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Health Risks to Female Workers in Occupational Exposure to Chemical Agents

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Preface

In 1980 the Directorate-General of Labor, Ministry of Social Affairs and Employment, the Netherlands, requested the Coronel Laboratory for Occupational and Environmental Health, Faculty of Medicine, University of Amsterdam, to carry out

> "a critical study of literature on health risks to women from industrial and occupational exposure to chemical agents which are different from risks to male workers, or which have only been observed in female workers."

The principal investigator was Mrs. A. Stijkel, medical biologist; a part of the study was carried out by R. L. Zielhuis, physician. M. M. Verberk, physician, and Mrs. M. v. d. Poel-Bot, librarian, provided continuous assistance. The final report (in Dutch) covering the literature up to and including 1981, was submitted to the government in October 1982.

A somewhat abridged and modified English text, updated to include 1982, was prepared. The Editorial Board and the publisher of the International Archives of Occupational and Environmental Health kindly made possible the publishing of this text in a special issue of the journal. The authors express their thanks to the Directorate-General of Labor, the Editorial Board and the publisher for making this publication possible. We sincerely hope that this report will be of assistance in making the industrial and occupational environment safer.

Prof. Dr. R. L. Zielhuis

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1 Introduction

1.1 Objective

In the last few decades women have entered the work force in ever increasing numbers; consequently, ever more female workers become occupationally exposed to various chemicals. In the United States in 1978 women constituted 41% of the work force, compared with 38% in 1973, although one-third were still in the traditionally female professions (Stellman and Stellman 1981). In other Western countries similar trends exist; the proportion of women employed is particularly high in the USSR.

In the same period there has been increasing awareness of adverse effects on reproduction by parental exposure to chemicals at home, in the general environment, and during employment. The increasing employment of women raises extra concern.

As early as 1942 the United States Department of Labor suggested that pregnant women should avoid accupational exposure to certain known toxic substances. However, the Threshold Limit Values (TLVs) recommended by the American Conference of Governmental Industrial Hygienists (ACGIH) have, until recently, largely ignored adverse effects on sexual function or reproductive capacity. Since 1971 the USSR has required that special investigations be carried out to determine the effect of industrial and occupational factors on gynecological and obstetric morbidity and mortality (Sullivan and Barlow 1979). Moreover, various countries, e. g., the Netherlands, have recently redefined the criteria for MAC values by including prevention of adverse effects on the offspring (Zielhuis and Notten 1979). The Dutch MAC is defined as follows: "The maximal accepted concentration of a gas, vapor, aerosol, or dust is that concentration in the air of the work place that — as far as the state of the art allows — in repeated exposure or over long periods of time, even over the whole working life, in general does not adversely affect the health of workers and their offspring." The MAC is usually expressed as time-weighted average per 8 h.

In recent years several reviews have been published, e. g., Sullivan and Barlow (1979) on behalf of the British Health and Safety Commission, and the Clement Association (1981) on behalf of the Council of Environmental Quality in the United States. In general, these reviews do not discuss evidence of differences in susceptibility between male and female workers, apart from effects on reproduction. Moreover, they often list studies which suggest on reproduction effects, with little consideration of the validity of the reported evidence.

1.2 Theoretical Possibilities for Extra Health Risks in Female Workers

1.2.1 Differences Between Women and Men Apart from Reproduction

There may be differences relating to *toxicokinetics* – differences in uptake (perhaps because of increased permeability of the skin), in retention and distribution, and in biotransformation. They may also relate to *toxicodynamics* – i. e., increased susceptibility of some critical organs.

1.2.2 Differences Related to the Reproductive System and Reproduction

Sullivan and Barlow (1979) listed the following possibilities:

1. Before conception	*2. During pregnancy*	*3. After delivery*
a) Menstrual disorders	a) Maternal	Abnormal development
b) Changes of libido	– Enhanced toxicity	because of exposure to
c) Infertility	– Toxemia	chemicals transmitted
d) Germ cell mutation	– Abortion	in breast milk or
	b) Fetal	brought home on work
	– Death	clothes, or in the
	– Malformation	environment
	– Functional deficit	
	– Biochemical change	
	– Growth retardation	
	– Mutation	
	– Cancer	

It is evident that the most important hazards to female workers compared with male workers will be those that have adverse effects on the female reproductive system and on the offspring. It should be realized that the same reproductive end points may be the result of different mechanisms and, moreover, that different end points may occur from exposure at different stages of fetal development. Moreover, adverse effects on the offspring may take place even *before* the female worker is aware that she is pregnant.

In this review the extra health risks to female workers are classified as follows:

1. Risks to female workers which differ from those to male workers, and which are not related to effects on reproduction and/or reproductive systems
2. Risks observed only in female workers, e. g., in occupations with predominant or almost exclusive exposure of women, and not covered by points 3, 4, or 5 following
3. Risks to the female reproductive system not covered by point 4
4. Risks to pregnancy and first-generation offspring due to exposure of women
5. Risks to offspring through lactation

Health risks which occur similarly in both male and female workers are not reviewed, neither are risks to reproduction and to offspring through exposure of the father. Most epidemiological and experimental studies have emphasized adverse effects of exposure during pregnancy. However, this does not necessarily mean that in this period the risks to the offspring are greatest; studies on genotoxic effects on oöcytes in occupationally exposed women hardly exist. The possibility cannot be excluded that some of the

reported evidence of effects on offspring may have been due to genotoxicity. Therefore, the health risks to offspring through occupational exposure of the parents are only partially reviewed.

The emphasis here is on reproductive effects and not specifically on embryotoxicity, fetotoxicity, and teratogenicity as such. The Environmental Protection Agency (EPA) in the United States (Karrh et al. 1981) defines teratogenicity as damage to offspring between conception and delivery; damage to genetic material is considered transplacental mutagenicity or carcinogenicity. However, in practice this distinction often cannot be made, because various mechanisms may lead to similar effects, e. g., abortion and congenital malformation.

1.3 Sources

The search of the literature was based upon a comprehensive bibliography published in Dutch, covering the period 1970–1975 (van der Poel-Bot 1976); a comprehensive coverage of literature, 1976–1981 (inclusive) mentioned in the data bases Toxline, Medline, and CIS (ILO); several abstracts journals; the lists of contents (1980–1982) of several journals on occupational and environmental toxicology; Index Medicus; and the Science Citation Index. Not only the Western literature, but also that of eastern Europe was covered as far as possible.

The review is based primarily upon *human* data on occupational exposure of female workers, i. e., epidemiological studies, observations in experimental exposure, and case reports. Some animal experimental data are presented where human evidence was limited, but a systematic review of animal data has not been undertaken. Observations of women exposed in the *general environment* (ambient air, food, water, soil, etc.) have not been systematically reviewed; they are discussed only when health risks from occupational exposure could be derived indirectly from such data.

This publication does not fully review all studies. Where several well-designed studies resulted in reliable conclusions about health risks from exposure to specific agents, separate studies are not always discussed at length. In a few cases review papers could be taken as a reliable source. Where limited data are available (which applies to most agents discussed), less well-designated studies are reviewed as well, because they might contain indications of health risks, particularly if confirmed by animal data.

Chapters 2–11 refer to specific (groups of) *agents*, Chaps. 12–17 to specific *work situations* for which no quantitative data on toxic exposure were given. Preference was always given to the first approach. Chapter 18 presents a general discussion and conclusions.

As far as possible, the exposure levels at which health effects are reported are compared with the TLVs for 1982 (ACGIH).

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2 Organic Solvents

Organic solvents are volatile organic liquids which dissolve lipids and high-molecular-weight compounds. Liposolubility determines both toxicokinetics and health risk. The effects on health are largely *nonspecific*, i. e., more or less common to all solvents: defatting of skin, irritation of mucosae, and depression of the central nervous system. The effects (acute, reversible) may occur in direct relation to exposure or after moderate, long-term exposure, and may be slowly reversible or lead to more or less permanent health impairment (e. g., organic psychosyndrome).

A few agents may induce so-called *specific* effects, not common to all solvents, e. g., benzene (hematotoxicity) and some saturated chlorinated hydrocarbons (hepato- and nephrotoxicity).

Solvents which are applied mainly in certain industries are reviewed in subsequent chapters, e. g., carbon disulfide (Chap. 3) and styrene (Chap. 5). Nonspecified exposure to solvents in certain work situations will also be discussed in Chaps. 15 and 16.

2.1 Health Risks

2.1.1 Different for Women than for Men

Seppaläinen et al. (Finland, 1980) examined 48 male workers (mean age 35.8 ± 11.4 years, mean duration of exposure 9.4 ± 8.4 years) and 59 female workers (42.0 ± 10.3 years and 7.6 ± 7.5 years respectively) with nonspecific signs and symptoms of solvent intoxication. Although the incidence of abnormal electroencephalograms was similar (67% in men, 64% in women), prominent beta activity was more frequently reported in women (64%) than in men (43%); in 17 of 31 men and in 31 of 40 women decreased nerve conduction velocity in at least one nerve was observed; impairment of memory and of concentration was reported to be more intense in women than in men. This study tentatively suggests increased susceptibility of women; however, whether the difference was related to sex as such or to a difference in exposure (intensity, type of solvent) could not be established.

