.03	0.17–0.06	0.7–0.5
24P	79–14–1	Glycolic acid	0.12–0.02	0.13–0.04	0.9–0.6
25P	96–48–0	g-Butyrolactone	0.11–0.04	0.02–0.01	5.0–3.6
26P	110–15–6	Succinic acid	0.09–0.05	0.14–0.11	0.4–0.6
27V	124–40–3	Dimethylamine	0.05–0.03	0.010–0.008	5.1–37
28P	65–85–0	Benzoic acid	0.027–0.051	0.028–0.014	0.9–0.6
29P	91–22–5	Quinoline	0.022–0.004	0.002–0.0005	11.0–8.0
30P	57–88–5	Cholesterol	0.019	0.022	0.9
31P	62–53–3	Aniline	0.011	0.00036	30.0
32P	581–49–7	Anatabine	0.010–0.0002	0.020–0.002	0.5–0.1
33P	16543–55–8	Nitrosonornicotine	0.009–0.0001	0.003–0.002	3.0–0.5
34P	486–84–0	Harman	0.005–0.0012	0.003–0.0017	1.7–0.7
35V	463–58–1	Carbonyl sulfide	0.005–0.001	0.070–0.018	0.1–0.03
36V	62–75–9	N-Nitrosodimethylamine	0.0040–0.0002	0.00004–0.00001	100.0–20
37P*		NNK	0.0040–0.0001	0.00100–0.00010	4–1
38P	95–53–4	2-Toluidine	0.0030	0.00016	19.0
39P	7440–02–0	Nickel	0.0024–0.00026	0.00008–0.00002	30.0–13
40V	55–18–5	N-Nitrosodiethylamine	0.0010	0.000025	40.0
41V	936–55–2	N-Nitrosopyrrolidine	0.00090–0.00004	0.00003–0.000006	30.0–6
42P	7440–43–9	Cadmium	0.00072	0.00010	7.2
43P	7440–66–6	Zinc	0.00040	0.00006	6.7
44P	56–55–3	Benz[a]anthracene	0.00028–0.00004	0.00007–0.00002	4.0–2
45P	92–67–1	4-Aminobiphenyl	0.00014	0.000005	31.0
46P	50–22–8	Benzo[a]pyrene	0.00014–0.00005	0.00004–0.00002	3.5–2.5
47V	302–01–2	Hydrazine	0.00009	0.00003	3.0
48P	116–54–7	N-Nitrosodiethanolamine	0.00008–0.00002	0.00007–0.00002	1.2–1.0
49P	91–59–8	2-Naphthylamine	0.00005	0.000002	30.0
50P	7440–68–1	Polonium-210	pCi 0.4–0.04	pCi 0.10–0.04	4.0–1

* 3-Pyridyl-3-3-(N-methyl-N-Nitrosoamino)propylketone

substances are labeled as "P", to mean particulates. Line 3P (total particulates) has a per cigarette range from 76 to 20 mg SSS, 40 to 15 mg MSS and SSS/MSS ratio of 1.9 to 1.3. The major component of particulates is in Line 5P (nicotine) ranging per cigarette from 8.2 to 2.6 mg for SSS and 2.5 to 1.0 per cigarette for MSS. Most of the remaining particulate constituents are in microgram quantities (see line 27V for dimethylamine, 50 to 30 microg); polycyclic aromatic amines and metalic constituents are in nanogram amounts (Lines 41V to 50P). Most vapor constituents have SSS higher than MSS emission; thus, SSS/MSS ratios exceed 1 (see highest ratio of 170 for Line 4V, ammonia). However, it should be noted that relatively higher SSS emissions are not directly inhaled by nonsmokers but diluted with air in the enclosure, adsorbed in room furnishings, and discharged in the ventilating system. The tabulated MSS quantities apply to nonfiltered cigarettes and are considerably reduced by incorporation of filters.

Sidestream Constituents with Workplace Standards

More than half of the 50 selected constituents are useful industrial chemicals and have threshold limit values (Table 3). The 26 constituents are arranged in the order of increasing estimated cigarette equivalents, starting with

- nicotine, then
- acrolein,
- formaldehyde,
- carbon monoxide, and
- ammonia.

Their cigarette equivalents are less than 10, i.e., it takes 8 or less cigarettes to approach the corresponding TLV consumed in an enclosed nonventilated space of 10 cubic meters. For (v) hydrazine, (w) aniline, (x) dimethylamine, (y) acetone, and (z) 2-toluidine, the cigarette equivalents exceed 1,000. The situation seems impossible because the amount of oxygen in a 10 cubic meter enclosure will not support combusion of 1,000 or more cigarettes. The most extreme equivalent of 29,600 cigarettes can be dismissed as ridiculous, because 29,600 cigarettes would almost completely fill 10 cubic meters of enclosed space. Therefore, a consideration of TLVs can not support the allegation that any one or more of the fifty selected constituents in ETS can cause smoking-associated diseases in nonsmokers. There is a margin of safety of 10 or more times TLV for an initial biologic effect to appear, and 100 to 1,000 times for poisoning and death. The target organs include mucosal lining, nervous system, lungs, skin, eyes, kidneys, liver and blood.

Sidestream Constituents Without Workplace Standards

The polycyclic aromatic amines, including benz(a)anthracene and benzo(a)pyrene, are formed during the combustion of organic matter and fuels. In animal experiments, repeated oral, dermal, subcutaneous or intratracheal administrations cause tumors (Table 4). However, inhalations of the same tabulated polycyclic amines or polonium, simulating human exposure to SSS or MSS, do not result in pulmonary tumors. A true inhaled carcinogen causes pulmonary lesions in both experimental animals and exposed humans. For example, bischloromethyl ether (BCME) and chloromethyl methyl ether (CMME) are proven inhaled tumorigens because human neoplasms seen in workers can

Table 3. Sidestream constituents with workplace standard

Chemical Name	Initial* Maximum		TLV	Cigarette	Line
	lethal	SSS mg/cig	mg/cum	equivalent	
(a) Nicotine	N/N	8.2	0.5	0.8	5P
(b) Acrolein	M/P	1.5	0.25	1.7	11V
(c) Formaldehyde	M/P**	5.0	1.5	3	8V
(d) Carbon monoxide	B/N	108	55	5	2V
(e) Ammonia	M/P	22	18	8	4V
(f) Nitrogen oxide	M/N	6.0	30	50	7V
(g) Hydroquinone	O/N	0.27	2	74	20P
(h) Acetic acid	M/P	2.9	25	86	9V
(i) Formic acid	M/P	0.78	9	115	15V
(j) Particulates	M/P	76	1,850	138	3P
(k) Pyridine	M/H	0.8	15	188	14V
(l) Carbon dioxide	N/N	440	9,000	204	1V
(m) Nickel	M/P	0.024	0.1	417	39P
(n) Phenol	M/P	0.42	19	452	18P
(o) Toluene	N/B	8.0	375	470	6V
(p) Methyl chloride	M/N	1.98	105	530	10V
(q) Catechol	D/K	0.32	20	617	19V
(r) Benzene	N/B**	10.0	30	625	16V
(s) Methylamine	M/N	0.18	12	672	21V
(t) Cadmium	M/P	0.00072	0.05	700	42P
(u) Hydrogen cyanide	B/N	0.12	11	880	22V
(v) Hydrazine	M/H**	0.00009	0.1	1,040	47V
(w) Aniline	B/B	0.011	8	4,400	31P
(x) Dimethylamine	M/H	0.05	18	6,250	27V
(y) Acetone	M/N	1.25	1,780	14,240	12V
(z) 2-Toluidine	M/B	0.003	9	29,600	38P

* Initial effects/lethal target organs: B = Blood; D = Dermal; H = Hepatic; K = Kidney; M = Mucosal irritation; N = Nerous system; P = Pulmonary

** Suspected tumorigen

be reproduced by inhalation exposure or experimental animals to BCME or CMME [15]. The suspected tumorigens in SSS and MSS administered by inhalation of tobacco smoke do not induce pulmonary neoplasm in experimental animals.

The last group of SSS constituents without workplace standards have been tested for mutagenicity. The results of mutagen testing have been positive for six constituents, and negative for seven others (Table 5). All of them have not been tested by inhalation route, and available biological activity are derived from oral, parenteral injection, or dermatomucosal application in experimental animals.

Conclusions

The consensus selection by the USPHS, NAS-NRS and IARC of fifty constituents in environmental tobacco smoke has been reviewed in terms of potential health effects. It is

Table 4. Sidestream constituents without workplace standards: suspected tumorigens based on oral, dermal or intratracheal administration in experimental animals

Chemical name	Maximum SSS mg	Route	Line
4-Aminobiphenyl	0.00014	oral, subcutaneous	45P
Benz(a)anthracene	0.00028	dermal, subcutaneous	44P
Benzo(a)pyrene	0.00014	oral, dermal, tracheal	46P
2-Naphthylamine	0.00005	oral, subcutaneous	49P
NNK*	0.004	Mutagen	37P
N-Nitrosodimethylamine	0.004	oral, dermal	36V
N-Nitrosodiethylamine	0.001	oral, dermal, tracheal	40V
N-Nitrosodiethanolamine	0.00008	oral, subcutaneous	48P
N-Nitrosopyrrolidine	0.0009	oral	41V
N-Nitrosonornicotine	0.009	oral, subcutaneous	33V
Polonium - 210	pCi 0.4	tracheal	50P

*3-pyridyl-3-(N-methyl-N-Nitrosamino)propylketone.

Table 5. Sidestream constituents without workplace standards: unsuspected tumorigens; some positive genotoxicity

Chemical name	Maximum SSS mg	Genotoxicity	Line
Anatabine	0.010	Negative	32P
Benzoic acid	0.027	Mutagen	28P
g-Butyrolactone	0.11	Negative	25P
Carbonyl sulfide	0.005	Negative	35V
Cholesterol	0.019	Mutagen	30P
Glycolic acid	0.12	Negative	24P
Harman	0.005	Mutagen	34P
Lactic acid	0.12	Mutagen	23P
3-Methylpyridine	0.47	Negative	17V
Quinoline	0.022	Mutagen	29P
Succinic acid	0.09	Mutagen	26P
3-Vinylpyridine	1.20	Negative	13V
Zinc	0.0004	Negative	43P

this reviewer's opinion that the selected constituents do not cause smoking-associated diseases in nonsmokers. The concentrations in sidestream smoke are so low that respective threshold limit values may be exceeded by igniting less than 10 cigarettes in 10 cubic meter enclosure for nicotine, acrolein, formaldehyde, carbon monoxide and ammonia. However, this is unlikely to occur in public places or dwellings. It will take 55 to 29,600 ignited cigarettes in a 10 cubic meter enclosure to exceed the respective TLV for 21 other constituents. The remaining 24 constituents with no recommended work standards have been tested for tumorigenicity and genotoxicity. Polycyclic aromatic amines do not cause pulmonary tumors when administered by inhalational route in experimental animals. Other constituents have not been investigated by inhalation route but instead, by oral, subcutaneous injection, or dermatomucosal application. Finally, it

should be noted that with the exception of carbon dioxide, carbon monoxide, particulates, ammonia and nicotine, the 44 other remaining constituents are present in cigarette smoke in microgram and nanogram quantities. Since the total emission is so small and diluted by environmental air, it is unlikely that any one of the fifty selected constituents can be a health hazard to the nonsmokers. Potentiation between two or more constituents has not been proven or disproven.

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Indoor Air Pollution from Tobacco Smoke as Seen by Scientists in Governmental Administration

C. Hugod

The purpose of the presentation is to describe the professional situation of a scientifically educated person who advises politicians and administrators, i.e., people without a professional background in biological science. Using tobacco smoking/passive smoking as examples, I will try to illustrate the importance of being clearly aware that interests in the scientific world (among scientists) and in the administrative/political world are not necessarily – or are even rarely – identical.

Scientists are searching for answers to questions, knowing that only one or a few questions – if any – are answered with each scientific project. Scientists often conclude that further investigations are needed, which is the same as saying that more money is needed to gain further information. For a scientist it is natural that all scientific results are connected with some or even much uncertainty, and therefore it is important and necessary for the scientist to make use of such results with care and caution.

Politicians and administrators never (or rarely) want to wait for "further investigations." They only rarely have the primary intention of spending more money for scientific investigations. Administrators want – and often mistakingly – scientific results to be unambiguous and indisputable and often pretend they are not. They do not want "noise" of scientific uncertainty connected with political decisions.

This should give an impression of the situation of scientific advisors who are trying to link the realm of scientists with that of politicians/administrators.

For at least 10 years the impact on the health of passive smokers has been discussed in Denmark. As advisors in the field, the Danish National Board of Health on the one hand has felt the obligation of supporting nonsmokers claiming their right not to be involuntarily exposed to tobacco smoke. On the other hand, the National Board of Health has the natural obligation to be aware of the considerable scientific uncertainty implied in literature in this field.

I shall briefly present the scientific basis for the advisory function of the National Board of Health when considering the health hazards of passive smokers.

The following parameters have been taken into account:

1) The amount of carbon monoxide (CO), "TAR," nicotine, and acrolein in tobacco smoke
2) Excretion of mutagens in passive smokers' urine
3) Lung cancer risk for passive smokers

Carbon Monoxide

Although it was once assumed that carbon monoxide (Table 1) is an atherogenic agent, we are now aware that this remains a hypothesis. However, we do know that in patients

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Table 1. Characteristic values of carboxyhemoglobine (COHb) for nonsmokers and passive smokers

Carboxyhemoglobine (COHb)	Normal values:	0.7–0.9%
	Passive smokers:	1.6–2.6%
	Nonsmokers in big cities:	50% > 1.5%

with coronary vascular disease a decrease in physical ability before an angina pectoris attack in some results from exposure to tobacco smoke.

It is indisputable that exposure to acrolein and other irritating agents in tobacco smoke may cause considerable discomfort, although in scientific terms it is still a matter of discussion which constituent(s) is/are most responsible for the annoyance.

At the moment the biochemical effects of nicotine, the probable indirect sympathomimetic effect(s), the problems of addiction and compensation possibly related to nicotine are being discussed in scientific circles, but it is easy to understand that these scientific problems are not suited for discussion with people who do not have a background in biological science. We know that nicotine is excreted in breast milk of passive smokers although no quantitative measures for the excretion or for the health effects on babies are available. Clearly, however, being acquainted with these problems requires us to integrate it into the advice offered by the National Board of Health. We are convinced that with respect to smokers' risk for developing lung cancer, smoking low-tar cigarettes should be preferred to smoking high-tar cigarettes, although we are aware that shifting to low-tar cigarettes does not affect the smokers' risk for developing cardiovascular disease. In Sweden a high court decided that a life insurance should be paid to the relatives of a woman who died from lung cancer, claimed to be due to passive smoking at her workplace.

Epidemiological studies seem to indicate an increased lung cancer risk in passive smokers of up to 30%; on the other hand, it must be kept in mind that in the studies which have been published hitherto a number of methodological problems make the evaluation difficult and imply great uncertainty as to the figures mentioned.

In our opinion, the problems connected with classifying smokers/nonsmokers and present or former smoking habits and describing exposure conditions of nonsmokers should be considerably improved to increase the validity estimating lung cancer risk in passive smokers. So far we consider it justified to bear the prevailing scientific uncertainty in mind when giving advice in this field from the National Board of Health.

In recent years the excretion of mutagenic substances in the urine of smokers and nonsmokers has been investigated. Of course some scientists may hope that this method will help to quantitate the risk of developing cancer in smokers/passive smokers, but so far it should be stressed that this kind of research only gives measures for exposure, not for effect of exposure.

We know for sure that women who smoke are at high risk of giving birth to babies with a relatively low birth weight and a secondary increased risk of early death, babies with a 100% increase in risk for respiratory disease during early childhood, and babies which are more frequently hospitalized during the first year of life. We also know that patients with cardiovascular disease and chronic lung disease, including bronchial asthma, are at special risk when exposed to tobacco smoke.

Based on this we encourage smokers in general to try to give up/reduce the habit of smoking, not embarrass their fellow humans with tobacco smoke, and to identify population groups at special risk; namely, pregnant women (considering the babies' or

embryos' risk), patients with cardiovascular and lung disease (including asthma), and children less than 1 year of age. We also advocate that these special risk groups be protected from exposure to tobacco smoke.

In conclusion, it should be stressed that from the point of view of public health it is important to realize that lack of definite scientific evidence for passive smoking causing lung cancer or other adverse health effects should not keep us from encouraging young people not to start smoking or encouraging adults to give up smoking and to avoid polluting indoor air with tobacco smoke.

Source, Nature, and Symptomology of Indoor Air Pollutants

G. Robertson

Introduction

ACVA Atlantic Inc. specializes in the study of indoor air pollution. Since we established ACVA in 1981, we have pioneered a multi-disciplined approach to the investigation of internal pollution. Investigators include chemists, microbiologists, and air conditioning engineers – three disciplines unused to working as a team. Our client list includes numerous government agencies; multi-national companies in insurance, finance, industry, banking, and property management; colleges, schools, and numerous hospitals. Most of our clients now not only ask us to examine other buildings that they own, but also enter into long term contracts of regular monitoring and preventive maintenance. In fact, as of November 1987, we have now studied the indoor air quality of over 40 million square feet of property.

Indoor Pollutants – The Sources

Virtually everything we use in the interior sheds some particulates and/or gases. When a building is new, some compounds are given off quickly and soon disappear. Others continue "off-gassing" at a slow pace for years. Common office supplies and equipment have been found to release dangerous chemicals – especially duplicators and copiers and we have even found formaldehyde being released from bulk paper stores.

People themselves are a major contributor since each person sheds literally millions of particles, primarily skin scales, per minute. Many of these scales carry microbes but fortunately the vast bulk of these microbes are short lived and harmless.

Clothing, furnishings, draperies, carpets, etc. contribute fibers and other fragments. Cleaning processes, sweeping, vacuuming, dusting, etc. normally remove the larger particles, but often increase the airborne concentrations of the smaller particles.

Cooking, broiling, grilling, gas and oil burning, smoking, coal and wood first also generated vast numbers of airborne particulates, vapors, and gases. If the windows and doors are closed all of these can only accumulate in that internal environment.

Classification of Indoor Pollutants

Perhaps the simplest classification can be shown in Table 1. We have gases and vapors – both organic and inorganic; fibers and dusts which can be subdivided into Total Suspended Particulates (TSP) and Respirable Suspended Particulates (RSP) – the latter being the more important since these are the particulates that can pass through the

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Table 1. Indoor pollutants

Gases – vapors (organic/inorganic)			
Examples:	Methylene Chloride	SO_2	NH_3
Formaldehyde	NO(X)	CO/CO_2	Radon
Fibers			
Asbestos			
Fiberglass: mineral wools			
Textiles/cotton			
Dusts			
Allergens			
Household dust (mites)			
Pollens: Feathers, danders, spores			
Smoke/Fume: Coal, wood, environmental tobacco smoke			
Microbes			
Bacteria			
Fungi			
Viruses			

natural filters of the nose and enter the lungs and finally the microbiological organisms which can be viable or nonviable fragments.

Organic Chemicals

These are arguably the widest range of pollutants with literally thousands of specific types fortunately occurring in very dilute concentrations which are usually expressed as parts per million or per billion. Most of these are presumed to be safe at the very low levels encountered, although some synergism between different organics or some incidences of organics "sensitizing" people to other pollutants cannot be ruled out. Usually the organics are more a problem in the typical home than the office and concentrations in the home are usually higher than the office mainly due to lower air exchange rates.

Perhaps two organics are of particular note, these being formaldehyde and methylene chloride. Formaldehyde has received considerable attention due to its widespread presence in adhesives, glues, urea-formaldehyde insulation, etc. Most of the documented case histories of severe formaldehyde pollution are in homes, especially insulated mobile homes, here the concentration of formaldehyde containing materials per unit area is higher than in typical offices and ventilation rates are lower.

A potentially more serious pollutant is methylene chloride, this compound has been shown to be carcinogenic in rats and mice when inhaled. With sublime ignorance, many of us spray a concentrated form of this material over our heads each morning as a hair spray and its widespread use in spray paints, insecticides, etc. is neatly disguised on the product labels as "chlorinated solvents" or "aromatic hydrocarbons".

Radon Gas

Radon, a decay product of uranium, is present in variable quantities in soils. It moves from the soil by diffusion into the soil's air pockets or into soil water. Then the radon can migrate from the soil air through unvented crawl spaces, building foundation cracks, etc. into the indoor space. Some building aggregates, cinder block, etc. also contain radon and out-gassing from these materials add to the indoor air levels. In other cases radon enters a building via the water supply. Some of this radon is released when there is turbulence of the water such as a running tap. It has been estimated by some researchers that anywhere from 10 to 15% of the average radon we are exposed to comes from such water. However, the general consensus is that the principal source of radon in buildings undoubtedly is the soil gas. Pollution by radon is far more prevalent in homes than in offices, again mainly due to the lower air exchange rates in homes plus the fact that homes have a larger area of exposure to soil relative to building volume and soil leakage area.

Inorganic Oxides

Carbon dioxide is produced by respiration and combustion, oxides of nitrogen and sulphur are combustion products associated with gas stoves, wood, coal fires, and kerosene heaters. Carbon monoxide is emitted from unvented kerosene heaters or wood stoves and it frequently diffuses into buildings from automobile exhaust fumes generated in adjacent garages. Small to trace quantities of each of these gases and other organics are present in cigarette smoke.

Ozone is another gas that is generated, usually in very small quantities, by miscellaneous copying machines and by certain electrostatic precipitators that are used to clean up the air. In one specific case that we studied, the maintenance staff of a building switched off the main air supply fans over the weekend, but omitted to switch off the central electrostatic precipitators. Thus, ozone accumulated inside the air handlers and was subsequently delivered to the staff first thing each Monday morning. When the fans were switched on this carried a severe, though temporary, period of discomfort to the people working in the areas involved.

Fibers

Asbestos

Prior to 1973, asbestos was the material of choice for fire-proofing, thermal insulation, and sound insulation. It was used as a spray-on insulation of ceilings and steel girders; as a thermal insulation of boilers, pipes, ducts, air conditioning units, etc.; as an abrasion resistant filler in floor tiles, vinyl sheet floor coverings, roofing, and siding shingles; as a flexible, though resistant, joining compound and filler of textured paints and gaskets; as a bulking material with the best wear characteristics for automobile brake shoes, and in countless domestic appliances such as toasters, broilers, dishwashers, refrigerators, ovens, clothes, dryers, electric blankets, hair dryers, etc.

The fact is that many asbestos bearing materials or products are of no health risk whatsoever when used in the normal course of events. However, if for any reason of wear, abrasion, friability, water damage, etc., any of the asbestos fibers are released into the air

and inhaled into people's lungs, there is a health hazard. The scientific evaluation of all available human data provides no evidence for a "safe" level of airborne asbestos exposure, thus any quantity should be considered potentially dangerous.

Glass Fibers

The glass fiber (usually referred to as fiberglass) industry is in its infancy compared with asbestos and since asbestos related illnesses only manifest themselves tens of years after exposure, there are some schools of thought that suggest glass fiber fragments will also accumulate in the lungs and cause later problems. This may be so, but it is unlikely to be anywhere near as severe. The fibers of glass are not shed in such large quantities as asbestos and most of the resins, etc. bonding the fibers together apear to be extremely effective and long lasting. However, some fragmentation does occur and this is especially noticeable when the loose fiberglass insulation, popularly used in attics and ceiling voids, is disturbed. Most of us have experienced itching of contact with fiberglass and dermatitis-type reactions are not infrequent due to airborne fiberglass particles.

Microbes

In our reviews of the literature, the one area of indoor pollution that has received least study or research has been contamination due to microbes. Nine percent of the first 125 major buildings studied by ACVA have exhibited high levels of potentially pathogenic or allergy causing bacteria, including Actinomyces and Flavobacterium species. In addition, Legionella pneumophila, the cause of the dreaded Legionnaires' disease has frequently been isolated from inside air conditioning systems.

Perhaps more significantly, we have found over twenty-eight different species of fungus contaminating air handling systems (see Table 2).

Of the 223 buildings studied by ACVA between 1981 and 1987, thirty-four percent have been found to contain high levels of potentially pathogenic or allergy causing fungi, including Alternaria, Aspergillus, Cladosporium, Fusarium and Penicillium species. In many buildings with excessive staff complaints, either Aspergillus and/or Cladosporium species of fungus were found growing to excess in the air conditioning ductwork systems. In some investigations, epidemiological tests run by various doctors have confirmed severe allergic reactions to the spores of these fungi in all affected staff. Subsequent

Table 2. Fungi isolated from air conditioning systems by ACVA systems 1981 to 1987

Alternaria sp.	Aspergillus sp.	Aureobasidium sp.
Candida sp.	Cephalosporium sp.	Chaetomium sp.
Chrysosporium sp.	Cladosporium sp.	Curvularia sp.
Diplosporium sp.	Fusarium sp.	Helminthosporium sp.
Monilia sitophila	Monosporium sp.	Mucor sp.
Mycelia sterila	Oospora sp.	Paecilomyces sp.
Penicillium sp.	Phoma sp.	Rhizopus sp.
Rhodotorula sp.	Saccharomyces sp.	Scopulariopsis sp.
Streptomyces sp.	Tricothecium sp.	Verticillium sp.
Yeasts		

cleaning and removal of the sources of these fungal contaminants have resuted in a complete abatement of complaints.

Dirt in Ductwork

HVAC systems also have been found to be poorly designed and negligently maintained. Excessive dirt accumulations are common in ductwork, even in hospitals. Frequently dirt is built into the systems during construction since the ducts are installed long before the windows, etc. and construction dusts from the site, plus wood shavings, lunch packets, coke and beer cans, etc. find themselves brushed into the vents then "out of sight – out of mind." Thereafter over the life of the building, more dirt enters with the supply and return air. Good filters reduce the rate of this accumulation, but the only perfect filter would be a brick wall. All filters, even the ultra-efficient HEPA filters used in hospital operating rooms allow fine particles through. Many of these fine particles coalesce, sticking to each other by adhesion or electrostatic attraction and larger particles simply grow with time. In commercial buildings, much cheaper and far less efficient filters are common. Many will stop birds and moths, but that is about all. Occasionally we find that the filters have been omitted and very frequently we find they are undersize, resulting in large air gaps that allow massive volumes of air bypass to occur. Then, there are the large electrostatic precipitators that theoretically provide ultra-efficient air. In one major building we found 16 out of their 18 precipitators were inoperative due to broken parts, many had not worked for over a year. In a major hospital, we found the power pack was missing from one of these units. When inoperative electrostatic precipitators provide zero filtration.

Dirty ductwork is a perfect breeding ground for germs. It provides an enclosed space, constant temperature, humidity, and food – which is the dirt. No germ could wish for more!

The extent of this potential problem is huge and it is very surprising what we have found in ducts. Dead insects, molds, fungi, dead birds and rodents are common. In 1984 we found two dead snakes in air supply ducts. We have also found rotting food, builder rubble, rags, and newspapers. All of these contaminate the air we breathe. It is the dirt that encourages germs to breed – germs which cause infections.

The dirt and dusts also may be allergenic, in fact most of the dusts are, by definition, household dusts which are notorious for causing allergies in many people.

In a recent survey of a 750,000 square foot hospital in Virginia, we found 14 miles of ductwork. Here are a few examples of the problems we encountered in that maze of ducts. Smoke detectors blocked by dirt and inoperative; fire dampers jammed open by dirt – they were unable to close; reheat coils completely blocked by dirt sealing off the fresh air supply; turning vanes and even the exhaust grilles completely sealed with dirt accumulations – in the operating suite the exhaust fan was still working against these duct blockages causing such immense negative pressure in the ducts that the ducts were bowing inward almost to the point of collapse, huge excesses of bacteria and fungi were present inside the air handling chambers and throughout the ductwork; cross infection rates were high and nurses, doctors, and patients complained about poor air quality. We have since cleaned all the air handlers and the 14 miles of ducts and have overseen the installation of more efficient filter systems. That hospital has been dramatically improved and its air quality is now well above average.

Symptomology of Indoor Air Pollutants

In general, when one hears of a polluted building or a so-called "sick building," one hears familiar symptoms from occupants including eye and nose irritation, fatigue, coughing, rhinitis, nausea, headaches, sore throats, and general respiratory problems. Without doubt, the pollutant most often blamed for these symptoms by the public is environmental tobacco smoke (ETS). However, there are usually confounding variables presented by a number of potential contaminants that precludes a quick analysis establishing a single source of contamination. The main problem being the incredible similarity between symptoms from widely different irritants or even environmental conditions. For example, identical symptoms have been reported for individual exposed for formaldehyde, ammonia, oxides of nitrogen, and ozone. In addition, similar symptoms are reported by those individuals suffering allergic type reactions to numerous dusts and to microbial spores such as Aspergillus. Penicillium, and Cladosporium fungi, among others. Similar symptoms have been reported from exposure to cotton dust and fiberglass fragments and an ever increasing and similar problem is encountered due to low relative humidities. The latter is well known to frequent flyers of airliners where relative humidity levels are frequently as low as 10%, compared to a normal lower comfort level of say 40%.

This similarity of symptoms is usually unappreciated by the public and in part it accounts for a bias against ETS which happens to be the sole visible air pollutant. Furthermore, due to their unreliability, we, as a policy, refuse to rely upon or otherwise use the information generated by subjective building occupant questionnaires. Only upon careful investigation of the entire indoor environment and ventilation system of a building can we draw informed conclusions about the various causes of poor indoor air quality. As a result, we have made it our business to perform precisely such investigations. Despite being the main suspect of the occupants in many of the buildings we have examined, we have determined high levels of environmental tobacco smoke to be the immediate cause of indoor air problems in only four percent of the 223 major buildings investigated by ACVA between 1981 and 1987 (see Table 3). This result has been corroborated. In a similar study of 203 buildings from 1978 to 1983, NIOSH found that only four of the buildings studied (two percent) had indoor air quality problems attributable to high concentrations of ETS (see Table 4). Significantly, in those few cases where high accumulations of ETS have been found, ACVA also has discovered an excess of fungi and bacteria in the HVAC system. These microorganisms usually are found to be the primary causes of the complaints and acute adverse health effects reported by building occupants.

Ventilation and Indoor Pollution

The fact is that the accumulation of many pollutants is itself a symptom of a more serious problem – a problem of inadequate ventilation. Medicine teaches us that treating the symptoms simply does not work, one has to go after the cause of the problem.

In the analysis of the NIOSH studies, approximately 50% of the "sick buildings" were found to be inadequately ventilated. Improper ventilation can sometimes be carried to extremes. The fresh air dampers were closed completely in over 35% of those buildings studied by ACVA (see Table 5). Three years ago we found a building where the "maintenance engineer" had bricked up the fresh air vents to save energy. In Washington State, one NIOSH investigator of a sick building found heavy duty polyethylene sheets

Table 3. ACVA systems experience 1981 to 1987

Total building studies	223
Number of square feet	39,000,000
Estimated number of occupants	225,000
Summary of most significant pollutants found:	
Major Pollutants in Air	*% of Buildings*
Allergenic Fungi	34
Allergenic or pathogenic bacteria	9
Glass fiber particles	7
Tobacco smoke	4
Carbon monoxide (vehicles)	3
Miscellaneous gases	2

Table 4. Completed NIOSH indoor air quality investigations by type of problem (through December 1983)

Problem	*Number*	*Total*
Contamination (inside)	36	17.7
Contamination (outside)	21	10.3
Contamination (building fabric)	7	3.4
Inadequate ventilation	98	48.3
Hypersensitivity pneumonilis	6	3.0
Cigarette smoking	4	2.0
Humidity	9	4.4
Noise/illumination	2	1.0
Scabies	1	0.5
Unknown	19	9.4
Total	203	

Source: Meluis J, Wallingford K, Keenlyside R, Carpenter J (1984) Indoor air quality – the NIOSH experience. Ann Am Conf Gov Ind Hygienists, vol 10, p 4

Table 5. Sick building syndrome – causes

Sample Buildings: 223 totalling 39,000,000 square feet; Period: 1981–1987		
(1) *Poor Ventilation*	No fresh air	35%
	Inadequate fresh air	64%
	Poor distribution of air	46%
(2) *Poor Filtration*	Low filter efficiency	57%
	Poor design	44%
	Poor installation	13%
(3) *Contaminated Systems*	Excessively dirty ductwork	38%
	Condensate trays	63%
	Humidifiers	16%

sealing off the fresh air intakes. It turned out that these had been installed two years earlier to reduce the levels of silica dust being carried into the building from the erupting volcano, Mount St. Helens. There are also numerous incidences of inadequate ventilation due to hidden blockages inside ducts. Using fiber-optic technology, we have found many classical examples of these where turning vanes, dampers, and reheat coils inside ducts have been totally sealed with massive accumulations of dirt, loose insulation, etc.

Perhaps the most serious problem of ventilation is that there is no effective legislation mandating the uniform use of minimum fresh air requirements. If authorities could agree on a specific design code, it would be relatively easy to enforce adherence to such codes during design and construction. However, the major problem at the design/construction phase is that there is no legislative structure, nor is there a practical policing methodology to ensure that the operators of buildings run their ventilation systems according to such designs.

The Effect of Energy Conservation

Some of these examples of inadequate ventilation were due to ignorance or accidents, however, the complex of symptoms that I have mentioned – the "sick building syndrome" – may result primarily from energy conservation efforts to seal buildings and reduce the infiltration/exfiltration of air. Such efforts have reduced the natural infiltration of fresh air that previously existed in many buildings, exacerbating the often undiscovered problem of a poorly designed or maintained HVAC system.

In addition to tightening buildings and sealing windows, building managers have shut down air conditioning systems at night and on weekends in an effort to lower energy costs. When the air conditioning is shut down in humid climates, condensation builds up and settles inside the ductwork. If dirt is present in damp ductwork, spores and microbes can flourish, only to be spread throughout the building once the HVAC system is turned on the next morning. This often results in Monday morning complaints of building odors or building sickness that disappear during the week, only to recur the following Monday morning. To save more energy, automatic temperature controllers are used to cycle fans on and off during the day. Vibrations from the start-up of these fans can cause dirt and microbes trapped inside ductwork to be dislodged and carried into occupied areas.

Another energy conservation effort that may contribute to sick building syndrome is the recirculation of indoor air, at the expense of fresh outdoor air. The 35% of the buildings mentioned above were saving energy by shutting off all the fresh air.

Extremely bad distribution of air throughout the building is common, especially in those systems using multiples of fan coil units mounted throughout the various floors of the building. Local thermostats switch off individual units independently of others and micro-environments are set up. Often it is necessary to ensure that when the heating or cooling is not required, all the fans should be left running to aid circulation throughout the areas concerned.

Variable air volume systems (VAV) using VAV mixing boxes mounted in the ceiling void frequently have louvers opening into the void. When certain temperature conditions are met, the louvers open and return or exhaust air from the void can be induced into the supply air, bypassing the filtration system We have found fiberglass, asbestos, fungi, and ETS to be recycled throughout an office due to this design.

More and more frequently one finds the following design condition, exhaust fans rated at say 70 to 80% of the supply fans. The supply fans are often automatically

throttled back for energy savings, say to 25% of their rated capacity. If the exhaust fan is not adjusted at the same rate the exhaust fan can overpower the supply fan and no fresh air gets into the building. The open fresh air louvers now act as addition exhausts and the whole building runs at negative pressure. When this occurs, unfiltered outside air infiltrates into the building or, worse still, exhaust fumes are sucked up from underground garages.

In addition, as described above, the substitution of low cost, low efficiency filters to reduce pressure drops and save energy seriously reduces the efficiency of building filtration systems, and can lead to serious indoor air quality problems.

Ventilation Costs

Without doubt, the major resistance to increasing ventilation rates has been the cost of such increases. Most companies have incorporated energy management problems and new operating budgets based on saving every energy dollar possible. In fact, the very salaries and bonuses of building engineers or energy managers are dependent on reduced costs. It would be an anathema for them to consider increasing energy usage and cost by increasing ventilation.

However, forward thinking companies should look way beyond the constraints of budgets of the energy managers. Consider the following: the average heating, ventilation, and air conditioning operating costs of a typical 100,000 square foot building in the Washington, D.C. area would be $ 50,000 per annum. A commendable target for energy saving by shaving on ventilation may be say 25% savings, giving a useful $ 12,500 per annum. Of course, many of you present operate buildings many fold larger than 100,000 square feet, so these savings are an attractive goal (see Table 6).

Now, consider the payroll costs for people in that building. Using typical averages, there are 150 square feet of space per employee, therefore each 100,000 square feet would house 667 people. Supposing we paid these staff only $ 15,000 per annum for the salary plus payroll costs, the salary bill (667 × $ 15,000) would be approximately $ 10,000,000 per annum per 100,000 square feet. Thus, each 1% absenteeism cost $ 100,000 per annum (see Table 7). Typical absentee rates run at 3 to 7% and no less than 30 to 50% of all absenteeism is estimated to be due to upper respiratory problems. How many of these are due to dusts, bacteria, fungi, fibers, chemicals, ETS, carbon monoxide, oxides of nitrogen, etc., i.e., how many are due to these internal pollutants.

In short, what does it profit a company to save $ 12,500 in energy savings if that small saving causes potentially hundreds of thousands of dollars in absenteeism, not to

Table 6. Energy conservation

Consider a 100,000 square foot building
Typical total utilities cost ($ 1.25 and $ 1.75/square foot)
Average: $ 1.50/square foot = $ 150,000 per annum
Typical HVAC fraction (25% to 40%)
Average: 33% = $ 50,000 per annum
Thus: All energy conservation steps by reducing ventilation, increasing air recirculation, etc. contribute a fraction of $ 50,000 per 100,000 square foot
Note: a 25% energy savings = $ 12,500 per year

Table 7. Payroll costs

Payroll Costs	Consider 100,000 square feet
	Average staffing = 150 square foot/employee
	$\frac{100{,}000}{150}$ square feet = 667 employees
	Assume average salary and benefits = $ 15,000 per annum 667 × $ 15,000 = $ 10,000,000 per annum
	i.e., each 1% absenteeism cost $ 100,000 per annum
Note on Average	Upper respiratory complaints = 50% of all absenteeism

mention lost worker efficiency. Small wonder that some European countries, including Denmark, West Germany, and Switzerland have introduced legislation mandating that steps must be taken to prevent the buildup of internal pollutants. This country is destined to follow that course either by slow evolution or legislation will be precipitated as a result of court actions brought by individuals or by trade unions making the building owners, architects, designers, and operators responsible for the health and welfare of their staff or tenants.

Health Aspects of Indoor Air Pollution by Organic Matter and Combustion Products

W. Stöber and G. Rosner

Summary

Urban industrial air pollution has been the primary concern of the public health authorities in the industrialized countries for a long time. However, during the last 15 years, industrial ambient air pollution control has been established successfully. In general, outdoor exposures to noxious air pollutants are reasonably close to the ambient air quality standards designed by the public health agencies for warranting health safety for the public. Meanwhile, after establishing low-pollution outdoor conditions, it has been increasingly recognized that indoor air pollution would frequently exceed the safe ambient air quality standards because of additional and poorly controlled sources indoors.

Much of this is due to the uncontemplated introduction of rather volatile or dispersable chemicals as dispensable products. New building construction technology and materials may have added to this. Therefore, enhanced accumulation of household chemicals, volatile construction chemicals, open-fire combustion products, and personal pollution like cigarette smoke make up an indoor pollutants' mixture which could be in excess of the few ambient air quality standards. The variety of chemicals and incomplete combustion products exceed by far the number of pollutants being of concern outdoors.

Since most people spend more than 80% of their time inside buildings, it is important to evaluate the health hazards attributable to typical indoor air pollutants and their combined effects. The paper discusses the occurrence and the healths aspects of the most prominent organic indoor air pollutants like formaldehyde and pentachlorophenol as well as typical organic and inorganic combustion products. Indoor exposures are assessed and the potential health problems are discussed and evaluated.

Introduction

Culminating in the post-World War II period, urban industrial air pollution has been the primary concern of public health authorities in the industrialized countries for a long time all over the world. This is exemplified by the legislation on air pollution between 1955 and 1975 in these countries. Like the British Clean Air Act of 1956, the Japanese Air Pollution Control Act of 1962, the American Clean Air Act of 1963 and the German Law for the Protection against Ambient Pollution in 1974, all of such regulations were aimed at curbing the emission of industrial pollutants and establishing safe and low pollution levels. The preoccupation with ambient industrial pollution was justified in those years, because in many industrialized areas, urban air pollution had reached proportions where the impact on public health could frequently be traced in epidemiological studies giving statistically significant data correlating air pollutants and acute or chronic morbidity.

H. Kasuga (Ed.) Indoor Air Quality

Since then, industrial ambient air pollution control has been established successfully. Today, epidemiological evidence of health effects of air pollutants in the public at large is hard to come by. In general, outdoor exposures to noxious air pollutants are reasonably close to the ambient air quality standards designed by the public health agencies to warrant health safety for the public.

However, under these low-pollution outdoor conditions, it has been increasingly recognized over the last ten years that indoor air pollution would quite frequently exceed the safe ambient air quality standards because of additional and poorly controlled sources indoors. Furthermore, it also was recognized that there are numerous airborne substances indoors which bear no significance as an outdoor pollutant and, thus, have never been considered for an ambient air quality standard, but, nevertheless, may constitute an indoor health hazard.

Much of this is due to the uncontemplated introduction of rather volatile or dispersable chemicals as dispensable products to alleviate household chores or hobby work or "do-it-yourself" home improvements. Also, new building construction technology and materials may have added to that. During recent years, the situation was definitely aggravated when the energy crises of the 1970's triggered efforts to economize on domestic energy consumption by improving heat insulation and reducing air exchange rates. Thus, enhanced accumulation of household chemicals, volatile construction chemicals, open-fire combustion products and personal pollution like cigarette smoke may make up an indoor pollutants' mixture which exceeds by far the number of pollutants being of concern outdoors.

Since most people spend more than 80% of their time inside buildings, it is important to evaluate the health hazards attributable to typical indoor air pollutants and their combined effects.

Typical Indoor Air Pollutants

As long as 100 years ago, the German hygienist Max von Pettenkofer noted that the mere presence of a person in a closed room would change the indoor air by human releases of carbon dioxide, water vapor and traces of odors. However, rather than simply from human perspiration, the significant contributions to indoor air pollution come from those human indoor activities which inherently disperse traces of gases, vapors and liquid or solid particulate matter into the room air. Furthermore, there may be releases from the building itself. Table 1 lists the sources and types of indoor pollutants in addition to urban background air pollution.

The use of certain commercially available materials for either the construction or renovation of a building may lead to the continuous release of substantial amounts of material components which could diminish the hygienic quality of the building as a working place or living quarters. Besides asbestos and radon releases, the continuous dispersion of organic components as used in glues and adhesives or for surface protection, insulation and pest control is of special importance.

Household appliance with open-flame combustion like gas stoves and gas ovens or bath room gas boilers emit a variety of components which are typical for poorly controlled combustion processes. Carbon monoxide as well as oxides of nitrogen and various organic products of incomplete combustion including soot will be generated. In fact, by building a fire in an open fire place, the indoor air quality may deteriorate way below the poor air quality of a bad outdoor smog episode which would cause a public smog alarm.

Table 1. Air pollution in buildings

Pollutant source		Pollutants
I	Urban Background Air	CO_2, CO, SO_2, NO_x, O_3, Pb Hydrocarbons, Particulate Matter
II	Building Materials	
	Bricks, Natural Rock	Radon
	Particle-Boards	Formaldehyde
	Wood	Pentachlorophenol
	Insulating Material	Formaldehyde, Glass-Fibres
	Fire-Proofing Material	Asbestos
	Glues	Organic Solvents
	Paints	Hg. Organic Solvents
III	Appliances and Supplies	
	Heating and Cooking,	CO_2, CO, SO_2, NO, NO_2,
	Fire Place	CO_2, CO, Particulate Matter, Polycyclic Aromatic Hydrocarbons (PAH), Aldehydes
	Water Supply	Organics, Odors
	Gas Supply	Radon
IV	Human Activities	
	Tobacco Smoke	CO_2, CO, HCN, PAH, Organics Odors
	Aerosol-Sprays	Fluorinated Hydrocarbons, Vinyl Chlorides
	Cleaning Materials	Hydrocarbons, NH_3, Inorganics, Odors
	Pest Control	Organochlorine Compounds
	Air Deodorizers	p-Dichlorobenzene

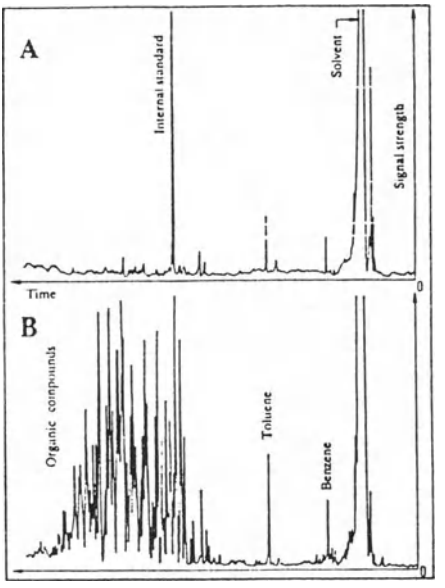

Fig. 1. Gaschromatograms of air samples collected in a conference room A) before, B) $2^1/_2$ h after a meeting in which only 2 out of 11 participants had smoked a total of 10 cigarettes plus one cigarillo. (Adapted from: Seifert 1985)

Table 2. Order of magnitude of indoor/outdoor ratios of concentrations of selected air pollutants. (Adapted from Seifert 1985)

Substance	Indoor/outdoor ratios	Comments
Sulfur dioxide	around 0.5	
Nitrogen dioxide	≤ 1	Without NO_2 indoor source
	2 to 5	With NO_2 indoor source
Carbon monoxide	≤ 1	Without CO indoor source
	1 to 5	With CO indoor source
Carbon dioxide	1 to 5	
Suspended particulate matter	0.5 to 2	Without tobacco smoke
	>2	With tobacco smoke
Radon	2 to 5	Living quarters
	5 to 10	Basement storages
Organic chemicals	$>>1$	Values of 10 to 50 are not common

In general, tobacco smoking in unventilated rooms, when occurring excessively, is one of the most important sources of indoor air pollution. It is not so much the smoke exhaled by the smokers, because they inhale directly only a small fraction of the cigarette smoke. This so-called main stream smoke constitutes only 15 to 25% of the total smoke of a smoldering cigarette, and most of the smoke is released as sidestream smoke which mixes directly with the indoor air. Figure 1 gives an idea of the variety of compounds added to the unventilated indoor air by smokers.

For an assessment of the potential health impact of foreign indoor air components, it is instructive to compare the pollutant levels with common outdoor concentrations. Table 2 gives a typical range of ratios. The numbers show that even the classical outdoor pollutants like carbon monoxide, nitrogen dioxide and respirable dust can easily have excessive indoor concentrations. However, the organic air pollutants are, indeed, the major components which make up the characteristic profile of indoor pollution of many buildings and private homes. In many cases, indoor levels of certain organic compounds exceed the outdoor concentrations more than 10 to 50 times. A few most prominent components and their potential health effects are described below.

Formaldehyde

Formaldehyde rates as an important indoor pollutant. Together with other organic substances, it is released by slow evaporation from urea-formaldehyde foam insulation (UFFI), particle boards, plywood, furniture and fabrics. To a lesser extent, tobacco smoke and open indoor fire contribute to airborne formaldehyde concentration in unventilated rooms. Since modern home construction as well as furniture manufacturing utilizes much foam insulation, particle boards and plywood, a low air-exchange rate in confined spaces can cause relatively high indoor air concentrations of formaldehyde as shown in Table 3. Average indoor concentrations from various surveys are in the range

Table 3. Formaldehyde concentrations in indoor air. (Adapted from Anon 1985)

Sources of emission Type of room	HCHO concentration (mg/m^3)		
Particle boards	0.36–1.1		
new schools			
school class rooms and living rooms	0.6–0.7		
school class rooms and living rooms	0.16–0.7		
prefabricated house	0.18–1.1		
UFFI mean values from 43 houses in Switzerland	0.48 (0.05–2.76)		
homes in Wisconsin, USA	0.24–3.5		
636 UFFI houses (USA)	0.13 (0.01–3.8)		
41 non-UFFI houses (USA)	0.038 (0.01–0.10)		
homes in Washington	<0.1	0.1–1.2	>1.2
430 mobile homes	14%	82%	4%
244 UFFI houses	71%	26%	3%
59 norm. homes	60%	38%	20%
Textiles/carpeting			
Paints/coatings			
storage of textiles	up to 1.6		
parquet floor sealing	0.24–0.48		
Tobacco smoke			
passive smoke (depending on situation)	to over 0.1		

from 0.1 to 1.0 mg/m^3 for prefabricated houses and extend from 0.05 to 0.1 mg/m^3 in conventional buildings (WHO 1985).

By comparison, natural background concentrations are around a few $\mu g/m^3$, and urban air annual averages range between 0.005 and 0.01 mg/m^3 with higher values near industrial sources. Short-term peaks may exceed these values by an order of magnitude.

Formaldehyde, primarily an irritant, can cause eye, nose and throat irritations in residents above 0.12 mg/m^3; sensitive individuals experience sensory irritation of the eyes from 0.06 mg/m^3. Direct skin contact with formaldehyde solutions can cause irritative skin reactions or allergic contact dermatitis, including sensitization. Inhalative exposure to formaldehyde may induce asthmatic response in sensitized individuals. Irritant effects on the airways occur at 2 mg/m^3 and above. Long-term lung effects appear to be possible at concentrations above 5 mg/m^3. Epidemiological studies do not clearly indicate carcinogenicity in humans. Recent animal studies have indicated that exposures of rats and mice to airborne formaldehyde induce nasal cancer. However, the risk of cancer was disproportionately decreased at low concentrations suggesting that only high, i.e. cytotoxic, concentrations of formaldehyde may induce nasal tumor. Thus, exposure of humans to non-cytotoxic concentrations of formaldehyde most probably represent a negligible cancer risk (WHO 1987a).

In order to avoid complaints about indoor air quality in non-industrial buildings, the World Health Organization (WHO 1985) recommends that the formaldehyde concentration should not exceed 0.1 mg/m^3. In the Federal Republic of Germany the guidance value for indoor air is 0.12 mg/m^3 (0.1 ppm) (Anon. 1985). However, one should take into account that for specially sensitive groups no threshold can be defined and that formaldehyde concentrations should, in this case, be kept as low as possible.

Pentachlorophenol

Few pesticides show such a broad efficiency spectrum at low cost as pentachlorophenol (PCP). Thus, PCP and its salts have been used for many years as algicides, bactericides, fungicides, herbicides, insecticides and molluscicides in industry, agriculture and in domestic fields. By far the major application is wood preservation. With the extensive use of wood in home construction and room decoration, PCP had become a significant indoor pollutant.

By 1976, there were first West German reports alleging serious health effects after chronic indoor PCP exposure. Aside from single severe cases of aplastic anemia, leukemia and liver damage, residents complained about relatively unspecific symptoms (headache, vertigo, loss of appetite, fatigue, hair loss, tonsillitis etc.). The complaints were carefully investigated by a Committee of the German Federal Health Office which found it difficult to confirm a causal relationship (Aurand et al. 1981; Krause et al. 1987). However, in view of the fact that the commonly used technical grade PCP product contains dioxins (PCDD/PCDF) as microcontaminants, the Committee could not rule out the possibility that such impurities could be held responsible for the alleged effects. As a precaution, the final recommendation to builders and consumers was to discontinue indoor applications of PCP. As of recent, such applications are now, in fact, prohibited in the Federal Republic of Germany, but past usage causes continued concern.

Indoor pollution levels of PCP vary widely (WHO 1987b). Homes and offices with previous indoor wood PCP treatment may have started with airborne concentrations of 30 $\mu g/m^3$ during the first months after applications and, for many subsequent years later, values between 1 and 25 $\mu g/m^3$ are not uncommon. Under unfavorable conditions, concentrations up to 160 $\mu g/m^3$ were measured. In contrast, in homes with untreated wood, the PCP concentration remains below convenient levels of detection, i.e. below 0.1 $\mu g/m^3$. Due to different evaporation and diffusion characteristics, the concentrations of PCP and PCP-specific dioxins in the indoor air are not correlated. However, indoor air samples have shown to have the same dioxin fingerprints, i.e. the same dioxin isomer composition, as found for the contents of the conserved wood, thus revealing their origin. Tetrachloro-dibenzo-dioxin (TDCC) equivalents of up to 2.5 pg/m^3 have been measured in West German kindergartens and private homes, and significant concentrations of this order of magnitude can persist over an extended period of time even when the concentration of the more volatile PCP had diminished considerably (Rosner 1987).

Health effects of PCP have been observed primarily in occupational settings at levels far in excess of indoor concentrations. But since there are few precise estimates of exposure, dose-response relationships can hardly be established. Chloracne, skin rashes, eye and nose irritations, neurological changes, headaches, nausea, and fatigue have been reported in numerous studies. At least chloracne and some subtle effects involving the liver and the immune system are suspected to relate to the dioxin impurities of the technical grade PCP.

As with many other substances, exposure to technical grade PCP in the home is usually for longer periods of time than exposures in the workplace and can affect subpopulations potentially at greater risk, for example children, the olderly, and those with an existing adverse health condition. Based on an ADI for PCP of 3 $\mu g/kg$ body weight per day (WHO 1987b) and assuming a breathing rate of 20 m^3/d or 5 m^3/d of an adult (70 kg) or a child (10 kg), respectively, tolerable PCP indoor concentrations would require values below 6 to 10 $\mu g/m^3$.

Although indoor PCP application has recently been abandoned or restricted in many countries, the continuous emission of PCP-specific dioxins requires a risk assessment on

Table 4. Major indoor air pollutants in US apartments (overnight personal air concentrations) as compared to outside concentrations. (Adapted from Wallace et al. 1985b)

Organic pollutant	Mean value (90 percentile) $\mu g/m^3$		Indoor/ outdoor ratio
	Indoors	Outdoors	
* 1.1.1-Trichloroethane	17 (78)	4.5 (11)	3.8 (7.1)
* Benzene	16 (54)	7.3 (15)	2.2 (3.6)
m, p-Xylene	14 (47)	9.6 (21)	1.5 (2.4)
Ethylbenzene	6.5 (22)	2.9 (8.3)	2.2 (2.7)
* Tetrachloroethylene	6.4 (26)	2.6 (6.9)	2.5 (3.8)
o-Xylene	5.0 (15)	2.9 (7.9)	1.7 (1.9)
* m, p-Dichlorobenzene	3.8 (82)	1.2 (2.5)	3.2 (33)
* Chloroform	3.4 (17)	0.7 (2.9)	4.9 (5.9)
* Trichloroethylene	2.3 (12)	1.3 (3.9)	1.8 (3.1)
* Styrene	1.8 (4.6)	0.6 (1.7)	3.3 (2.7)
* Carbon tetrachloride	1.5 (5.7)	0.8 (1.9)	1.9 (3.0)

* Mutagenic, carcinogenic or co-carcinogenic properties.

the basis of these congeners. A recent conservative approach proposed that the action level above which curing measures should be considered should be in the range of 0.2 to 0.6 pg/m^3 TCDD equivalents (Rosner 1987). However, it should be noted that the concept of TCDD equivalents as well as the tolerable daily intake level of 1 pg/kg body weight per day presently discussed in risk assessment are only preliminary.

Other Organic Compounds

Besides the organic emissions from pretreated wooden furniture material and wooden structural elements as discussed above, there are numerous other organic substances found indoors which were introduced by the use of modern dispensable products in private homes and offices. Many of these compounds are of little or no significance outdoors. A US-EPS-study (Wallace et al. 1985a) in senior citizen homes led to the identification of some 350 organic gaseous trace components, and 53 of these were found to be common in all living quarters. At least 14 of these substances are considered to be carcinogens, co-carcinogens or mutagens.

A personal sampler study of tenants of 355 apartments in two US cities revealed 11 major components occurring at elevated levels indoors (Table 4), 8 of which are considered to be potentially instrumental in carcinogenesis. Of these, 1.1.1-trichloroethane rates highest and, by average, is 4 times enhanced compared to outdoor concentrations. Similar studies in homes and apartments in Italy (De Bortoli et al. 1985) and the Netherlands (Lebret et al. 1985) indicated somewhat different frequencies of organic compounds and generally higher concentrations as well as higher indoor/ outdoor ratios. Comparing the top 11 components reported in the three studies, the compounds benzene, xylene, dichlorobenzene, toluene, limonen, undecane, trimethylbenzene and n-hexane were listed at least in two studies. Data analyses revealed that the occurrence of n-hexane, toluene, xylene, benzene and others were correlated to smoking

habits of the tenants. However, there were also other indoor sources for these compounds. Toluene, for instance, which was found at rather high concentrations in the European studies (55 and 127 $\mu g/m^3$ is most likely released from interior decorations, shoe polish, furniture varnishes and printing ink of newspapers and magazines. The complexity of the indoor sources does not permit a unique identifications of single sources; however, the occurrence of dichlorobenzene appears to relate primarily to the use of moth crystals, room air deodorizers, and toilet bowl deodorizers. Similarly, elevated dichloromethane and 1.1.1-trichloroethane levels are related to their widespread use in spray cans as solvent or propellant. Limonen indicates the utilization of kitchen detergents and floor wax. Most of the alcanes and alcylbenzenes are closely related to the solvent mixtures for paints, conservation agents and other household chemicals.

An assessment of the toxicological implications of these organic indoor pollutants is difficult. Acute toxic effects as observed in applications of certain household chemicals have not attracted much attention and have been thought of lightly. However, it is questionable whether it is sufficient to label the containers of such chemicals simply as not suitable for indoor applications. There have been reports of eye irritation and respiratory problems after detergent treatment of carpets or the use of oven cleaning agents and leather cleaners. The observed symptoms appear to be reversible and disappear soon with the dissipation of the chemical agent. Apparently, if there is no chronic exposure involved, occasional exposures are simply assumed to be inconsequential. It remains to be seen whether this is a correct assumption in view of the multitude of compounds and the possibility of combination effects of these organics which add up to average indoor concentrations of more than 200 $\mu g/m^3$, thus constituting variable chronic exposure. Besides, there are several compounds involved most prominently, for instance benzene, which are known to be carcinogenic. The chronic exposures to potential carcinogens is indeed a crucial issue, but suspicion of indoor pollutant carcinogenicity is mostly focussed on cigarette smoke which is, indeed, one of the prominent indoor pollutants but may not contribute significantly to the indoor level of known carcinogens. However, it should be noted that the mere detection of trace levels of carcinogenic organics in indoor air does not necessarily imply an elevated cancer risk for residents.

Sick Building Syndrome

Another source of concern which is possibly related to organic trace components has been termed the "sick building syndrome" because it occurs and persists primarily in occupants of modern office and apartment buildings. Office workers and tenants complain of building-related symptoms like headache, vertigo, nausea, diarrhea, eye and nose irritation, skin rashes etc. This set of symptoms resembles to some degree the effects of irritant gases and vapors or organic solvents as they occur indoors. However, there are no significant correlations to specific pollutants, like formaldehyde, or certain groups of organics, like n-alcanes, benzene and its derivates etc. As much as the complaints about "sick buildings" are real, the cause of the irritations is still subject to speculation. Among other hypotheses, the influence of flaws in the air-conditioning systems are suspected to contribute to the cause. Conducts of cool air, humidification devises, faulty air filters and even carpets can incubate and disperse bacterial aerosols contributing to irritations. It was reported that more than one third of the employees in a US office building developed skin and mucosa irritation, headache and lethargy after a new humidifier system had been installed (Pickering et al. 1985). Certain microorganisms and other biological

material as well as allergens have also been considered as cause for discomfort in sick buildings. Thus, the sick building syndrome needs definitely increased attention and research efforts in the future.

Tobacco Smoke

Tobacco smoke may be considered a product of destillation and incomplete combustion, and may be dealt with in that context. However, tobacco smoke is the most prominent and easily identifiable source of indoor pollution, and thus, deserves to be specifically addressed. Indoors, tobacco smoking, contributes significantly to the levels of particulate pollutants, and many of the undesirable organic compounds of tobacco smoke are directly associated with the smoke particles. However, tobacco smoking adds also to the levels of gaseous pollutants like carbon monoxide, nitrogen dioxide and organics, like nicotine, which occur as vapor traces as well as on the smoke particles. Since indoor pollution by tobacco smoke requires smokers as a source the indoor concentrations may vary widely as demonstrated in Figure 1. Indoor measurements indicated CO values between 2.5 and 45 mg/m^3 (2 to 35 ppm) and particulate matter attributable to tobacco smoking was ranging from 10 to 1000 $\mu g/m^3$ in public places (Repace and Lowrey 1980). In private homes, a moderate smoker consuming a pack per day will contribute approximately 20 $\mu g/m^3$ of particulate matter to the 24-hours average value. With several smokers in a family, it may well be possible that, by smoking alone, the 24-hour standard for particulate matter for ambient air (US-National Air Quality Standard 260 $\mu g/m^3$) may be exceeded if there is insufficient air exchange indoors.

Health concerns with regard to indoor tobacco smoke pollution originate from the fact that smokers have a substantially increased risk of lung cancer from smoking. Thus, there is the suspicion that, in confined spaces, non-smokers would involuntarily be exposed to tobacco smoke and would, thus, share a certain fraction of the risk accepted by smokers. Besides, non-smokers claim that there are other health effects of "passive smoking" ranging from eye and throat irritation to circulatory and cardiovascular problems due to increases in carboxyhemoglobin (COHb) in the blood or other influences of tobacco smoke components. There are, indeed, studies showing that "passive smokers" have cotinine levels in their saliva and urine which are directly correlated to the number of cigarettes smoked in a closed room. Cotinine is a metabolite of nicotine, and thus, indicates the uptake of airborne nicotine by non-smokers.

To date, however, epidemiological studies do not yet significantly indicate any irreversible long-term effects in passive smokers. Rather than discussing various studies which claim relative lung cancer risk increases of non-smokers between 20 and 100 percent, it may suffice to quote the summary of a recent IARC survey: "Several epidemiological studies have reported an increased risk of lung cancer in nonsmoking spouses of smokers, although some others have not. In some studies, the risk of lung cancer in nonsmokers increased in relation to the extent of spouses' smoking. Each of the studies had to contend with substantial difficulties in determination of passive exposure to tobacco smoke and other possible risk factors for the various cancers studies. The resulting errors could arguably have artefactually depressed or raised estimated risks, and, as a consequence, each is compatible either with an increase or with an absence of risk. As the estimated relative risks are low, the acquisition of further evidence bearing on the issue may require large-scale observational studies involving reliable measures of exposure both in childhood and in adult life.

The studies on childhood cancer do not provide clear evidence as to whether or not there is a clear association with parental smoking" (IARC 1986).

However, earlier in 1981, the US National Academy of Sciences (1981) accepted limited evidence of lung cancer acquired by passive smoking and recommeded at that time that "public policy should clearly articulate that involuntary exposure to tobacco smoke ought to be minimized or avoided where possible".

Combustion Products

In many instances, the indoor use of open fire will significantly reduce the indoor air quality. Main indoor sources of this kind are tobacco smoking, candle lights, open fire places for space heating or cooking and the use of certain kitchen appliances fueled by wood, coal, charcoal, or organic liquids and gases. With insufficient or non-existent exhaust vents and ducts, these fuels can be the source for various inorganic and organic pollutants in form of vapors and particulate matter. Major products of concern are carbon monoxide, carbon dioxide, various oxides of nitrogen, sulfur dioxide as well as hydrocarbons, certain aromatics and organic products of incomplete combustion, like polycyclic aromatic hydrocarbons, nitrosamines and the like.

As already mentioned, tobacco smoking may be the main contributor to carbon monoxide indoor pollution, however, the contribution of domestic use of gas stove and heaters may also contribute significantly. While in non-smokers homes with electric stoves and heaters an indoor/outdoor ratio of 1.14 was found for CO, this ratio went up to 3.76 in homes using natural gas for cooking and heating (Coté et al. 1974).

Carbon dioxide is not considered an outdoor pollutant, and values between 0.01 and 0.05 volume percent are considered normal. The indoor concentrations vary typically between 0.015 and 0.22 volume percent (Moschandreas et al. 1985), but depending upon the degree of ventilation, values exceeding 0.5 volume percent can occasionally be expected which, for instance, would violate the German Standard for acceptable work place conditions.

The most prominent indoor sources for nitrogen oxides are gas stoves and gas or kerosine space heaters. Again, in the absence of these sources the impact of tobacco smoking can be traced, although the smoke contribution is not very important and, in fact, is typical for a characteristic release of nitrogen monoxide, NO. In homes with electric stoves, hourly averages of 19 $\mu g/m^3$ have been measured for nitrogen dioxide, NO_2 (Melia et al. 1985), while gas cooking increased these concentrations up to 140 $\mu g/m^3$. Indoor/outdoor ratios in the presence of indoor sources generally rate between 2 and 5 (cf. Table 2).

Except for kerosine stoves and heaters, the indoor pollution by sulfur dioxide does not pose a particular problem. Major sources outdoors keep the indoor/outdoor ratios generally below 1.0. However, defect chimneys may cause up to 10-fold increases.

The organic products of incomplete combustion have attracted particular attention because certain classes of compounds of this nature are known to be carcinogenic in animal experimentation. Thus, the focus has been on certain polycyclic aromatic hydrocarbons and nitrosamines. Their analysis as indoor components is complicated by the fact that many of these compounds are readily adsorbed by particulate matter like indoor dust or other particles subject to sedimentation.

Considering the health effects implications of indoor combustion products, there is much similarity to the health effects suspected in outdoor exposures of carbon monoxide, nitrogen dioxide and particulate matter. In assessing risk, smokers whose health effects

will include the induction of lung cancer certainly rank highest and their problems may be aggravated by excessive indoor pollution by nitrogen dioxide. The risk of "passive smoking" is less well defined, but there are indications that chronic exposure to increased indoor levels of nitrogen dioxide as well as cigarette smoke may have an influence on the long-term well-being and the development on children, particularly on very young children below the age of 2 years. The preliminary findings will be probed in prospective studies and reliable data should be available in the future.

Conclusions

Modern human life can be subdivided into three domaines: life outdoors, life at the working place and private life at home. Of these, the private home cannot easily be subjected to enforceable exposure regulations. In fact, since personal life style, besides social strata, is so highly determinant in indoor pollution by hygienic attitudes, smoking habits, wood burning, and cooking, it may be an intrusion of privacy to promulgate indoor air pollution regulations which cannot be enforced anyway. However, since people are generally unaware of the potential dangers of many of the present day household or home construction chemicals, regulation should concentrate on the environmental quality of the commercially available chemical products for applications in and around homes.

Here, future may bring certain improvements. Many countries have provisions in their toxic substances control laws which prohibit the marketing of new chemical products if no evidence is submitted that, according to a variety of required tests and analyses, the new product is compatible with the environment and does not constitute an unreasonable risk. Although this may apply to new products only, such provisions would be effective in the long run because of the usual turnover time of new products on the market. One can expect that, a decade from now, potentially hazardous household products will have considerably decreased.

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Indoor Tuberculosis Infections in Small Offices in Downtown Tokyo

M. Minowa, T. Shimo, T. Oi, and I. Shigematsu

Summary

Three episodes of tuberculosis outbreaks which occurred in company offices in downtown Tokyo since 1979 will be described and discussed with special reference to indoor environment.

Episode I. Between May 1979 and June 1980, four cases of tuberculosis occurred among company employees working in the same building. The first case, a 36-year-old man with a positive smear and cavities in both lungs, was considered to have been in an infectious state for about 1 year before his admission to a tuberculosis hospital in June 1979. Follow-up investigation of 99 contacts until October 1987 revealed the occurrence of 17 secondary cases. The desks of these secondary cases were aggregated near and around that of the first case. Although this building had central air conditioning, the office room where the first case and most of the secondary cases worked was overcrowded, and ventilation was often closed for energy conservation purposes. An environmental survey revealed elevated levels of carbon dioxide concentration and floating dust.

Episode II. Two cases of tuberculosis in which cavities had developed were detected by chest X-ray examinations for company employees in September 1983. A 20-year-old woman with a positive smear who had been admitted to a tuberculosis hospital in August 1982 was suspected to be the source of infection. Eight new cases occurred among 67 contacts followed-up until October 1987. Windows of the first floor were almost always closed because of traffic noise outside. The office room on the first floor of the main office was overpopulated and showed higher carbon dioxide concentration.

Episode III. On June 16, 1987, a 36-year-old individual with smear-positive tuberculosis and cavities in both lungs was reported to the health center which had jurisdiction for his area of residence. Five additional cases were detected by chest X-ray examinations of 81 employees working in the same office. The other contacts are being followed-up. Two rooms of the office were not equipped with central air conditioning and were very crowded by Office Sanitation Standards Regulations.

These three episodes suggested that the indoor infection of tuberculosis was attributable to insufficient ventilation or overpopulation of the office rooms.