Sato et al. (Japan, 1975) exposed five female and five male volunteers to *benzene* (75 mg/m^3 at rest — 2 h). During exposure the concentration in blood was higher in men than in women ($P < 0.05$); after exposure the concentration in blood and in exhaled air decreased faster in men than in women ($P < 0.05$); at 4 h after exposure the levels were highest in women. Apparently, in women benzene remained longer in the body. Animal studies (lean and fat male and female rats) confirmed these findings; moreover, decrease in the number of leucocytes occurred earlier in fat than in lean rats. The difference in toxicokinetics was very probably at least partly due to the higher (factor about 2)

average fatty mass relative to body weight in female rats than in male rats; consequently, the fat-soluble solvent is taken up in larger amounts in female than in male fatty tissues, which leads to lower concentrations in blood and a smaller increase in the blood level in short-term peak exposure. The solvent concentration in body fat is not higher in female than in male rats; however, a larger amount has to be eliminated after exposure in female rats. In the case of benzene the female fatty bone marrow is therefore exposed for a longer period of time, which may result in a greater susceptibility of females as regards hematotoxic effects. However, the authors could not rule out a role played by the difference in hormone status, because (female) estrogens inhibit the activity of metabolizing enzymes, in competition with the promoting effect of (male) androgens.

This difference in toxicokinetics between men and women is not specific for benzene, but may occur with exposure to all fat-soluble agents.

2.1.2 Reported for Women Only

Several studies of women exposed to various solvents have been summarized in Table 1. The symptomatology of toxic effects in female workers is, to a large extent, similar to that in male workers; the studies do not permit the conclusion that there is an increased susceptibility in women as comparison with men. However, the data reported are often limited and essential information may not be presented: e. g., age distribution per subgroups, comparability between exposed and nonexposed groups with regard to age, life style, body weight, or exposure to other chemicals. The reported effects may be poorly defined; some studies have an insensitive design, because of the small numbers examined or the application of nonsensitive methods.

2.1.3 To the Female Reproductive System

2.1.3.1 Disturbed Menstruation

Table 2 summarizes six studies of effects on menstrual function. These studies suggest an increased risk of disturbed menstrual function, particularly of increased menstrual bleeding, and probably even at relatively low exposure levels. There may be decreased coagulability. Benzene, moreover, exerts its specific hematotoxic effects, with increased propensity to bleeding. However, the studies are often poorly designed, having the same deficiencies as those mentioned in Sect. 2.1.2.

2.1.3.2 Uterine Cancer

Blair et al. (USA 1979) examined the causes of death of 330 workers, 279 of whom had worked exclusively in chemical cleaning works with exposure mainly to *tetrachloroethylene;* 50% of them were women. Among men and women 87 cancer deaths were observed, and 67.9 expected ($P < 0.05$) in the period from 1955 to 1977. In women, ten cases of cervical cancer were observed and 4.8 were expected (proportional mortality ratio [PMR] = 208, $P < 0.05$). Subsequently, Katz and Jowett (USA, 1981) studied the causes of death (1962–1977) of 671 women who had worked under similar conditions in Wisconsin. The authors did not observe an increased cancer death rate; however, for

cervical cancer the risk was increased (ten cases observed, 5.1 expected; PMR = 195; $P < 0.05$). Blair et al. did not take into account the socioeconomic status (SES); after correction for SES Katz and Jowett no longer observed a significantly increased risk (PMR = 141). Together, the studies do not provide evidence of a relationship between exposure to tetrachloroethylene and death from cervical cancer.

2.1.4 To Pregnancy and Offspring

Syrovadko (USSR, 1977, quoted by the WHO 1981) did not observe any difference in the number of children born to 140 women exposed to *toluene* (25–140 mg/m^3) when compared with 201 controls, in the course of pregnancy, or in average birth weight, although in the exposed group twice as many children were born with a birth weight of 2500–3000 g ($P < 0.02$). In their study Syrovadko and Malysheva (1977, available as summary) examined women exposed to *vinylflex chlorobenzene*, and *tricresol*. They reported an increase in perinatal deaths; the available data were limited. Postolache (1977, available as summary) reported greater prevalence of abortion and prematurity in about 100 women exposed to *acetate*, *butylacetate*, and *toluene* (further details not given); most women also had nonspecific symptoms of general toxicity.

A few papers suggest an increased incidence of *malign tumors* in children whose father or mother had been exposed before and/or during pregnancy to various hydrocarbons, among other solvents; others could not confirm this. Zack et al. (1980) carried out an extensive in-depth study in the United States; they did not observe any relationship between exposure of the parents to hydrocarbons and the incidence of malignancy in their offspring. Gold et al. (1982) reviewed eight studies of the effects of parental exposure, adding one of their own, and concluded that the evidence is conflicting. Although an excess risk cannot definitely be excluded, the relative risk (RR) is generally small; usually RR = < 2 to 3. In their review, van Raalte and Grasso (1982) concluded of benzene that women and their offspring are not more susceptible to the clastogenic or leukemogenic action of benzene.

In a case-control design in Finland, Holmberg (1979) and Holmberg and Nurminen (1980) studied the relationship between the incidence of congenital abnormalities of the central nervous system (40% anencephaly) and occupational exposure of the mother during pregnancy. From 130 497 births between June 1, 1976 and May 31, 1978, there were 132 cases of such congenital abnormalities; 120 of these cases were compared with 120 controls (birth preceding a case in the same district). Extensive information on exposure was drawn from routinely registered data, from interviews with the mothers, and from visits to work places. The cases differed from the controls in exposure to dust (relative risk – RR = 3.4, $P < 0.01$) and to organic solvents (RR = 5.5, $P < 0.01$), and in smoking (RR = 2.1, $P < 0.05$); no relation with smoking habits of the fathers was observed. There was evidence of a synergism between combined exposure to dust and solvents (RR = 10). The "dust" referred to textile, cleansing, cement, and wood dust. Smoking habits proved to be a confounding factor, because there was a positive relationship with exposure to solvents (RR = 2.1, $P < 0.05$). The corrected RR for solvents was 3. No information could be provided on the intensity of exposure and type of solvent. However, only when trained hygienists estimated exposure probably exceeding one-third of the TLV, was exposure accepted as such. The hygienists made the

Table 1. Findings in women occupationally exposed to solvents

Author, year of publication, country	Exposed group, type of exposure (E)	Control group (C)	Reported effects	Comments
Helmer (1944) Sweden	$n=169$ women, 15 men; exp. up to 17000 mg benzene/m^3, in later periods 440–700 mg/m^3; rubber industry	–	58 of 169 (34.3%) women and 2 of 15 (13.3%) men with chronic benzene poisoning; headache 73%; fatigue 88%; propensity for bleeding 48%; itching skin, pustulae, dermatitis; paresthesia	Quoted by NIOSH (1974), see also Table 2
Butarewicz et al. (1969) Poland	$n = 300$, up to 120 mg benzene/m^3; shoe industry	$n = 246$, only exposed to glue (C_1); $n = 169$, not exposed to benzene and glue (C_2)	Changes in blood cells in 18.6% (E), 5% (C_1), 3.6% (C_2)	Quoted by NIOSH (1974), limited data
Sobczyk et al. (1973) Poland	$n=100$, benzene (?) for 0.5–10 yr; age 22–60 yr; increased phenol excretion	–	Increased incidence of pathologic electroencephalogram (EEG) when phenol excretion increased; positive relation between changes in EEG and in psychologic/psychiatric symptoms; in 40 subjects with pathologic EEG psychoorganic syndrome in 17%, neurosis in 60% (in the case of normal EEG 47%)	–
Zielinski (1973) Poland	$n=140$, 25–2000 mg trichloroethylene/m^3; av. 60 mg TCA/liter urine	$n=44$	Dizziness in 40% (E), 1% (C) Neurasthenic syndrome 43% (E), 21% (C)	Limited data
Syrovadko et al. (1973) USSR	$n=168$, white spirit, toluene, xylene; electrotechnical industry	–	Increased incidence of disturbed circulatory and nervous system	Limited data
Postolache (1974) Poland	$n=$about 100; acetone, butylacetate, toluene, probably below 200, 200 and 50 mg/m^3 resp.	–	In 94% nonspecific symptoms	See also Table 2
Matsushita et al. (1975) Japan	$n=38$; up to 225–375 mg toluene/m^3 for $3\frac{1}{3}$ yr; age	$n=16$	Fatigue in 26% (E), 6% (C), $P<0.1$ Toxic granulae in leukocytes 34% (E), 6% (C), $P<0.05$	See also Table 2; sometimes also exposed to benzin

	20.7 ± 5.2 yr; shoe industry		Itching skin, dermatitis in 29% (E), 6% (C) $P<0.05$ Abnormal tendon reflexes 37% (E), 6% (C), $P<0.05$.	
Lob (1976), Switzerland	Laboratory technicians; up to 66 mg benzene/m^3	–	Several cases with hematotoxic effects	Case reports; also exposure to other chemicals
Syrovadko (1977) USSR	$n=140$; 24–450 mg toluene/m^3 4–20 yr	$n=201$	Autonomic vascular dysfunction in 28% (E), 15% (C), $P<0.05$	See also Table 2; quoted by WHO (1981); limited data
Maroni et al. (1977) Italy	$n=23$; 550–1884 mg 1,1,1, trichloroethane/m^3 for 6.7 ± 2.5 yr; age 32.4 ± 9.9 yr	$n=7$	No health effects; no increased susceptibility	Insensitive design
Funes-Cravioto et al. (1977) Sweden	$n=73$, men and women, laboratory and chemical printing shop; 14 children (4 d–11 yr) of 11 women who worked during pregnancy	$n=42$ adults; 7 (or 9) children	Incidence of chromosomal gaps increased 2 to 3 times ($P<0.01$), also in children ($P<0.01$); no relation between chromosomal changes in children and their mothers	Exposure to various solvents and other chemicals; controls not sufficiently comparable, no age correction
Triebig and Burkhardt (1978) FRG	10 females, 3 males, 100–800 mg/m^3 1, 1, 2, trichloro-1,2,2, trifluoromethane; 22–54 yr of age	–	In three women headache and/or dizziness	According to authors, probably not due to solvent exposure
Britanov (1979) USSR	$n=113$, acetone and/or noise for 8–10 yr; 23–29 yr of age; polymer production	–	Suggested synergistic effect of combined exposure to noise and acetone (~200 mg/m^3): nervousness, cardiac pain, fatigue/weakness, increased blood pressure and/or heart rate	No data on age of subgroups; probably differences in other working conditions
Watanabe et al. (1980) Japan	$n=16$, up to 150 mg benzene/m^3 for 1–20 yr (not in last 6 months), age 33–63 yr	$n=7$	No structural and numerical chromosomal changes; slightly decreased incidence of sister chromatid exchange (SCE)	Insensitive design

Table 2. Disturbed menstrual function in women occupationally exposed to solvents

Author, year of publication, country	Exposed group, type of exposure (E)	Control group (C)	Reported effects	Comments
Helmer (1944), Sweden	$n=169$ women, 15 men, exposed to benzene; see Table 1	–	In 58 of 169 women chronic benzene poisoning, with increased propensity for bleeding	Quoted by NIOSH (1974); very high exposure
Michon (1965), Poland	$n=500$; age 20–40 yr; exposed to benzene, toluene, xylene probably below 5.50 and 50 mg/m^3 resp.; shoe production	$n=100$	Greater prevalence of disturbed menstruation, particularly profuse and/or extended bleeding; no increased irregularity	Quoted from summary; limited data; no classification according to age and obstetric history; possible effect of work posture (standing)
Postolache (1974), Poland	$n=$about 100; exposed to acetone, butylacetate, toluene; see Table 1	–	Greater prevalence of disturbed menstruation	Quoted from summary; limited data
Matsushita et al. (1975), Japan	$n=38$; age 20.7 ± 5.2 yr; toluene; see Table 1	$n=16$	Painful menstruation in 19 of 38 (E) and in 3 of 16 (C)	Sometimes also exposed to benzin
Syrovadko (1977), USSR	$n=140$; exposed to toluene; see Table 1	$n=201$	Up to five times greater prevalence of disturbed menstruation Prolapse of uterus 6.5% (E), 0.5% (C) ($P<0.05$)	Quoted by WHO (1981); limited data; prolapse may be due to working posture
Izmerow et al. (1978), USSR	Exposure to benzin in rubber (tire) production $n=63$, exposure to dimethyldioxane (20–25 mg/m^3) and formaldehyde (1–2 mg/m^3)	– $n=90$	No changes in vaginal cells, indicating absence of disturbed function of ovary In women exposed for >4 yrs disturbed menstruation in 31.7% (E), 6.6% (C) ($P<0.05$); increased frequency in 17.4% (E), 1.1% (C); irregularity and profuse bleeding in 11.1% (E), 2.2% (C)	Review of eastern European literature; limited data

estimation without knowing whether they were dealing with a case or a control (Holmberg and Kurppa 1982). In another study (Holmberg et al. 1982), on oral clefts, mores se mothers than controls (referent mothers) had been exposed to solvents during the first trimester of pregnancy ($P < 0.05$).

Kucera (1968, quoted by the NIOSH 1975) examined the incidence of congenital abnormalities of the spine, observed in Czechoslovakia from 1959 to 1966 (births, 1 500 000; congenital abnormalities, 20 000). In five of nine cases of skeletal abnormality the mother had been exposed to solvents during pregnancy. This study is less informative than the above-mentioned Finnish studies.

This review of effects on pregnancy and/or offspring provides hypotheses for further study; most studies allow no more than tentative theories. However, the Finnish studies suggest a relationship with various congenital abnormalities. Conclusions on the relationship with exposure intensity and duration and on the role of specific solvents cannot yet be drawn. Further studies are certainly needed.

Animal studies provide supporting evidence for an effect of solvent exposure on pregnancy and offspring. Reviews have been presented in various NIOSH criteria reports and by the WHO (1981). However, the experiments were usually carried out with high exposure concentrations. Meklman et al. (1980) reviewed effects of *benzene* on the fetus; they concluded that if no effects of poisoning are observed in mother animals, no indications exist for any adverse effect on the offspring. Izmerow et al. (1978), in their review of eastern European studies, reported that exposure of female rats to 30 mg *dimethyldioxane*/m^3 for 4 months (no information was available on exposure duration per day) did not elicit general systemic toxic effects, but only specific effects on the estrous cycle (at first shortening, afterwards lengthening of the cycle). The WHO (1981) quoted a not yet published study from Bulgaria in which pregnant rats, exposed to 50 or 681 mg *xylene*/m^3, 6 h/per day for 20 days, produced offspring with skeletal abnormalities (dose related). The EPA (TSCA 1978) issued a warning of increased risk of congenital abnormalities in offspring and of infertility in women exposed to *benzene*, but it did not provide any basic data to support this warning.

2.1.5 Through Lactation

Urusova (USSR, 1953, quoted by the NIOSH 1976) examined the concentration of *1-2-dichloroethane* in breast milk at 0, 1, 1.5, 2, and 2.5 h after occupational exposure of lactating women; the concentration increased up to 1 h after exposure. In one woman exposed to 58 mg/m^3 (duration not stated) the concentration was 5.4–6.4 mg/liter; at 18 h after exposure it was 1.9–6.3 mg/liter. Sykes and Klein (1957, quoted by the NIOSH 1976) fed cows with 100–1000 mg 1.2-dichloroethane/kg in their food for 22 days; the concentration in milk was highest at day 5 (nearly 0.3 mg/liter). Syrovadko and Malysheva (USSR, 1977, only summary available) reported decreased appetite and even refusal of breast milk by infants of mothers exposed to *chlorobenzene* and *tricresol;* this might have been due to the taste of the milk.

Bagnell and Ellenberger (Canada, 1977) described a case of obstructive jaundice in a 6-week-old infant; the concentration of *tetrachloroethylene* was 10 mg/liter in breast milk 2 h after the mother had lunched with her husband at a dry cleaner's. The mother's blood contained 3 mg/liter. At 24 h after exposure the concentration in breast milk had

decreased to 3 mg/liter. This single case does not permit the conclusion that the obstructive jaundice was caused by ingestion of tetrachloroethylene.

Recently, Pellizari et al. (USA, 1982) investigated whether breast milk could be used as an indicator of environmental pollution (ambient air, drinking water) with volatile organic compounds, among them several solvents widely applied in industry. Milk was collected at four urban sites from 12 women at each site; eight samples were analyzed by thermal desorption (glass-capillary gas chromatography), electron-impact mass spectrometry. The authors identified, among others, 26 halogenated compounds, 17 aldehydes, 20 ketones, ten alcohols, six esters, two ethers, 14 furans, 13 alkanes, 12 alkenes, seven alkynes, and 11 cyclic and 14 aromatic compounds. Practically all solvents used widely in industry and/or at home were qualitatively identified in at least one, and some in all eight of the samples. Concentrations were not reported. This study implies a high probability that practically all fat-soluble solvents will be excreted in breast milk. The few quantitative data presented above suggest that the concentrations in breast milk may reach several milligrams per liter.

The available data on exposure of infants to solvents ingest through breast milk do not yet lead to any general conclusion, but they may serve as a signal for further study (see also Chap. 3).

2.2 Discussion and Conclusions

One animal study which has been carried out in rats exposed to benzene is highly suggestive of an increased susceptibility to benzene (hematotoxic effects) for female rats. In general, the relative fatty mass in women is about two times higher than that in men. In exposure to organic solvents the concentration of the solvent in women's blood does not follow intermittent peaks in exposure as quickly as in men's; during exposure the level is lower, after exposure higher, in women than in men at the same concentrations in inhaled air. When the duration of the presence of solvents in fat-containing effector organs is also decisive for induction of an effect, women may be more susceptible than men. Nothing can yet be suggested about difference in susceptibility with long-term exposure.

Disturbed menstruation is reported in several studies of women occupationally exposed to various solvents, particularly aromatic solvents. The findings reported are not conclusive, although they usually point in the same direction; further studies are needed.

Various studies suggest an increased risk of abortion, complicated pregnancy, prematurity, and perinatal death, but the separate studies are not conclusive. Indications of an increased frequency of chromosomal abnormalities in one study have to be confirmed.

There is evidence suggestive of an increased risk of congenital abnormality; the reported synergism of combined exposure to "dust" and solvents raises concern, but further studies are needed.

Practically all solvents can be excreted through breast milk; the highest concentration may be reached sometime after exposure. This may result in decreased appetite of the infant and even refusal to feed. However, the possibility of exposure of the infant from the environment (when on the factory premises) or from clothes should also be considered

(see Chap. 3). Excretion is a potential risk to the infant; however, no data are available to establish such a risk.

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3 Carbon Disulfide

Carbon disulfide (CS_2) is used particularly in the half-synthetic fiber (rayon) industry; in addition it may be used as a solvent. Its main effects on health are neurotoxicity with (sub)acute and long-term exposure, and vascular diseases (heart, brain, kidney, eyes) with long-term exposure. In addition, it may have adverse effects on the endocrine and reproductive systems. The present TLV is 30 mg/m^3 (10 ppm) — TWA 8 h.