Introduction

Since 1980, indoor environment in buildings with total floor area of 3,000 square meters or more in Japan has been subject to control by the "Law for Maintenance of Sanitation in Building" which prescribes standards for sanitary management of buildings, such as regulation of the air environment including floating dust, carbon monoxide, carbon

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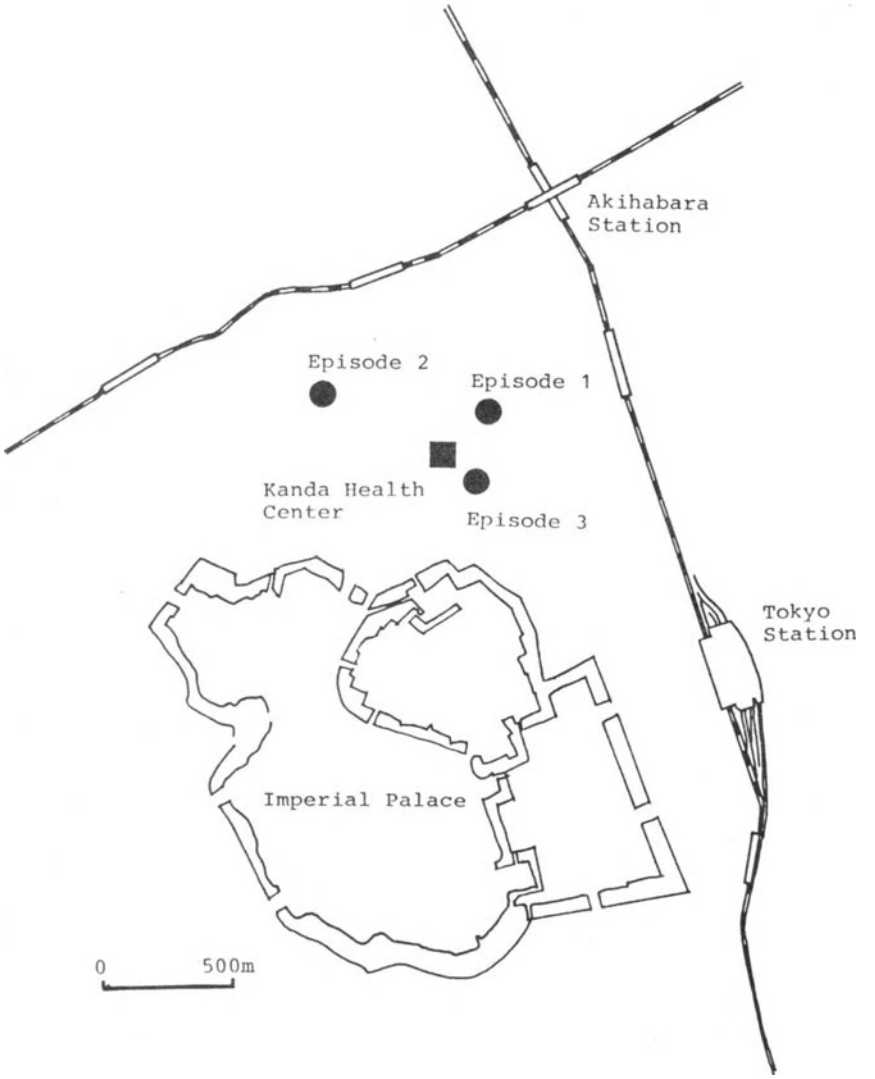

Fig. 1. Locations of 3 tuberculosis outbreaks

dioxide, temperature, relative humidity and air current, control of water supply and drainage, cleaning, and rodent control. Beside this Law, "Office Sanitation Standards Regulations" have been applied to office rooms since 1972. These regulations stipulate air space per person, ventilation and air-conditioning for offices.

During the past eight years, we have experienced three outbreaks of tuberculosis among the office workers in an area under the jurisdiction of a health center in Downtown Tokyo (Fig. 1). In addition to the epidemiological surveys, a detailed environment study on the office rooms was made for the first episode and simplified

Table 1. Number of secondary cases among contacts by floor (May 1979–October 1987)

Floor	Number followed-up*	Number of secondary cases	(%)
1	8	1	12.5
2	13	2	15.4
3	11	2	18.2
4	29	11	37.9
5	9	1	11.1
6	8	-	-
Total	78	17	21.8

* As of May 1979.

environment studies were made for the other episodes. These three episodes of tuberculosis outbreaks were discussed with special reference to the indoor environment of the office rooms.

Episode I

In the First Episode, the occurence of four tuberculosis cases among the employees of an advertising company was reported by the industrial health physician in June 1979 [Shigematsu and Minowa 1985]. Epidemiological surveys revealed that the primary patient who had been the source of the outbreak was a 36-year-old male with cavities in both lungs. The primary case who was smear-positive for tuberculosis had been discharging tubercle bacilli in the office for approximately one year prior to hospitalization. Ninety-nine contacts (56 males and 43 females including former employees) were followed up until October 1987. A total of 17 secondary patients were thus detected. The attack rate in the Business Department (occupying the fourth floor of the building) to which the primary patient belonged was as high as 38% (11 out of 29) (Table 1). On the fourth floor secondary cases were aggregated around the primary case (Fig. 2).

The office was located in a seven-floor ferro-concrete building with one basement floor and had a total floor area of 1,150 square meters to which the Building Sanitation Law is not applicable. The entire building was air conditioned by a single system. There was a fresh-air inlet on the roof, but the fresh-air damper was always completely closed. Temperature control of the air conditioning system was done manually and when the system was stopped the entire function including ventilation ceased.

Inspection of the office revealed that air space per person on the fourth floor where the primary case and eleven secondary cases had developed was far less than the standard value of 10 cubic meters per person stipulated by the Office Sanitation Standards Regulations (Table 2).

To examine the indoor environment, measurements of the carbon dioxide concentration, floating dust concentration and number of floating bacteria were made in the office on the fourth floor. Most of the time during the working hours with the presence of many workers, the carbon dioxide concentration on the fourth floor exceeded 1,000 ppm which is the the indoor environmental management standard stipulated by the Building

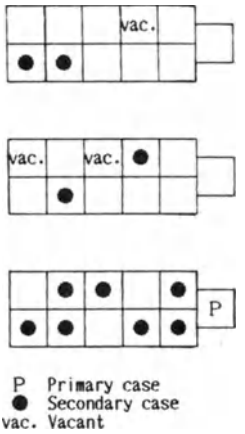

Fig. 2. Distribution of desks and tuberculosis cases on the 4th floor (Business Department)

Table 2. Space and ventilation of the office rooms (Episode 1)

Floor	Workers	Area		Air space* m^3/worker	Air supplied m^3/h/worker
		m^2	m^2/worker		
B1	10	70	7.0	14.0	161
1	9	24	2.7	5.3	90
2	17	120	7.1	14.1	96
3	16	120	7.5	15.0	119
4	33	105	3.2	6.4	74
5	7	33	4.7	9.4	224

* Standard: ≥ 10 m^3 by Office Sanitation Standards Regulations.

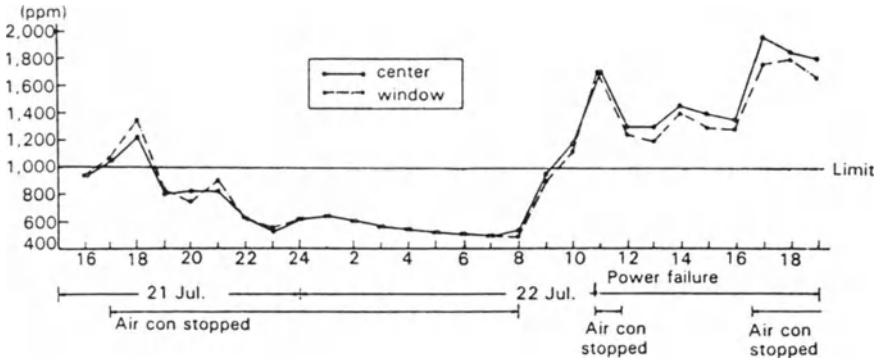

Fig. 3. CO_2 concentration by time (4th floor, 21–22 July 1980)

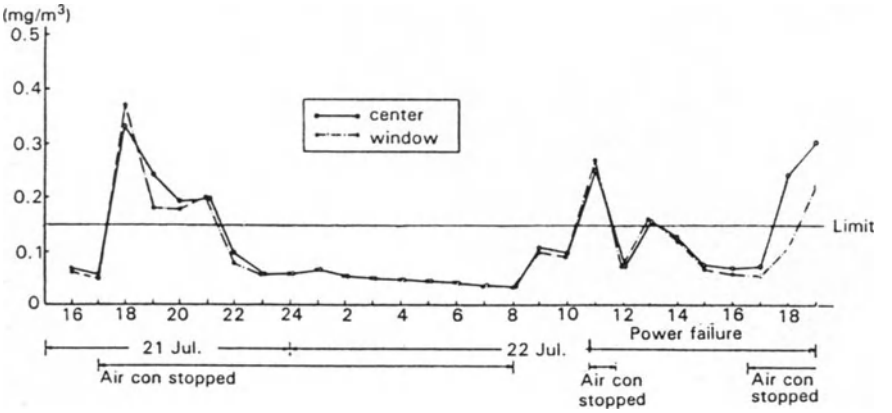

Fig. 4. Concentration of floating dust by time (4th floor, 21–22 July)

Table 3. Number of floating bacteria by species*

Species	Air con. on 13:34–14:30	Air con. off 18:30–19:00
Staphylo. albus	135.0	283.9
aureus	37.2	61.2
other	8.2	7.1
Gram-positive bacilli	7.6	15.3
Fungi	8.8	17.7
Proteus	1.3	–
Unidentified	107.9	373.4
Total	306.0	758.5

* Number of colony/m^3 by slit sampler

Sanitation Law. Especially when the air conditioning system was stopped, this value rose to approximately 2,000 ppm (Fig. 3).

Floating dust concentration, as in the case of carbon dioxide concentration, changed with time closely corresponding to the number of people occupying the room and the operation of the air conditioning system. However, unlike the carbon dioxide concentration, during most of the working hours it did not exceed 0.15 mg per cubic meters which is the indoor environmental management standard, but it exceeded this level only when the air conditioning system was stopped (Fig. 4).

Among the floating bacteria, staphylococcus albus accounted for the largest population, followed by staphylococcus aureus and fungus. When the air conditioning system was stopped, the total number of floating bacteria increased by more than two times (Table 3).

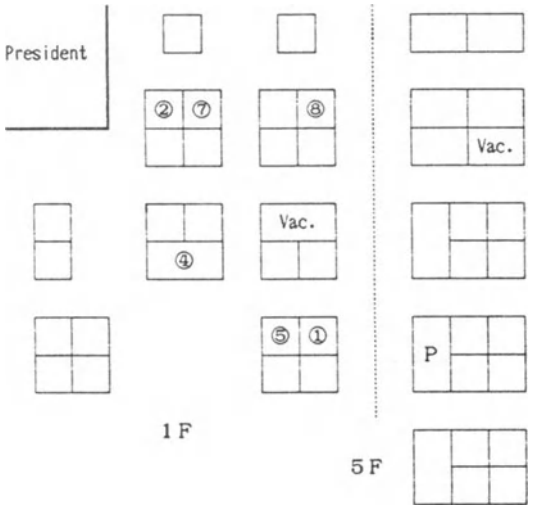

Fig. 5. Distribution of desks and tuberculosis cases in the main office of Episode 2. P Primary case, O Secondary cases, Vac. Vacant

Episode II

In Episode II, two tuberculosis cases with cavities in both lungs were detectedd in regular chest X-ray examinations for employees of a company in September, 1983. Following chest X-ray examinations for the rest of employees, three more cases were found. In total five cases were detected among 67 employees. The suspected source of infection was a 20-year-old female employee who had been admitted to a tuberculosis hospital with smear-positive for tuberculosis in the previous year. Eight secondary cases were detected among 67 contacts followed-up until October, 1987.

The company had its main offices on the first and fifth floors in a building and the second office in another building. The primary case worked on the fifth floor of the main office, but the most of the secondary cases developed on the first floor. It was suggested that the tuberculosis was first transmitted to the secondary case 1 who worked on the fifth floor before the admission of the primary case and caused an outbreak on the first floor (Fig. 5).

The total floor space of the building was 2,054 square meters, and not covered by the Building Sanitation Law. There was no central air-conditioning system, but there were steam heaters for winter and room coolers for summer. Windows of the first floor were almost always closed because of traffic noise outside. The office room on the first floor of the main office was overpopulated as shown by the value of 3.8 square meter per person of space, 8.4 cubic meters of air space per person and 1,300 ppm of carbon dioxide concentration (Table 4).

Episode III

Episode III began with the report of a 36-year-old male, smear-positive tuberculosis case with cavities in both lungs to the health center which had jurisdiction for the area of his residence in June 1987. The information was transfered to Kanda Health Center which

Table 4. Environmental indices of the office rooms (Episode 2)

Floor	Workers	Area		Air space*	Co_2**	CO**	Suspended** particles
		m^2	m^2/worker	m^3/worker	ppm	ppm	mg/m^3
Main office							
1	25	96	3.8	9.6	1,300	2.0	0.09
2	23	207	9.0	22.5	1,250	1.8	1.04
Second office							
2	5	62	12.5	31.0	1,450	2.2	0.07
3	6	62	10.3	25.8	750	1.2	0.10

* Standard: $\geq$ 10 m^3 by Office Sanitation Standards Regulations.
** Standard: $CO_2 \leq$ 1,000 ppm, CO $\leq$ 10 ppm, suspended particles $\leq$ 0.15 mg/m^3 by Law for Maintenance of Sanitation in Buildings.

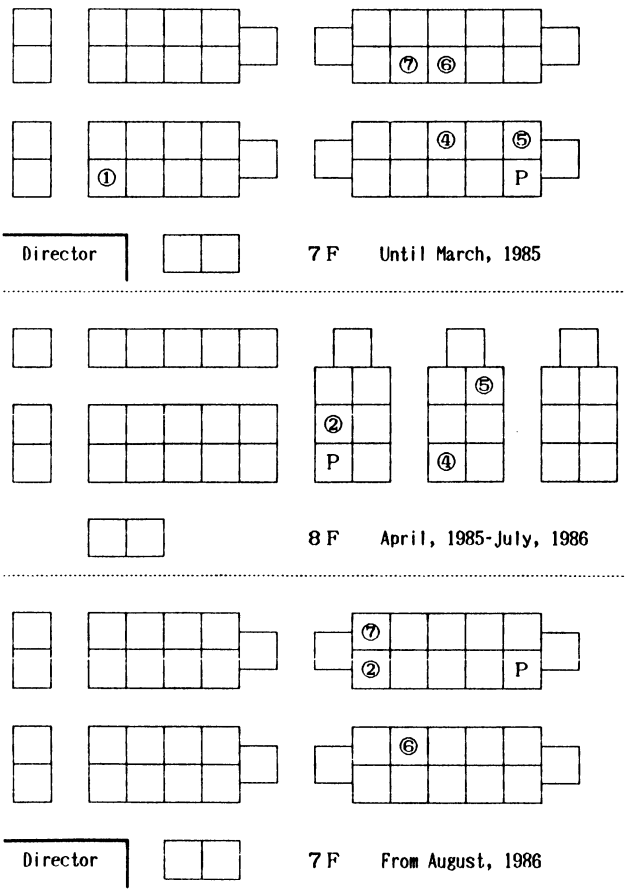

Fig. 6. Distribution of desks and tuberculosis cases around the primary case in the major office rooms of Episode 3. P Primary case, O Secondary cases

Table 5. Environmental indices of the major office rooms (Episode 3)

Floor	Workers	Area		Air space*	Co_2**	CO**	Suspended** particles
		m^2	m^2/worker	m^3/worker	ppm	ppm	mg/m^3
7***	48	161	3.4	8.4	1,470	2.0	0.09
8	39	115	2.9	7.4	900	3.9	0.05

* Standard: ≥ 10 m^3 by Office Sanitation Standards Regulations.
** Standard: $CO_2 \leq 1{,}000$ ppm, $CO \leq 10$ ppm, suspended particles ≤ 0.15 mg/m^3 by Law for Maintenance of Sanitation in Buildings.
*** A kerosene stove was used supplementarily in the office room.

covers the area of his office. Five additional cases were detected by chest X-ray examinations of 81 employees working in the same office. Thus, the above-mentioned smear-positive 36-year-old male employee with cavities in both lungs was suspected to be the primary case.

The offices in which the episode occurred occupied the seventh to nineth floors of a building that had been constructed in 1971. The total floor area was 1,260 square meters and not covered by the Building Sanitation Law. The office rooms had, instead of central air conditioning, two fans, two room coolers and steam heaters. Desks of employees were rearranged twice from 1980. Secondary cases, however, developed around the primary case (Fig. 6).

As shown by the floor area and air space per person which were less than the standard, overpopulation of the office rooms was obvious. Carbon dioxide concentration was higher than the standard only on the seventh floor where a kerosene stove was used supplementarily. Suspended particles did not exceed the standard by the Office Sanitation Standards Regulations (Table 5).

Discussion

There may be different factors in each of these episodes which had caused these tuberculosis outbreaks, such as mahjong and drinking after work, and misdiagnosis of chest X-ray films taken at times of regular health examinations. There are, however, common factors to the three outbreaks. Namely, these buildings were not covered by the Building Sanitation Law, and consequently overpopulation and poor air-conditioning of office rooms resulted. Besides, inadequate management of the ventilation system was suggested in one episode. Small buildings which are not covered by the Law are occupied often by small companies where other working conditions are also poor.

Thus, poor indoor air quality caused by overpopulation and poor ventilation may have resulted in inhibiting the dispersion of tubercle bacilli and may have increased the change of infection. The standards for the sanitary management by the Law should be applied correspondingly to the smaller offices.

Acknowledgement: The authors are grateful for the cooperation and effort of Drs. S. Yoshizawa, K. Ikeda, S. Yamazaki, H. Miyaji and F. Sugawara, and staffs for Kanda Health Center, with whom this study was done.

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Experimental Studies on the Odor of Cigarette Smoke

K. Nishida, K. Ohtsuka, K. Sasaki, M. Yamakawa, and Y. Kita

Summary

Lately, the unpleasantness of cigarette smoke has become a matter of great public interest and a new antismoking trend has spread rapidly in order to protect the nonsmoker.

However, few studies on sensory evaluation of cigarette smoke (mainstream and sidestream) have been done. In this paper, we report on a study in which the odor intensity and unpleasantness of cigarette smoke were measured using a panel of smokers and applying the triangle bag test, which was developed to evaluate the degree of odor pollution. The test sample smoke was obtained using an automatic smoking device under the conditions of international smoking mode and the "Mild Seven." In order to compare the change of odor intensity and unpleasantness with different treatments for mainstream and sidestream smoke, the sensory tests were done before and after passing through the Kenbridge filter, water filter, silica gel, and activated charcoal column. Odor intensity was measured as odor concentration (dilution/threshold), and unpleasantness was evaluated by the six-stage sensory scale.

Many studies on cigarette smoke and smoking have been done from the point of view of harmful effects and carcinogenic action.

Tests subjects washed their hands with odorless cleanser prior to the test, and smoking, drinking, and eating were prohibited from 30 min before the test to the end.

Rooms

Three different rooms were prepared, to collect sample smoke, for the panel to wait in, and for sensory measurement; the air in the rest room and measuring rooms was kept clean, and smoking was prohibited in this room.

Samplings of Mainstream and Sidestream Smoke

As the odor intensity and quality of cigarette smoke are liable to change with the passage of the time, the samples were collected on the day of sensory tests. Polyester bags (5 to 10 l) were used as the sample container and the mainstream smoke was put into the bags by the motion of piston, passing through the exit of the automatic smoking device. For the collection of sidestream smoke, the indirect vacuum box was used as shown in Fig. 1, and the sidestream smoke was sucked in at a rate of 2 l/min through the outlet of the glass tube (id 5 cm), covering the cigarettes, as shown in Fig. 2. The glass tube used to collect the samples has been cleansed by steeping it into EtOH solution (70%) for about 10 h and washed with distilled water and odorless cleanser.

H. Kasuga (Ed.) Indoor Air Quality

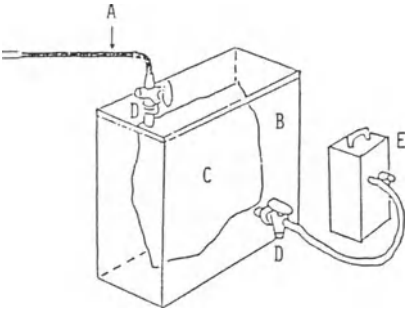

Fig. 1. Indirect sampling box. *A*, sampling line; *B*, airtight box (transparency); *C*, plastic bag; *D*, valve; *E*, vacuum pump

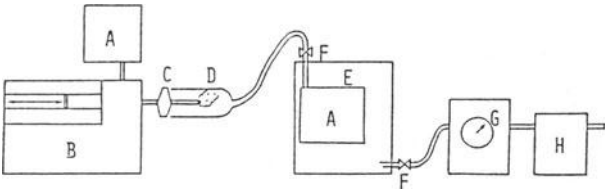

Fig. 2. Outline of sampling method. *A*, plastic bag; *B*, automatic smoking device; *C*, cigarette holder; *D*, cover tube for sidestream sampling; *E*, indirect sampling box; *F*, valve; *G*, flow meter; *H*, vacuum pump

The original mainstream smoke for sensory measurement was collected under the conditions of the international smoking mode on an automatic smoking device. Six cigarettes were consumed for one sample collection, the collected volume of smoke was about 1.6 l, and the length of each butt was about 35 mm. The collected volume of original sidestream smoke was about 5 l with 0.4 parts of a cigarette.

Lately, it has become a matter of public interest that indoor air pollution is caused by pollutants in cigarette smoke, such as aldehydes, nitrogen oxides, and particles. Also, most nonsmokers must find the odor of cigarette smoke very unpleasant and campaigns against smoking are widely spreading in the world [1]. However, few studies on the odor of cigarette smoke have been performed. Because a quantitative method of sensory evaluation of cigarette smoke odor has not been established.

In this paper, we report the results of a study in which the odor intensity and unpleasantness of cigarette smoke were measured using the triangular bag test which was developed by the Tokyo Institute for Environmental Pollution [2]. The sensory tests with panels were done for samples which were collected in the plastic bags after passing through the Kenbridge filter, water filter, silica gel filter, and activated charcoal filter, in order to find out whether they reduced the effects of the unpleasant odor.

Sensory Measurements for Odor of Cigarette Smoke

Smoking Conditions and the Automatic Smoking Device

Individual smoking modes, in general, vary with the personality, and physical and psychological conditions of subjects and surroundings. A typical smoking pattern in Japan had been reported as having an inhalation duration of 2 s at 35-s intervals, length of butt 40 mm, and the volume of inhaled smoke 35 ml for every inhalation, according to the results of the survey at Ueno and Tokyo station [1]. However, it does not describe the typical smoking pattern of the Japanese at present because this survey was done about 20 years ago.

In this study, the international smoking mode [3] was adopted to collect test smoke for the sensory evaluation of odor. It consisted of the following: duration of inhalation is 2 s and the interval of inhalation is once per min, the time of each inhalation is 2 s, the total volume of inhaled smoke is 35 ml per smoke, and the length of butt is 23 to 40 mm. The mainstream and sidestream smoke were collected in the plastic bags (polyester bag) with the automatic smoking device (type-1, Chuo Sansyo Co., Tokyo) and the brand of cigarette tested was Mild Seven (made in Japan, 5.5 cm in total length, 2.4 cm of the attached filter), and also the tested cigarettes were kept in a constant condition at 20 °C and RH 60%, until the sampling of smoke was started.

Test Panel

Eight students (male) aged 21–24 were involved in the sensory test. They had passed the T&T Olfactometer test [2] which was applied to exclude persons who had an abnormal olfactory sensitivity. Three of them smoked 10 to 20 cigarettes per day.

Filtrated Samples

The mainstream smoke was collected after it passed through the filters connected to the exit of the automatic smoking device. The filters used were the Kenbridge filter, a water filter which was a bottle of bubbling water (30 ml of distilled water), a silica gel filter which was a glass tube (id 10 mm, L 50 mm) pack with 40 to 60 mesh of silica gel (10 g), and an activated charcoal filter (glass tube, id 10 mm, L 50 mm) which was packed with 11 g of granular activated charcoal (40 to 60 mesh). In the case of sidestream smoke, the tested smoke were passed through those filters from the original exit of sample bags, and the flow rate of smoke passing through those filters was always maintained at 2 l/min.

Sensory Measurements of Cigarette Smoke

Preliminary Test: In order to grasp the approximate figures of odor concentration for the samples, the operator roughly measured it by a 10-fold dilution method. Based on the results of this preliminary test, samples to be given to the panel were prepared with a 3-fold dilution, by diluting it with odorless air which was purified by passing it through the activated charcoal column. Here the odor concentration is, dilution/threshold, defined as the required dilution with odorless air until that odor is no longer unpleasant.

Sensory Measurement: The triangular bag test was started from the sample which was diluted one step lower than the maximum dilution ratio on the preliminary test, applying the exit method of the triangular bag test [2]. However, the results given by this method [4] are not more reliable because the values estimated by this method are always influenced considerably by the appearance of a hit by chance while sniffing, so that each panel was forced to repeat the sniffing for the same sample twice. Then, if two hits were given by one panel for different samples in the same dilution ratio, one correct answer for this dilution rate was counted in the calculation for the ratio of the correct answer. The sniffing test was continued until the panel could not judge whether an odor was present for the sample or his response was incorrect after sniffing twice. And also, the largest or smallest value of dilution ratio on each panel was left out in order to reduce the probability of a chance error, following the ordinary method [2].

An individual odor concentration was calculated as below.

$$X\iota = \log X\iota = \log (X\iota_1 \cdot X\iota_2) \tag{1}$$

$X\iota$: threshold of the panel ι ($\iota = 1$ to 7)
$X\iota_1$: the maximum dilution ratio in the collect answer of the panel ι
$X\iota_2$: the maximum dilution ratio when the answer of panel ι was an error or unknown

Omitting the maximum and minimum values among the individual threshold value which derived by formula 1, the mean value for all panels (X_m) was given as below:

$$X_m = 10^x \tag{2}$$

X; the mean threshold value for all panel

Odor Intensity and Quality of the Cigarette Smoke

The odor quality table as shown Table 1 was presented to each panel and they selected the number in this table corresponding to their judgement, and the odor intensity for given samples was judged using the sensory scale as shown in Table 2. Although odor intensity was measured, in general, according to the six-step scale recommended by Japan EPA [2], in this study, the sensory scale improved the explanation for each category and the

Table 1. Odor quality

00 Unknown	
10 Ether	11 Fruity 12 Ether
20 Aromatic	21 Camphor 22 Spice 23 Lavender 24 Lemon 25 Almond
30 Fragrance	31 Jasmin 32 Polyanthus 33 Violet 34 Vanilla
40 Amber	41 Musk 42 Ambergris
50 Garlic	51 Garlic 52 Onion 53 Leek 54 Fish
60 Scorched	61 Tar 62 Coffee 63 Bread 64 Naphthalen 65 Tobacco 66 Benzene
70 Caprylic	71 Cheese 72 Rancid fat 73 Sweat 74 Secretion
80 None	81 Bedbug 82 Putrefaction 83 Nausea
90 Other	

Table 2. Sensory scale: odor intensity scale

Step	Contents
0	None
1	Faintly detectable (detection threshold)
2	Perceptible, clearly unpleasant (recognized threshold)
3	Strong desire to avoid that odor if possible
4	Very strong, cannot endure even for a moment

Table 3. Odor concentration of the smoke

Samples		Threshold $\bar{X}$	Square root of unbased variance	Odor concentration hold	Elimination rate (%)
Mainstream	Original	5.34	0.22	220,000	–
	Kenbridge filter	5.54	0.27	350,000	–
	Water filter	4.54	0.45	35,000	84.1
	Silica gel filter	3.24	0	1,700	99.2
	Activated charcoal filter	3.14	0.22	1,400	99.4
Sidestream	Original	5.24	0.50	170,000	–
	Kenbridge filter	4.74	0.58	55,000	–
	Water filter	3.37	0.25	2,300	98.6
	Silica gel filter	2.74	0.29	550	99.7
	Activated charcoal filter	1.84	0.22	70	99.9

number of steps, in order to include the factor of unpleasantness into odor intensity, as shown in this Table.

Results and Considerations

Odor Concentrations of Cigarette Smoke

The results of sensory measurement for the original sample of main- and sidestream smoke are shown in Table 3, and the values are also shown for the smoke which was passed to the filters. The odor concentration of the original mainstream smoke was about 220,000-fold, in spite of the fact that it had passed through the attached filter and the original sidestream smoke was about 170,000-fold. These results indicate that the cigarette smoke must be diluted over 10^5-fold by fresh air to keep the level of odor in the rooms such that it is not unpleasant for nonsmokers. The lowest value was given by the activated charcoal filtration, about 1,400-fold for the mainstream and about 70-fold for sidestream smoke.

Although reduction rates exceeding 99% in the odor concentration were given for main- and sidestream smoke after passing through the activated charcoal filter, the values

for the remaining odor concentration are still high in comparison with the environmental value, about 10-fold [5], which should not cause complaint of being unpleasant [5].

Using the values of odor concentration obtained in this study, a one-sided t test was done. There were no significant difference ($d = 0.005$) between the original smoke and samples which had passed through the Kenbridge filter in both main- and sidestream smoke, and between the smoke which had passed through silica gel and activated charcoal filters. There was a significant difference ($d = 0.001$) in combinations of samples other than the above three.

The Kenbridge filter has been used, in general, to measure tar in cigarette smoke, as the collection method of particles in the smoke. As there were no considerable differences in odor concentrations between the original smoke and samples which were passed through Kenbridge filter, it seemed that the particles in the cigarette smoke does not have a great influence on the unpleasantness of cigarette smoke. And the total particulate matter collected on the Kenbridge filter was about 13 mg for one cigarette after excluding the water in the tar.

From the filtration tests, the odorants which were adsorbed on silica gel and activated charcoal must have a great influence on the unpleasantness of the smoke in comparison with the components which dissolved in the water. For sidestream smoke, the higher reduction in odor concentration was obtained by activated charcoal treatment as 70-fold more than the case of silica gel (550-fold). From the difference of the reduction rate in the mainstream and sidestream smoke, it was considered that the different components would affect their unpleasantness, respectively, and also, the amount of particles in the smoke must have greatly influenced the reduction rate of odor concentration on the filtration, as the sidestream smoke showed 0.01 mg and the mainstream had 406 mg in 5 l of each sample of original smoke.

The Influence of Smoking on Odor Sensitivity

In this study, as the tested samples were cigarette smoke, it was assumed that the subjects who smoked daily would give considerably different values than nonsmokers. About 68% of the measured values were from the panel of smokers and 60% of data in the upper range on the calculation of odor concentration came from the smokers, but the ratio of data in the lower range did not differ between smokers and nonsmokers. So, it seems that fair differences were noted in the ability to detect the sensory intensity of cigarette odor between the smoker and nonsmoker, but the judgement of the unpleasantness of cigarette smoke must differ with each other to a fair extent.

Odor Intensity of Cigarette Smoke

The sensory scale for odor intensity employed here did not secure regular intervals within the steps of the scale because the categories were improved so as to include an expression of unpleasantness. Therefore, the percentages on each step of the scale were counted from the number of responses for each respective step, and the odor concentrations measured for each step. The relationships between the percentages of the subjects who indicated above 2 on the scale and odor concentration are shown for mainstream and sidestream smoke in Fig. 3. The results of measurement of samples which were passed through the filters are shown in Fig. 3, too. The dotted line represents the 50% level, which means that half of the subjects were able to perceive an odor to a fair degree since dilution levels were

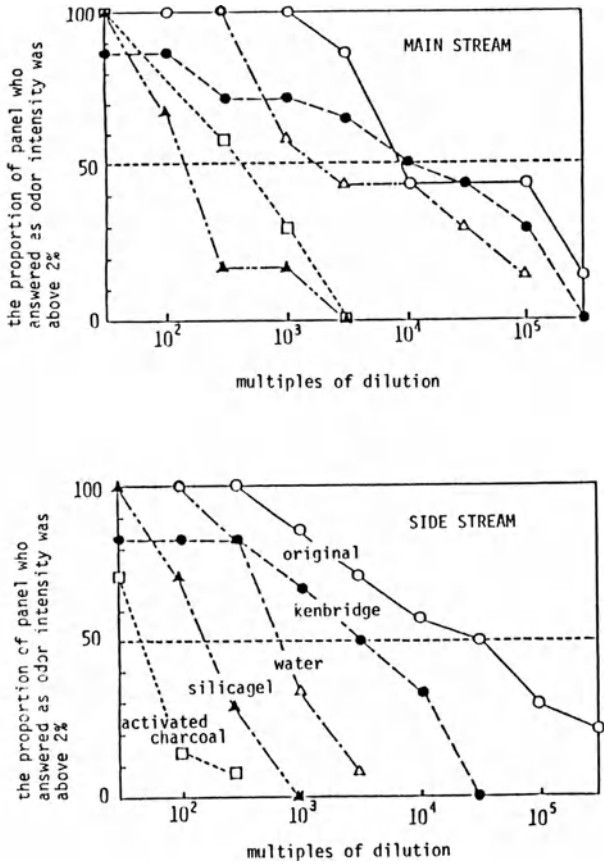

Fig. 3. The relationships between the change of odor intensity and multiples of dilution

10,000-fold for mainstream and about 70,000-fold for sidestream smoke, and these values were clearly decreased after passing through an activated charcoal filter as shown in the figure.

The decreasing tendency of the plots differ according to the kind of filter. This is due to the respective components which have been removed from the smoke.

The Odor Qualities

The odor qualities for cigarette smoke were judged by each subject, selecting suitable words from the given table, and it seemed that the subject's feeling must have changed with the dilution rate of the samples of smoke.