3.1 Health Risks

3.1.1 Different for Women than for Men

In Czechoslovakia Kovarik et al. (1972) did not observe any evidence of different health risks among male and female workers exposed to 50 mg CS_2/m^3. Kulajova et al. (Czechoslovakia, 1979) examined 35 male and 16 female workers exposed to <30 mg/m^3; 25 men and 24 women served as controls. Excretion of 4-pyridoxic acid (4-PA) was decreased in morning urine in exposed male workers ($P<0.01$) but not in female workers ($P>0.05$); during exposure the excretion did not differ. The authors considered decreased excretion of 4-PA an indication of increased risk to the nervous system. Herbig (German Democratic Republic, 1971, 1973) examined 137 female and 138 male workers by means of the neuroticism questionnaire of Eysenck and by testing intelligence, alertness, and concentration. Women and men were of similar ages; duration of exposure was shorter for women than for men (average 3.7 years and 6.2 years respectively), and the concentration of CS_2 in exhaled air was lower for the women (<10 mg/m^3 and about 10 mg/m^3 respectively). Psychopathological symptoms were observed more often in male workers than in female workers, probably due to a difference in exposure.

These studies do not provide evidence of different susceptibility of female workers to CS_2 with regard to effects of general toxicity.

3.1.2 Reported for Women Only

Kramarenko et al. (USSR 1970) examined two groups of women, aged 17–19 years, who were being trained for work in the rayon industry. Group I was exposed to 20–30 mg CS_2/m^3 for 64% of their work time, and to 3–10 mg/m^3 for the remaining time. Group II was exposed to 3–10 mg/m^3. Both groups were also exposed to SO_2 and SO_3 (<10 mg/m^3). The trainees were examined before starting work and at 5, 7 and 9 months

thereafter. Various tests suggested an increased incidence of decreased neurophysiologic and motor performance and decreased blood pressure in group I; the excretion of catecholamines was not affected. However, the data do not allow the conclusion that the reported effects were due (only) to exposure to CS_2.

Model et al. (USSR, 1974, quoted by the WHO, 1981) repeatedly examined 102 women, 17–22 years of age and regularly exposed to <10 mg CS_2/m^3, for 3 years. Changes in the regulation of the cardiovascular system and of the electroencephalogram were reported, in some women as early as the first year of exposure. According to the authors, exposure at first induced effects that indicated decreased sympatheticotonia, but with longer duration of exposure, effects of decreased vagotonia. No control group was examined.

Terescenko et al. (USSR, 1977, quoted by the WHO 1981) examined 678 workers in the rayon industry, of whom 613 were women; 83% were younger than 40 years; 48% had less than 10 years of exposure. They were exposed to 5–8 mg CS_2/m^3 (31% of workers) or to 10–30 mg/m^3 (69%); no control group was examined. In 41% of subjects symptoms and signs of intoxication (disturbed vegetative nervous system in 37%, neurasthenic syndrome-polyneuropathy-encephalopathy in 4%) were reported, more so (47%) in those with higher exposure than in those with lower exposure (24%). Tarlov et al. (1977, quoted by the WHO 1981) carried out a cardiovascular examination of 541 subjects from the above-mentioned group and of 75 controls; they found cardiac pain in 29% and palpitations and extrasystoles in 13.5%; the cardiac effects became evident after 2–5 years of exposure, following the effects on the nervous system. Diagnostic criteria and methods of measurement were inadequately defined and the influence of age was not taken into account.

Petrov (USSR, 1977) assessed the sickness, absenteeism, and health status of 1422 female workers exposed to <20 mg CS_2/m^3 and of 5430 women exposed to caprolactam and biphenyl (see also Chap. 6); 2575 nonexposed women served as controls. The age distribution was not reported. In women between 20 and 39 years of age absenteeism was highest, probably due to pregnancy and/or care of sick children. Absenteeism because of gastrointestinal diseases was lower for women than for men, but numerical data were not presented.

The data reviewed do not suggest an increased susceptibility of female workers with regard to effects not related to the reproductive function. However, the reports were deficient in details and design.

3.1.3 To the Female Reproductive System

Bezversenko (USSR, 1967, quoted by the WHO 1981) examined 280 women between 25 and 38 years of age, 50% of them working for >10 years in the rayon industry; 120 nonexposed women served as controls. In the spinning department the exposure level was 30–80 mg CS_2/m^3, elsewhere usually ≤ 10 mg CS_2/m^3. In women exposed to 30–80 mg/m^3 either profuse or too little menstrual bleeding, premenstrual tension in the breasts, and abortion (see Sect. 3.1.4) occurred two to three times more frequently than in those exposed to ≤ 10 mg CS_2/m^3. In 70 of the exposed and in only 15 of the controls urinary excretion of estrogens was measured. Increased ($+50\%$) excretion was reported in exposed women, particularly those exposed to 30–80 mg/m^3; in 30 of 38 women with

increased excretion of estrogens the level of albumin in serum was decreased and that of gamma globulin and urobilin increased. Moreover, 23 subjects showed decreased excretion of hippuric acid after administration of benzoic acid.

Vasilieva (USSR, 1973) observed findings in 1118 women between 20 and 40 years of age working in the rayon industry. The group was divided into three subgroups:

I. $n=500$, spinning department; exposure up to 20 mg CS_2/m^3 and up to 10 mg H_2S/m^3; relative humidity (RH) 80%–88%, temperature (T) up to 26 °C;
II. $n=209$, exposed to ≤ 10 mg CS_2/m^3 and ≤ 10 mg H_2S/m^3; RH 80%–88%, T up to 30 °C;
III. $n=409$, not exposed to CS_2 and H_2S; RH 60%–75%, T up to 26 °C.

The data are presented in Table 3. Women with a changed cytogram (vaginal cells) excreted less pregnanediol during the corpus luteum phase; at day 11 the excretion of estradiol was increased. In groups I and II the basal temperature also indicated a disturbed corpus luteum phase. In this study age and parity were not taken into account; the data on exposure were limited; the general working conditions (e. g., RH and T) were probably more favorable in group III than in groups I and II.

Finkova et al. (Czechoslovakia, 1973) examined two small groups of women working in the rayon industry: group I had 18 women working in the spinning department, where in former years many cases of acute intoxication had occurred, but since 1967–1969 the conditions had improved; group II had 17 women employed in a "dry" department. No data on age were given, but at least a few subjects were ≥ 65 years old; no data on exposure were presented. In this statistically insensitive study the authors did not observe any effect on menstruation, fertility, pregnancy, libido, or excretion of steroids.

In 87 women exposed to 30–60 mg CS_2/m^3 Aghadzhanova (USSR, 1978) observed almost the same prevalence of irregular menstruation (42%) as in 167 women exposed to ≤ 10 mg/m^3 (40%); this also applied to profuse menstruation (11% and 10% respectively) In 344 nonexposed women the prevalence was 1.3% ($P<0.01$). In the group with the highest exposure the excretion of estrogens was increased. This study had shortcomings similar to those of the Vasilieva report.

Table 3. Findings in women exposed to CS_2 (Vasilieva 1973)

	I	II	III	Comments
n	500	209	409	
Menstruation				
Menarche	–	–	–	No difference
Duration ≥ 5 days	17.8%	10.5%	5.1%	Particularly after 5 to 10 years' exposure
Irregular	7.6%	1.6%	no data	$P<0.01$; increasing with duration of exposure
Profuse bleeding	12.5%	11%	2.3%	$P<0.01$
Painful	37%	38%	17%	Increasing with duration of exposure
Hormonal function	48	$n=29$	35	
Decreased activity of corpus luteum	25%	36%	8%	

In 11.8% of 321 women between 20 and 40 years of age, most of whom were exposed to ≤ 10 mg CS_2/m^3 for < 3 years, Timoshenko and Petrov (USSR, 1977) reported either too much or too little menstrual blood loss, as compared with 2.8% of 385 nonexposed controls. There were no differences in regularity and duration of the menstrual cycle (see also Caprolactam (Chap. 6). This study also had several shortcomings in design.

Shi Xiong Cai and Yu Shu Bao (China, 1981) carried out a well-documented study of 183 women exposed (E) to CS_2 and H_2S in the rayon industry. In summer the average exposure was 56 mg (range, 22–135 mg) CS_2/m^3 and 8 mg (1–25 mg) H_2S/m^3 (T, 28 °–35 °C; RH, 69%–90%); in winter it was 37 mg (11–92 mg) CS_2/m^3 and 5 mg (2–9 mg) H_2S/m^3 (T, 22 °–30 °C, RH, 55%–89%). This resulted in an estimated respiratory intake of 300–400 mg CS_2/8 h as a group average. Nonexposed women ($n = 197$) from the finishing department served as controls (C). Table 4 presents the main findings.

Although the designs of various studies reviewed do not allow reliable conclusions, the overall data suggest an increased risk of disturbed menstruation, presumably (partly) due to derangement of hormonal balance, at exposure levels on the same order of magnitude as, or even below, the present TLV.

3.1.4 To Pregnancy and Offspring

In the study by Bezversenko (see Sect. 3.1.3 an increased risk of abortion in women exposed to 30–80 mg CS_2/m^3 was reported. Aghadzhanova (Sect. 3.1.3) examined the course of pregnancy in 170 women exposed to CS_2 (either to ≤ 10 mg/m^3 or to 30–60 mg/m^3), and in 100 nonexposed females. In those exposed to > 10 mg/m^3 the incidence of abortion was increased; 4.7% of those exposed, but none of the nonexposed women, delivered prematurely; the incidence of toxicosis was three times higher than in controls; moreover, there was 2.5 times more hypotonic bleeding. In the study reported by Timoshenko and Petrov (Sect. 3.1.3) abortion occurred in 31% of 321 women exposed to ≤ 10 mg/m^3, and in 19% of 385 nonexposed women; the respective toxicosis rates were 25% and 13%. Among the controls both rates were unexpectedly high. Correction for age and obstetric history was not done. Judging from the published data, the three

Table 4. Effects on reproductive functions in women exposed to CS_2 and H_2S (Shi Xiong Cai and Yu Shu Bao, 1981)

		E $n = 183$	C $n = 197$	Comments
Age < 25 years		85%	76%	Range 18–32 years
Duration of exposure (years)	1–3	37%	–	
	3–6	63%		
Married		37%	50%	
Disturbed menstruation		41.6%	20.9%	$P < 0.001$; particularly frequent in those who started work at < 18 years of age
Changed duration of cycle		34.4%	18.3%	
Painful menstruation		12%	7.6%	

E, exposed; C, controls

studies show several shortcomings in design. Conclusions cannot yet be drawn, although the data may serve as a signal for further study.

The findings from the study by Shi Xiong Cai and Yu Shu Bao (Sects. 3.1.3 and 3.1.5) have been summarized in Table 5. The increased incidence of abortion as reported in the Soviet studies was not confirmed in this study, but the increased risk of toxicosis suggested by Aghadzanova (1978) and Timoshenko and Petrov (1977) was also reported in the study from China, albeit with lower frequency.

In Finland Hemminki et al. (1980) examined the abortion rate (1973–1976) for 9000 women employed in the chemical industry; the national registry system served as data source (see also Chap. 15). Among women employed in the rayon industry the abortion rate was increased: relative to the number of pregnancies RR = 2, $P < 0.05$; relative to the number of live births RR = 3, $P < 0.001$. However, the absolute number was only nine cases of abortion.

The WHO (1981) reviewed relevant animal data: exposure of pregnant rats to 100 or 200 mg/m^3 (8 h per day for 21 days) induced increased fetal loss and congenital abnormalities; these findings were not observed with exposure to 50 mg/m^3. With exposure to 10 mg/m^3 (8 h per day for 21 days) the learning performance of neonates was slowed down, but not with exposure to 0.03 mg/m^3. In another study of exposure to 10 mg/m^3 (4 h per day for 20 days) adverse effects on kidney function and increased relative weight of internal organs was observed in neonates; the last finding was reported to also occur with exposure to 1 mg/m^3.

The data reviewed above are suggestive of pregnancy complications (toxicosis, abortion, perhaps congenital abnormalities and decreased learning performance) in women exposed to relatively low concentrations of CS_2. Although they may not yet be regarded ad conclusive, they are a matter of concern and further studies are needed.

3.1.5 Through Lactation

Shi Xiong Cai and Yu Shua Bao (1981, see also Sects. 3.1.3 and 3.1.4) measured the concentration of CS_2 in breast milk at the end of the working day in 17 mothers exposed to 200–250 mg/m^3 per/h (concentration in air 23–125 mg/m^3). The concentration in milk

Table 5. Pregnancy complications in women exposed to CS_2, according to Shi Xiong Cai and Yu Shu Bao (1981)

Married	E $n = 100$	C $n = 104$	Comments
Pregnant women[a]	79	84	
Number of pregnancies	92	108	
Number of deliveries	79	98	
Toxicosis	12.7%	3.6%	$0.025 < P < 0.05$
Premature delivery	11.4%	5.1%	$P < 0.01$
Abortion	10%	10%	
Stillborn	1%	1%	

[a] Refers to no. of women who had been pregnant one or more times
E, exposed; C, controls

ranged from 21 to 306 μg/liter; there was a positive relation between the product of concentration and the duration of exposure during the work day. In seven women exposed to ≤ 2 mg/m^3, no CS_2 was found. In eight of ten exposed women CS_2 was still present in breast milk 16 h after the end of exposure: 80–126 μg/liter. In the case of one woman who worked until delivery, 50 μg CS_2/liter was found in umbilical blood.

The authors followed up 14 infants for 2–7 months; the impression existed of a slight retardation of growth, compared with growth in 13 infants from nonexposed mothers (difference not statistically significant). Moreover, when they examined the concentration of CS_2 in the urine of ten infants (first group) they found a level of 1.5–7 μg/liter in six of 28 samples from five infants.

On the factory premises where lactation took place no CS_2 was found in the air; however, in examining four mothers 40–750 μg CS_2 was found in hand-washing fluid (diethylamine-copper solution). In the clothes 0.03–0.16 μg CS_2/m^3 was measured. Uptake of CS_2 in infants may also be due to direct contact with mothers' hands or clothes (see also Chap. 2).

3.2 Discussion and Conclusions

There is no evidence of a difference in susceptibility to CS_2 between women and men as regards general toxic effects.

Five studies indicated an increased risk of menstrual disturbances (two to five times as many), two increased excretion of estrogens, and one decreased excretion of progestogens. Although the studies themselves may be deficient, the overall trend suggests a causal relationship at levels on the same order of magnitude as the present TLV, and even below this level.

Three studies indicate an increased risk of toxicosis (two to four times as much), four an increased risk of abortion (RR: 1.5 to 2.5), although neither are confirmed by a fifth study; two studies reported an increased risk of premature delivery, one uterine hypotonia and blood loss. The studies as such may show deficiencies, but the overall indication cannot be neglected. Moreover, animal studies also suggest adverse effects on offspring at low dosage levels.

CS_2 may be excreted through breast milk and in some infants it was found in urine.

As mentioned before, several studies were deficient in design and data reported. Most studies were carried out in eastern European countries and in China; the NIOSH (1977) stated, — however without providing factual data — that "findings of reproductive system disorder have not been confirmed in this country" (the United States). The WHO (1981) concluded that, although several studies may be deficient in design, there is reason to tentatively recommend a health-based occupational limit of 3 mg CS_2/m^3 — TWA 8 h for female workers of fertile age, a limit lower than that for male workers (10 mg CS_2/m^3 — TWA 8 h). The adverse effects reported probably do not occur at exposure to less than 3 mg CS_2/m^3. This raises doubt about the present TLV.

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4 Pesticides

During production of pesticides exposure occurs mainly by inhalation, but during application in the field dermal penetration may be the main route of entry. It can be hypothesized that dermal resorption may be greater in female workers than in male workers. Moreover, fieldwork may have to be carried out in a hot, humid climate, with long, strenous working days, lack of hygiene, and poor supervision. Fieldworkers in particular are often exposed to "cocktails" of pesticides, simultaneously or one after the other.

Not only workers but also the general population may be exposed. Recently Gordon (USA 1981) examined the relationship between environmental exposure and the incidence of cleft lip and/or palate in the offspring of the general population of two regions (in Iowa and Michigan), where the use of chemicals in agriculture was large. The authors stated the following hypothesis: "Fetuses exposed in utero to agricultural chemicals during peak use period(s), coincident with their first trimester of gestation, will show greater risk of birth defects of the organ systems developing at that time than fetuses whose first trimester of gestation is in the dormant (cold) part of the year." The data were drawn from routinely registered data (1974–1975) and processed according to a case-control design. It was not possible to estimate exposure per individual. Cases and controls (white live-birth cases in Iowa, 53 and in Michigan, 134; controls 314 and 671 respectively) were taken from rural areas. Exposure was calculated from the ratio of surface of acres treated to total surface of agricultural land; scores were developed per county for combined use of various agricultural chemicals. Sex, age of parents, obstetric history, and education of mother could be excluded as confounding factors. In both Iowa and Michigan there appeared to be a significant relationship between being conceived in areas with relatively high use of chemicals and the presence of cleft lip/palate:

	Iowa	Michigan
Relation with use of all agriculatural chemicals (fertilizers, insecticides, herbicides)	$P=0.034$	$P=0.093$
Relation with use of insecticides, herbicides	$P=0.005$	$P=0.050$

The relationship with use of insecticides and/or herbicides was stronger than with all agricultural chemicals combined. The authors regarded the results as a signal for further study and as not yet conclusive evidence.

In this chapter pesticides will be treated in four groups: cholinesterase inhibitors, cyclic chlorinated pesticides, chlorinated aliphatic pesticides, and miscellaneous pesticides. Within the first three groups the toxic effects are to a large extent qualitatively similar, although the actual risk may differ.

4.1 Cholinesterase Inhibitors (Organophosphates and Carbamates)

The effect of short-term exposure is due to inhibition of the activity of acetylcholinesterase (AChE) in the nervous system; acetylcholine is not broken down, and this may lead to serious poisoning. Decreases of activity of total cholinesterase (ChE) in blood, of AChE in erythrocytes, and of pseudocholinesterase (pChE) in plasma are used as indicators of health risk and indirectly of total exposure. In addition, long-term exposure to various organophosphates may induce neuropathy, and perhaps myopathy and organic psychosyndrome.

4.1.1 Health Risks

4.1.1.1 Different for Women than for Men

Cavagna et al. (Italy, 1969) measured the activity of AChE in erythrocytes and of pChE in plasma of 250 men and 100 women (nonexposed) between 15 and 72 years of age; no differences were observed.

4.1.1.2 Reported for Women Only

Jordanova et al. (Bulgaria, 1974) examined 12 women aged 27–53 years who had been intensively exposed for 6–18 years to Intrathion (*O*, *O*-dimethyl-*S*-[2-(ethylthio) ethyl] dithiophosphate) and 40 healthy controls. Exposure occurred in 20- to 30-min periods in the field during spraying by airplanes (concentration in air not reported). Most exposed women complained of headache, sensitivity to light, dizziness, gastrointestinal symptoms, and muscle fasciculations; recovery took place within 3–4 days. This report presented too little information to allow reliable conclusions.