In this test, the scorched smell, such as "tar," "coffee," "burned breads," and "scorched tobacco" were selected as the common expression in both main- and sidestream smoke at any dilution rate. On the other hand, the odor quality of the samples which were passed through the filters changed considerably and the expression "like onions" appeared after smoke passed through the water, and also, "tar" and "scorched tobacco" did not appear for the samples which passed through the activated charcoal filter. This would be brought

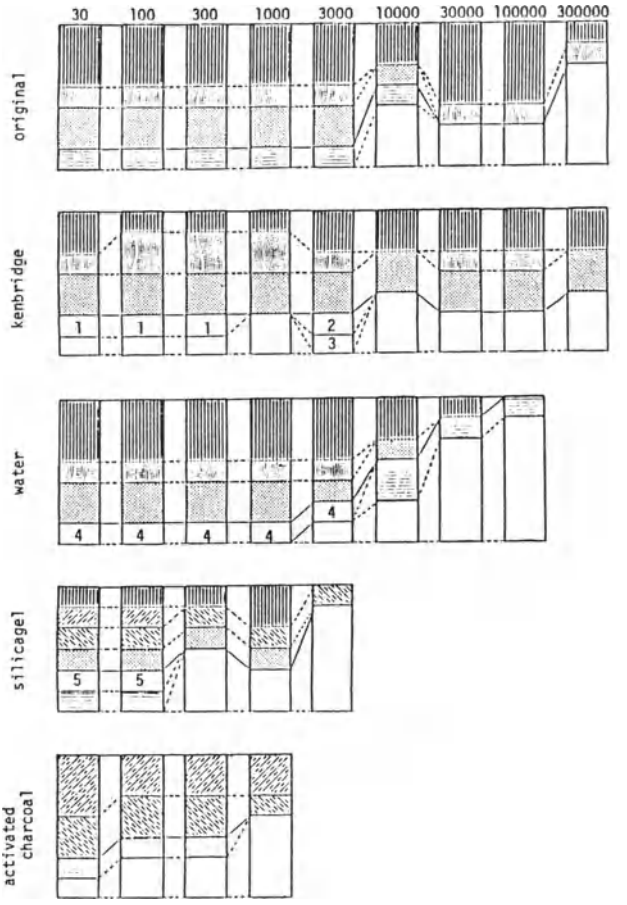

Fig. 4. The relationships of mainstream smoke between the change of odor quality and the multiples of dilution. ▥ scorched odor; ▩ tar; ▩ tobacco; ▨ coffee; ▧ bread; ▤ unpleasant; ▭ unknown; *1*, onion; *2*, aromatic; *3*, rancid fat; *4*, garlic; *5*, cheese

about by the elimination of different odorants in the smoke by those filters. The changes of odor qualities by filtration and dilution are shown in Fig. 4 (mainstream) and Fig. 5 (sidestream).

Odor Emission Rate (OER)

Odor emission rate [2] is adopted, in general, to show the source intensity of odor and is given as follows:

$$\text{Odor emission rate } (m^3/\text{cigarette}) = \text{the smoke volume per cigarette } (m^3/\text{cigarette}) \times \text{odor concentration (fold)}. \quad (3)$$

Here, as generated smoke volume must be known from one smoked cigarette, the measurement was done while the cigarette was burning as shown in Table 4; the brand of cigarette tested was "Mild Seven" and 28 of them were consumed. Table 4 gives the required

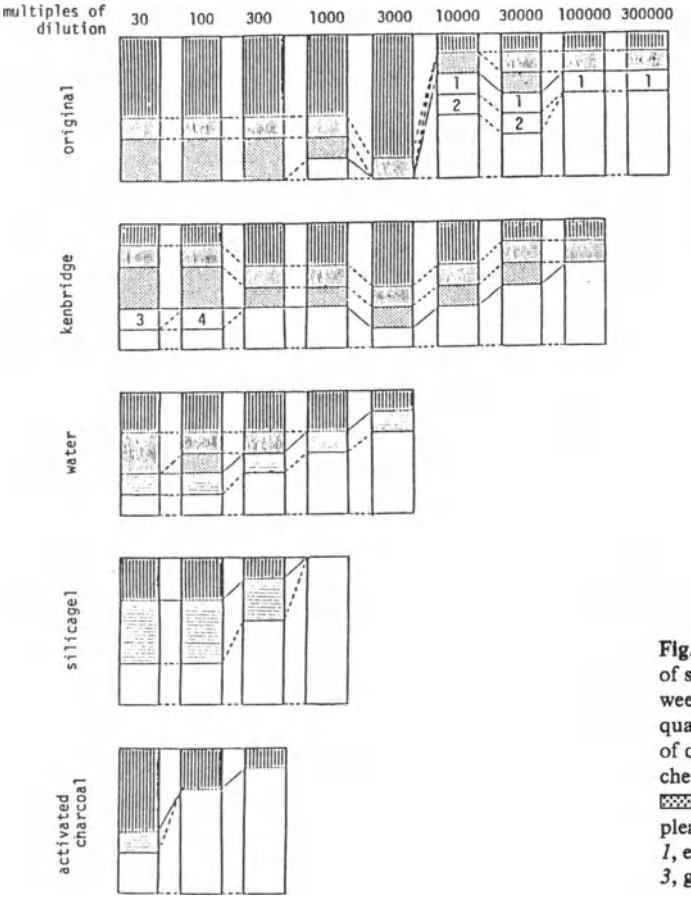

Fig. 5. The relationships of sidestream smoke between the change of odor quality and the multiples of dilution. ▥ scorched odor; ▩ tar; ▩ tobacco; ▤ unpleasant; ▭ unknown; *1*, ether; *2*, aromatic; *3*, garlic; *4*, onion

number of puffs and burning time, until the length of the butt is 35 mm smoking according to the conditions of the international smoking mode by automatic smoking device.

From this test, the mean number of puffs per cigarette was 7.75 and the mean burning time was 426 s per cigarette. Accordingly, the mean volume of generated smoke was given for mainstream smoke as below:

$$\text{Volume of smoke for one cigarette } (m^3/\text{cigarette}) = 426\ (\text{s/cigarette}) \times 2\ (\text{l/min})/60\ (\text{s/min}) \times 10^{-3}\ (m^3/\text{l}). \quad (4)$$

After measuring the generated volume of smoke and odor concentration as mentioned above, the odor emission rates were calculated, as shown in Table 5. The estimated $OER_{2,50}$ are shown in Table 5, too; these values represent the OER of the sample when the odor intensity exceeds 2 and the perception rate is over 50% for given smoke.

Table 4. Condition of the burning cigarette

Number of puffs	Length of butt (mm)	Burning time (s)	Number of puffs	Length of butt (mm)	Burning time (s)
8	34	422	8	35	430
8	37	422	9	35	482
8	35	422	9	35	530
7	35	380	7	35	420
7	35	390	8	34	422
8	34	440	8	35	440
8	35	422	8	35	422
8	35	470	8	35	422
8	35	470	8	35	422
7	35	400	7	35	410
7	35	410	8	33	422
8	34	422	8	35	422
8	35	422	7	34	410
7	36	390	7	35	400
Mean			7.75	34.9	426
Standard deviation			0.51	0.70	30

Table 5. Odor emission rate (OER) of cigarette smoke

		OER (m^3/cigarette)	$OER_{2.50}$ (m^3/cigarette)
Mainstream	Original	60	2.1
	Kenbridge filter	95	2.7
	Water filter	9.5	0.52
	Silica gel filter	0.46	0.038
	Activated charcoal filter	0.40	0.11
Sidestream	Original	2,400	430
	Kenbridge filter	780	43
	Water filter	33	9.4
	Silica gel filter	7.8	2.4
	Activated charcoal filter	1.0	0.68

The value of OER indicates the volume of air required to reduce the smoke odor to below levels which 50% of subjects perceived as not being unpleasant and where odor intensity was rated above 2 when they were exposed to the smoke generated by smoking one cigarette.

Conclusion

Odor concentration, odor intensity, and odor quality of cigarette smoke was measured in order to obtain the fundamental data on the sensory evaluation of cigarette smoke. The triangular bag test was employed, and the results obtained are as follows.

1) Among the odorants in the cigarette smoke, water soluble compounds influence smoke odor less than adsorbed compounds on silica gel and activated charcoal.
2) Considerable differences in the perception of odor intensity of the smoke were not found between smokers and nonsmokers, but fair differences in the judgement of odor quality and unpleasantness of the cigarette smoke.
3) The odorants which were removed by the silica gel and activated charcoal filters have a great influence on the odor quality of mainstream smoke, but this was not seen in the case of sidestream smoke. Also, the quality of odor changed with the dilution rate of the smoke.
4) The odor concentration was shown to be about 220,000-fold for mainstream and 170,000-fold for sidestream smoke. The generated volume of smoke was about 0.27 l of mainstream and about 28 l of sidestream smoke for one smoked cigarette. Odor emission rate was calculated to be $60\,m^3$ for the mainstream and $2{,}400\,m^3$ for sidestream smoke from one cigarette. From these results, it was recognized that the odor of sidestream smoke must have more effect on nonsmokers than the unpleasantness of the odor of mainstream smoke does.

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Lung Cancer and Indoor Air Pollution in Xuan Wei, China: Current Progress

X. He, R. S. Chapman, R. Yang, S. Cao, J. L. Mumford, and C. Liang

Summary

Xuan Wei County is a rural area in Yunnan Province, China. The population is about 1 million people, more than 90% of whom are farmers. Indoor air pollution levels are very high. Lung cancer mortality is among China's highest and, especially in women, is more closely associated with indoor burning of "smokey" coal, as opposed to wood or "smokeless" coal, than with tobacco smoking. Indoor air was sampled in Xuan Wei homes in which smokey coal, smokeless coal, and wood were burned. Levels of submicron particles containing mutagenic organics, especially in aromatic and polar fractions were generally highest during smokey coal burning, intermediate during wood burning, and lowest during smokeless coal burning. Animal natural inhalation experiments were conducted in Xuan Wei. The results showed that the lung cancer incidence in the smokey coal group was higher than in the wood and control groups. These studies suggested an etiologic link between domestic smokey coal burning and lung cancer in Xuan Wei.

Xuan Wei County, in northeastern Yunnan Province, China, has an area of 6257 square kilometers and lies on high plateau punctuated by mountain ridges. Its total population is about one million people, over 90% of whom belong to China's predominant ethnic group, the Han. Xuan Wei is rural – over 90% of residents are farmers – and until the 1980s was relatively untouched by modernization. Non-agricultural occupations include homemaking, coal mining, office work, and industrial work in chemical fertilizer plants, two coal-fired electric power plants (including one of Yunnan's largest), and a cement products plant. All of these plants were built after 1960.

Xuan Wei has 20 communes with populations of about 30,000 to 60,000. Each commune is divided into "large production teams," of which there are 385 in the County. Each large team is further divided into 15 to 25 "small production teams." The population is residentially stable; fewer than 20% of households experienced in- or out-migration from 1965 to 1985. Xuan Wei is well kown for its export of ham, though the typical local diet consists of corn, potatoes, rice, and about 400 grams of unsmoked pork per week.

Tobacco smoking is very rare in Xuan Wei females but common in males. Factory-made cigarettes and locally grown tobacco are used. Cigarettes are frequently smoked through water pipes. Tobacco is seldom used orally or nasally. For generations Xuan Wei residents have used three major fuel types, "smoky" coal, "smokeless" coal, and wood, for home heating and cooking. Smoky coal is glossy black, has a low sulfur content, and smokes heavily on firing. Smokeless coal is dull black, has high sulfur and ash contents, and produces little smoke. Because smokeless coal is powdery, it is usually mixed with clay to form briquets prior to burning.

Most Xuan Wei residents live in mud-brick or wooden two-story homes in which the cooking, dining, and living area is downstairs and the sleeping area is upstairs. The

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Table 1. Annual lung cancer mortality rates in China and the U.S.

Place and time period	Lung cancer mortality rate, per 100,000					
	Unadjusted		Age-adjusted to 1964 China population		Age-adjusted to 1970 U.S. population	
	Males	Females	Males	Females	Males	Females
China 1973–75	5.0		6.8	3.2	12.3	5.7
U.S. 1970	53.7	12.0	30.0	6.3	53.7	12.0
Yunnan Province 1973–75	2.8		4.3	1.5	6.9	2.5
Xuan Wei County 1973–79	27.0	24.5	27.7	25.3	43.2	38.7
Three Xuan Wei communes of highest lung cancer mortality (Cheng Guan, Lai Bin, Rong Cheng) 1973–79	114.4	120.6	118.0	125.6	186.8	193.4
55–59 year age group in high-mortality communes	849.4	904.0				
Three Xuan Wei communes of low lung cancer mortality (Pu Li, Yang Liu, Re Shui) 1973–79	4.0	2.8	4.3	3.1	5.8	4.3
55–59 year age group in low-mortality communes	17.1	18.1				

average household contains about five people, including children, parents, and often grandparents. Women generally start the domestic fire in the morning and prepare the two or three daily meals eaten at home, while men spend most daylight hours outside the home. Females generally start cooking at about age 12. Domestic fuel has traditionally been burned in a shallow, unvented pit in the floor of the dwelling's main room.

Annual unadjusted and adjusted lung cancer mortalities in China, the U.S., Yunnan Province, and Xuan Wei are presented in Table 1 [1]. In the table, as throughout this report, the term "lung cancer" includes carcinomas of lung, bronchus, and trachea. During 1973–75, males' and females' lung cancer mortalities in Yunnan Province were 19th and 25 th, respectively, among China's 29 provinces, municipalities, and autonomous regions [2]. In marked contrast, females' rates in Xuan Wei were higher than in any other Chinese county, and males' rates were among China's highest. Males' and females' absolute mortalities were similar, a surprising finding in view of the rarity of smoking in women. In the Chinese national cancer survey of 1973–75, lung cancer was the only type of cancer for which mortality in Xuan Wei exceeded the national average. Of 115 tumor specimens examined pathologically in Xuan Wei, 58% were squamous cell carcinomas, 28% were adenocarcinomas, and the remainder were mixed cell, undifferentiated, or alveolar carcinomas [3].

The marked difference in lung cancer mortality among Xuan Wei communes was especially striking. This difference is apparent in Table 1 and Fig. 1 [1], which shows a map of Xuan Wei County with commune boundaries, annual adjusted lung cancer mortalities in each commune, and locations of mines supplying smoky and smokeless coal for domestic use. That commune population denominators are reasonably large,

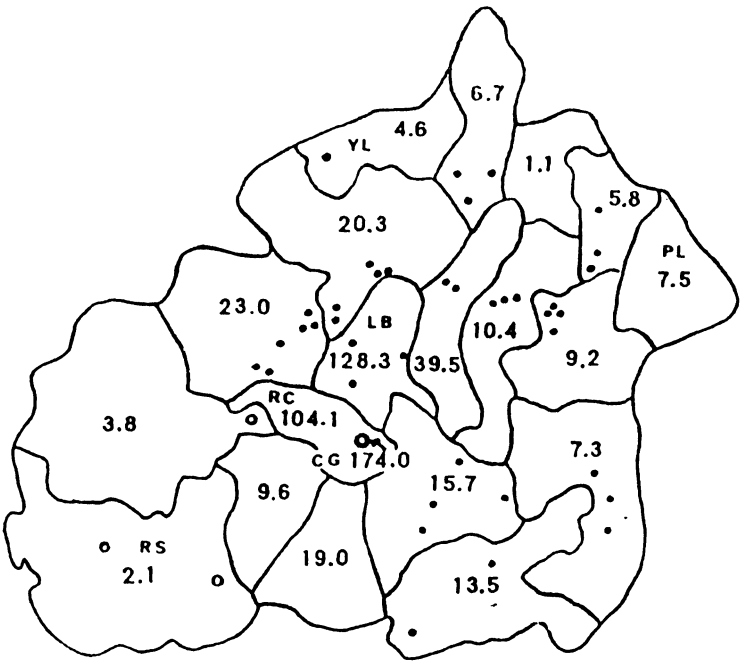

Fig. 1. Map of Xuan Wei County, showing commune boundaries, each commune's adjusted annual lung cancer mortality rate per 100.000 (both sexes, 1973–79), and mines supplying domestic coal (● = smoky coal. O = smokeless coal). Designated communes: high mortality – CG: Cheng Guan. LB: Lai Bin, RC: Rong Cheng; low mortality – PL: Pu Li, RS: Re Shui, YL: Yang Liu

and that vigorous lung cancer surveillance is conducted throughout the County, strongly suggest that the observed intercommune variation in lung cancer mortality is real.

On balance, Xuan Wei constitutes a very unusual natural experiment in lung cancer production. The marked local variation in the dependent variable (lung cancer mortality) presents a rare opportunity to investigate the relative etiologic roles of independent variables (known and suspected risk factors). That such important independent variables as population mobility and lifestyle are reasonably well "controlled" further enhances Xuan Wei as a setting for quantitative, interdisciplinary investigation of lung cancer etiology. Since the 1970's investigators from Beijing and Yunnan Province have conducted epidemiologic, aerometric, and chemical studies in Xuan Wei. In 1982 they were joined by investigators from the U.S. Environmental Protection Agency.

In 1982 we conducted a survey of fuel use and tobacco smoking in 11 Xuan Wei communes. The proportion of households in each commune using smoky coal before 1958 was highly correlated with commune-specific lung cancer mortality between 1973 and 1979 ($r = 0.78$, $p < 0.005$).

Table 2 shows 1982 survey results for 11 Xuan Wei communes, with very different lung cancer mortality rates. Sex-specific smoking habits differed little among 11 communes. But fuel use habits differed greatly, with all of CG, and none of RS, using smoky coal. In a previous survey [2], higher lung cancer rates were detected in farmers

Table 2. Percentage of tobacco smoking, households burning, smoky coal before 1958 and 1973–1979 adjusted lung cancer mortality in 11 Xuan Wei communes

Commune	Tobacco smoking [%]			Smoky coal [%]	Adjusted lung cancer mortality (per 100,000)
	Males	Females	Combined		
Cheng Guan	38.27	0.01	16.36	100.0	174.21
Lai Bin	45.11	0.08	22.85	89.7	128.31
Rong Cheng	37.62	0.01	16.08	81.9	104.09
Long Chang	32.64	0.03	16.67	76.1	39.46
Long Tan	37.02	0.03	18.83	78.0	22.96
Hai Dai	33.50	0.02	16.98	49.7	13.48
Pu Li	42.44	0.23	21.42	35.2	7.49
Ban Qiao	35.94	0.06	17.62	34.0	19.03
Luo Shui	45.79	0.01	22.50	2.7	9.55
Xi Ze	42.69	0.03	21.63	0.0	3.81
Re Shui	40.42	0.10	20.42	0.0	2.08

Table 3. Interim distribution of cigarette smoking 10 years prior to study in 33 male case-control pairs in Xuan Wei

		Cases		
		Not smoke	L.E. 16 cigarettes per day	>16 cigarettes per day
Not smoke		2	0	2
Controls	L.E. 16 cigarettes per day	0	6	2
	>16 cigarettes per day	3	7	11

than in coal miners or office workers, tending to exclude non-agricultural occupations as an important lung cancer risk factor.

A case-control study is currently in progress in Xuan Wei. In this study each lung cancer patient is matched on age and sex with a control subject whose residence is selected randomly from throughout the County. Interim findings from the first 39 case-control pairs of females and 33 pairs of males are presented in Tables 3 and 4. Among females, there were no smokers 10 years prior to the study. Among males, the great majority of case and controls had been smokers (Table 3), leaving few discordant pairs for consideration. At the same time, the number of controls smoking heavily, 21, was larger than the corresponding number of cases, 15. These observations suggest that smoking may not be as serious a lung cancer risk factor in Xuan Wei as in numerous other locations.

If length of using smoky coal were positively associated with risk of lung cancer, one would expect the odds ratio associated with smoky coal use to increase with increasing remoteness in the time at which smoky coal was used. In the interim case-control

Table 4. Interim odds ratios associated with smoky coal use now, 20 years ago, and at age 12 in Xuan Wei lung cancer patients and controls

Time using smoky coal	Males (33 pairs)	Females (39 pairs)
Now	1.5	2.6
20 years ago	1.3	2.9
Age 12	4.0	3.7

Table 5. Ames test mutagenic potency of total organics and organic fractions* of Xuan Wei indoor air pollution, 1983, by type of fuel burned

Potency revertants × 1000 per mg of sample	Total organic sample	Organic fractions			
		Aliphatic	Aromatic	Moderately polar	Polar
Smoky coal	2.6	0	2.1	1.4	4.0
Wood	0.9	0	3.4	2.6	0.5
Smokeless coal	2.6	0	2.5	3.0	2.0

* Organic fractions were extrated with different solvents, as follows: aliphatic, hexane; aromatic, hexane; moderately polar, dichloromethane; polar, methanol.

distributions, such a trend was observed in both sexes (Table 4). However, the absolute magnitudes of the odds ratios were not as great as might have been expected in light of evidence summarized above. Because females customarily spend much more time than males near the domestic fire, one might expect smoky coal-associated odds ratios to be substantially higher in females; in fact, the interim odds ratios did not differ greatly by sex.

Indoor air was sampled in Xuan Wei homes in which smoky coal, smokeless coal, and wood were burned in 1983. Concentrations of particulates and total organics (dichloromethane-extractable portion of particulate samples) were measured. Results showed that extremely high levels of particulates and total organics were observed in homes burning smoky coal (Suspended particulates is 24.4 mg/m^3, Dichloromethane-extractable organics is 17.6 mg/m^3) and wood (22.3, 12.3); levels during smokeless coal burning were considerably lower (1.8, 0.5). Levels of individual polycyclic aromatic hydorcarbons, including benzo(a)pyrene, were generally highest during smoky coal burning, intermediate during wood burning, and lowest during smokeless coal burning. In the smoky and smokeless coal samples, most organics were in the aromatic (hexane/benzene-extractable), moderately polar (dichloromethane-extractable), or polar (methanol-extractable) fractions. Aliphatic (hexane-extractable) concentrations were relatively low for all fuel types.

The Ames test mutagenicity (revertants per cubic meter of air) of total organic combustion samples from smoky coal was considerably higher than that of smokeless coal or wood samples [1]. The mutagenic potency (revertants per milligram of sample) of organic smoky and smokeless coal samples was higher than that of wood samples (Table 5). The potency of the polar fraction was highest in smoky coal combustion

Table 6. Concentration of chemical pollutants in the field of animal experiment in Xuan Wei County (mg/m^3

Group	Bap*	TSP	SO_2	H_2SO_4	CO
Control	1.47	0.91	0.02	0.02	1.87
Wood	43.09	14.99	0.05	0.27	80.82
Smoky coal	506.44	14.38	0.18	0.19	97.63

* $\mu g/100\,m^3$

samples and lowest in wood samples, but the potency of each of the other organic fractions did not differ greatly among the three fuel types. On balance, differences in mutagenic potency among the fuel types were not as great as differences in lung cancer mortality among the communes using the different fuel types.

Natural inhalation studies consisting of 345 Wistar rats and 558 Quming mice were conducted on March, 1982 – October, 1983 in Xuan Wei County. Both rats and mice were divided into three groups: smoky coal, wood and control groups and were kept in three separate rooms in which animals inhalated different smoke from smoky coal or wood burning. The smoky coal used in this study was from local mine (Lai Bin commune) in which high mortality of lung cancer was found, the wood from area with low mortality of lung cancer (Re Shui commune). The temperature of room for control group was kept by using electronic oven. The burning habits for smoky coal and wood in this inhalation study, and consumed quantity for smoky coal and wood per day were similar to that usually for local residents (average: 8.4 kg per day). During the study, the samples of the air pollutants for each inhalation rooms were taken for 6 times per day, 3–9 days for one month. The results of concentration for some chemical pollutants are listed in Table 6. This study showed that the incidences of lung cancer for the squamous cell, adeno-squamous and adenocarcinoma in mice were 0% (0/171), 0% (0/171) and 17% (29/171) for control group; 2.3% (4/177), 1.1% (2/177) and 42.4% (75/177) for wood group; 11.4% (24/210), 21.4% (45/210) and 56.6% (119/210) for smoky coal group, respectively. The total incidence of lung cancer for mice is displayed in Fig. 2. For rats, the incidences of lung cancer for squamous and adenocarcinoma were found to be 0% (0/110) and 0.9% (1/110) for control group; 0% (0/110) and 0% (0/110) for wood group; 62.7% (84/125) and 0% (0/125) for smoky group, respectively. The total incidences of lung cancer for rats were 0.9% (1/110) for control group, 0% (0/110) for wood group, and 67.2% (84/125) for smoky group, respectively.

On balance, this animal study indicated that air pollutants from smoky coal burning was related to high incidence of lung cancer observed in the study. The differences due to lung cancer incidences between smoky coal group and wood group or control group were statistically significant ($P < 0.01$).

Conclusion

In industrially developed countries tobacco smoking and some types of occupational exposure have consistently emerged as important etiologic factors of lung cancer.

Though tobacco use in Xuan Wei has not yet been fully characterized, available evidence renders it most unlikely that tobacco appreciably affects women's lung cancer rates.

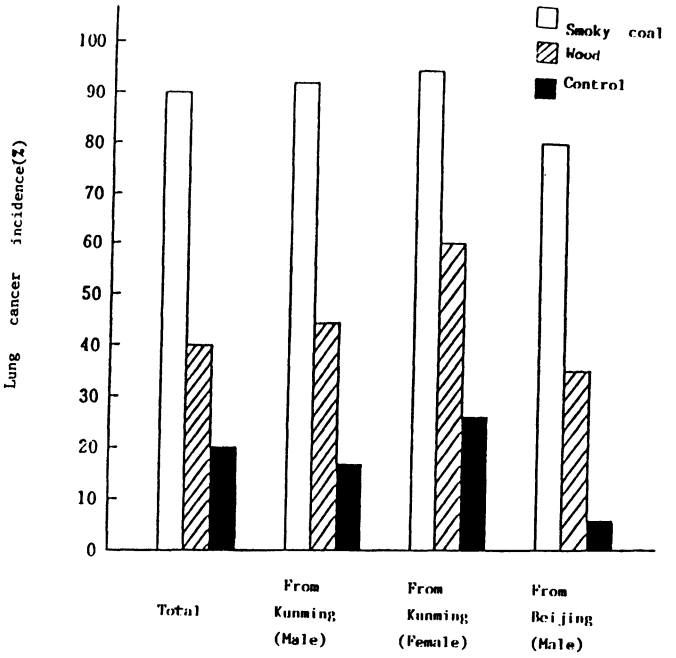

Fig. 2. Lung cancer incidence in mice

These observations lead us to the hypothesis that: Indoor air pollution from smoky coal burning is the prime determinant of lung cancer in Xuan Wei County, especially in women.

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Characterization of Indoor Pollution in Korea

C.-W. Cha and S. H. Cho

Introduction

Carbon monoxide poisoning is one of the most serious public health problems in Korea. According to the results of recent surveys on the incidence of CO poisoning, the severity of health hazards by this invincible demon is a threatening one.

In Korea, "Ondol," a very unique heating system built under the floor, has been employed. Coal briquettes are widely and economically used in the "Ondol" system as a domestic fuel since few natural resources exist in Korea.

Carbon Monoxide Poisoning in Korea

According to Korean government statistics, coal briquettes provide more than 50% of total energy consumed in households. And 56% of households in Korea use coal briquettes as heating fuel. Given this situation, we assume that half population, about 20 million, of Korea have a chance of being poisoned by coal briquette gas, mainly CO gas (Table 1).

An epidemiological study of CO poisoning, which surveyed about half a million people nationwide during 1984, showed that one million Korean people might have suffered from coal briquette gas poisoning, especially from CO. More than 85% of those intoxicated by CO were mild cases with symptoms such as headache, emesis, and chest pain, but around 14% were in semicomatose or comatose states which strongly indicated intensive oxygen therapy.

Figure 1 shows the monthly distribution of patients hospitalized in the Seoul National University hospital due to CO poisoning for a period of 10 years from 1969–1978 and the monthly mean temperature in Seoul. As expected, CO poisoning cases occurred during the cold season, especially from November through January. The peak monthly variation occurs in December and is several times more than the corresponding variation in July.

As regards the relation between CO poisoning cases and weather, one report suggested that the incidence of CO poisoning might be correlated with meteorological

Table 1. Energy consumption using coal briquettes as fuel in Korea

1 Coal briquette fuel hole system	42.5%
2 Piped coal briquette boiler system	13.9%
Total	52.6%

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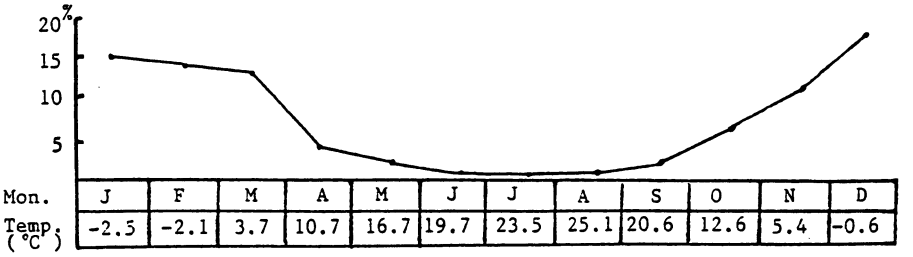

Fig. 1. Monthly distribution of CO poisoning estimated through National Survey 1984. Total number of CO poisoning estimated was about 1 million. Mild case, 86.2%; Severe case, 13.5%; Death, 0.3%

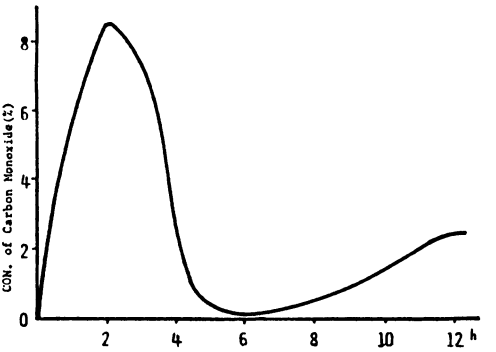

Fig. 2. Percent distribution of CO gas from a briquette by hour under natural conditions. Amount of CO gas/briquette, 225 which can kill 376 persons (* Lethal dose/day = 0.6 l)

parameters such as temperature, wind speed, and humidity. Among these meteorological parameters, ambient temperature was shown to have a highly significant correlation with CO poisoning cases.

However, other survey results suggested that factors other than meteorological effects which influence the seasonal pattern of CO poisoning are likely to include the kind of socioeconomic environment in the household.

Figure 2 shows the distribution in percent of the concentration of carbon monoxide after 12 h of burning coal briquettes with sufficient air supply. In general, a coal briquette which is made of 22 holes emitted about 2251 of carbon monoxide gas. This amount of CO gas per briquette can kill about 376 people. Carbon monoxide concentration was highest 2–3 h after the coal briquette was burned. Since a coal briquette was changed 2–3 times per day in the heating system in most Korean households and it was in general changed before sleeping, many people might be at risk intoxication of CO gas while sleeping.

We can say that various types of intoxication from CO may depend on the concentration of CO and actual exposure time. However, we can not measure on-site concentrations of carbon monoxide to which household members are accidentally exposed.

Dr. Jack Peterson [1] developed one formula for estimating CO concentration. He first estimated COHb in blood by using the hours of exposure to CO and hours after CO

Table 2. Estimated on-site concentration of carbon monoxide to which the comatose patients were exposed[a]

Concentration of CO (ppm)	No. of patients	Duration of exposure (h)						
		1	1–3	3–5	5–7	7–9	9–11	11–13
100– 300	7	–	–	–	–	2	3	2
300– 500	17	–	–	–	2	7	8	–
500– 700	17	–	–	3	8	6	–	–
700– 900	13	–	1	9	2	1	–	–
900–1,500	7	–	4	3	–	–	–	–
1,500–3,000	4	2	2	–	–	–	–	–
3,000–6,000	2	2	–	–	–	–	–	–
Total	67	4	7	15	12	16	11	2

[a] Estimated with using the mathematical model proposed by Jack E. Peterson [1].

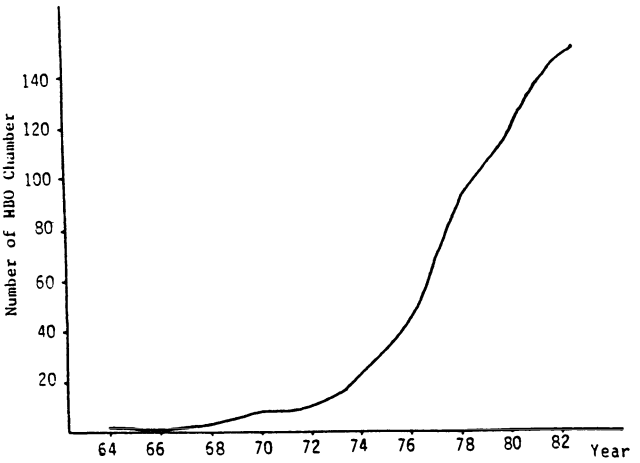

Fig. 3. Number of monoplace hyperbaric chambers in Korea by year

exposure to measure the COHb and then estimated the on-site CO concentrations to which intoxicated persons were exposed, based on reverse calculation of the first formula.

Table 2 shows the estimated on-site CO concentration to which the comatose patients were exposed, based on Peterson's mathematical model from people with CO poisoning admitted to the emergency room of Seoul National University Hospital during 1980–1982.

We can say from Table 2 that CO poisoning cases occur with greatest frequency in the range of 500–900 ppm of carbon monoxide after exposure 3–7 h. Since these CO concentrations were mathematically estimated, we will initiate a pilot study in the future to try to measure on-site CO concentrations.

Table 3. Age and sex distribution of the patients with carbon monoxide poisoning treated by hyperbaric oxygen therapy*

Age	Male		Female		Total	
	No.	[%]	No.	[%]	No.	[%]
0–14	55	5.7	62	4.8	117	5.2
15–29	514	53.3	662	52.3	1,182	52.7
30–44	195	20.2	193	15.1	388	17.3
45–59	99	10.3	148	11.6	247	11.0
60–	93	10.0	198	15.5	291	13.0
unknown	8	0.8	9	0.7	17	0.8
Total	964	100.0	1,278	100.0	2,242	100.0

* Data from S.N.U.H., Korea, 1969–1978.

Table 4. Admission rate of the patients with carbon monoxide poisoning by arrival time*

Arrival time	No. of patients	No. of admissions	Rate of admission
– 4:00	32	3	9.4%
4:00– 6:00	61	5	8.2
6:00– 8:00	115	17	14.8
8:00–10:00	202	24	26.7
10:00–12:00	118	52	44.1
12:00–14:00	40	23	57.5
14:00–16:00	36	15	41.7
16:00–	37	15	22.4
Total	671	184	27.4

* Data from S.N.U.H., Korea, 1969–1973.

In an effort to confront the social problem of CO poisoning, a hyperbaric oxygen (HBO) chamber has been introduced to Korean medical institutions since 1964.Thanks to the Korean government's support there are now more than 300 of these units available. Figure 3 shows the cumulative number of monoplace hyperbaric chambers in Korea during 1964–1982. These hyperbaric chambers have even been provided to local clinics. In general, the recovery rate of CO poisoning patients by hyperbaric oxygen therapy is about 98% according to the SNU hospital report.

Table 3 shows the age and sex distributions of the patients with CO poisoning admitted to the Seoul National University Hospital from 1969–1978. The peak age group is from 15–29 years. The sex ratio shows 1 over 1.3. This table suggests that young, working age individuals may be at higher risk of accidental CO poisoning in an urban area. Also, women are at great risk to CO exposure in their household environment.

Table 5. Complications of admitted patients*

Complications	No. of patients	Percentage
Pulmonary edema and aspiration pneumonia	29	34.1
Trophic changes such as decubitus, burns, and myositis	31	36.5
Neurologic disorders	20	23.5
Psychologic disorders	5	5.9
Total	85	100.0

* Data from S.N.U.H., Korea, 1969–1973.