4.1.1.3 To the Female Reproductive System

Adebahr (1966, quoted by Deichmann 1970) reported adverse effects of *parathion* on the ovaries of women who died after acute intoxication. According to Nakazawa (Japan, 1974, available as summary) more than 50 cases of infertility and/or menstrual disturbances were observed in women intensively occupied in the application of *organophosphates* (OPs). In women living and/or working in a fruit-production area menopause came earlier than in those from another area without field application. No data were presented on age, type, intensity, and duration of exposure to OPs; the report is not very informative. Il'ina (USSR, 1977) examined women (mainly between 20 and 45 years of age) who had suffered 1–3 months previously from slight-to-moderate *polychloropinene* poisoning (concentration in air <0.01 mg/m^3; about 70% had been

exposed for more than 6 years). They had also been exposed to other cyclic chlorinated pesticides and cholinesterase inhibitors (OPs). Nonexposed women ($n = 155$) served as controls. The following incidence of signs and symptoms (for exposed and controls respectively) was reported: disturbed menstrual cycle in 34% and 3% ($P < 0.001$), secondary infertility in 13% and 1% ($P < 0.001$), salpingitis in 18% and 5% ($P < 0.001$), erosion of cervix in 11% and 4% ($P < 0.01$), and uterine fibromata in 5% and 3% ($P < 0.02$). Menstrual disturbance started as early as the first month of exposure, increasing in frequency with duration of exposure. In addition, the author reported a relationship between gynecological disturbances and adverse effects on the nervous system. However, the data were limited in detail: the number of exposed women was unknown, signs and symptoms were not clearly defined, and there were no data on age and obstetric history in relation to effects, and none on (combined) exposure. Therefore, this report does not allow conclusions.

The WHO (1982) reviewed animal experiments in which 100 mg/kg per day of carbaril, given orally to rats for 90 days, affected the estrous cycle; 50 mg/kg per day did not; in another study covering 12 months, the effect threshold was between 7 and 14 mg/kg per day; in a four generation study 5 mg/kg per day for 90 days decreased fertility in generations 2–4.

4.1.1.4 To Pregnancy and Offspring

Nakazawa (Japan, 1974) suggested evidence of an increased incidence of toxicosis in an area treated with OPs; no increased incidence of congenital abnormalities was observed among 6000 births in a fruit-production area. See comments in Sect. 4.1.1.3.

Cavagna et al. (1969) and Cavagna and Vigliani (1970, see also Sect. 4.1.1.1) examined the effects of the application of *dichlorvos* (Vapona, DVVP) in hospital wards; the concentration in air (24-h exposure) was ≤ 0.28 mg/m^3. In nonexposed women pChE during delivery and puerperium was lower ($P < 0.005$) than in nonpregnant women; this decrease may have been due to a larger blood volume or to an effect of pregnancy on liver function. Neonates ($n = 16$) were exposed for 9–33 days to a maximum of 0.21 mg/m^3; pChE decreased. In women exposed to 0.095–0.25 mg/m^3 during delivery and puerperium no effect on pChE and AChE was observed. The data on neonates suggest an increased susceptibility as regards inhibition of pChE if compared with adult women or with 2-to 7-year-old children. Clinical effects on health were not observed.

In reviews of animal experiments Derache (1977) and the WHO (1982) concluded that effects on reproduction and on offspring occurred only after administration of high doses.

No information exists on excretion of cholinesterase inhibitors through breast milk.

4.1.2 Discussion and Conclusions

Because various cholinesterase inhibitors are easily absorbed through the skin, it may be hypothesized that uptake might be higher in female than in male workers at similar levels of external exposure but no data have been published to test this hypothesis. There is no evidence of increased susceptibility in women in comparison with men at the same levels of uptake.

Human observations suggesting an effect on the female reproductive system, though supported by a few animal data (high dosage), do not allow any firm conclusions; they may serve as a signal for further study.

Although there is some evidence that through exposure to *dichlorvos* (Vapona, DDVP) infants may be more susceptible to inhibition of pChE (but not of AChE), no health effects have been observed. In animal experiments with high dose levels adverse effects have occurred; according to the WHO (1982) and Derache (1977) these data do not warrant different acceptable occupational exposure limits for male and female workers.

The general conclusion can be drawn that if AChE and/or pChE activities are not inhibited to less than 70% of pre-exposure levels, there is no reliable evidence of extra health risks in women and/or offspring.

4.2 Cyclic Chlorinated Pesticides

The group of pesticides known as CCPs specifically includes *DDT, aldrin-dieldrin, endrin, heptachlor, endosulfan, hexachlorocyclohexane* (notably *γ-HCH or lindane or γ BHC*), *chlordane, methoxychlor,* and *hexachlorobenzene* (HCB). Most compounds are persistent and accumulate in fatty tissues; elimination usually takes place very slowly (over several months). CCPs are strong enzyme inductors, and may consequently disturb the hormone balance. They may also be absorbed through the skin, albeit less than the cholinesterase inhibitors. The most important effector organ is the central nervous system. No data are available on health effects in female workers.

4.2.1 Health Risks

4.2.1.1 Different for Women than for Men

The liposoluble CCPs may be expected to have toxicokinetics similar to those of organic solvents (see Chap. 2): the relative amount accumulated in the body is larger in women than in men at the same exposure levels; the biological half-life may be longer. However, no studies comparing men and women with the same external exposure have been carried out.

4.2.1.2 To the Female Reproductive System

Il'ina (USSR, 1977) reported increased incidence of menstrual disturbance, infertility, salpingitis, cervical erosion and uterine fibroma in women occupationally exposed to *chloropinene* and various CCPs and OPs. Il'ina (1978) also examined another group of 306 women aged 18–40 years, exposed for 5 to 15 years, 79 to *hexachlorane* (BHC), 97 to *tetramethylthiuram disulfide* (TMTD), 130 to *complex CCP-OP compounds* (Sect. 4.3), and 105 to *chloropinenes* (see Sect. 4.3); 105 women served as controls. At the start of exposure most women had a regular menstrual cycle (average age at menarche 12.06 years). During exposure irregularity occurred in 42% of those exposed to BHC, in 25% exposed to TMTD, in 10% exposed to CCP-OP, in 30% exposed to complex CCP-OP compounds, and in only 2%–6% of controls ($P < 0.001$); the irregularity was believed to

be due to effects on the hormone balance. Those with menstrual disturbances also often had disturbed function of liver, bile production, and the nervous system. The cyclic excretion of estrogens achieved lower peaks in those exposed to BHC or TMTD than in the controls; no clear-cut corpus luteum phase could be observed. Exposure apparently was intensive; BHC or chloropinene was even found inside the vagina. As Il'ina reports no quantitative data on exposure and no data on the relationship with age and obstetric history, and as the effects were poorly defined, a firm conclusion cannot be drawn from this study.

In his extensive review of health effects of pesticides Hayes (1975) did not mention any effects on the female reproductive system.

4.2.1.3 To Pregnancy and Offspring

Cyclic chlorinated pesticides cross the placental barrier and accumulate in the fetus. It has been shown that the level of DDT (and its metabolites) is lower in umbilical blood than in maternal blood; however, the levels are higher in the lipids of placenta, amniotic fluid, and fetus than in the lipids of the mother (NIOSH 1978c, WHO 1979).

Rappolt et al. (USA, 1970) measured the concentrations of CCPs in the human placenta in a general population; because placental tissue contains only a little fat (0.4%–1.2%) CCPs usually could not be detected; in ten placentas and umbilical cords only *p,p'*-DDE was found (4.8 and 5.1 mg/kg fat respectively); in four cases of stillbirth and/or congenital abnormality the level was not increased. The WHO (1979) quoted various studies in which the levels of DDT (or metabolites), α- and γHCH, heptachlor, and dieldrin were not excessively increased in various internal organs in stillborn children. Thieleman et al. (German Democratic Republic, 1982) examined the total DDT (*p,p'*-DDT + *p,p'*-DDE) level in fetuses and placentas; in ten of 80 fetuses (age not given) the level was 0.05–7.5 mg/kg; in five of 40 placentas there were only traces of DDT; in five samples of fatty tissue the level was 0.2–3 mg/kg.

Krauthacker et al. (Yugoslavia, 1980) repeatedly observed *p,p'*-DDE in maternal and umbilical cord serum (18 and 6.8 µg/liter respectively; ratio 2.7); the level in nonpregnant women did not differ from that in pregnant women at the time of delivery.

Siddiqui et al. (India, 1981) measured levels of total BHC in total blood; they averaged 22 µg/liter (maternal) and 30.5 µg/liter (umbilical). The levels for lindane were 7.5 µg/liter and 5.6 µg/liter respectively; for total DDT equivalent, 20 µg/liter and 15.3 µg/liter respectively; for dieldrin, 21 µg/liter and 14.9 µg/liter respectively. All these data refer to the general population. Saxena et al. (India, 1981, same reasearch group) observed partly different data, which have been summarized in Table 6.[1]

In the case of abortion the concentrations in the mother were increased 3- to 18-fold; in normal full-term deliveries the concentrations were the lowest. This study suggests that exposure to CCPs interferes with the outcome of pregnancy. Again, the data refer to nonoccupationally exposed women.