Table 6. Sample courses of CO poisoning since medical treatment

- 11.7% of inpatients of Yonsei Hospital (1976–1984) showed brain syndrome as delayed sequela (Min)
- 11.8% of inpatients of Yonsei Hospital (1976–1981) showed delayed neurologic sequela (Choi)
- Among 73 patients discharged from SNU Hospital (1985)
  4.1% partial recovery
  6.8% delayed sequelae
  5.5% death confirmed through follow-up at 10, 30, 70, 180 day survey (Kang)

Table 4 shows the admission rate of the patients with CO poisoning by arrival time to the SNU hospital. The arrival time seems to be a good index for predicting the prognosis because a lower admission rate means a higher discharge rate on the first hospital day with complete recovery.

Among the types of complications of admitted cases, acute decubitus was the most frequent, followed by pulmonary complications, and neurologic disorders (Table 5).

Several investigators have studied the various types of complications among paients admitted due to CO poisoning.

For example, as shown in Table 6, Dr. Min surveyed 2,967 people with CO poisoning admitted to the emergency room at Yonsei University Hospital from 1976–1984. Among 738 inpatients, based on the above cases, 86 patients (11.7%), mostly in the old aged group, showed brain syndrome with CO delayed sequelae. Also, Dr. Choi surveyed 2,360 CO poisonings that occurred from 1976–1981. About 12% of inpatients were diagnosed with delayed neurologic sequelae. Dr. Kang and other researchers did a follow-up survey at 10, 30, 70, 180 day intervals of 73 CO poisonings cases after discharge from the SNU Hospital. Among these, about 84% had recovered completely, whereas 6% had died.

Conclusion

CO poisoning is an important phenomenon in Korea. It will occur in the home as long as Koreans use coal briquettes or maintain the traditional "Ondol" system.

Despite efforts to prevent CO poisoning in homes throughout the nation, knowledge about it is not yet complete. Home monitoring of carbon monoxide concentrations can provide a means of preventing fatal CO exposure.

Reference

1. Peterson JE et al (1970) Arch Environ Health 21:165–171

Indoor Air Quality and the Pollution Transition

K. R. Smith

Summary

Accompanying economic development there has been a transition in the type and magnitude of environmental risks facing nations. The traditional risks associated with rural poverty such as those due to infectious diseases and poor village air and water quality and are supplanted by modern risks such as chemical wastes, air pollution from fossil fuel combustion, and chronic diseases. Under some development scenarios, however, societies can be subjected to excessive amounts of both types at the same time.

This paper examines this risk or pollution transition from the standpoint of indoor air quality, which is often the chief determinant of total exposure on each side of the risk transition. It follows the evolution of cooking technology in South Asia to illustrate the changes in indoor air quality that accompany development. It ends with a call for an International Kitchen Study to characterize these changes more completely and provide the basis for mitigation and control.

Economic development and international trade result in transitions in the type and pattern of environmental risks affecting different regions of the world. As shown in Fig. 1, one aspect of this transition is the gradual substitution of traditional risks relating to rural poverty (the declining curve on the left) by those characterizing industrial cities (the rising curve on the right). In the presently developing countries, because of the direct and indirect influence of developed nations, modern technologies and their risks are introduced during earlier phases of economic development than in the past. On Fig. 1, this would be represented by the modern risk curve shifting to the left. Consequently, undue risks of both types may exist side by side, for example when uncontrolled and excessive pesticide use occurs in regions where poor sanitation still persists and thus people are subjected to both threats through their water supplies. While this risk transition involves a range of natural and environmental risks, here I will focus on those related to air quality, part of what might be called "the pollution transition".

In some cases risk enhancement can occur from the interaction of modern and traditional sources. Most rural Chinese, for example, burn crop residues for cooking and heating but many live in areas that have started to use modern agricultural chemicals. As a result, pesticide residues may exacerbate the danger of indoor cookstove smoke. At a different level of development, in the Los Angeles air basin, automotive air pollutants settle onto natural vegetation and can be released again in significant amounts during brushfires.

Figure 1 shows only one of several different possible paths for the two curves. For example, the density modern sources of air pollution may rise rapidly at first during urban development while accompanied still by significant numbers of traditional sources such as biofuel-fired cookstoves. In later stages of economic development, however, the traditional sources are supplanted nearly entirely by modern fuels and, eventually, by

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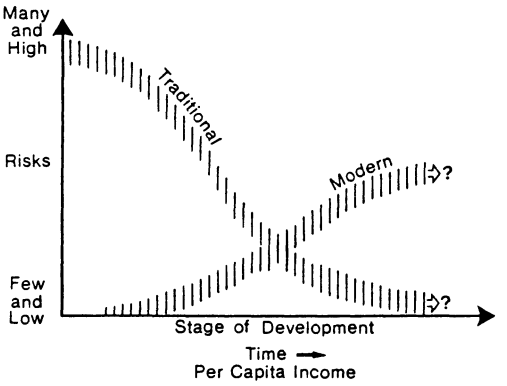

Fig. 1. The risk transition. As nations develop the nature of the environmental risks that affect them changes. The traditional sources of risk that come about in mainly rural societies, where subsistence agricultural dominants, slowly decline and the risk associated with modernization and industrialization rise. Depending on how a nation manages this transition, it may find itself exposed to a significant amount of both kinds at once. Examples are India and China, where urban air pollution from fossil fuels is growing alongside yet-to-be-alleviated sources of rural air pollution exposure such as poor quality cooking fuels

cleaner fuels such as gas and electricity generated with emissions control (Bennett et al. 1985). Combining this with the changes in the urban: rural population ratios, make a determination of exposure trends more complicated than shown by Fig. 1.

For many years, the localization of traditional air pollution sources such as household cookstoves, led the air pollution community to ignore them and to focus on the more obvious and growing ambient air pollution from industries and motor vehicles. Application of the concept of total exposure assessment, however, has important effects on this view of the pollution transition (USNRC 1985). For example, it is clear that most people spend most of their time indoors where their exposure is not directly indicated by ambient air quality. In addition, most of the world's person-hours are spent in developing countries inside village houses in rural areas. This is the environment that most closely represents the bulk of human experience, throughout history as well as today. Thus, the most important location for air quality monitoring in terms of total human exposure is in places that represent the other end of the spectrum from the sites most commonly monitored, which have been outdoors in industrial cities.

Total exposure to many air pollutants is largely determined by indoor conditions on both sides of the pollution transition. That indoor air pollution levels in both conditions can lead to significant exposures has become widely recognized in recent years. It may be valuable, however, to look at this situation in its evolutionary sense, as stages in a continuous development path.

Cookstove Evolution and Indoor Air Pollution

The effect of the pollution transition on indoor air quality can be illustrated by the evolution of the most common combustion device in history, the household cookstove. In the presently developed countries, nearly all cooking is done with gas or electricity.

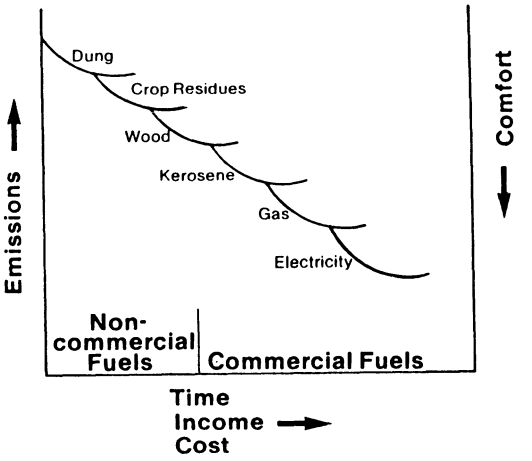

Fig. 2. The evolutionary path for cookstoves. As evidenced by both cross-sectional and historical comparisons, there is a path of evolutionary change in cookstove technology. At the left are the dirtiest fuels requiring the least capital and technology, but costly in terms of human effort, health, and lost opportunity for other uses. At the right are the cleanest and most efficient fuels, although requiring more capital investment and technology. The arrow marks the approximate point for two important and related transitions. The first is that between the non-commercial fuels that lie below and which households gather or barter for on their own and the modern fuels and fraction of woodfuel that is bought and sold. The second is between centralized fuel cycles characterized by the petroleum-based fuels and the distributed systems characterizing most biofuels. This point also, coincidently marks the approximate global median point, i.e., about half the world's households lie both below and above this mark. Since stove efficiency rises along the continuum, however, there is considerably more heat released by stoves in the lower half

Indeed, the difference between them in cleanliness (air emissions) has been the subject of much indoor air quality concern and research. While gas may appear much more polluting than electricity, these two sources of cooking heat actually lie relatively close together at the end of a long path of evolution in cooking technology over which most of the world's households have not yet traversed. While the details of this path differ somewhat geographically and historically, the general outline is similar.

The situation in South Asia provides an opportunity to describe a typical path. As shown in Fig. 2, the worst conditions are experienced by the least economically developed groups. These people have so little access to fuels that they must rely on dried animal dung, a resource that in most circumstances has a higher value as fertilizer and construction material. This is because cooking fuel is one of the most basic needs and, like food itself, almost anything else must be sacrificed for it if necessary. It thus serves the poorest and is the poorest fuel, as shown by its level of "comfort", which might be interpreted as a three-way combination of non-independent factors: 1) time spent in fuel gathering, storage, and use; 2) efficiency of combustion; and 3) air emissions (Foundation for Woodstove Dissemination 1987).

Somewhat more comfortable (quicker, more efficient, and cleaner) is the use of crop residues for cooking fuel. Much preferable, if available and affordable, is wood, the most prevalent cooking fuel in the world now and throughout history. These three biofuels are still used daily for cooking by more than half the world's households (Hughart 1979). As

shown in Fig. 2, there is an increasing trend of cost (and thus income group served) and comfort with these fuels.

Somewhere in the wood phase occurs another important transition, from noncommercial to commercial fuels. People begin to buy some of their fuel instead of gathering it all themselves. This transition is important for a number of reasons, not least of which is that people who pay for their fuel are more likely to be motivated to spend money on improved cookstoves designed to raise fuel efficiency.

The fuel phase beyond wood is kerosene, often the first of the modern cooking fuels to be used in rural areas and, along with another middle distillate, diesel, one of the two classic fuels of development. The increase in comfort and cost by shifting from wood to kerosene is substantial. Afterwards come gas, usually first as bottled gas (LPG) then natural gas followed eventually, perhaps, by electricity.

Obviously, this is an oversimplified and overgeneralized illustration. In some areas, dung is not used at all. In others, such as China, there is so little wood remaining that modern fuels come directly after crop residues. The first modern fuel is sometimes not kerosene, but coal, as in China. In some areas, upgraded biofuels such as charcoal and biogas play roles (Smith 1987a). In addition, special requirements for cooking, related to local cultural practices for example, can affect the definition of comfort and efficiency.

Nevertheless, the pattern shown in Fig. 2 reveals several interesting relationship. Consider, for example, the effect of the oil crisis on this evolutionary path. By increasing the relative cost of petroleum-based fuels (including kerosene and gas), the oil crisis effectively moved these first modern fuels to the right in the figure, putting them further out of the reach of the poor. This has the effect of stretching out the use of biofuels, i.e. people are willing to spend more for them than in the past. Payment may be in the form of money or in additional effort spent to gather fuel, but in either case, the result is substantial additional pressure on biofuel resources such as forests, and a longer exposure duration for a larger population than was the case in the past (Smith 1987a).

Another impact of this stretching out is that it may open up niches for new fuels, upgraded biofuels or coal, for example. No one would use coal instead of kerosene, if they had a choice, but because of the change in relative costs, they may be forced to do so. Indeed, the shift of prices has led to cases of devolution where communities have been forced backwards down the path. This has happened at every level: kerosene stoves are now used for heating, for example, where gas or electricity were used in the past as in Japan and the USA. Some groups that once relied on wood, now must use crop residues and dung because the rise in relative costs of fossil fuels has helped drive up the price.

By comparison to almost any other combustion device, there has been little research on the air emissions of cooking stoves, except those using gas. Nevertheless, enough work has been done to obtain some empirical verification for the hierarchy of comfort illustrated in Fig. 2 (Ahuja et al. 1987; TERI 1987; Smith 1987b). Table 1 lists newly available data for two major categories of pollution: total particulates and carbon monoxide (CO). The first emissions index shown, the emission factor in grams of pollutant per kilogram of fuel, does not show a consistent trend although there is a general decrease in going down the list. For determining impact on household comfort, however, the second index, emissions per standard cooking task (bringing three liters of water to boil and simmering for 15 min), is probably superior. By this measure, there is a sharp and consistent trend of improvement.

The two indices differ according to variations in fuel efficiency among the fuels. In addition, of cource, efficiency and emissions are functions of stove design and operation as well as fuel. The data shown are based on tests of typical stoves used in India. Improved stoves with higher efficiencies, fuels, or flues would result in different numbers.

Table 1. Air pollution emissions from different cooking fuels: the evolutionary trend (Sources: TERI 1987; Smith 1987b; Davidson et al. 1985)

Cooking fuel	Carbon monoxide		Total suspended particulates	
	E[a]	E_t[b]	E	E_t
Dung	35 g/kg	36 g	5.3 g/kg	1.6 g
Crop residues	55	16	4.7	1.4
Wood	29	5.3	1.9	0.4
Kerosene	69	2.6	3.3	0.1
Gas	8.6	0.3	0.1	0.002
Electricity	–	–	–[c]	–[d]

[a] E = emission factor, g/kg, grams of pollutant per kilogram of fuel.

[b] E_t = emissions (g) per standard cooking task.

[c] Indian coal power plants with well-operating first-generation emission controls (85%) might have a particulate emission factor of about 30 g/kg (Smith, 1987b).

[d] The exposure commitment of a typical Indian coal plant has been calculated to be about 50 times less than that of a wood-fired stove for each unit of energy delivered to the cookpot (Smith, 1987b). Energy losses at each step of both fuel cycles have been taken into account: It takes 0.3 kg Indian coal of 20 MJ/kg and 20% ash burned at 30% thermal efficiency to send electricity over wires with a 20% loss to a stove with 80% efficiency to obtain 1 MJ in the pot. It takes about 0.33 kg wood of 15 MJ/kg burning in a moderately efficient woodstove of 20% efficiency to accomplish the same task.

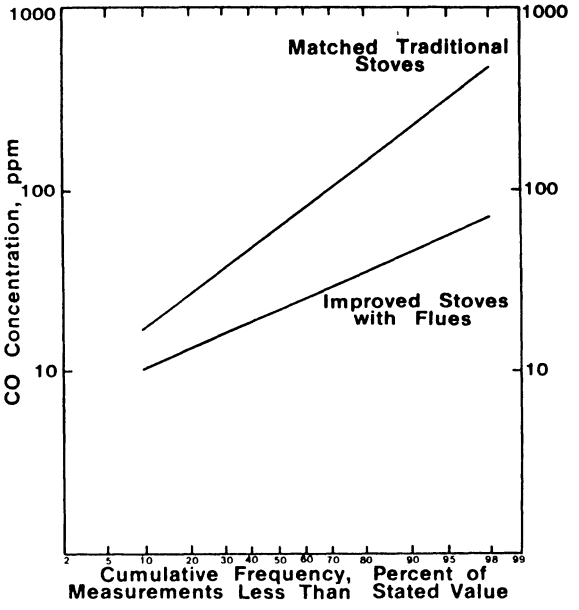

Fig. 3. The difference in indoor carbon monoxide concentration in households with improved compared to traditional wood-fired cookstoves in a study in western India. Based on cross-sectional measurements in about 50 households during cooking. (From Smith and Durgaprasad 1987)

Figure 3, for example, shows the impact on measured indoor carbon monoxide concentrations of a change from traditional to one type of improved stove in India (Smith and Durgaprasad 1987).

It should also be noted, however, that a change to improved stoves would not only result in a shift downwards in Fig. 2 because of improved comfort, but also to the right because of greater cost. This could be represented in Fig. 2 if each of the fuel curves shown were subdivided into sections of traditional and improved stoves.

Electric stoves release no combustion products in the house but may be responsible for substantial emissions from power plants, depending on fuel and technology. Rough calculations show, however, that in Indian conditions the particulate exposure commitment of one meal cooked by electricity supplied by a typical coal power plant is some fifty times less than that for a simple wood cookstove (Smith 1987b). As shown in the notes to Table 1, however, this would mean that such a system has a particulate exposure commitment somewhat higher than a gas cookstove but still substantially less than kerosene. Cleaner fuel or more effective pollution controls at the power plant could bring the level down below gas (e.g., to 0.5 mg per standard cooking task by changing particulate control from 85% to 99%).

Just as fuels and stoves cannot really be considered separately, indoor air quality is as much a function of mixing volume and ventilation as of emissions. These interact with emissions rate as well as total emissions, and thus cooking time must also be considered. Nevertheless, the general trends seem clear.

Comparison with Environmental Tobacco Smoke

Since most other contributors to this volume have focused on environmental tobacco smoke (ETS), it may be worthwhile to compare typical ETS concentrations with those found in kitchens at different points along the cookstove evolutionary path. This may help put both in perspective.

There have not been enough measurements among the thousands of house-stove-fuel combinations that make up cooking patterns in developing countries to know average indoor concentrations and exposures. Only available are a handful of studies in what, it can be hoped, are fairly typical situations in their locale. In addition, although it is known the biofuel smoke, like tobacco smoke, contains hundreds of chemical species, only a few have been monitored.

Table 2 presents a rough comparison. Starting from emissions and then moving to concentrations and exposures, the table compares the pollution derived from combustion of cigarettes (mainstream and sidestream), and wood. It uses five common pollutants as indicators: CO, respirable particulates (RSP), particulate benzo(a)pyrene (BaP), formaldehyde (HCHO), and nitrogen dioxide (NO_2).

It is easy to see from the table that for these pollutants, ETS is not likely to be much of a concern in that majority of the world's households using biofuels unless ETS contains substantially more toxic materials than revealed by the five indicators shown. By extension from the emission factors in Table 1, it would seem that the same could be said of ETS in households cooking with kerosene. Considering the relative populations at risk, the population exposure (in terms of exposure units = microgram-person-years/cubic meter) is likely to be much higher on a global basis from traditional cooking fuels than from ETS (Smith 1986). Indeed, for some pollutants, the total cooking fuel population exposure probably rivals that from active smoking.

Table 2. Comparison of emission factors, concentrations, and nominal doses for active smoking, environmental tobacco smoke, and woodsmoke from cooking. (Source: Modified from Smith 1987b)

	Active smoker (mainstream)	Passive smoker (sidestream)	Village cook (wood smoke)
Emission Factor (per kg of biomass)			
CO	17 g	43 g	40 g
TSP	14 g	24 g	4.0 g
BaP	0.018 mg	0.06 mg	0.5 mg
HCHO	0.03 g	1.5 g	0.4 g
NO_x	0.35 g	2.7 g	0.5 g
Concentration (per cubic meter of air)			
CO	1,800 mg	2.6 g	50 mg
TSP	1,500 mg	1.5 mg	5.0 mg
BaP	1,900 ng	3.5 ng	1,500 ng
HCHO	3.1 mg	0.08 mg	1.0 mg
NO_x	33 mg	0.14 mg	1.0 mg
Nominal dose (per day)[a]			
CO	680 mg	12 mg	130 mg
RSP	530 mg	6.0 mg	13 mg
BaP	660 ng	16 ng	3,800 ng
HCHO	1.2 mg	0.33 mg	2.6 mg
NO_x	13 mg	0.6 mg	2.6 mg
Assumptions			
TSP and BaP 95% respirable Adult women	940 ml/breath; 10 puffs/cig; 2 packs/day	200 m^3 room; 20 cig/h; 2 ACH; perfect mixing; 4-hour meeting; 1.1 m^3/h air	Data from Indian, Nepal, Guatemala, and, New Guinea; 2.6 m^3 total air

[a] Nominal dose equal to mass inhaled. A cigarette smoker in the same 4-hour meeting as the passive smoker would receive a total nominal dose equivalent to approximately the two added together. If the smoker is assumed to exhale half of the respired pollutants, the passive smoker's concentrations and doses could be expected to be larger by CO: 20%; TSP: 30%; BaP: 15%; HCHO: 1%.

Only when a community evolves to the point of using gas stoves does the kitchen environment become clean enough to worry about ETS. Whatever the health impacts of ETS exposures, therefore, this comparison would seem to indicate that much larger effects might be expected in these other situations. The relative importance of respiratory disease in developing countries, where it is the chief cause of mortality and morbidity, is consistent with, although not proof of, this point.

Conclusion

One final point might be illustrated with Fig. 2. If access to adequate cooking fuel is a basic need, then it is not too much of a leap to the idea that a minimum degree of kitchen comfort (time and fuel efficiency as well as cleanliness) is a basic human right. At the least, this minimum might be set at the level of an improved vented cookstove using wood or upgraded solid fuel (charcoal or clean coal). As shown in Fig. 3, however, this may still not be very clean by many standards. Perhaps, therefore, it should be set at the level of the cheapest of the liquid fuel stoves. The appropriate level would, of course, depend on local circumstances.

If such a basic right were to be added to the handful of others generally accepted, such as education, food, and shelter, there would be additional reason for government intervention to help achieve it for the poorest groups that now lie below this point on the path shown in Fig. 2. The goal would be to move them up to the minimum by subsidy or other government intervention until the time came that they could afford to support themselves at this level. It would imply that, just as the government should subsidize education and other basic needs, it should intervene to achieve a minimum of household comfort because it brings such social benefits as improved maternal and child health and increased efficiency of household work.

I would like to end by seconding a proposal made recently by Wieslaw Jedrychowski (1987) that the international indoor air pollution community consider the scientific and welfare benefits to be gained by embarking on an International Kitchen Study. Included would not only be examination of stoves and fuels, but also of ventilation and other aspects of comfort and health. Due consideration would need to be given to local cultural and social factors. The purpose would be to document in more detail the human exposure and efficiency characteristics of several important evolutionary paths such as the one in Fig. 2. Such an effort could help direct government policy in the encouragement of household conditions that are compatible with longterm development goals.

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Domestic Smoke Pollution and Acute Respiratory Infection in a Rural Community of the Hill Region of Nepal*

M. R. Pandey, R. P. Neupane, and A. Gautam

Acute respiratory infection (ARI) is the cause of death of at least 5 million children under 5 years of age. Most of these deaths occur in developing countries. Domestic smoke pollution is very common in many parts of the developing world. The present study was undertaken in a rural community of the hilly region of Nepal to find out if domestic smoke pollution is a risk factor of ARI in infants and children below 5 years of age. A positive correlation was found between moderate and severe ARI and exposure to domestic smoke pollution as measured by the time spent near fireplace.

Introduction

More than five million children under five years of age die in the world each year from acute respiratory infection (ARI) and most of these deaths occur in developing countries [4]. About 20 percent of infants born in developing countries fail to survive their fifth birthday. One fourth to one third of these deaths may be attributed to ARI as an underlying contributing factor. Nepal, one of the least developed countries in the world, has unacceptably high infant and childhood mortality rate. ARI is an important cause of illness and death among infants and children under 5, especially in the hilly and mountainous region of the country [6].

It is generally considered that air pollution is a problem of industrially developed countries. But, the problem of indoor air pollution in rural locations in developing countries, where combustion of biomass fuels are the principal source, is considerable. This problem is common in northern Indian belt, Nepal, large parts of China, northern Burma, northern Thailand, Papua New Guinea, Irianjaya region of Indonesia, Guatemala, Central and Southern America. It is estimated that about half the world's households cook daily with biomass fuels. Most of this cooking is done indoors in unvented stoves. The highest exposures are probably experienced by women, infants and young children. Measured levels of air pollution in these houses of developing countries greatly exceed indoor and outdoor concentration found in developed countries [8]. Epidemiological study of chronic bronchitis among adults has shown a statistically significant association between prevalence of chronic bronchitis and exposure to domestic smoke pollution [7].

There have been very few studies to observe the effect of environmental factors such as air pollution as a risk factor for ARI in developing countries. ARI is a particularly important problem in Nepal perhaps because of the climate, terrain and living conditions

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of the people. The present community based study has been undertaken to find out if there is any relationship between domestic smoke pollution and ARI.

Methods

The study area comprised two contiguous village panchayats, Talku Dundechaur and Chhaimale, and their adjacent villages, Dakshinkali and Phakhel, situated on the south-west edge of Kathmandu valley (about 18–24 kilometres from the city centre at the altitude of 4,000–6,000 ft. above sea level). The area is totally free of industrial and general atmospheric pollution. The terrain and living conditions of the area are typical of rural communities in the hill region of Nepal. The villagers are predominantly farmers with a subsistence economy. In the study area, as in most other parts of hilly Nepal, traditional stoves burning biomass fuels, such as firewood and straw, are used for cooking and heating in ill-ventilated houses. Domestic smoke pollution is considerable as the houses have no chimney.

The eligible population for this study comprised everyone under 5 years of age who permanently resided in the area. In the scattered rural population, the eligible infants and children were visited fortnightly by trained lay reporters under the supervision of health assistants. The recording of information on ARI was done using a method for classifiying severity (Grade I, II, III and IV) which was originally developed and used in studies in Papua New Guinea. Data from the observed infants and children under 2 years were analysed to determine whether there was any relationship between domestic smoke pollution and ARI. Exposure to domestic smoke was assessed by asking the mothers about the average time per day spent near the fireplace by the infants and children under 2 years. In older children, aged 2–4 years, estimates of exposure to smoke could not be made because the children were too mobile. For this reason, no attempt was made to collect the data on smoke exposure in this age group. In contrast to the first sub-study, which covered an earlier 6 months period (February-July 1984), the new sub-study covered 3 months (November 1984 – January 1985) among the same population. It employed, however, separate investigators to determine ARI and smoke exposure times, thereby assuring a greater degree of independence in observation of the two variables. Random checks by senior medical staff were also undertaken to raise the level of quality control.

Results

A picture of general pattern of the relationship between ARI among infants and preschool children and exposure to domestic smoke pollution has been portrayed in Tables 1 and 2. It is to be noted that the average time spent near the fireplace per day by the child is taken as a measure of the extent of exposure to the domestic smoke pollution.

Table 1 shows the ARI episodes among infants and children under 2 years in association with exposure to domestic smoke pollution as recorded during the first substudy (February–July 1984). A positive correlation was found between all grades of ARI and hours of exposure to domestic smoke pollution among infants below 1 year. Among children between 1–2 years similar positive correlation was observed in ARI grade II, III/IV, but not in the mild ARI grade I.

Table 2 shows the ARI episodes among infants and young children under 2 years in association with exposure to domestic smoke pollution as recorded during the second

Table 1. ARI episodes according to time spent per day near the fireplace (February–July 1984)

Average time per day (in h)	0–1 year				1–2 years			
		ARI episodes				ARI episodes		
	n	I	II	III/IV	n	I	II	III/IV
0–0.9	33	40 (1.21)	9 (0.27)	1 (0.03)	17	42 (2.47)	4 (0.24)	1 (0.06)
1–1.9	90	120 (1.33)	33 (0.37)	6 (0.07)	64	118 (1.84)	15 (0.23)	8 (0.13)
2–3.9	94	170 (1.81)	48 (0.51)	16 (0.17)	95	179 (1.88)	32 (0.34)	11 (0.12)
4+	16	30 (1.88)	13 (0.81)	9 (0.56)	40	81 (2.03)	31 (0.78)	11 (0.28)
Total	233	360 (1.55)	103 (0.44)	32 (0.14)	216	420 (1.94)	82 (0.38)	31 (0.14)

(Figures in parenthesis are average ARI episodes per child during six-month period)

Table 2. ARI episodes according to time spent per day near the fireplace (November–January 1985)

Average time per day (in h)	0–1 year				1–2 years			
		ARI episodes				ARI episodes		
	n	I	II	III/IV	n	I	II	III/IV
0–0.9	142	118 (0.83)	24 (0.17)	–	70	62 (0.89)	3 (0.04)	–
1–1.9	61	63 (1.03)	10 (0.16)	1 (0.02)	75	90 (1.20)	8 (0.11)	1 (0.01)
2–3.9	24	42 (1.75)	5 (0.21)	4 (0.17)	36	69 (1.92)	9 (0.25)	3 (0.08)
4+	20	36 (1.80)	4 (0.20)	10 (0.50)	27	45 (1.67)	9 (0.33)	8 (0.30)
Total	247	259 (1.05)	43 (0.17)	15 (0.06)	204	268 (1.31)	29 (0.14)	12 (0.06)

(Figures in parenthesis are average ARI episodes per child during three-month period)

substudy (November 1984 – January 1985). A positive correlation was found in 0–1 age group in ARI grade I and III/IV but there was only a slight increase in grade II episodes with increase in exposure hours. In 1–2 years age group, positive correlation was found in all the grades observed.

Thus both the substudies show consistent positive correlation between life-threatening ARI grade III/IV and domestic smoke exposure.

Discussion

Most ARI research so far has focussed on microbiological causes, immunization and case management. There have been relatively very few studies of the effect of environmental factors like air pollution as a risk factor. The present study has focussed particular attention on domestic smoke pollution and its relationship to ARI.

The possible mechanism by which passive inhalation of smoke may contribute to the respiratory infection in infants and children are i) cilial paralysis; ii) the facilitation of attachment of respiratory bacteria to mucosa; and iii) the depression of immune responsiveness.

The possible role of domestic cooking fuel in contributing to ARI has also been investigated in Britain and the USA where it seems that exposure to nitrogen dioxide from gas cooking stoves may increase risk [5, 9]. Biomass fuels produce high nitrogen dioxide levels as well as other toxic pollutants, and it is probable that these pollutants have a range of effects on the child's respiratory defence mechanisms. The problem is believed to be especially critical in countries such as Nepal, where biomass fuels are burned in unvented fireplace and stoves resulting in very high levels of indoor air pollution.

In the present study area, the cooking and heating is done on traditional stoves by burning biomass fuel such as firewood and straw in ill-ventilated houses without chimney. Nitrogen dioxide levels in these homes are much higher than in gas cooking houses of USA, UK and are associated with complicated mixture of other toxic pollutants [3]. Our findings show a positive correlation between domestic smoke pollution and ARI, especially the life-threatening moderate and severe grades, suggesting that domestic smoke pollution is an important risk factor in ARI. Anderson was not able to find any difference in the prevalence of acute lower respiratory infection between children in coastal and highlands areas of Papua New Guinea [1]. He concluded that smoke indoors in huts and chill are unlikely to be major determinants of severe disease. However, it should be noted that his work was confined to the school children only.

A study on acute respiratory infections among children under 5 years in Kenya has shown no correlation between ARI incidence and pollution levels or housing characteristics. But no definite conclusion could be made from this study as the pollution levels were homogeneously distributed among the houses [2].

Ideally smoke exposure assessment should be done by conducting extensive personal air pollution monitoring involving several infants and children in each of the homes for several of the important pollutants in smoke, over several seasons. Only in this way could overall exposure be quantitatively and completely defined. Such an active monitoring programme however, was beyond the resources of the present study.

The present study has shown that domestic smoke pollution is an important risk factor of ARI, which is a leading cause of infant and child mortality in the developing countries. The ideal way of tackling the problem of ARI is to prevent life-threatening moderate and severe ARI by control of risk factors. So, national programme for prevention of ARI should also incorporate the control of domestic smoke pollution.

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Panel Discussions

ETS Measurements, Biological Effects of ETS, and Indoor Air Pollution

Chairmen: Y. Tsunetoshi and Y. Yanagisawa

Chairman: My name is Tsunetoshi, Miyazaki Medical College. I am the chairman of this session. The co-chairman is Dr. Yanagisawa, HSPH.

I would like to introduce the panelists whom you all know: Dr. Kira, Juntendo University; Dr. Norpoth, Essen University; Dr. Schwartz, School of Medicine, Georgetown University; Dr. First, School of Public Health, Harvard University; Dr. Roe, Consultant in Toxicology, Experimental Pathology and Cancer Research; Dr. Spengler, School of Public Health, Harvard University; Dr. Lebowitz, University of Arizona Medical Center; Dr. Lehnert, University of Hamburg; Dr. Aviado, Atmospheric Health Sciences, Inc.; and Dr. Kasuga, Tokai University.

Dr. Yanagisawa will explain the format of this Panel Discussion.

Co-chairman: The theme for this session is ETS relating to issues besides lung cancer and cancer epidemiology which were already covered in yesterday's panel discussion. I suggest that we concentrate on four areas during our discussion today. The first topic is ETS Measurements; second, Field Survey on ETS Effects; third, Criteria for the Evaluation of ETS Biological Effects; and the last topic, Toward a More Comfortable Environment.

In each of these sessions I will call upon the panelists to give a presentation of about five to ten minutes each, and we will then base our discussions on these initial comments.

First, I would like to call on Dr. First to give us a short presentation on ETS Measurements.

Dr. First: Epidemiologists concerned with ETS seem to be obsessed by counting the number of cigarettes consumed by anyone in the vicinity because they can be counted and this seems to make the analytical process more quantitative. Most epidemiologists I know are physicians, and physicians might love to rummage through old hospital records since they contain voluminous data on the diagnosis and progress of diseases of interest. Unfortunately, they contain little else of value to the epidemiologist. Epidemiologists cannot obtain the blood cotinine level from a 20-year old corpse, and must rely, therefore, on infallible memories of family members and associates to do the cigarette counting for them.

Should the environmental health scientists decide to hang out their shingles as epidemiologists, I feel certain that exposures would be evaluated in exquisite detail. It is obvious to all of us that epidemiologic studies must involve the best efforts of environmental scientists working closely with physicians. In the area of epidemiology of occupational diseases, we put this concept into practice when we investigate occupational diseases such as cancers. We cannot resurrect the victims to measure their absorbed dose, but what we can do is to go into the factories that employ the same technology and equipment and measure, with reasonable certainty and reliability, what their exposure

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must have been. Just so, we should be able to improve enormously our ability to quantify the dose.

What is it that we have to measure? The contrast between mainstream and sidestream smoke has been commented on repeatedly over the past three days, but the physical, chemical factors that are responsible for the differences have not been explored systematically. I will mention a couple of prominent differences. First, freshly formed main-stream smoke is concentrated and the particulate phase is in an equilibrium with its own gas phase, so that the volatile chemicals are distributed between the two phases roughly in proportion to their vapor pressure.

Particle size of main-stream smoke has been variously estimated between 0.4 and 0.5 μm. That is close enough considering the variation between measurement methods. When size measurements of main-stream smoke were made in our laboratories with an aerosol centrifuge, the aero-dynamic equivalent diameter was found to be 0.42 μm.

Now, let's look at environmental smoke. Under most natural conditions dilution approaches infinity and the equilibrium shifts sharply towards the gas phase. This explains why nicotine in ETS is largely in the gas phase, whereas nicotine in main-stream smoke is largely in the particulate phase.

If we create a closed room without ventilation and introduce many smokers for hours, it is by no means certain that nicotine is still all in the gas phase. Furthermore, it has been demonstrated that nicotine and total suspended particulate matter decay much faster than the fixed gases, even in a closed unventilated room.

Where does it go? We find that nicotine deposits on surfaces like absorption, and total suspended particulate matter does the same by agglomeration followed by sedimentation. If you doubt that this occurs, wipe a white kleenex paper against the window or wall of a room of a heavy smoker and you will come up with a dense, yellow-brown stain, characteristic of tobacco smoke tar. I think that in public places with ample mechanical ventilation, nicotine will be largely, but not necessarily exclusively, in the gas phase, and the loss of volatile matter including water-vapor and other major components of the tobacco smoke will shrink the particles from the 0.4 to 0.5 μm size characteristic of main-stream smoke to somewhere in the vicinity of 0.1 to 0.2 μm.

How do we come to this conclusion that it is not all in the gas phase?

First of all, there are three different methods for measuring nicotine. Two of them, the TENAX and the XAD-4, are absorption of nicotine on chromatography packing. The other is the treated filter often called the Harvard Method where you absorb it on a chemically treated filter. Now, the point to be made here is that the two methods using chromatography packing give lower values quite consistently than the filter paper method, and this would lead us to conclude that if you filter the particles as well as absorb the gas phase, you are getting more of the nicotine than if you only absorb the gas phase. One of the interesting points of this is that the chemists have chosen to use the XAD-4 method even though it gives lower levels because the method can be automated. The filter paper method is more of a manual method, and this apparently is the reason for going in that direction which is somewhat questionable.

Co-chairman: Thank you very much. Then I would like to call upon Dr. Roe to talk to us about ETS measurements. Can you give us your initial comments?

Dr. Roe: Thank you Mr. Chairman.

I think there is a great danger in this day and age, that people measure things purposelessly, without any purpose, just because they have the methods to do so or because they can get funding to develop methods or to improve methods to do better

measurement, without any clear idea of how those methods might be used to solve any real problem.

At this meeting we've had some discussion of measuring the concentrations of certain ETS derived chemicals in ambient air and the methods are getting better and more sensitive all the time. One example is Dr. Matsushita's elegant and sensitive methods for measuring ambient mutagen.

We've made some but less progress on the measurement of the uptake of smoke constituents, and when we come to look at the effect of exposure to ETS or ETS derived chemicals, I think we are perhaps in scientific areas there. We've got some data that can be relied upon, but that is about as far as it goes. By contrast, in all these very sensitive methods we have developed there is no bridge between the data we can get from those methods and the thing that most people are primarily interested in, and that is any relationship with chronic health effects.

I think there is a consensus view that clinical and epidemiological methods are just not sensitive enough for us to be able to meaningfully investigate the possible effects of ETS on the incidence of chronic diseases.

There are several problems, and I have grouped them into four categories. One, and most important, is the inadequacy of historical exposure data, and combined with that is the multiplicity of confounding variables. Theoretically you can overcome some of the confounding variables by finding out what people were being exposed to yesterday. But when you go back to childhood or earlier these confounding variables become an insuperable problem in epidemiological studies.

Secondly is that measurements of the uptake of one ETS constituent such as carbon monoxide or nicotine do not provide a reliable index of the uptake of any other. Despite this, and I think there is a more or less consensus view on that at this meeting. We will continue to see many papers which are based on the false assumption that you can use any of these as a reliable marker of exposure. This is especially true in the case of nicotine. If you are measuring urinary cotinine, it doesn't matter how the nicotine gets in, whether it is swallowed or inhaled. Thus urinary cotinine does not give you any real idea of the inhaled dose.

Turning to cardiovascular effects, and we had one paper by Dr. Asano I think on this, I think we are in deep trouble here. We have heard papers today about the sensitivity of the human olfactory system a very very sensitive mechanism for detecting odors, such as tobacco odors. This means that you cannot do a single blind study, let alone a double blind study, and look for cardiovascular effects. I have referred, during this meeting, to the importance of distinguishing between the effects of actual exposure and the perceptions of exposure. There are two aspects of perception: one is that if you can smell something and think that you are being exposed to a much higher concentration of it than you are, in fact, being exposed to. And secondly, if you have been primed to believe that exposure to a substance at whatever concentration may evoke a response, then the effect may no longer be related quantitatively to dose. The effects particularly on bloodpressure and pulse rate maybe quite different depending of what your perception on risk of exposure is. So, I think this poses enormous difficulties in relating measurements with effects.

In the last case I would say there is a great need for trying experiments to find out the effects of perception of hazard. Thank you, Chairman.

Chairman: Thank you very much. We have heard from Dr. First and Dr. Roe, let us continue with a discussion on these two presentations. The question is, "What are the indicators of ETS?" Of course nicotine is one indicator that is unique to tobacco, but

is that sufficient as an indicator? Dr. First, would you like to make the first comments?

Dr. First: I differ rather significantly from my colleague, Dr. Roe, with regard to the adequacy of the surrogates that we have selected for the gas phase and the particulate phase of tobacco smoke. I think we all recognize that you cant't make much sense out of an analysis of thirty-eight hundred compounds. We do have precedence. Those of you who are familiar with the progress of air pollution control will realize the effects of sulphur dioxide and total suspended particulate matter in the levels that we have set for standards for the United States and other places. They are surrogates for all of thecompounds that are associated with the emissions from the burning of fossil fuels.

Another example, completely out of our field, would be the use of E-coli as a surrogate for sewerage contamination of drinking water and swimming water. We've been using that quite successfully for over a hundred years. Nobody believes that the E-coli is toxic in the concentrations that we have. My point is that we shouldn't get too discouraged with the surrogates we have selected.

Chairman: Thank you very much, Dr. Roe.

Dr. Roe: Well, if I could only point out, I wasn't really saying you can't use surrogates, but I think when you get down to the sort of levels that we are talking about in ETS exposure, then I don't think the same thing applies. When you get to chronic effects you are outside the range which you can really hope to measure any relationship between exposure and effect.

Chairman: Okay, Dr. Spengler.

Dr. Spengler: We are recently seeing that the cadmium component of cigarette smoke is serving as a very reliable and consistent tracer for the particle phase ETS component. So, we have this kind of evidence or a stable marker for the particle phase.

I would also like to make another point, clearly the concentrations that we are typically finding in office buildings and homes for individual ETS components, are not anywhere near a level that would be necessarily hazardous in itself. They could be in irritation effects range. Let's look at some recent work coming out of Denmark where subjects are exposed in a chamber to a mixture of volatile organics. Every single component of these VOCs is far below any threshold limit value. But the combination, the mixture of about fifteen to twenty of these compounds are showing very demonstrable effects over a range of 1 to 10 milligrams per cubic meter. These concentrations are way below the toxic effect levels of any individual compound.

Chairman: Thank you very much. Are there any other comments?

Well, I would like to make a brief summary. Dr. First mentioned SO_2 as a surrogate for the combustion of fossil fuels, and E. coli as a surrogate for the degree of contamination in sewage or swimming water. Dr. Roe questioned whether nicotine can be used as an indicator of chronic effects of ETS. Dr. Spengler suggested cadmium as a good indicator of particulate phase. These are some of the very important comments that we have just heard.

Can we have further comments?

Dr. Hirayama: I have to make again my plea which I made in 1984 at the Vienna Meeting. If Dr. Roe were smoking now, his smoke would be inhaled by Dr. Schwartz who is seated within thirty centimeters of Dr. Roe. I call this NTS, neighbor tobacco smoke. What I consider very important, is the proximity effect of side-stream smoke. Wives in Japan are exposed to heavy-smoke by their husbands who sit very close, within one meter of their wives. I think this important proximity effect should be considered in ETS measurements. Thank you.

Dr. First: I completely agree with what you have said and I find it deplorable that people are taking the very intimate situations that exist in the home, the mother cuddling the child and blowing smoke in the child's face, and translating that information into the situation that exists in public places with mechanical ventilation where concentrations are a couple of orders of magnitude less. What we see happening constantly is this transformation being made, and it is not valid.

Chairman: As was pointed out by Dr. Hirayama, there might be some physical, chemical or biological changes of the effect of the smoke according to the aging of the tobacco smoke. But we do not know the aging process of the smoke and the changes of the constituents of the smoke. Are there any comments on this point? If not, then the Chair suggests that the aging process of smoke should be studied further in the future.

Now, I would like to go on the sub-session two. The session is on the Field Survey on ETS Effects, we would like to have brief presentations from four Speakers, Dr. Lehnert, please.

Dr. Lehnert: Thank you Mr. Chairman, there is no doubt that scientifically based assessment of health risk and passive smoking requires exact dogmatic data on the uptake of compounds being present in ETS. Commonly used by German researchers are nicotine, cotinine and carboxy-hemoglobin. These substances, however, are mainly suitable to estimate the uptake of gas phase components.

Additionally, they are not related to the carcinogenic properties of the ETS which should be of special concern with respect to long-term health effects. Concerning the problem under discussion, urinary-mutagenicity could be an appropriate parameter for risk assessment in so far as this kind of bio-monitoring considers even the most unknown mechanisms of toxification and re-toxification of the complex mixture inhaled.

But one has to keep in mind that the prevalence of an increased urinary-mutagenicity, with respect to cancer risk, is unclear as yet.

Chairman: Thank you very much. Dr. Kira, please.

Dr. Kira: Yesterday I reported that the estimation of personal exposures to nicotine due to passive smoking is difficult because of the spatial unevenness of the concentration, and because of the unpredictable behavior of the non-smoking subject in the respective indoor environments. Therefore we have designed a personal sampler which may be carried by the individual non-smoking subject.

The sampling tube is 2 cm in length, 5 mm in diameter and it contains 4.5 g of diotomyte. It is connected to a portable pump. By comparing it with a Japanese cigarette, you can see how big this device is. A tiny girl can carry this equipment.

Although a bartender and a waiter work in the same small bar, the exposures to nicotine are far different as you can see. The bartender is surrounded by many smokers

while the waiter is walking around the bar for serving drinks. The number of smoked cigarettes from 5 p.m. to 11 p.m. is very high, close to four hundred.

This slide shows a record of a non-smoking office worker measured for 6 consecutive days (S. Kira et al.: Passive exposure to nicotine in daily environment), Fig. 7, in this publication). She is a non-smoker but her husband is a smoker. Her office permits smoking and has many smoking guests every day. As you see the results of the respective studies is composed of three time categories; from 10 p.m. to 6. a.m., from 8 a.m. to 4 p.m. and from 4 p.m. to 10 p.m.

From this study it is clear that she is exposed to her husband's smoking when she gets back to her home, but high exposure to the nicotine is more serious in her office rather than in her house.

On Saturday the nicotine concentration during the business time is the lowest. As the conclusions of our study which I reported yesterday and today, room size and amount of ventilation as well as the amount of tobacco smoked in the unit time strongly inferred the nicotine concentration of the room and the nicotine level fluctuated widely from spot to spot, and time to time in respective space.

Therefore, measurements of passive smoking may not be identical even for non-smoking individuals who are working in the same office during the same business hours.

As for personal exposure to nicotine, it is clearly heavier in subjects who are living with smokers in the family, than for subjects living without a smoker. It is also clear that even tiny children who are from non-smoking families cannot escape from nicotine exposure in their daily lives, because of unexpected source of nicotine.

The problem that remains is to determine what correlation exists between nicotine exposure and tobacco exposure as measured with these methods and the physical and psychological responses of individuals.

Thank you.

Chairman: Thank you very much. Next, Dr. Lebowitz, please.

Dr. Lebowitz: I will depart a little bit from my colleagues and discuss specific health effects.

My primary statement is that many previous epidemiologic studies dealt with the carcinogenic effects of tobacco. This fact has determined how and why we look at the effects of passive smoking, since it must have a similar relationship to dose and response as active smoking.

And in the previous very basic epidemiologic studies, chronic-lung disease and cardiovascular disease etc as well as acute respiratory illness have been related to smoking.

In fact sometimes the studies go further and allow us to say how such effects might occur through the influence of host effects mechanism, such as clearance of the airways by neurophils which can release protease and clean up the lung. More recently, these results have been influenced by genetic factors and inherited effects.

Without going into all the details, we have found immunologic markers of active smoking that have a strong dose-response relationship, and we have found genetic factors that may explain why certain smokers are susceptible to chronic-lung effects or to cardiovascular effects.

Modern epidemiologic studies start with genetic determinants that help us determine who might be susceptible to the long-term effects including the immunologic and biochemical markers that determine which children are going to have acute respiratory experiences that lead on to childhood chronic respiratory disease and adult respiratory disease.

They also start with testing lung function very early in life. This helps determine the responsiveness in the individual, and, in fact, can predict who might have slower lung growth and who might develop respiratory track infections and so forth.

So, we can look at these immunologic markers, like I've looked at IgE to determine if I can see changes in passive smokers that I've seen in active smokers. I've looked at T-cell changes to see if that would occur. I've looked in sub-populations that already have poor lung function or a family history of chronic respiratory disease and so forth, to see if in fact I can measure changes in those people where I can't in others.

So, what I would suggest is that, depending on the effects we have seen, we should try to fit passive smoking into the same dose response relationship, and the same host characteristics as we have for active smoking, and we should use those same techniques to determine the non-carcinogenic effects. Thank you.

Chairman: Thank you very much.

Next I would like to call upon Dr. Spengler.

Dr. Spengler: I would like to make two points. One is the interest in looking at some genetic effects that Dr. Lebowitz just raised and I want to share with you some very recent data that was reported in an International Meeting in Berlin.

This is a measurement system used by US-EPA in a very large study of personal exposures to volatile organics in an individual person's house, outside that house and the exhaled breath. This is a Tenax sampler connected to a pump that draws air and VOCs analysed by GC-MS, and from that analysis they could quantify between twenty and thirty volatile organics.

Lance Wallace from EPA has developed a large data set of over several hundred homes. The indoor concentrations of benzene are higher in homes with cigarette smoking; 10 $\mu g/m^3$ vs 7 $\mu g/m^3$. Non-smokers who report workplace exposure to cigarettes also showed a significant increase in benzene in their breath. It is quite striking in the fact that the amount of cigarettes and the actual benzene concentrations are highly correlated.

I think this kind of information is important. Infants, children and fetuses are exposed to benzene from cigarette smoke.

It behooves us to examine other end-points beyond respiratory outcomes. We should be considering childhood leukemia in future health studies of passive smoke effects.

The other point I want to return to, is the issue of childhood symptoms, respiratory symptoms and the evidence of the effects of parental smoking, in particular maternal smoking. If one looks across the recent evidence published from a variety of cohort studies in the last five to ten years, you are struck by the consistency of this finding. I am fully convinced that the effect manifested in children of school age population is associated with the smoking in their households.

If you examine the strength of this relationship you will note that it is most pronounced in maternal smoking households. About thirty percent of the mothers of schoolaged children are smoking. This is increasing lower respiratory illnesses by about twenty percent. This has substantial health and economic impacts when aggregated across society. I think one has to take this information seriously and do something about it. Now at this point we have a situation just a subtle form of child abuse.

Two studies haven't been conducted yet. One, we have to ascertain the contribution of exposures in early childhood to this effect that is seen in the seven, eight, nine, ten year old kids. The other thing that needs to be done is the ultimate experiment. Are respiratory effects in children reversible in the absence of a continuing irritation due to ETS exposure

at home? These two studies are still on our agenda, and I really feel it must be done to fully resolve this issue.

Chairman: We have received initial comments from the four Speakers; Dr. Lehnert mainly touched upon markers, and he mentioned that further studies are necessary with regard to urinary-carcinogens. Dr. Kira mentioned the confounding factors in personal exposure estimation based upon the actual measurements. Dr. Lebowitz emphasized the importance of susceptible individuals and of the indirect effects through metabolism. Dr. Spengler mentioned that there was consistency between ETS and respiratory effects and his belief that we need to take measures to deal with the situation.

In the next sub-session we will discuss the effects of ETS. Now we would like to talk about markers. Dr. Lehnert mentioned a number of types of markers that have been reported up to now. For example, nicotine is a constituent of ETS and is directly measurable. CO is one of the ETS components and is measured as co-hemoglobin, while hydroxyproline is a marker through the ETS effect on collagen and elastin. We would like to focus our discussion on what are the appropriate markers of acute or chronic effects of ETS exposures, and how we may evaluate these markers. We call upon Dr. Kasuga to talk about markers.

Dr. Kasuga: I think perfect markers and effects are comparable. For example, if the prevalence of asthma increases with ETS as reported in other session, that may be one marker. However, I believe in the case of juvenile asthma, ETS is not the causative factor. We have various other causative factors such as fungi, house-dust and mites which are suspected factors. We can find mites in carpets and in the Japanese tatami. Thus we should not really confuse the effects of ETS with fungi or with mites.

Dr. Spengler mentioned cadmium in ETS. "Itai itai" disease, a very well-known pollution caused disease in Japan, is caused by cadmium discharged by the industries. And hydroxyproline is very closely related with cadmium uptake. We have not yet carried out any studies concerning the relationship among cadmium, hydroxyproline and tobacco smoke: these three are forming a triad which we believe will be extremely interesting in our further studies.

Chairman: Are there any comments and questions? Dr. Koo please.

Dr. Koo: I just have a question directed back to the previous speaker. I think that it is important to have consistent results in showing the relationship between ETS and respiratory illnesses in children.

What bothers me about this is that we may not know whether it is really due to ETS, especially ETS by maternal smoking, or to the fact that the mother would also be more liable to have flues, colds and other communicable respiratory diseases, and she is passing these air-borne agents to her children?

Dr. Lebowitz: I think it is both. As we demonstrated in 1976, you can't separate them; you start with the intra-uterus effect if it exists, and that does impact on the immunologic system and the lung function which then impacts on biological host defense mechanisms. In fact the lower the social status, the worse in the nutrition, the lower the immunologic defense. So you have these respiratory track illnesses occurring earlier and creating much more damage in an earlier stage. And it goes on from there, because they continue. It is not just as if they have one episode. They have multiple episodes which have multiple impacts on the lung. We know the biological process is not a simple thing. It's a chain.

It is very difficult to explain in a setting without going into how these might be occurring; namely, the biological hypothesis about the biochemical changes, and the immunological changes that are occurring from the genetics through the intra-utrium development, etc.

Many of these steps were skipped in the discussion.

Dr. Spengler: The odds ratios are reduced, but remain significant after controlling for parental illness, in accordance with what Professor Lebowitz has said.

Dr. Koo: I hope we can separate those effects more, I mean it may not be biologically possible, but maybe it is.

Dr. Spengler: You can start looking at the changes in the immunological markers and the micro-cilia clearance in the airway caliber and changes through the methods well functioning in the contributions of different parts of the lung. For instance, if the boys have exposure already and have smaller lungs, they are much more likely to have viral impact and viral response at an earlier age.

And you can go into the actual immunologic changes that are going on for instance, what leads to this as well as the structural changes that have led to it.

Dr. Koo: ETS is in rather low concentration. As several people pointed out we have many pollutants in the home environment, what are the rates of contributions of the various factors in relationship to ETS?

Dr. Spengler: In the absence of elevated ambient concentration, ETS is the most dominant source of particles. However, put in the perspective of other sources of particles including open wood burning or kerosene heating, then it may have a different role. Other agents such as fungi, bacteria may be important.

Yes, the work does have to continue to determine in each case, who are the susceptible people and what are the contributions to that.

Chairman: Dr. Lehnert please.

Dr. Lehnert: From my clinical experience I would like to ask Dr. Lebowitz, if in his opinion the biochemical methods presently available are sensitive enough to detect susceptibilities especially with regards to biological variances.

Dr. Lebowitz: Biochemical markers like protease inhibitor which is genetic, and some of the anti-oxygens like cilia plasma which is in fact also genetic, can distinguish those who may go on to have structural difficulties due to biochemical processes that start with exposure to irritants. Other markers that we use now are very sensitive too.

We could discuss a range of factors that have been evaluated which distinguish who is responding and who is likely to respond. The best known case that they will use is the protease inhibitor homozygosis deficiency status which leads very early in life to major damage in other organs, and then, eventually if they survive, to much better likelihood of structural damage in the lung when exposed to irritants, especially cigarette smoke.

Chairman: Thank you very much. I think we are running out of time. We would like to discuss one more item before we close this sub-session, namely the marker of

chronice exposure. Or what kind of methods are possible to show the risk of long-term exposure. Would anybody like to talk about the question of long-term, or chronic, indicators?

Dr. Schwartz: For long-term evaluation of ETS exposure, I think we will have to identify some singular, clinically significant biochemical effect rather than the identification of some marker.

Markers are useful for acute maybe sub-chronic effects, but not for long-term exposures.

Dr. Kira: I worry about the chronic effect of passive smoking. As Dr. Lebowitz indicated, there are many reports of the acute effects of smoking, such as the decrease in neutrophils, the activation of macrophage, or the exhibition of alpha-1-antitrypsin and so on.

A typical chronic effect of smoking is emphysema. If emphysema starts after twenty years or thirty year's smoking, I worry about how we can consider all the factors simultaneously. There are many acute effects, but the real risks appear after twenty year's smoking.

Between the acute effects and the appearance of the chronic effects we must consider what kind of indicators may be available to choose from. The search for such indicators demands further study. Thank you.

Chairman: Dr. Aviado.

Dr. Aviado: I don't think it is time to suggest that one biologic test or genetic test is sufficient to detect some long-term biological effects.

I agree with Dr. Koo that whatever effects you describe, you cannot prove that it is exclusively arising from exposure to ETS. There are so many environmental factors that it is practically impossible to identify a cause and effect relationship if there is a change in a genetic marker. Thank you.

Chairman: Thank you very much. We would like to have one more speaker to make a comment.

Dr. Lebowitz: I certainly agree with Dr. Kira that some of the long-term, chronic effects do occur twenty years or forty years after exposure starts. Fortunately sometimes we are able to detect those changes beginning, for example, in the decline of function which is already an objective tool that we use sometimes.

Of course we do need long-term studies to make sure that this is in fact occurring. I think that these are issues that need to be addressed continuously in the cohort studies. I believe that my sixteen-year study should go longer, and that my other two cohort studies should be allowed to go for twenty years each too, to do this. So, I certainly cannot disagree with Dr. Kira.

Chairman: Thank you Dr. Lebowitz. I think Dr. Lebowitz's comments concluded this session. So, I would like to move on to the next sub-session. This is on the ETS biological effects, Dr. Schwartz will make some comments on the ETS biological effects.

Dr. Schwartz: Thank you Mr. Chairman. Pharmaco-kinetics is a description of clearance, volume of distribution and concentration-time curves. Pharmaco-kinetics

and epidemiology share something in common. That is that it is easy to over-estimate the importance of the data and to under-estimate the difficulty of doing the studies. As a practitioner of pharmaco-kinetics, I can appreciate how epidemiologists feel. I am ill at ease when pharmaco-kinetic data is manipulated while unaccompanied by appreciation for fundamentals of experimental design.

Consider at the present situation with ETS, single samples of blood, urine or any other body fluids analysed for cotinine tell us only a few things about exposure to tobacco smoke. They may tell us whether somebody is a smoker or not a smoker, and they probably can tell us if someone lives or works with a smoker. All that is qualitative or, at best, only semi-quantitative.

The biological marker in a tissue fluid is an indication of dose, if we are really careful.

The dose has to be equated to the exposure of the surrogate, that is, what is taken into the body. This is a little more difficult, and for it to take place, those of us in pharmaco-kinetics need the cooperation of the people who are doing atmospheric analysis.

And then finally, the third step is that we have to take the exposure level of the surrogate and see how it relates to what compounds or what substances of the total mixture we are interested in.

All three must be satisfied before we can say very much about what markers mean with respect to total exposure. And it's the last one that I would like to point out that markers do not have to be a marker for cancer, or for risk analysis. I suggest that the proper use of markers may help us much more so in identifying potential, or associating exposure of ETS with potential acute or sub-acute or sub-chronic effects.

Chairman: Thank you very much. I am sure there are many questions and comments, but we would like to hear from Dr. Norpoth first, and then we will receive questions.

Dr. Norpoth: Ladies and gentlemen, let me point to the part of experimental toxicology, possessing vast effects of passive smoking. Well established toxicological methods strengthen my opinion but I have some reservations concerning the epidemiological approach.

Apart from the aspects of cost and time, you can be sure that with better design studies, definite and commonly accepted decisions will be possible in the next ten years on whether ETS is a proven human carcinogen. In the meantime, we have to answer a number of urgent questions and I think we have a good chance to be successful.

Coming back to the discussions of the yesterday evening, I may emphasize that we argued in terms of probability but there is a great difference between a probability level required for clear scientific decisions or for gaining convincing evidence in the context of damage compensation on the one hand, and a probability level which demands of protection measures on the other hand.

In our country, West Germany, the committee for establishing limit values at the workplace came to this conclusion two years ago. The Committee stated that on the basis of epidemiological evidence, which leads to a serious hypothesis and on the basis of our knowledge of proven animal carcinogens in the side-stream smoke protection measures are recommended at heavily contaminated working places.

This statement, where Lehnert and I were involved in it, is quite relevant in my opinion. We tried to avoid exposure to any animal carcinogen at working places, not only for proven human carcinogens. I am ready to give you some more convincing arguments for it. Hence ETS cannot be considered as a harmless principle.

By no means would we tolerate such a mixture of toxic substances at working places without regulations.

It is not decisive that passive smoking causes a cancer excess of, let's say, five percent or that it is the most important cause for lung cancer in non-smokers. Nevertheless, we are interested, for a number of reasons, in determining the order of magnitude of adverse effects. We should therefore consider the approach of experimental toxicology.

At first I will give you an example of what we can learn from carcinogenicity using rodents. When side-stream smoke is condensated and fractionated in the fractions of nitrosamine and of polycyclic hydrocarbons, and these fractions are applied into the lung directly, only the polycyclic compounds seem to produce carcinomas. This result has been found by Grimmer's group in not yet published experiments.

In 1977 Grimmer and coworkers measured BaP concentration in an extremely loaded test-room. In such a room the uptake of about one hundred ng of BaP by a non-smoker is an equivalent of two to three cigarettes actively smoked. From such data, the respective carcinogenic effects and the carcinogenic equivalent of BaP may be extrapolated.

Similarly, the purpose of experiments performed to measure the urinary mutagenicity in passive smoking was not the same as experiments to develop a method of biological monitor. We found the urine mutagenicity of highly exposed non-smokers was in the range of that produced by a smoker after having smoked four to five cigarettes.

But again, we have to look to the fraction of polycyclic hydrocarbons among the urinary mutagens and to use also methods of trace analysis. It could show that the mutagenicity is mainly due to the fraction of polycyclics in urine.

A number of experimental models are available for side-stream smoke and main-stream smoke effects. Effects on chromosomes, SCE, the effects on DNA, effects on repair processes, and defense mechanisms as by example, thio-ether production. The information available from a variety of models may tell us whether or not side-stream smoke must be considered more carcinogenic than main-stream smoke.

Two other items are also important; one is that we need models to control the refinement of cigarettes not so as to reduce the risk to smokers, as well as the burden of non-smokers. The other is a means for measuring the combined effect of ETS with occupational and non-occupational carcinogen exposure. It is hard to believe that this problem can be solved by epidemiologists. Animal experiments are therefore indicated. A promising approach in my opinion is to use of the markers of the critical effect in humans, the effect on DNA adducts for example, as well as hemoglobin adducts, and these adducts may reflect the carcinogenic mechanisms to a certain extent. It may be helpful in clarifying the questions of carcinogenicity. Thank you very much.

Chairman: Thank you very much. Now, Dr. Aviado please.

Dr. Aviado: Since I made my presentation this morning, I don't want to add more to what I said. And simply I will immediately comment on the remarks of the previous speaker.

It is very obvious to you that there are two schools of thought regarding TLVs. One from Germany, and an opposite view expressed by me from the Philippine Islands and the United States. The TLV in the United States is set up by the American Conference of Governmental and Industrial Hygienists. This is a group of governmental personnel. The values I gave to you this morning are valid only for the United States.

As far as the carcinogens in the workplaces are concerned, I agree with the Professor from Germany that the current opinion now all over both sides of the Atlantic Ocean is to reduce as much as possible the amount that are in the workplace. However, if you

examine the pertinent evidence on the carcinogenicity relating to lung cancer, you will notice that all of these so-called carcinogens were proven to be carcinogens not by inhalation but by very, very artificial means, such as intra-tracheal injections, dermal application of the skin, oral administration, and as far as I know these groups of administration do not apply to passive smokers.

I think that is all I need to say. Thank you.

Chairman: Thank you very much.

Then we will open up discussion based upon the initial remarks. Dr. First please.

Dr. First: I would like to say that I am in sharp difference of opinion with Dr. Aviado's use of TLVs. They are not at all applicable to this problem and I think it just represents a red herring to what we are talking about.

In the first place, the American Conference of Governmental Industry Hygienists say very clearly in the first paragraph of their publication that these TLVs are not to be used for any purpose other than eight-hour per day five days per week, exposures of workers. The workers are to some degree a self-selected population of adults who are reasonably healthy, not too old and they don't represent the population at large by any stretch of the imagination where we have infants, elderly and ill people and so on.

People who are exposed to environmental smoke or to anything else, may be exposed for more than eight hours a day, five days a week. That's the first correction.

The second correction is the fact that they are not healthy adults and when we apply TLV, because there is nothing else to be looked at, we are going to have to reduce them by at least two orders of magnitude for most of the substances that cause chronic disease. And if we are talking about carcinogens, maybe we are talking about three orders of magnitude because if you start with a newborn child, it obviously has a long way to go to absorb this material.

So, I don't think that's an appropriate way to approach this problem at all.

What we have just heard reminds me of the advice we were getting during the Vietnamese War which was to declare that we had won the war and get out of there. What you are telling us I think is that we should adopt the public health viewpoint, that if there is any danger of damage we should avoid it. This is a good principle for a health director, because if the Director of Health isn't for you who else will be?

Dr. Schwartz: With regard to regulatory decisions I don't think we say that we don't know, and therefore we will throw darts at it and come up with some decision.

I think a lot of considered intelligent thought is given to these matters, and agencies such as IARC and WHO, and our individual governmental agencies, which in spite of all the snide remarks that they receive from the press and others, put in a good deal of thought into making a decision. All I was saying is that we should apply the same thing to ETS.

If you want to talk as if the war is over, and we won, you can merely look at the Surgeon General's report which simply declares ETS causes cancer and suggests that we now go on to something else.

Dr. First: That is exactly what I was saying.

Dr. Schwartz: Dr. First said that was what he was saying, so I agree with him there.

Chairman: Thank you very much. There seems to be no end to this argument but of course this is not the last conference we are going to have on TLV so we don't have to really draw any conclusions.

I think we have had a variety of opinions here and I think that when it comes to emphysema or lung cancer or various other respiratory disease, for someone who is involved in preventive medicine, the TLV results are extremely disheartening.

So, as the Chairperson of this discussion, I would like to say in conclusion, that we should come up with some TLVs that will give us some preventive effect or maybe of some use in preventive medicine.

We have really fallen behind in our schedule, and must proceed to one more item. That is Session D, "for a more comfortable environment." We are supposed to discuss ways to establish a more comfortable environment whether in Asia or in Europe or the United States.

We will receive some comments from our panelists on what they are doing to create a more comfortable environment in their respective countries. Is there anyone from the United States who will volunteer to give us comments on how the United States is creating a more comfortable environment? Dr. Lebowitz:

Dr. Lebowitz: We have seen an extension from the question of carcinogens to the question of other chronic effects, to their acute effects. And some very interesting points were raised in today's discussion and yesterday's, about very similar pollutants occurring in the environment at the same time.

I think that if we have to look at total exposure, so we also have to look at total control. That is, what are the mechanisms we can use to minimize effects of pollutants whether they be chronic or acute, whether they drive us up the wall, as we would say in America, from the annoyance or just kill us after eighty years. And I think that in order to do this, several conferences have conceived of the ways to control each of the different pollutants and each of the different sources.

Some people have even written articles to try to postulate this I believe that in fact there are technical controls, there are some regulatory controls (we heard of some in Japanese buildings this morning), there are also social controls and educational controls, and we have very little of that. There is one final control of course, and that is to hope that individuals themselves can modify their own environment sufficiently for their own benefits and for those with whom they work or live.

I think that for each pollutant and for each source, there are some technical controls. I think that ETS, as I said in West Berlin, is a slightly different issue because in fact it is a public policy type and behavioral type control. With ETS much more is done to control the individuals who are the sources, than to control the technical aspects of the substance.

I think also that we perceive ETS in a broader context. If we want to avoid ETS, for whatever reason and we want to avoid people who are generating it, that is, actively smoking, then what we want is smoking cessation as one of the methods of control.

I think this is really the issue. I would like to promote cessation of smoking more strongly than any of the other possible control, certainly for ETS. And, this is especially important for certainly every cessation during certain times of life, such as during pregnancy for females and in some cases special work place situations, etc.

But I would prefer to work on cessation as the basis of control, having worked in the field of active smoking, long enough to know that there is no question that it is causing things. Thank you.

Chairman: Thank you very much, Dr. Lebowitz. Dr. First, please.

Dr. First: We should resort also to engineering control efforts, because we are measuring the same things over and over again. There is no question that if you have an unventilated kerosene stove in your home, you are going to have certain affects. This is the same in the U.S., the same in South America. Why don't we, using all of our efforts to make measurements, look at it from a control standpoint. Let's look at it from an engineering standpoint and really help the world.

Chairman: Thank you very much Dr. First. Any more suggestions from the panelists? I would like to get suggestions from the floor. Any suggestions? Okay, no suggestions.

It is now time to close the last session. We think we have had too little time in comparison to the tremendous number of items that we had to discuss. I would like to apologize to the panelists for the small amount of time we have had. I am sure each of you had more things to say, and many more questions to ask. I hope you make up for this loss, not in cigarette smoke but by touring and enjoying the rest of your days in Japan. Thank you so much.

Epidemiology of Passive Smoking and Lung Cancer (I)

Chairmen: K. Maeda and T. Namekata

Dr. Maeda (Chairman): Good afternoon ladies and gentlemen. Welcome to the panel discussion on epidemiology of passive smoking. I am the chairman of this session. My name is Kazuho Maeda, Professor of the Department of Epidemiology, School of Health Sciences, University of Tokyo. It's our extreme honor to have such distinguished scholars as panelists from various parts of the world. I would like to introduce the co-chairman of this session, Dr. Tsukasa Namekata, epidemiologist at Battelle Memorial Institute – Human Affairs Research Centers, Seattle, Washington, USA.

Dr. Namekata (Co-Chairman): The purpose of this panel discussion is to improve future epidemiological studies of passive smoking and lung cancer. We will cover a variety of topics, including questionnaires, problems of misclassification, statistical analysis, and passive smoking at home and at the workplace. We will ask each question, then have answers from panelists, and then open the discussion.