Nikitina (USSR, 1974) examined 390 women occupationally exposed (in vineyards) to DDT, sulfur, nitrofen, metafos, and copper; 209 farmers' wives and 100 women who took care of children served as controls; age ranged up to 30 years. At day 40 after pesticide spraying the DDT in air levels still averaged 0.35 ± 0.03 mg/m^3 (skew distribution). The average DDT (and metabolites) concentration in the placentas of

1 see also chapter 19

Table 6. Concentrations of various CCPs in mothers and offspring ($\bar{x} \pm SD$, in μg/liter)

	Full-term deliveries ($n=25$)		Premature deliveries ($n=15$)		Abortions ($n=10$)	
	Maternal blood	Placenta	Maternal blood	Placenta	Maternal blood	Placenta
BHC	52.2 ± 18.2	27.2 ± 11.4	93.8 ± 22.6	62.3 ± 18.4	209.2 ± 141.2	90.7 ± 31.7
Lindane	18.9 ± 8.8	8.9 ± 4.3	39.7 ± 14.3	20.4 ± 8.8	73.3 ± 32.2	30.6 ± 15.5
Aldrin	11.1 ± 7.3	4.1 ± 3.96	30.1 ± 18.8	17.9 ± 26.1	33.1 ± 18.2	15.9 ± 7.6
p,p'-DDE	12.6 ± 7.0	11.9 ± 11.6	57.8 ± 65.3	31.2 ± 15.0	163.8 ± 15.0	83.6 ± 69.3
p,p'-DDD	6.9 ± 7.9	4.9 ± 8.3	15.2 ± 12.5	10.7 ± 10.7	65.5 ± 129.4	20.6 ± 22.8
p,p'-DDT	4.5 ± 4.1	4.1 ± 3.9	58.8 ± 88.5	19.8 ± 14.9	136.8 ± 152.8	57.2 ± 71.8
DDT	26.2 ± 18.1	23.6 ± 11.9	140.8 ± 164.5	66.3 ± 13.9	393.8 ± 355.2	162.2 ± 134.0
Total CCPs	87.3 ± 37.1	55.7 ± 27.2	241.8 ± 216.5	146.6 ± 43.8	586.2 ± 499.8	258.9 ± 153.8

exposed women was 0.19 mg/kg, a 5.6-fold increase. In exposed women the incidences of *abortion* (RR = 2.1, $P < 0.05$), toxicosis, uterine hypotonia, bleeding at delivery, lassitude, and asthenia increased and histological changes (infarction, increased thickness) in the placenta were observed. The RR for congenital abnormalities (particularly of the central nervous system) was 1.5, for lower birth weight (< 3000 g) 1.5 to 2.0 ($P < 0.05$). According to Nikitina, the provision of the fetus with oxygen and nutrients might have decreased. However, the data reported were not detailed enough to permit firm conclusions.

Wassermann et al. (Israel, 1982)[1] collected blood from ten women with normal pregnancies and from 27 who had delivered prematurely (PD: birth weight 500–2500 g, delivery after week 20 and before week 37). They examined PCBs (see Chap. 5) and CCPs in serum. The total DDT concentration was 11.9–149.2 μg/liter in the PD group and 8.1–78.9 μg/liter in the controls; the PD group was divided into PD-1: < 100 μg/liter, and PD-2: > 100 μg/liter. All five PD-2s also had high γ-HCH and heptochlorepoxide levels. The high total DDT level in the PD groups occurred because of *p,p'*-DDT and *p,p'*-DDE and *o,p'*-DDT, *o,p'*-DDD, and *o,p'*-DDE. The authors do not conclude a causative relationship, but do suggest the possibility; they quote a study by Yamada (Japan), who observed an association between γ-HCH levels and PD and other pathology in pregnancy. Procianoy and Schwartzman (Brasil, 1982) did not observe any difference in the DDT blood level of 30 nonoccupationally exposed mothers with full-term delivery (average 39 weeks, birth weight 3180 g) and those with preterm delivery (average 33 weeks, birth weight 1930 g); however, the total DDT level in cord blood correlated negatively ($r = -0.3$, $P < 0.05$) with birth weight, but not with gestational age. Although a causal role of DDT could not be ruled out, the lower DDT level may also be a secondary effect of the low fatty mass in preterm neonates. Observations in animals point in a similar direction; a disturbed hormonal balance might have precipitated labor.

Infante et al. (1978) described five cases of neuroblastoma (diagnosis made at age 2 years, 8 months – 6 years, 5 months), three cases of aplastic anemia (15–68 years), and three cases of acute leukemia (9–37 years) in offspring exposed before or after birth to chlordane and heptachlor; moreover, they found 25 cases in the literature of hematopoetic diseases related to CCP exposure (sometimes exposure to OPs, solvents,

1 see also chapter 19

and drugs as well). The authors suggested a possible causal relationship. David and Fairchild (1980) reviewed the literature on hematopoetic diseases; the number of cases observed in association with exposure appeared to be very small with respect to the huge number of persons exposed. A causal relationship may have been accepted too easily; combined exposure to various chemicals makes it difficult to draw firm conclusions. According to David and Fairchild, pesticides applied at present probably do not play any causal role.

Reviews of animal experiments have been presented by the European Colloquium (CEC, 1975), Hayes (1975), the WHO (1979, DDT; 1982, lindane), and the NIOSH (1978c, DDT): effects on fertility, the estrous cycle, and offspring have been observed with high dosages. A few recent studies raise concern. Gray et al. (1981) observed an effect on behavior of the offspring of hamsters after repeated oral exposure to 0.75–1.5 mg endrin/kg body wt. during pregnancy. When Olson et al. (1980) administered 0.35 μg dieldrin/kg per day (only three to four times the ADI) orally to two generations of rats (same dose as in Dutch infants, see Sect. 4.2.1.4), an effect on behavior was observed in the offspring. According to Jager (1970), the exposure of the general population of the Netherlands (in the 1960s) was 10–20 μg dieldrin per day, i. e., on the same order of magnitude as in the experiment by Olsen et al.; in occupationally exposed (male) workers the average exposure was 107 μg dieldrin per day (about the same for endrin). The data of Olsen et al., therefore, may be a matter of concern in regard to the offspring of women occupationally exposed to CCPs.

The EPA (USA 1979) prohibited the use of mirex (chlorooctahydrometheno-1H-cyclobutapentalene) by women of fertile age, because of adverse effects on the offspring reported in animal studies.

4.2.1.4 Through Lactation

It has often been shown that CCPs are excreted in breast milk, even among the general population; reviews have been presented by Hayes (1975), the CEC (1975), Greve (1979) and the WHO (1979 for DDT). Generally the levels of CCPs in breast milk are higher than those in cow's milk; for infants this may lead to an oral intake which temporarily exceeds the ADI for adults. In 35 women Krauthacker et al. (Yugoslavia, 1980) found the levels of DDT (and its metabolites) an average of 2.1 times higher than those in maternal serum (at day 3–5 after delivery). Siddiqui et al. (India, 1981) observed a high positive correlation between levels in total blood and in breast milk: for BHC $r = 0.88$, for DDT $r = 0.92$ ($P < 0.01$). The respective average levels of total BHC and total DDT in milk were five and six times those in maternal blood; the site of preferential accumulation for BHC was milk > cord blood > maternal blood; for DDT, milk > maternal blood > cord blood. According to Nikitina (1974), the DDT (and metabolites) levels in breast milk of occupationally exposed women were 4.8 times higher than those in nonexposed women; no effects on the infants were mentioned. In the Netherlands, Eckenhausen et al. (1981) studied the levels of seven CCPs in infants who received breast milk from non-occupationally exposed mothers. They observed that the levels usually were not higher in mothers on a weight-reducing diet than in mothers who did not follow such a diet; there was no consistent increase in the levels in infants' blood during the first 3 months of life; there was neither a significant difference in maternal blood before and after delivery, nor a difference between the levels in umbilical blood and in infants' blood during

lactation. The levels in infants' blood were lower than those in maternal blood, and the levels in blood, milk, placenta, and meconium were similar to those reported in the literature for comparable nonoccupationally exposed women and offspring. The authors estimated that the elimination through lactation was 12% of the daily intake of dieldrin at delivery and 23% after 3 months, for DDT 36% and 61% respectively; the intake by the infant was 0.35 μg dieldrin/kg body wt. (see sect. 4.2.1.3) and 5 μg DDT/kg body wt. No effects on the infant were observed.

4.2.2 Discussion and Conclusions

There is no evidence to suggest an increased susceptibility to CCPs for women compared with men, although in women the internal level (due to body fat) may be higher at similar total exposure.

Some papers suggest adverse effects on the female reproductive system, but they do not present conclusive evidence.

Cyclic chlorinated pesticides cross the placenta and accumulate in the fetus; the concentrations in umbilical blood are usually lower than those in maternal blood, but they can sometimes be higher. In one Soviet study of occupationally exposed women adverse effects on pregnancy and neonates have been reported; the findings were supported to a certain extent by studies in India, Brasil, and Israel of nonoccupationally exposed women. Animal studies on the effect of low doses of dieldrin on the behavior of offspring also raise concern in regard to exposure of pregnant women; the experimental dosage was considerably lower than the equivalent dosage received when exposed to the TLV of 0.25 mg/m^3 -S.

Cyclic chlorinated pesticides are excreted in breast milk. Because the concentration in breast milk is positively related to the concentration in maternal blood, increased levels in breast milk can be expected to occur in women who are occupationally exposed before and/or during pregnancy. Increased exposure of the fetus and the neonate may be expected. It should be noted that the WHO (1974) recommended that "baby foods", which constitute the main diet of infants, should not contain any pesticides.

4.3 Halogenated Aliphatic Pesticides

The volatile Cl- and/or Br-containing halogenated aliphatic pesticides are applied as fumigants. Well-known compounds are monobromomethane (*methylbromide*), 1,2-dibromoethane (*ethylene dibromide*), 1,2-dichloroethane (*ethylene dichloride*), and various halopropane and halopropene compounds, e.g., *dichloropropane*, *bromochloropropane*, and 1,2-dibromo-3-chloropropane (*DBCP*). The toxic effects are to some extent similar to those of solvents (see Chap. 2).

DBCP exerts a strong effect on male reproduction (decreased spermatogenesis); no data are available on effects on female reproduction, although according to the NIOSH (1978a), animal studies in the USSR provided indications of an effect on estrus and embryogenesis.