Chairman: Question 1. Johnson and Letzel published a paper entitled "Measuring Passive Smoking: Methods, Problems and Perspectives" in *Preventive Medicine* in 1984. In the paper they describe Dr. Wynder's idea about three time frames: prenatal, the first 16 years of life, and adulthood. Then they propose the concepts of the exposed M-time of a person ($T_{\dagger}^{M}$) or group ($T_{\dagger}^{M}$). We would like to ask Dr. Überla to clarify this concept.

Dr. Überla: Let me begin by commenting on evaluating ETS with questionnaires (see Appendix I.) Two years ago, we developed a quantitative instrument for assessing exposure to ETS. We developed a one-page questionnaire, which shows on the left side the hours of the day. You ask the person being interviewed where he was at each hour – at home or at the workplace or somewhere else. Then he is asked whether he was exposed to environmental tobacco smoke during each hour and for how long. Using this questionnaire you can obtain a measurement of quantitative exposure in about 5 to 10 minutes.

There are a variety of ways to evaluate the data from the questionnaire; for instance, the counting rule. If you apply counting rule 1 to these data (which would mean for any exposure), in this case for the 24 hours, you have 7 hours with no exposure, 8 hours with some exposure, 7 hours with a little more exposure, and 2 hours with really high exposure. Using counting rule 1, you count 70% of the time exposed. With counting rule 2, 9 hours of the 24 hours have exposure, which would be 37%. Counting rule 3 would give you only 8% exposure. The questionnaire allows you to evaluate the data in many different ways. For instance, you could ask whether the intensity of the exposure has changed, or you could evaluate working place and other locations separately. And it can be used to measure exposure for 24 hours, or for a whole lifetime.

H. Kasuga (Ed.) Indoor Air Quality

The reliability of the questionnaire, from day to day, is 0.76, and the validity is 0.62, which I think is rather high. If we apply such questionnaires for quantitative estimates of passive smoking, we will be more reliable in future studies.

Mr. Lee: May I, Mr. Chairman, make the obvious point? And that is that the questionnaire is fine for finding out what people were exposed to yesterday, but for an end point like lung cancer, it's absolutely meaningless. People do not remember accurately what they ate yesterday, nor how much they ate, and they certainly would not remember what level of air pollutants they were exposed to a week ago, a year ago or 20 years ago. They'd have no idea at all. Although it's the right approach for acute symptoms, it is of little value for cancer studies.

Co-chairman: However, this kind of method can be useful in prospective studies.

Chairman: Question 2. The quality of information obtained by interview or self-administered questionnaires may vary among studies. Data quality for ETS exposures can be affected in many ways by differential and nondifferential misclassification of exposure. Therefore, it is important to determine whether non-smoking subjects are people who have never smoked or ex-smokers who are non-smokers. Another source of bias is the misclassification of exposure among non-smokers. That is, non-smokers who say they have not been exposed but may in fact have had significant exposures. In both cases, detailed probes are needed. 1) How can such misclassification of smoking status be reduced? 2) How can survey techniques be improved to increase the reliability of exposure data? 3) What methods of verification have been successful in the past and what methods would you recommend? I would like to ask Dr. Hulka to reply.

Dr. Hulka: This question is one we could discuss all afternoon. The whole area of misclassification in questionnaires as a general topic could be reviewed under this question, but let me just make a few comments specific to the issue of passive smoking.

Clearly, we want reliable questionnaires, questionnaires that are repeatable when administered at different points in time, and valid questionnaires – questionnaires that give accurate, true information as measured by sensitivity and specificity. Those are general principles of questionnaires.

There are special issues related to passive smoking. I would start out by saying that we want complete information. One of the problems that's arisen through the studies that we have so thoughtfully reviewed today is the problem of various sources and sites of exposure. We've used the measure of spouse smoking as a proxy for exposure to environmental tobacco smoke, and we all know we would like more complete information. We certainly want information on a variety of micro environments in which people can get exposed. Home is one of them, as well as work, leisure-time activities, and travel.

I was interested in Dr. Überla's questionnaire and the effort to quantitate information on an hourly basis related to exposure. I like the idea and the effort to quantitate and come up with a number. I like it because it tends to refine our interest and the detail and effort we put into a questionnaire.

I don't like it because we come up with a number that we then believe in. Once we have a number, there's something magical about that number, even though it may not reflect reality. So I think we have to be careful in terms of what a person can actually respond to. You might be reasonably accurate about your exposures of yesterday, but certainly you're not humanly capable of being accurate about your exposures of a year or five or ten years ago. And if you're interested in adverse health effects with a long latent period,

you want to know about exposures over a prolonged period of time. I don't think the issue of whether it's a cohort study or a case control study makes any difference. Because if it's a cohort study you still have to collect data repeatedly over a period of time.

One other comment is that we have a special problem in that passive smoking is not like active smoking. When people start smoking actively they get hooked! And they're going to continue smoking, although there may be periods of trying to stop the habit. So you can get more accurate information from active smokers than you can from passive smokers because for passive smoking there's going to be more variability in exposure over a lifetime than there is with active smoking.

Co-chairman: Thank you. Dr. Hayashi has a special comment about this.

Dr. Hayashi: I have carried out various social surveys, and tried to see how reliable the responses are. We carried out a national survey using a random sampling method. We asked people, for example, did you vote in the last election? When we checked to see whether they actually did vote, we found that about 15 percent were lying. So I think that there are certain items about which people tend not tell the truth.

With 1,800 subjects we had 50-90 percent reliability. We thought this was a Japanese problem, but then in the social survey carried out in West Germany there was also a reliability of about 70 percent.

So no matter how reliable or how accurate the questionnaire itself is, we are really dependent on the reliability of the people who are questioned.

I'd like to give one example of Data A and non-A (see Appendix II, Explanation 1). This is one example of the probability of misclassification to 0.7 and 0.8. The true figure is 5,500 and 4,500, but the data is actually 4,750 and 5,250 respectively. And looking at this we get data which is totally inaccurate. We have to adjust based on the probability of misclassification. So we have to look at the odds of misclassification and adjust the figures accordingly.

Now, looking at the responses (see Appendix II, Explanation 2). If we look at the previous example, the true passive smokers and the true non-passive smokers, the percentage would be the apparent number of PS and non-PS in the data. We have to see who are the true smokers and who are the apparent true smokers, and similarly with the passive smoker.

And now we also have problems with incipient lung cancer, or primary lung cancer and metastatic lung cancer (see Appendix II, Explanation 3). The probability of misclassification is also seen.

We would like to know the true rate of primary and metastatic lung cancer, but we cannot get the true rate in the data themselves. It is objective to find what is the true rate, because we can only see the apparent rate from the surveys and questionnaires.

So we get the apparent data, and the apparent data has to be calculated to give us the true result. We will get the true answer from the apparent data. Is this really possible, you may ask? Well, this very detailed explanation (Explanation 3) will show you that it is possible. We can use the method of calculation shown in Explanation 3. And in the interests of time I will skip over the details of the equation, but it can be calculated and adjusted in the manner shown.

This is the apparent lung cancer data or the ratio of non-lung cancer, and these can be estimated if we can only know the P and Q (probabilities of misclassification) matrices. If we use only the apparent data without carrying out reasonable calculations, we will come up with very misleading information. Furthermore, such kinds of misclassifications are inevitable. But because these are inevitable, we have to identify the P and Q matrices, keep

in mind that there is a misclassification, carry out the calculation I've just mentioned, and then we can really obtain very detailed and valid epidemiological information.

Dr. Überla: I very much agree with your proposition, but I would like to make a comment about the question Barbara Hulka and you raised about the validity of such questionnaire measurements. I think we have only two possibilities: either use personal samplers for cohort studies for about 10 to 20 years, which will be an awful, impossible task, or, apply some kind of measurement, relying on the memory of the persons for the last 20 years.

The reliability of such an instrument would be the crucial point because all our results would have an upper limit which is defined by this reliability. Our risk ratio estimates can't be better than the reliability of our instruments. So we have to adjust them for this reliability. And there are statistical ways to do this. The confidence intervals for the risk ratios would be much wider.

There seems to me to exist an empirical threshold for epidemiological knowledge which can be gained. And this empirical threshold for epidemiological knowledge will be rather low – perhaps far away from the odds ratios of the size order 1.3 or so.

Dr. Wynder: I would like to suggest, since the questionnaire is a relatively inexpensive instrument compared with those chemists use, that we agree on an international standardized version so that we can evaluate a common questionnaire. We should also agree on who should conduct the interviews. At the American Health Foundation we have a careful program to train the interviewers who conduct the interview.

Secondly, we should consider what population we should study. We have only used hospital cases and hospital controls. In the United States, investigators use neighborhood controls. We like to use hospital controls because a hospital control is the same hospital; the same hospital environment has been lying there for the same length of time. If we could agree, as part of this conference, on the structure of the interview and where and how the interviews should be conducted, the epidemiological part of this conference would gain a great deal.

Co-chairman: Next, question 3: To evaluate the role of major confounding exposures, what kind of information should be included in a questionnaire? For this question, could you reply, Dr. Stellman?

Dr. Stellman: I think Dr. Wynder mentioned validity, and one dimension to establish validity for any questionnaire would be to include in it all factors that possibly could confound the interpretation of results. I think we have covered most of them today, and all I have to do is to review them. First, we have the lifestyles: food, smoking, drinking, and other vices. Now here's where we'll probably miss out because people do not like to speak about their vices. They lie a little bit about smoking and they lie a great deal about drinking. Nevertheless, one has to accept these errors for measurements. One measure of lifestyle that was not mentioned was artistic hobbyists. A lot of people do artwork that brings them into contact with very toxic materials, such as solvents. For instance, airplane glues are probably one of the real risk factors for lung cancer. The second class of confounding exposures has to do with occupation. This involves both the husband and wife. Does any one of them have the possibility of being exposed to risk factors? And here, especially, because we are doing so many studies on women married to smokers or non-smokers, it is important to look at the wife's activity if she's a housewife. One should not overlook the fact that housewives use a great deal of such things as solvents, and that

in some countries, such as Japan, they used to be involved with kerosene heaters and stoves and received heavy exposure to fumes from these portable heaters.

Another possible factor would be pollution in the area. There might have been an increase in lung cancer incidence of people living downwind from certain industrial complexes. I think that is a fairly comprehensive list.

Co-chairman: Thank you very much. Do you have any further comments, Dr. Sterling?

Dr. Sterling: Occupation is my special interest, and listening to the discussion of misclassification I was quite struck by the whole discussion of questionnaires, because it seems to me the problem is not in designing a good questionnaire. The problem is the small number of cases upon which to base the questionnaire. Any scientific instrument has an imprecision associated with it, whether it is a gas chromatograph or a questionnaire. The extent to which the imprecision of the measuring instrument has an impact on the outcome is a function of the number of cases or the size of the sample.

I have been thinking about women – because we are likely talking about women – who might be exposed on their jobs and that could have an impact on the evaluation of passive smoking.

For instance, in the United States there are half a million cosmetologists who up until 1973 were exposed to aerosolized hair spray. The Food and Drug Administration now estimates that one out of every 100 cosmetologists is under the risk of lung cancer from the methylene chloride in the spray.

Dr. Wynder and Dr. Kappa did a study on passive smoking in which they found a large number of textile workers among their cases. Textile workers are exposed to formaldehyde, and to chloromethyl ether that's generated from the formaldehyde in acid solution.

The EPA has just released a study on dioxins and paper products. Many of the paper converters are female. They may be exposed to dioxins.

Dr. Hoffmann at the American Health Foundation did some analyses of nitrosamines in the paper industry from the cutting oils, because in the paper industry one has to keep the knives very sharp, and cutting oils are often nitrite-contaminated. Levels of nitrosamines exceed OSHA standards in many cases.

Workers in central supply in a hospital will be exposed to ethylene oxide. Nurses may be exposed to cancer chemotherapeutic drugs and formaldehyde. For instance, in clinical laboratories in the United States the workers are still allowed to be exposed to polychlorinated bi-phenyls by law, because they are used in the immersion oils in the microscopes. They may also have a formaldehyde exposure. Dry cleaning workers are exposed to chlorethylene and trichlorethylene.

Stewardesses in airplanes are exposed to very high levels of indoor air pollution, as are waitresses in bars and restaurants, and some offices have indoor air quality pollution problems not related to ETS that can offer exposure to carcinogens, so that the potential for confounding effect is there, particularly when one is talking about as weak an effect as has been observed throughout these few days of conferences.

Mr. Lee: Mr. Chairman, I have an important question to ask. There seem to be two things left out of the questionnaires, which have not been mentioned by the people who are measuring environments, and that's two questions relating to perception.

I would like to know if anybody has compared what is being measured in an environment with a person's perception of whether they're being exposed to environmental tobacco smoke.

And, secondly, there should be a question regarding a person's perception of the hazard from environmental tobacco smoke, or whatever he's looking at.

Co-chairman: How about Dr. Hulka?

Dr. Hulka: It's a very interesting idea, and I certainly understand the gist of what you're trying to get across. What we get on a questionnaire is a person's perception of exposure, and I think you're trying to get at how does that perception influence how the person responds.

Dr. Überla: I think you are asking a very important question. I can remember an experiment which we performed. We randomized 200 people into two groups and exposed one group to our questionnaire, without giving them information on the relationship between passive smoking and lung cancer. The other group got a 20-minute introduction on how well-established the relationship between lung cancer and passive smoking is, before answering the questionnaire. We then looked at the questionnaires from the two groups to see whether the exposures of passive smoking were different. In the 24-hour questionnaire there was definitely no measurable difference. In the lifetime history there was a very small effect. So we could demonstrate that one could influence it, but it was on the borderline of statistical significance.

Chairman: Thank you. Let's move to question 4. In order to obtain an adequate assessment of total ETS exposure, how far do we expand survey areas? Should we conduct surveys in homes, at school, at work, in vehicle and recreation areas in terms of the duration of time an individual is exposed in each area?

For this question, could you answer, Dr. Lehnert?

Dr. Lehnert: My special interest is the influence of the workplace. I am very glad that I have the opportunity to introduce this problem. From my point of view there are three aspects to it: The first aspect is, what is the influence of the workplace itself in developing lung cancer risk? The second is, what about the influence of passive smoking itself at the workplace? And the third is, what about multiplicative effect of passive smoking and workplace influences? In other words, it seems to me to be important to check the workplace conditions exactly, not only if women are working, but also if the husbands are working. We have good information that influences from the working place of the husband can result in diseases of the wife.

For example, it is well-known that mesothelioma in women can be induced by asbestos exposure of the husband. He is bringing the asbestos fiber home and the woman is exposed.

Therefore, I think it is necessary to ask not only about the husband's profession but about the kind of work he actually does on the job. To my knowledge, up to now this has not been done.

The third aspect, namely the interaction between passive smoking and workplace conditions, could be of importance, too. We know from active smoking studies that there is a cumulative effect of workplace conditions and active smoking especially with asbestos, arsenic, and some other substances.

My opinion is that these influences would be somewhat more meaningful than the passive smoking alone. I fear that all the discussions about passive smoking overlook the influences of the workplace.

Co-chairman: Next, question 5: It is extremely important to have accurate ETS exposure information that enables us to estimate lung cancer risk due to ETS exposure. Should we collect information from both self and surrogates regarding smoking habits and history and ETS exposure? If we have interviews with surrogates, who do we consider them to be: spouse, sons or daughters, and brothers or sisters?

Could you answer this question, Dr. Wynder?

Dr. Wynder: This is a very important question. Listening to the various reports and case-control studies, I think sometimes we mix apples and pears. We mix replies from the patient with replies from the spouse, with replies from a surrogate. Those who are married know that if you ask the husband how much he drinks he gives you one amount. If you ask the wife, she gives you twice the amount. There can clearly be different responses between spouses.

The retrospective study by Garfinkel, which has been previously mentioned, is a case in point. He finds great differences between the answers given by the patient and those given by a surrogate, such as the daughter or some other next of kin. We combine what the spouse has said with what the patient has said, and what the daughter or son has said, as if it were one unit.

We should limit ourselves to what the patients have said, particularly in a weak association like passive inhalation. It's a very difficult question that only the patients themselves can answer. If we do report on the replies of the spouse and on some surrogate, at the very least we should report those results separately.

It is difficult enough simply to get the appropriate information from the patients themselves. As far as we are concerned at the American Health Foundation, we limit all of our studies to the patients themselves.

Co-chairman: Thank you. Any other comment? Mr. Lee?

Mr. Lee: I have a question about your example on alcohol. You said that the husband said one figure and the wife said twice the amount. Who do you think was right?

Dr. Wynder: That would be a study in itself. All I'm saying is that at the very least, we should have separate analyses for the answers given by the case, the spouse, and the surrogate, rather than lumping them all together as if they all came from the same source.

Mr. Lee: Pooling information from various sources is a problem, but I really wonder, to get around the misclassification point, whether there is a case for getting information on one person from more than one source in order to validate the answer. If you get information from two sources, and they give you different answers, then you're much less happy about the data.

Dr. Wynder: I agree. The Garfinkel study is of particular interest because it shows a great bias in what the distant relative says. In a separate study on diesel exhaust we found very similar parameters. The patient admitted to a much lesser exposure to diesel exhaust than the daughter or the son had reported. These problems are among the most intricate in epidemiology.

Chairman: Thank you very much. Dr. Lebowitz.

Dr. Michael Lebowitz (University of Arizona): It is not appropriate when we are looking at these factors to ask the spouse because the information provided is usually highly incorrect. It can go both ways – errors of omission and commission. We've used in these different studies several methods of validation, including medical records,and including expired carbon monoxide. People may lie; I think that this was shown in terms of the election example given by Dr. Hayashi, and it's certainly shown at certain times in terms of drinking and smoking. The tendency to lie is greater if the other spouse is present or in the child if the parent is present. However, if you do a confidential interview with the individual, as we do with the children, you do get accurate answers that are quite different from what they give when they fill out a questionnaire or are interviewed in the house.

So, I would agree with Dr. Wynder, that it's absolutely essential to do a confidential interview with the individual to get a close approximation of the right answer.

Co-chairman: Thank you very much. We'll move to the second problem, the problems of misclassification.

Chairman: Question 6. One source of potential bias that would influence the estimates of relative risk is that some people who occasionally smoke or who have smoked in the past may report that they have never smoked. Having smoked, these people are somewhat more likely to develop lung cancer than would true lifelong non-smokers. Because smokers tend to marry smokers, they are also more likely to have a spouse who smokes or did smoke in the past. Table 12-5 shows that the bias produced by this misreporting could be serious.

Could you explain this table for us, Mr. Lee?

Mr. Lee: This table came from the National Research Council's Report on Environmental Tobacco Smoke (1986), and illustrates a bias likely to affect passive smoking studies. It's a hypothetical example. It is assumed that the true proportion of smokers among women is 35 percent, and the true proportion of smokers among men is 50 percent, and there is an aggregation. This is the same thing as the concordance ratio I explained yesterday. The tendency for smokers to marry smokers is 3.5. You start at the top with 100,000 women, of which 35 percent are smokers, 65 percent non-smokers. You then suppose 8 percent are misclassified as non-smokers. As 8 percent of 35,000 is 2,800, you have 2,800 misclassified smokers. Now it has been assumed that among smokers the numbers married to smokers and married to non-smokers are in the ratio 2.28 to 1. And so you split the distribution of the 2,800 this way. Whereas among the 65,000, for every two married to a non-smoker, there's 1.3 married to a smoker. The differential split comes because of the aggregation ratio (here 2.28:1 divided by 1.3:2 equals 3.5 as assumed).

The 65,000 and 2,800 both appear to be non-smokers, although the latter group are actually smokers. Assigning a lung cancer rate in the true smokers that is 40/10,000/10 years, 8 times higher, than that assigned in the true non-smokers, you get the numbers of lung cancers shown. Eventually you get an apparent effect of passive smoking of 1.3, when in fact we have assumed at the outset that there is no real effect of passive smoking.

I should make it clear that this table isn't actually the way I personally would have gone about presenting the problem. One difficulty is that the relative risk of 8 they assumed for the true effect of active smoking was based on a risk observed in epidemiological studies, without taking account of the fact that misclassification means that the observed risk is an underestimate. There is also a confusion between true and observed concordance, though that is not so serious.

I think I have said enough as I know Dr. Mantel wants to consider misclassification also.

Dr. Sterling: In our recent paper in which we compare changes in smoking by occupation between 1970 and 1980 in the United States, we find a dramatic increase in the number of people who refuse to answer smoking questions to the surveys conducted by the National Center for Health Statistics. For some occupations, such as blue collar workers, the refusal rate is very large. About 8 percent of people refuse to answer questions on smoking. The unwillingness of people to say something about smoking might very well influence the amount of misclassifications that occur.

Mr. Mantel: I want to say something which I consider more important before answering those questions asked here. They are very important questions, but in the context of passive smoking and lung cancer these are all irrelevant questions. The reason for this is that it would appear that if passive smoking leads to an increase in the risk of lung cancer, that increase is not more than about a relative risk of 1.10. And one of the things set down by the International Agency for Research on Cancer, earlier this year, was that before a causal relationship could be inferred,then in view of the difficulties of epidemiological investigations, a high relative risk should be found.

Recently they decided against ascribing a causal role to alcohol in breast cancer, even though the studies on that point gave relative risks of about 1.5. Some 30 odd years ago, when work of this kind was started, it was suggested that a relative risk might have to be about a 2 before one might accept it as demonstrating anything, because of the biases in studies.

Chairman: Question 7: Disease misclassification refers to the incorrect classification of the lung as the primary site of a cancer that originated elsewhere. Garfinkel stated in his 1981 American Cancer Society Cohort Study that, on the basis of medical record verification,the death certificate diagnosis of lung cancer in non-smoking women was incorrect for 12 percent of the cases. Because some studies did not verify death certificate diagnosis, do you consider disease misclassification to be a major concern which may distort the study result? Dr. Wynder?

Dr. Wynder: I don't think it's a major concern, but if in fact these cases are not lung cancer, and if ETS does cause lung cancer, then you would get an underestimation. But while on the subject of histology, I think it's absolutely vital that every case that is included in the study has confirmed histological data.

I'm rather impressed that so many studies in the literature do only cytology. I would suggest that every case should be examined by the pathologist, and we would like to see squamous, small-cell, adeno, large-cell carcinomas be analyzed separately.

Chairman: Question 8. Someone says that the number of cigarettes smoked should be counted at home and at work separately.

When we conduct an epidemiological survey, is it feasible to include such questions and is it reliable to follow back 10-20 years ago?

Dr. Hulka, could you answer this question?

Dr. Hulka: I have to ask a question about the question first. It says "Number of cigarettes smoked". Do you mean the number of cigarettes to which one is passively exposed? We're not talking about active smoking now, I gather.

Co-chairman: I think as a proxy we are always asking the number of cigarettes smoked by the husband or any others.

Dr. Hulka: I see what you're saying. I would guess that this probably does vary by workplace and by home. To what extent one would know the number of cigarettes smoked by a co-worker or in a variety of different locations other than the home, and people who occupy the home, is doubtful. I think that the number of hours or minutes that one is exposed to environmental tobacco smoke is probably the best we can do in most locations and for most people. Spouses perhaps are somewhat different in that one might have a pretty good idea of how much one's spouse smokes.

Now, when we conduct an epidemiologic survey is it feasible to include such questions? Is it reliable to follow back 10 to 20 years ago? The answer here is that we don't have other alternatives if we want to get data from the past.

If biological markers that measure cumulative ETS exposure are developed in the future, that would be a substitute.

Dr. Überla: Barbara, I wonder why we talk about cigarettes only when discussing passive smoking. The cigarette smoker inhales deeply and the mainstream smoke passes through his lungs. But those of you who know cigar and particularly pipe smokers, know that we inhale much more of their smoke than we do of cigarette smokers'. I wonder whether we shouldn't include, as indeed we are, a question on passive cigar and pipe-smoking because, as all of us know, it's just as carcinogenic as cigarette tar is.

Dr. Hulka: I agree ...

Dr. Überla: I think that in counting cigarettes, we aren't getting any indicator for ETS exposure. We have to separate the immeasurable from the measurable. In order to do this we have to calculate reliability, which is quite a common construct in psychometric tests. So for every study using an exposure indicator there should be in the same study a reliability estimation of this indicator. I expect those reliability estimates would usually be in terms of a correlation coefficient somewhere between 0.60 and 0.80.

Then we have an estimate which is an upper limit of what we can get regarding information from this questionnaire, by counting cigarettes. And then we try to incorporate this into our relative risk estimation. This would mean that the confidence intervals of the relative risks become much wider. We will come up with a statement that the things we want to know, namely the relative risk of being exposed, are not measurable with the necessary accuracy. And it seems to be better to me to have such a statement than a statement that we have a relative risk, but without an estimation of the reliability of exposure.

Dr. Gerhard Winneke (F.R.G.): Concerning the problem of reliability of exposures to measurements, an important aspect in this is assessing a dose-response relationship. But in the absence of such information, wouldn't it be true that if exposure assessment is not possible with adequate reliability that the actual risk is diluted? If the reliability of the exposure estimation is low, then one would not expect dose-response information to be quite accurate.

It seems to me that if we had more reliable instruments, and if there's any association whatsoever, then the dose-response information and the odds ratios would most likely be higher than those reported so far. I may be wrong. I'd like the Panel to comment on that.

Mr. Lee: Well, it doesn't follow. As I have shown, misclassification can make your relative risks become higher or lower. It all depends on the situation. It's a fallacy to believe that, just because you're measuring an effect inaccurately, what you see is less than what exists. It may be more.

Chairman: Let's move to the next question. Question 9: What do you suggest in order to obtain accurate or reliable information on ETS at home and at work? Could you answer this question, Dr. Überla?

Dr. Überla: I think that even at the workplace it remains absolutely impossible to measure ETS routinely over the lifetime. In some cases it would be useful and possible to do so, but this could be done only in special situations.

In this context, there seems to me to exist no other idea than using the same procedure as at home, namely asking in a questionnaire for the number of cigarettes consumed ...

Dr. Melvin First (Harvard University): We're talking about doing very accurate and reliable measurements. My question to the panel is, how accurate and how reliable do you have to have the information? Obviously there are limitations to what you can obtain. And I think before we try to answer these questions we ought to ask the epidemiologists what they need in the way of precision and accuracy. Dr. Überla has talked about his very detailed questionnaire. And one of the factors in the questionnaire was: Is the environmental smoke light, moderate or heavy? Now, what does this question mean? To whom is it light? To whom is it medium? To whom is it heavy? And what do you use as your definition, and what do you use as your guidepost? So I think these are questions of precision that we need to look at.

Dr. Überla: In the second version we didn't ask whether there was light or heavy exposure to the opinion of the subject. We simply used the hour during which he said he was exposed. This is more accurate and more reliable. We also tried to validate this instrument by measuring fractionally the cotinine of the urine in patients, which gave some reliability of about 0.70. That's the best one can expect to get, I think, and we come down to the fact that we simply cannot measure exactly enough in order to establish a relationship. We must live with the fact, at least presently, that our instruments are not accurate enough.

Dr. Wynder: The question has been asked, why we are here? There are clearly more important issues for us to discuss than the relationship between ETS and lung cancer. I certainly agree with Jeanne and others that the effects on respiratory disease in others are very important. The problem we're discussing here is to me of great epidemiologic interest; to others, of great political interest.

We have organized a conference sponsored by the National Cancer Institute on alcohol and breast cancer. This association would not have been an issue unless epidemiologists had suggested that alcohol might be a cause of cancer of the breast. If so, it would have a great effect on American women. There was a headline in The New York Times, with all the media carrying the story. Epidemiologists must be very careful before we determine an association to be causative. This exercise here has been an exercise in the epidemiology of weak associations which has been of interest to us for a long time.

We need to look at the totality of this problem. One of the issues that I realized at the beginning, and I haven't heard any comment on it: How common is lung cancer in non-smokers? I'm reminded of when, in 1949, I did my first work on lung cancer and smoking. Dr. Graham used to tell me that when a lung cancer patient was brought into Barnes Hospital in St. Louis in 1933, all the residents were brought in to see this unusual case. Since then, we now have more than 125,000 deaths from lung cancer in the United States per year. But today when I see a lung cancer patient at Memorial Hospital who is a non-smoker, I look at this case very carefully because it is so rare.

So we must look at the epidemiology of smoking, of ETS and lung cancer, in light of what type of problem is it for society? Has lung cancer in the non-smoking population increased? Why do Chinese women and Mexican women have a particularly high rate of adenocarcinoma, as Dr. Koo indicated?

In terms of establishing how meaningful this exercise is, beyond what we learn as epidemiologists by new methodology, the issue is how many cases does ETS cause, if any, in the United States? And has lung cancer in non-smokers increased?

Before the meeting is over we need, under "Criteria of Judgment," to consider all the other factors that are mentioned, realizing that in terms of interview studies alone we may have problems that we cannot overcome.

Dr. Hayashi: I do see the intent and attitude [of the previous speaker] about getting reliable and accurate data. Of course, reliable data is self-explanatory. But what do you mean by "accurate" data? I think there are many discussions involved here.

How much tobacco was smoked 20 years ago? How much tobacco is really smoked now? I think we have to think of accuracy in such terms. And I think this term is used because you are all thinking of conducting studies in the laboratory. But in studies in the field, this kind of accurate measurement is impossible, because data always has some kind of bias. How to evaluate such data is very important. And based on the data that is actually evaluated, you have to handle the data cautiously and draw the information from that data. I think that is important because if you're always looking for accurate data or accuracy in your data, its going to be like a bluebird. When you think you've got it, you find that it's not quite what you want.

I think the mistake here is to handle the data formally, disregarding the quality, or to believe you have got accurate data. Rather you have to work on the data to draw from it relevant and reliable information, taking into consideration the quality of data based on its mathematical property and numerical evaluation. I think that is how we have to approach data and data assessment.

As was mentioned by Mr. Mantel, we have to handle data cautiously, and have the wisdom to look at the wider perspective. And I think that is the angle from which we have to think of measurement.

Appendix I

Question 1. Response from Dr. Überla: Questionnaire instrument for ETS exposure

Time	Exposure			
	None – High			
	0	1	2	3
0 ~ 1	×			
1 ~ 2	×			
2 ~ 3	×			
3 ~ 4	×			
4 ~ 5	×			
5 ~ 6	×			
6 ~ 7	×			
7 ~		×		
		×		
		×		
~ 11		×		
11 ~			×	
			×	
			×	
			×	
~ 16			×	
16 ~		×		
		×		
		×		
~ 20		×		
20 – 21				×
21 – 22				×
22 – 23			×	
23 – 24			×	
Total	7	8	7	2

Rule 1 (any exposure):

$$\frac{8 + 7 + 2\,(= T_i^m)}{24 \text{ hours}} \times 100 = 70.8\%$$

Rule 2 (moderate to high exposure):

$$\frac{7 + 2\,(= T_i^m)}{24 \text{ hours}} \times 100 = 37.8\%$$

Rule 3 (high exposure):

$$\frac{2\,(= T_i^m)}{24 \text{ hours}} \times 100 = 8.3\%$$

T_i^m = maximum exposed time of individual i
T_6^m = average T_i^m of group 6

Appendix II

Question 2. Dr. Hayashi's response:

Explanation 1

Opinion Survey of Social Attitude:		In Japan In Germany	average about 70%	
	data	A	$\bar{A}$	
	true			
n_+ 5,500	A	0.7 (3,850)	0.3 (1,650)	(P)
n_- 4,500	$\bar{A}$	0.2 (900)	0.8 (3,600)	
	data	4,750 m_+	5,250 m_-	

$(P)'(n) = (m)$
Est. $\hat{n} = (P)'^{-1}(m)$

Explanation 2

	data	S	$\bar{S}$
size	true		
N_s	s	P_{11}	P_{12}
$N_{\bar{s}}$	$\bar{s}$	P_{21}	P_{22}

s: True passive smoker (PS); $\bar{s}$: True non-passive smoker (NPS)

Apparent number of PS and NPS in data

$N'_s = N_s P_{11} + N_{\bar{s}} P_{21}$
$N'_{\bar{s}} = N_s P_{12} + N_{\bar{s}} P_{22}$

$\begin{pmatrix} P_{11} & P_{12} \\ P_{21} & P_{22} \end{pmatrix}$: Matrix of probabilities of misclassification

Explanation 3

	data	L	$\bar{L}$
true			
$\alpha_s(\alpha_{\bar{s}})$, L		Q_{11}	Q_{12}
$\beta_s(\beta_{\bar{s}})$, L		Q_{21}	Q_{22}

L: true primary lung cancer (PLC); $\bar{L}$: true metastasized lung cancer (MLC)

$\begin{pmatrix} Q_{11} & Q_{12} \\ Q_{21} & Q_{22} \end{pmatrix}$: Matrix of probabilities of misjudgment

α_s: Rate of primary lung cancer in S
β_s: Rate of metastasized lung cancer in S
$\alpha_{\bar{s}}$: Rate of primary lung cancer in S
$\beta_{\bar{s}}$: Rate of metastasized lung cancer in S

It is our purpose to find α_s, $\alpha_{\bar{s}}$, β_s and $\beta_{\bar{s}}$.

But we have the errors mentioned above in the data of both PS and LC.

Apparent rate of PLC in data (S): $\alpha_s Q_{11} + \beta_s Q_{21}$
Apparent rate of PLC in data (s): $\alpha_{\bar{s}} Q_{11} + \beta_{\bar{s}} Q_{21}$
Apparent rate of MLC in data (s): $\alpha_s Q_{12} + \beta_s Q_{22}$
Apparent rate of MLC in data (s): $\alpha_{\bar{s}} Q_{12} + \beta_{\bar{s}} Q_{22}$

Data

$N'_s = N_s P_{11} + N_{\bar{s}} P_{21}$: Apparent PS in data

$N'_{\bar{s}} = N_s P_{12} + N_{\bar{s}} P_{22}$: Apparent NPS in data

$N''_s = N_s P_{11} \alpha'_s + N_{\bar{s}} P_{21} \alpha'_{\bar{s}}$

$$\frac{N''_s}{N'_s} = \frac{N_s P_{11} \alpha'_s + N_{\bar{s}} P_{21} \alpha'_{\bar{s}}}{N_s P_{11} + N_{\bar{s}} P_{21}}$$
$$\Big\| \; A_s$$

Apparent Rate of PLC in apparent passive smokers in data if

$\alpha'_s = \alpha_{\bar{s}}$, $\alpha'_{\bar{s}} = \alpha_{\bar{s}}$

$P_{11} = 1$, $P_{21} = 0$

$$\frac{N''_s}{N'_s} = \alpha_{\bar{s}}$$

P'_s are known $\Rightarrow (N'_s, N'_{\bar{s}}) \rightarrow (N_s, N_{\bar{s}})$

$\frac{N''_s}{N'_s} (= A_s)$ and $\frac{N''_{\bar{s}}}{N'_{\bar{s}}} (= A_{\bar{s}})$ are known (data),

$\frac{N'''_s}{N'_s} (= B_s)$ and $\frac{N'''_{\bar{s}}}{N'_{\bar{s}}} (= B_{\bar{s}})$ are known (data)

Apparent rate of PLC in apparent NPS: $A_{\bar{s}}$

$$A_{\bar{s}} = \frac{N''_s}{N'_s} = \frac{N_s P_{12} \alpha'_s + N_{\bar{s}} P_{22} \alpha'_{\bar{s}}}{N_s P_{12} + N_{\bar{s}} P_{22}}$$

Apparent rate of MLC in apparent PS: B_s,

$$B_s = \frac{N_s'''}{N_s'} = \frac{N_sP_{11}\beta_s' + N_{\bar{s}}P_{21}\beta_{\bar{s}}'}{N_sP_{11} + N_{\bar{s}}P_{21}}$$

Apparent rate of MLC in apparent NPS: $B_{\bar{s}}$

$$B_{\bar{s}} = \frac{\acute{N}_{\bar{s}}''' }{N_{\bar{s}}'} = \frac{N_sP_{12}\beta_{\bar{s}}' + N_{\bar{s}}P_{22}\beta_{\bar{s}}'}{N_s'P_{12} + N_{\bar{s}}P_{22}}$$

$$\begin{pmatrix} N_sP_{11}Q_{11}, N_{\bar{s}}P_{21}Q_{11}, N_sP_{11}Q_{21}, N_{\bar{s}}P_{21}Q_{21} \\ N_sP_{12}Q_{11}, N_{\bar{s}}P_{22}Q_{11}, N_sP_{12}Q_{21}, N_{\bar{s}}P_{22}Q_{21} \\ N_sP_{11}Q_{12}, N_{\bar{s}}P_{21}Q_{12}, N_sP_{11}Q_{22}, N_{\bar{s}}P_{21}Q_{22} \\ N_sP_{12}Q_{12}, N_{\bar{s}}P_{22}Q_{12}, N_sP_{12}Q_{22}, N_{\bar{s}}P_{22}Q_{22} \end{pmatrix} \begin{pmatrix} \alpha_s \\ \alpha_{\bar{s}} \\ \beta_s \\ \beta_{\bar{s}} \end{pmatrix} = \begin{pmatrix} A_s' \\ A_{\bar{s}}' \\ B_s' \\ B_{\bar{s}}' \end{pmatrix}$$

known

where $A_s' = A_sN_s'$
$A_{\bar{s}}' = A_{\bar{s}}N_{\bar{s}}'$
$B_s' = B_sN_s'$

and $B_{\bar{s}}' = B_{\bar{s}}N_{\bar{s}}'$

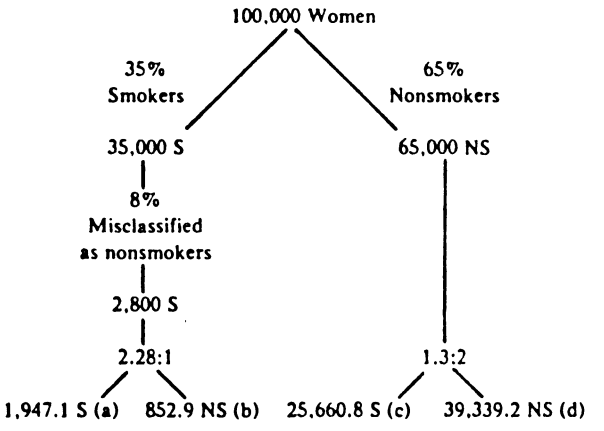
Appendix III

Question 6. Mr. Lee's response:

Illustration of a bias likely to affect passive smoking studies. (Source: National Research Council: Environmental Tobacco Smoke, p. 236, 1986)

ASSUME: (i) proportion of smokers among women = 35%
(ii) proportion of smokers among men = 50%
(iii) aggregation of smokers with smokers and nonsmokers with nonsmokers[a] = 3.5

True Situation



Assume true *RR* of lung cancer associated with smoking (8.0) and spouse smoking (1.0)	8.0	8.0	1.0	1.0
Rate/10,000/10 years	40.0	40.0	5.0	5.0
Number of lung cancers	7.79 (e)	3.41 (f)	12.83 (g)	19.67 (h)

Observed Situation

Observed no.	67,800 (65,000 NS + 2,800 smokers misclassified as nonsmokers)	
Observed no. in spouse groups	27,607.9 S (a+c)	40,192.1 NS (b+d)
Observed no. of lung cancers	20.62 (e+g)	23.08 (f+h)
Observed rate/10,000/10 years	7.47	5.74
Observed RR of lung cancer associated with spouse smoking	1.30	

CONCLUSION: Misclassification error would increase the true relative risk of 1.0 to 1.30.

[a]Ratio of cross-products in a 2 × 2 table of smoking status (Yes or No) by spouse smoking status (Yes or No).

ABBREVIATIONS: S = smoker; NS = nonsmoker; RR = relative risk.

Epidemiology of Passive Smoking and Lung Cancer (II)

Chairmen: K. Aoki and T. Namekata

Chairman: Good evening, ladies and gentlemen. We'd like to resume our panel discussion. I'd like to introduce myself. My name is Kunio Aoki, Professor of the Department of Preventive Medicine, Nagoya University School of Medicine, Nagoya.

I will introduce one new panelist, Dr. Fukuma. He's a consultant (and former director) of the Chiba Cancer Center. And I would like to introduce the co-chairman, Dr. Tsukasa Namekata, epidemiologist at Battelle Memorial Institute-Human Affairs Research Centers, Seattle, Washington, USA.

We learned many things from this afternoon's session and now have a sketchy background on the epidemiological survey on passive smoking. It seems to be a good time for the discussion about the counter-relationship between passive smoking and lung cancer. Most epidemiological studies can be evaluated based on five criteria which were used in the Surgeon General's report in 1964: strength of association, specificity of association, temporal relationship, coherence of association, and biological plausibility.

We know the large role of active smoking in lung cancer and many other diseases. How about passive smoking? Epidemiological studies have already been conducted. Now we would like to discuss this problem by evaluating those epidemiological studies.

We have divided the discussions into three parts: 1) the issue of cohort and case-control studies; 2) pathophysiological consideration of lung cancer; and 3) the interpretation of lung cancer risk due to passive smoking.

Let us begin the discussion. Question 10. Three cohort studies of passive smoking and lung cancer have been published by Hirayama (1981), Garfinkel (1981) and Gillis et al. (1984). Could you discuss the significant results or the questionable points in these studies and also comment on the problems of cohort studies?

Also, considering the reduction in the smoking population in the US, could you tell us if large-scale cohort studies are still feasible?

Co-Chairman: Dr. Hirayama, first.

Dr. Hirayama: I would just mention the advantages of cohort studies over case-control studies. First, we can forget the psychological response bias. With so many people now informed of the impact of passive smoking on lung cancer, the psychological bias is a headache when a case-control study is introduced. But if we conduct a cohort study, I think we can forget this kind of bias.

The second advantage of cohort studies is the control of selection bias, the controls. It is sometimes extremely difficult to solve such problems in a case-control study. But in the cohort study we do not have to select controls.

And, finally, multiple disease and multiple hazard can be studied. If we do case-control studies, we can study only lung cancer or a specific disease. In a cohort study, on the other hand, we can study not only lung cancer, but also other diseases.

H. Kasuga (Ed.) Indoor Air Quality

Chairman: Thank you very much. Dr. Hayashi, could you make another comment?

Dr. Hayashi: Large-scale cohort studies are very helpful, I think, and I realize the importance of that kind of a study. I actually conducted such a study myself and I agree with that. But when we conduct a cohort study, very careful follow-up procedures are required. And to do so requires a lot of energy and effort, which is easy to say, but very difficult to practice. It's a task that will require lifelong studies. Those who have conducted that kind of cohort studies must have made a great deal of effort, and I respect them.

Careful consideration has to be paid to the cohort study. How are we going to deal with the dropout cases? If we miss dealing with the dropout cases, the results may be different. Bias is a question that we have to deal with.

And in large scale cohort studies, at every stage of the research plan, it is important to control the bias that may lead to distortion of the result. It is easy to say, but according to my experience, it is very difficult to control this. Even in the 2,000 or 3,000 samples it's very difficult to maintain the samplings because you have to deal with many items over which you cannot possibly check. Also in large scale cohort studies you cannot conduct or manage very careful studies, so you come up with misclassification, misanalysis or response error. You require a lot of effort, and this is regarded as a disadvantage in the cohort study. It's a very difficult proposition.

Because the study is on a large scale, the wrong results will be very misleading. The possibility of miscalculation or misclassification will be great. So, in order to conduct these cohort studies, you require many excellent people. And, therefore, you have to organize a very big team and with the cooperation of this big team, you have to actually conduct this large-scale study. You have to check every stage of the cohort studies so as to come up with data that can stand up to the review all over the world. This is very important – that is to say, you have to collect the data that is worthwhile disclosing or publishing. If we have only one or two studies of this kind it will be very ideal and desireable.

Dr. Überla: I think we all agree that we need both cohort and case-control studies. But within the cohort studies it is a question of how detailed the information should be for the individual subjects. In the States there are now studies starting which are called large studies with simple protocols. So you have very little information on a huge number of subjects. This is quite different in comparison to other cohort studies where you have a lot of detailed information on not so many subjects. This question in my opinion is not yet settled. Under what conditions one should have such large studies with simple protocols and under what conditions one should have cohort studies, say, of the size of the Hirayama studies?

We probably need the combinations because of what is the reason for the studies. We want to get risk estimates. From cohort studies we get incidence estimates, and from case-control studies we get odds ratios. And in estimating the risk we have to bring them both together for one reasonable estimation. When the cohort study is the weaker part then this will be the bottleneck. And if the case-control study is the weaker part then the odds ratio will be the bottleneck. So we have to have a careful balance between cohort studies and case-control studies. We need them both.

Dr. Gerhard Winneke (F.R.G.): We have learned from the previous discussion that the crucial point is the small number of cases. I would like the panel to discuss the possibility of running a coordinated international study according to a common protocol – be it

cohort or be it case-control. Combining international efforts according to a common protocol would be a feasible and useful endeavor to arrive at more detailed and more reliable answers than we have available today.

Dr. Wynder: This was exactly the recommendation that I made earlier. Certainly in case-control studies, we ought to work on a common protocol, common training of interviewers, and common analysis. I would like to support what Dr. Überla just said.

I'd like to remind all of us that long before we did the cohort study on lung cancer and smoking the case-control studies had already established a connection. We must remind ourselves that cohort studies are expensive, require a large population, and are difficult to do on relatively rare diseases such as lung cancer in non-smokers.

Most of the information that has come forward in cohort studies has already been demonstrated previously in well-conducted case-control studies. Case-control studies will continue making important contributions to our knowledge in epidemiology.

Dr. Sterling: Your question is a good one. It seems that if we make an international effort we should succeed more. But, as a practical epidemiologist, I doubt that. We need to include in our studies observations on occupation, style of life, age, and others. Unfortunately, in the computation of risk ratios, it is not the number of people at risk, but the number of cases that constricts any analysis. For example, we have for sex two possibilities; for age, four possibilities; for exposure, three possibilities; for occupation, three possibilities; and for nutrition, two possibilities. We end up with 144 cells, each one combination of classifiers. Any analysis we use is limited by the number of cells that have zeroes in them. One of the big problems with logistic analysis is that we can feed in hundreds of variable to evaluate, and end up with thousands of cells – most of them empty. The result is that our analyses really don't conform to the model which we use.

Even if we start off with a large population, as Dr. Hirayama had, we end up with perhaps 200 lung cancer cases, which are barely enough to compute a risk involving 4 or 5 variants. The problem is not a simple one. I don't think that international cooperation is going to solve it.

Dr. Franz Adlkofer (F.R.G.): You have discussed the methodological problem of epidemiology separately from the passive smoking issue. I think that no one will doubt the importance of epidemiologic approach, and in all its possibilities, it is a very important scientific approach to find out what's going on.

But coming back to passive smoking: After all that we have heard during the first panel discussion, would you believe that there is a proper approach to designing a case-control study or a cohort study on passive smoking today? Or would you believe that the tools available to the epidemiologist are not good enough to pick up the risk?

Dr. Sterling: It's a matter of how much money you want to spend. If you spend enough money, and examine a larger population, you can. If you were willing to spend enough money you could have a very large population. You could use a very detailed questionnaire. You could follow enough people. The question is whether it's worth it.

Mr. Lee: The problem also is how small an effect you're looking for. I mean if one thinks passive smoking could only cause a ten percent increase in risk of lung cancer, one probably needs to have a study with something like 1,000 lung cancer cases to pick it up, which would mean something four or five times as large as Dr. Hirayama's study, or even bigger still.

If, as I do, you have doubts about the validity of the questionnaire data in such studies, you're going to feel that you need bio-chemical markers as well to test the validity of responses obtained. The cost of the study is going to be astronomical, but one may need to spend that sort of money if one wants to get any sort of reliable answer.

Dr. Francis Roe (U.K.): Is there not always the problem that you set about several years planning a big international study and then for some reason or other the study overlooks a variable which comes to be seen important? I mean a couple of years ago the EPA, rather late in the day, discovered radon. Now if what the EPA was saying about radon causing one-third of lung cancers in the States, if that happened to be true – I don't think it is true – but if it happened to be true, then it would make a complete nonsense of even the planning of all the passive smoking studies that have been designed so far.

If it's not radon, there may be something else. So the idea that you can really solve the issue once and for all by designing the perfect study, I think it is probably a "pie in the sky".

Dr. Adlkofer: I would like to continue the question raised by Dr. Sterling. You have answered my question by saying it's possible to do such a cohort study, so that one can find out the risk due to passive smoking; it's just a question of money. Mr. Lee said it might cost an astronomical amount of money. Then I have to ask this question: if we see the risk due to passive smoking as it is discussed within this panel, is it worthwhile to spend this astronomical amount of money? Don't we have other problems which might be more important than this one?

Co-Chairman: Any comment from the panel?

Dr. Wynder: I would like to make a general statement of the question. When we talk about good epidemiology we really talk about good medicine. As a physician I'm not just a healer, I'm an etiologist and as an etiologist I ought to take a proper history.

The American Health Foundation has set a good example: We take a good history that not only includes passive inhalation, but includes other pertinent parameters. Sometimes people ask me, "aren't you asking a lot of questions?" – well, I need to ask the questions, not only to get etiological information, but also to practice good preventive medicine.

The suggestion that I would like to make is that we, as epidemiologists and physicians, learn to take the best history we can on all of the patients coming to our hospital and put all of this data on a computer. We're using computers for many other things, but rarely do we use them in recording good historical data.

The question we really address here is how much does it cost to take a good history? It doesn't cost very much. If we take a good history, including passive inhalation, it's the cheapest expenditure and perhaps the most worthwhile undertaking we can do today in medical practice.

Dr. Hulka: Well, I've been thinking about the possibilities for cohort studies and also case-control studies. In general in the United States it's not easy to put together a cohort of the size that would be required to get sufficient numbers of non-smoking lung cancer cases.

I would feel differently about the issue of a multi-center international case-control study. I believe it certainly could be done. I really do think that there is enough public interest; there's enough political interest; there's enough economic interest involved with this passive smoking issue that it would be well worthwhile. And I would recommend an

international, multi-center study in order to get enough cases, and enough power in the study to come up with a clear result.

Dr. Ian O'Neill (International Agency for Research on Cancer): Following this discussion you should know that the IARC is about to coordinate a multi-center study, using case-control method. The early planning for this is now proceeding. But this follows several years of work to validate the questionnaire method as a way to ascertain exposure.

The first step that was done was to try and correlate cotinine in urine measurements; this was performed at the American Health Foundation with questionnaires which were utilized in thirteen centers worldwide.

That followed on an examination of questionnaires being used. There were major differences between the questionnaires which were used in the different studies which have been published so far. So there's a fair way to go in getting the proper study design. And I wonder, for example, whether you have really flushed out the problem of ascertaining exposure, using the questionnaire method, when the degree of exposure in different places may vary enormously due to local factors such as ventilation and room size.

Co-Chairman: Thank you very much. We'll now move to the next question. Question 11: Knowing that lung cancer cases are very rare among non-smokers, how many cases are required in case-control studies to examine the relationship between lung cancer and passive smoking? Could you answer, Mr. Lee?

Mr. Lee: Well, to look for a 10 percent difference you probably need nearer to 2,000 than 1,000 cases. If you just see it as a two-group problem ending up with 1,600 deaths – 840 in one group and 760 in the other, that would give you about a 10 percent difference that would be just statistically significant at the 95 percent level. Obviously if one is going to look for a 30 percent difference, you could do it on a study nine times smaller, since the size of the study depends on the square of the difference in risk you're looking for. To some extent the study size required depends on the maximum level of likely true effect and this depends on dosimetric extrapolations. If you believe some of the dosimetric evidence that suggests any effect of passive smoking is likely to be less than one percent of that in relation to active smoking, then you probably need all the non-smoking lung cancer cases in the world to study it epidemiologically. That's the sort of order of result.

Dr. Wynder: As I emphasized before, we must do the study by type of lung cancer because it's quite likely that the data will show that the risk is different for squamous compared to adenocarcinoma. And we cannot lump all lung cancer together. And if you do that, Mr. Lee, you will find that probably we need even more. But I'd just like to emphasize this because sometimes I think we lose track of it.

Dr. Hayashi: I was very much impressed by what has been discussed. The size of the sample has been discussed in order to prove something about it. But with only an incremental number of cases required, there will be errors with respect to implementation; practical errors will also increase. This is one of the difficulties faced by epidemiological studies. Increasing the number of cases does not mean that we will be free from the problem of controlling the samples. And also we have miscalculations and non-sampling error and so forth. We have to be mindful of the type of difficulty involved in the implementation of the study.

Chairman: The next question is 12: Many case-control studies have been carried out throughout the world to measure the risk of lung cancer among non-smokers exposed to ETS. Could you tell us if it is still worthwhile to conduct such case-control studies? Dr. Wynder, please.

Dr. Wynder: The answer is yes.

Co-Chairman: Mr. Mantel, do you have any comments about Question 12?

Mr. Mantel: I had already said earlier that for many purposes there is no point to having case-control studies because people already know what the suspect factor is and their reply to questions may be influenced by this knowledge. The case-control studies could be very useful elsewhere. But specifically on smoking and lung cancer or even passive smoking and lung cancer you will not get proper replies. And therefore I think we have to depend more on cohort studies.

Chairman: Question 13. The next question – Pathophysiological Consideration of Lung Cancer. With regard to lung cancer, there exists apparent sex difference in distribution by histological types. According to the Kreyberg's study, epidermoid carcinomas and small-cell anaplastic carcinomas (Group I) were more common than adenocarcinomas, bronchiolar alveolar-cell carcinomas, carcinoids and mucous gland tumors (Group II) among men (78% vs. 22%), but this proportion was reversed in women: 18.5% for Group I vs. 81.5% for Group II. Because most lung cancer cases among men happen to smokers, is it possible to relate epidermoid carcinomas and small-cell anaplastic carcinomas (Group I) to smoking-related tumors? Dr. Fukuma, could you answer this question?

Dr. Fukuma: With regard to whether squamous cell carcinoma is a smoking-related tumor or not, as far as I have known, most pathologists seem to accept this statement and squamous cell carcinoma is called a smoking-related tumor. There are several pieces of evidence to support this statement. I would like to draw your attention to the phenomena called squamous cell metaplasia, which has two types. One, which does not have cell atypia, is somehow related to inflammation in the case of pneumonia, for example. This is a consequence of such inflammation, fibrosis and infarction which is considered to be reversible pathological change. Another type of squamous cell metaplasia is called dysplasia, which is irreversible and closely related to lung cancer.

If you look at a group of heavy smokers and try to observe some of the changes in their lungs, you can observe the higher frequency of the squamous cell metaplasia, developing the cell dysplasia. Therefore, pathologists tend to link and relate squamous cell to smoking-related tumors.

Now I will comment on the other type, adenocarcinoma. We do not identify any evidence to support the idea that adenocarcinomas are smoking-related tumors. About 30 years ago adenocarcinoma was considered to be developed from scars, which may become the place for carcinogen to accumulate and develop into carcinoma subsequently. If that is the case, we may remotely relate the occurrence of adenocarcinoma to smoking. However, people do not seem to believe in it. So at least the case of the adenocarcinoma up to this moment is that there seems to be no evidence to support the idea that it is a smoking-related tumor.

The small-cell carcinoma is a type which will develop in the sites which is somehow similar to squamous cell mctaplasia. So small cell-anaplastic carcinoma is categorized and treated the same as squamous cell metaplasia, according to Kreyberg's study. In that

study, he said that only Type I, or the squamous cell carcinoma and small-cell anaplastic carcinoma, are smoking-related tumors.

Dr. Wynder: Among non-smokers adenocarcinomas are somewhat more common, and that's part of the reason why the odds ratios for adenocarcinoma on smoking are always lower than that for squamous. But clearly in the United States adenocarcinomas are related to tobacco smoking.

The only type of glandular lung cancer that is not related to smoking is terminal bronchiolar or alveolar type of cell cancer. In a recent report we pointed out that in the United States, at Memorial Hospital, in particular (which I emphasize because we had the same pathologists working there over many years) there appears to have been in recent years a relative increase of adenocarcinoma in the male population. One explanation Dr. Covey and I had is that as the tar yield of cigarette is decreasing, the depth of inhalation is perhaps greater, and therefore reaches the lower portions of the lung. This is speculation, but adenocarcinoma in our smoking population is increasing.

It is for that reason that we had assumed that if environmental tobacco smoke does relate to lung cancer it ought to be the adeno-type of lesions that would be primarily affected. But the paper by Pershagen and the data from Correa suggest it is only the squamous that is affected, and it's for that reason that I have emphasized throughout this meeting that we must have accurate histological diagnosis.

Chairman: Next question, Question 14: Interpretation of Lung Cancer Risk Due to Passive Smoking. Since we discussed possible changes in relative risk due to misclassification, another possible estimation of lung cancer risk from ETS exposure among non-smokers can be made by using biological markers. Urinary cotinine is considered to be at present the best marker of tobacco smoke intake for passive smoking dosimetry because it is highly sensitive and specific for tobacco smoke.

Based on the dosimetric considerations, the risk of lung cancer from ETS exposure among non-smokers in the United Kingdom and the United States would be small. Assuming linearity in the dose-response relationships, the risk would be about 1% of the excess risk in active smokers. This is equivalent to a relative risk of 1.14 in males, given that the relative risk in average male active smokers is 10 to 15 times greater than in non-smokers (Hammond 1966; Doll and Peto 1978). For ETS-exposed women, the average relative risk may be less.

Could you provide further explanation of this risk estimate and make any comments on its accuracy?

Dr. Hulka: Well, I believe this is the epidemiologists' effort to be toxicologists. Assuming that environmental tobacco smoke, and inhalation of that, represents the low dose range of mainstream smoke, then what you're trying to do is to get an estimate of the internal dose levels of low dose mainstream smoke constituents. And this is where the study of cotinine in body fluids has been used to come up with an estimate of the relative proportion of smoke constituents found in body fluids of ETS-exposed persons compared to active smokers.

On the basis of cotinine studies in the United Kingdom, (I believe the data in Japan are a little different) it's been estimated that approximately one percent of the dose that an active smoker would get occurs with the inhalation of environmental tobacco smoke. That observation is based on the measurement of cotinine levels.

So if you take the prior estimates of risk, say that there's a 15-fold excess risk for active smoking, you subtract one from that for the risk of a non-smoker, and then you have 14.

You multiply that 14 by 0.01, which is the one percent, then you get the 14 percent excess risk and that's where you get the 1.14 relative risk.

Using this sort of dosimetric extrapolation to the low dose levels is how you come up with the 1.14.

Dr. Überla: I think I would be extremely cautious with such extrapolations. First, they presuppose that there is a dose relationship and a causal relationship between environmental tobacco smoke and lung cancer, which is not yet established, in my opinion. They start with a presupposition, or with a statement which might be wrong. And such extrapolations are outside of the empirical observations that we have. My opinion is that epidemiologists should refrain from such extrapolations because they might be far away from reality. One easily could establish similar extrapolations with a variety of possible results, and we have only an insufficient, empirical basis for it. My advice would be to be extremely careful.

Dr. Nortwood (F.R.G) : Dr. Überla, I would agree if we had any indication that the sidestream smoke would be less carcinogenic than the mainstream smoke. But, on the contrary, we have the analytical data and there is no evidence that the carcinogenic potency is less pronounced than that of the mainstream smoke. This is a good argument for using this extrapolation, I think.

Dr. Schwartz: You say that environmental tobacco smoke is more carcinogenic than mainstream tobacco smoke. That does not make cotinine a marker for the risk for environmental tobacco smoke and Dr. Überla is absolutely correct.

Dr. Hulka: I'd make one other point. I was asked to describe the process whereby this 1.14 relative risk came about, and I did that. I didn't make any value judgment about that process. But I would say it isn't my favorite thing to do. I like data. I like real data, real observations on people and exposures. But so much of the risk assessment activity that's undertaken, at least within the United States, is based on animal models and low dose extrapolations from animals who are fed or in other ways receive very high doses of carcinogens, and we must live with that. It seems to me that at least in this situation we're dealing with the human species, so that there's one less extrapolation, one less assumption that has to be made. That would be at least one argument in favor of this approach.

Dr. Sterling: This discussion touches on a number of interrelated problems, and actually goes to the heart of our estimation of risk due to passive smoking. One way to approach the problem (of estimating the risk of passive smoking) is to take epidemiological studies on women married to smokers and non-smokers, and obtain risk estimates from them. These risk-based estimates tend to be much higher than exposure-based estimates. There's a mystery here.

Now there are two ways out of this dilemma: First, we can assume that sidestream smoke is much more carcinogenic than mainstream smoke. If we assume that sidestream smoke is a hundred times more carcinogenic than mainstream smoke, we can explain that difference. The problem is that physiologically we have no evidence that this may be the case. There are some carcinogens which seem to be in higher quantities in sidestream smoke, but then there are others that seem to be in lower quantities. Certainly we do not know of any justification to say that sidestream smoke is a hundred times more toxic than mainstream smoke. Also, the smoker is most exposed to sidestream smoke because the smoker is nearest to the cigarette.

Second, there are a lot of holes in epidemiological studies: confounding, misdiagnosis, failure to include occupation, recall bias. Perhaps it would be more comfortable to say the risk models based on population studies are faulty. I would pay more attention to extrapolation models than to the risk model based on human data.

However, I think we have to keep one thing in mind. These are models. These are speculations that assume a risk exists. Using the models, we start off with the assumption that a risk exists so that we can never find a risk of less than one. And these models have to be treated as pure speculations.

Chairman: Last question, Question 15: Since 1980 three cohort studies and more than ten case-control studies have been published throughout the world. Relative risks range from 0.8 to 4.3 with large confidence limits. Do you think we have enough evidence that passive smoking can cause lung cancer? Otherwise, do you think we must continue to conduct more, better-designed epidemiological studies to determine such a risk?

Co-Chairman: I'd like to ask each of the panelists to answer this question, and in this way we can conclude this panel discussion. First, Dr. Stellman.

Dr. Stellman: I think that there is some evidence that it may cause lung cancer. I am opposed to large-scale studies of passive smoking and lung cancer because of other health programs of higher priority. And in my scope of public health priorities, investing a great deal of money in epidemiological studies of lung cancer and passive smoking is very low on the list.

Mr. Mantel: I think it is hopeless to try to continue any more epidemiological studies on this because if the relative risk is as low as 1.1, and even if it might be as high as 1.2, which I just don't think it can be, we cannot meet the requirement put down by the International Agency for Research on Cancer – that we must have a high relative risk to infer causality. But I think the problem of passive smoking and lung cancer is a non-problem for the reason that we are pretty much convinced that there is a role of active smoking. And I think we're going to resolve the question of the role of active smoking in due time. Maybe it'll take another three generations but when that goes away, so will the passive smoking problem.

Dr. Hirayama: I'm not talking about other countries, but I'm talking about Japan. In Japan at least three studies were done. Our cohort study and two case-control studies, one by Dr. Akiba and Dr. Blot in the Hiroshima and Nagasaki areas, and another one by Mrs. Inoue and myself in Kamakura and Miura, which will be reported soon. All of these three studies clearly showed that the effect of the husband smoking on the risk of the non-smoking wife is higher than in other countries. The risk of 1.5 plus or minus would be the proper estimate. I think that now – at least in Japan – is the time for action, rather than study.

Mr. Lee: Given the effect of active smoking and given that passive smokers absorb smoke constituents, I think it's likely that there is some effect for passive smoking. But I think it may be getting close to infinitesimally small. I certainly don't think the epidemiological evidence suggesting a 30 or 40 percent increase in lung cancer is anything remotely like convincing. And so I don't think it's been shown that passive smoking causes any serious effect.

If we want to find out more about the issue we need to do more research.

Dr. Sterling: I will join Dr. Lee.

Dr. Fukuma: Dr. Hirayama was very persuasive and convincing, but my response is a bit different. I can't but help feel that there are enormous efforts still required to clarify and elucidate the relationship.

Lung cancer is a very serious issue. There are opposing views, and we have to, as scientists, try to clarify. In order to do that we have to generate some scientific data. If someone wants to negate the relationship between passive smoking and lung cancer, an epidemiological study has to be done.

Dr. Hayashi: It seems to me that two opinions exist: (1) lung cancer is an important (public health) issue (regardless of passive smoking); and (2) the effects of passive smoking are not important. Because of ambiguity and problems in the studies reviewed, it is better to conduct a better study to determine the risk of lung cancer due to passive smoking. Under the conditions of later disclosure, researchers should produce high quality data which can tolerate criticisms of other scientists and should evaluate data with appropriate statistical techniques. Even if the risk is none, I would like to see the epidemiological study which can convince us of its result.

Dr. Überla: My answer to the first question, whether we have enough evidence that passive smoking can cause lung cancer, is "no". I don't think we have enough evidence. And I don't think this needs more specification after the discussion of today.

The answer to the second question, whether we should continue to conduct more epidemiological studies, is a value judgment. And my value judgment would be that we should conduct studies. The truth will become evident in due time. The only method to answer questions is to conduct adequate studies in man and to stop discussing inadequate evidence.

Dr. Lehnert: Very shortly. Question 1: no. Question 2: Yes, but the design should become better. And my feeling is that the epidemiological tool should become more sensitive.

Dr. Hulka: Considering all the evidence that we have, it seems that passive smoking can cause lung cancer. What we don't know is the magnitude of that risk. Is it very small, or is it modest? Therefore I think it's essential that we continue to conduct major epidemiologic studies of the nature we've been told will be conducted or are in progress by IARC studies that will be multi-center, multi-country.

Dr. Wynder: Being the eternal epidemiologist, the answer is two "do", two "don't", and six "maybe".

In my opinion, the relationship has not been established, but it's possible. The reason why we will continue epidemiological studies on passive inhalation is because it is part of a general program to determine what causes lung cancer in non-smokers, and as part of that it may give us some new information about other factors that may relate to this relatively unusual occurrence.

Co-Chairman: Thank you. I'd like to ask Dr. Kasuga for a final comment.

Dr. Hitoshi Kasuga: Yesterday morning I mentioned that three years ago in Vienna there was a Congress, and at that time Dr. Lehnert mentioned that with this level of evidence epidemiologically it is difficult to determine the relationship between lung cancer and

ETS. However, despite that opinion, at the end of last year the Surgeon General of the United States issued a report on passive smoking, which said the correlation between passive smoking and lung cancer were clearly delineated.

So, for the past three years do you think there was great progress in epidemiologic studies of passive smoking and lung cancer? This is a question that I would like to ask Dr. Lehnert. Since three years ago when we had the Congress in Vienna, have we made a very remarkable progress in epidemiologically establishing a relationship between lung cancer and ETS?

Dr. Lehnert: No, we have not.

Chairman: Thank you very much for substantial presentations and discussions.

We have discussed various problems on methodology of epidemiology and interpretation of the data, and heard comments and advice from social, biophysical and biological points of view.

ETS is one of the major current health problems in the world. It should be addressed through the study of human subjects, and it is the role of epidemiologists to continue these studies and discussions. Thank you again.

Outline of the International Conference on Indoor Air Quality, Tokyo, 1987

H. Kasuga

The International Conference on Indoor Air Quality was held to stimulate research into the effect of ETS, or passive smoking, on the human body, currently a topic of great interest, by reporting on research findings to date. The 3-day conference was attended by over 100 specialists in the fields of epidemiology, medicine, analytical chemistry, and statistics from Japan, the USA, and European and Asian countries. It provided a forum for scientific reports and frank discussion.

Below is an outline of the research papers and discussion.

1) Human Exposure to ETS

(a) ETS Concentration Indicators: Nicotine, carbon monoxide, and particle matter have been regarded as indicators of ETS concentration. However, there are problems in choosing any one of these as an ETS indicator as the speeds at which their concentration declines differ.

(b) Human Exposure to ETS: Concentrations of nicotine, cotinine, and COHb in the body fluids have been considered indicators of human exposure to ETS. Currently cotinine, which is metabolized from nicotine, is thought to be the most appropriate. However, individual differences have to be taken into account.

2) Relationship Between ETS and Lung Cancer

Most participants were of the opinion that it would be very difficult at the present time to reasonably establish a correlation between passive smoking and lung cancer because a detailed examination of all published data (statistical bias in relationship between ETS and lung cancer, estimated ETS levels, incidence of lung cancer in nonsmokers, histological types, etc.) shows that the relationship, if one exists at all, is very slight. Others, however, strongly asserted that there is a correlation.

It was also suggested that there are many other problems in the area of public health, and it would be better to direct our energies towards solving them rather than ETS, as the correlation between it and lung cancer is thought to be slight. The conference, however, felt that steady efforts should be continued to determine the relationship between passive smoking and lung cancer by introducing an objective method of measuring ETS exposure and by thorough research into the cancer site and histological type of nonsmoking cancer patients.

There were also some reports and discussion on the effect of ETS on the respiratory and circulatory organs, and although some acute effects have been seen with asthmatics and children, there were no papers reporting any chronic effects.

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3) In addition to ETS, some papers dealt with other indoor air pollutants and their relationship to respiratory diseases. There were reports on the probability that air pollutants from household cooking and heating raised the incidence of lung cancer and respiratory diseases in some countries or regions. Other papers suggested that it was possible that inadequate maintenance of air conditioning systems in buildings could encourage the outbreak of infectious diseases. Furthermore, another paper indicated that restricting industrial atmospheric pollutants was a major task in reducing the incidence of lung cancer in a particular city.

Thus it is obvious that the air itself contains many factors that could have an adverse effect on health. We must encourage scientific research not only into exposure to ETS, but also into the effects that a variety of factors have on living bodies.