Van Velsen and van Logten (1980) reviewed the toxicity of methylbromide. No data are available on reproductive effects. Sikov et al. USSR, 1981) recently provided data on

animal experiments in which rats were exposed 7 h per day, 5 days a week for 3 weeks; after subsequently breeding, they were again exposed at day 1–19 of pregnancy, then killed at day 21. Rabbits were artificially inseminated and subsequently exposed for 7 h per day, 7 days a week up to day 24 of pregnancy, then killed at day 30. Exposure to 480 mg/m^3, but not to 80 mg/m^3, caused serious neurotoxicity (70%) and a high death rate (96%) in the mother rabbits; there was no clear evidence of embryotoxicity. In rats no effect on fertility was observed but in rabbits fertility decreased. Further study is needed.

4.4 Miscellaneous Pesticides

4.4.1 2, 4, 5-Trichlorophenoxyacetic Acid (2, 4, 5-T)

The herbicide 2, 3, 5-T may contain, as an impurity, the highly toxic *2, 3, 7, 8-TCDD* (*2, 3, 7, 8-tetrachlorodibenzo* p-*dioxin*); see Chap. 5. In several incidents workers and/or the general population have been exposed to TCDD, e. g., Seveso (Italy) and Vietnam. It has been claimed that TCDD may induce effects upon reproduction and offspring, through exposure of men and/or women; only the last claim will be discussed. Studies from Vietnam do not lead to conclusive evidence, because the war situation very much hampered reliable registration of such effects. Among the general population of Seveso the incidence of stillbirths, abortions, and malformations did not increase (Reggiani 1980); however, an unknown number of women may have practiced contraception or undergone induced abortion.

In 1979 a panel (Coulston and Olajos USA, 1980) assessed a decision of the EPA, which had provisionally prohibited the application of 2, 4, 5-T because in Alsea (an area sprayed by airplanes in the state of Oregon) an increased incidence of abortions among the general populations had been reported. The panel concluded that the evidence was based upon poorly designed studies: only hospital patients were included; geographic and demographic factors were not taken into account; the area studied was not representative for the area sprayed; the relationship between period of conception and of spraying was not examined; abortion rates were not calculated in consistent ways; seasonal peaks were not accounted for; and the actual exposure of the mothers was not measured.

Smith et al. (1982) and Hanify et al. (1981) studied the outcome of reproduction in New Zealand. Smith et al. compared 548 married chemical (2, 4, 5-T and other pesticides) appliers with 441 married agricultural contractors (postal questionnaire) as controls. Wives often helped their husbands in the field and were exposed by handling and washing clothes soaked with chemicals. For congenital defects the RR was 1.19 (90% confidence interval 0.58–2.45); for abortion, 0.89 (0.61–1.30). Only three stillbirths were reported, all cases where the father (and mother?) was exposed to 2, 4, 5-T; there were 13 and nine cases of congenital defects: all comparisons are between families in which the father (and the mother) was exposed to 2, 4, 5-T and families in which neither parent was exposed, and cover the period 1969–1980. The authors concluded that this study did not indicate any adverse effect on reproductive outcome; further analysis, however, was still considered necessary, e. g., taking into account the season of conception. Hanify et al. analyzed the incidence of congenital malformation in the general population of Northland, an agricultural area in which spraying of 2, 4, 5-T was done by airplane. The

congenital defects among 37 751 neonates born in hospitals between 1960 and 1977 were related to data on location of birth and amounts sprayed. Assuming that the causative factor disappeared from the environment within 1 month, no association between application of 2,4,5-T and the incidence of congenital malformation was observed; assuming that only one-quarter disappeared within 1 month, a significant association was observed between application of 2,4,5-T and the incidence of clubfoot. According to the authors, the data available did not point unequivocally to a causative role of 2,4,5-T (or of 2,3,7,8-TCDD). It should be realized that, when an increased RR was observed in the above-mentioned studies, one still could not conclude that this was due to exposure of women (workers, general population) themselves.

Wassom (1977, 1978) studied the prevalence of chromosomal abnormalities in Seveso (general population, children, workers): no increased RR was observed. Morganti and de Carli (1981) reexamined the blood of 21 subjects who had the highest frequency of chromosomal abnormalities: no difference was observed in the frequency of sister chromatid exchange, but the DNA-repair activity in exposure to UV was increased. This study did not indicate a causative role of TCDD.

In animal experiments TCDD has induced congenital defects in mice and abortion in rhesus monkeys, albeit at comparatively high dosage levels. Further study of health risks from exposure to this extremely toxic compound is needed.

4.4.2 Organic Mercury Compounds

See Chapter 11.

4.4.3 Tetramethylthiuramdisulfide

A study by Il'ina (1978) was discussed in Sect. 4.2.1.2; exposure to tetramethylthiuramdisulfide (TMTD) was reported to result in an increased incidence of menstrual disturbances (25.7% after exposure as compared with 1.03% before) and in a decreased excretion of estrogens. However, the data presented and the study design do not permit any firm conclusion.

4.4.4 Dinitro-o-cresol

The WHO (1982) evaluated the health risks from occupational exposure to dinitro-*o*-cresol (DNOC). Osipova et al. (USSR, 1971, quoted by the WHO 1982) examined nine women exposed for 3 months to DNOC (no data on concentrations in air are available) by working in a room painted with DNOC-containing paint. After 1 month of exposure adverse effects on the autonomic and central nervous systems were reported, in addition to evidence of liver toxicity. Varnai and Kote (Hungary, 1969) examined 45 young women (most of them under 20 years of age) from a group of 81 subjects who had worked in a field that had been sprayed the previous day. Uptake may have occurred mainly by dermal absorption. On the first working day there were signs and symptoms of slight intoxication in 32 women, of moderate in 12, and of serious in three; in the last two groups the DNOC in blood levels increased to between 20 and 55 mg/liter (20 mg/liter is

considered the maximum acceptable). Three women were pregnant, but no effect on pregnancy outcome was observed. The WHO (1982) concluded that no different health-based occupational exposure limits for male and female workers need be recommended regarding occupational exposure to DNOC.

4.4.5 Anticoagulants

Theoretically, one may expect women to run extra risk in occupational exposure to anticoagulants, if compared with men, i.e., profuse menstruation in case of over-exposure; however, no such data have been reported.

4.4.6 Zineb

Makletsova (USSR, 1979) examined 162 pregnant women occupationally exposed to zineb; 148 pregnant women served as controls. The data are summarized in Table 7.

The author concluded that there was an increased risk of abortion and of complications with delivery and puerperium. However, findings were not related to age and obstetric history and reported effects were not clearly defined. In the controls the frequency of complications with pregnancy and delivery appeared to be excessively high. No data were presented on intensity of exposure; only the data on an increased risk of abortion weakly suggest an adverse effect. Further study appears necessary.

4.4.7 Nicotine

No data have been presented on adverse effects of nicotine in occupationally exposed women. The agent has been extensively studied as responsible for some of the effects of smoking. Two reviews (Abel 1980, the US-DHEW 1979) may serve indirectly to assess the risk in occupational exposure.

Table 7. Effects on pregnancy and offspring of women who are occupationally exposed to zineb in pregnancy (Makletsova, 1979)

	E $n=162$	C $n=148$
Abortion	26 (16.1%)	12 (8.1%) ($P<0.005$, RR = 2)
Imminent abortion	14.8%	11.0%
Prematurity	12 (8.8%)	7 (5.2%)
Prolonged pregnancy	6 (4.4%)	5 (3.7%)
Pregnancy complications	69.3%	57.3%
Anemia	14.8%	8%
Complicated delivery	73.8%	61.4%

E, exposed; C, controls

Nicotine is inhaled and dermally absorbed; being readily soluble in water and in lipids, it is quickly distributed throughout the body. It exerts cholinergic effects (increased irritability of the nervous system) and releases catecholamines, causing increased heart rate and vasoconstriction, increased O_2 consumption, increased metabolism of free fatty acids, and hyperglycemia. Such effects also may occur in the fetus, because nicotine crosses the placenta, particularly in the first weeks of pregnancy. Moreover, it is excreted in breast milk: in women smoking 1–4 or 5–10 cigarettes per day the concentration of nicotine in breast milk averages 0.12 or 0.23 mg/liter respectively. Adverse effects in the infants have not been reported, but they have hardly been studied. Nicotine poisoning, however, has been reported in infants of mothers who smoked 20–40 cigarettes per day. If one assumes an alveolar volume of 8 m^3/ 8 h, and 100% pulmonary absorption, at the TLV of 0.5 mg/m^3-skin the uptake during work will be 4 mg/8 h. If one cigarette is smoked the uptake of nicotine is about 1 mg; exposure to the TLV as a TWA of 8 h, therefore, corresponds to smoking about four cigarettes; in that case the concentration in breast milk may be expected to be 0.1–0.2 mg/liter. Although adverse effects on the infant have not been reported, such an occupational exposure may be considered undesirable. Studies of nonsmoking, occupationally exposed women are needed.

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5 Polychlorobiphenyls and Polybromobiphenyls

Polychlorobiphenyls (PCB) and polybromobiphenyls (PBB) may contain toxic impurities such as TCDD (see Sect. 4.4.1) and polychlorodibenzofuranes. No data exist on sex related differences in susceptibility.

5.1 Polychlorobiphenyls

Health effects due to exposure to PCBs were detected in 1968 in Japan, when consumption of contaminated rice oil caused extensive food poisoning (Yusho disease), with about 1300 victims. The PCBs carried polychlorodibenzofuranes as impurities. Neonates of mothers with Yusho disease had darkly colored skin and mucosae, chloracne, and lower than normal birth weight (review by Wassermann et al. 1980). The daily intake of PCBs by Yusho infants had been about 70 μg/kg (Yakushiiji et al. Japan, 1978). According to Kuwabara et al. (1978) the daily intake by nonoccupationally exposed women (in Osaka) was 3–20 μg per day, mainly by ingestion (food); the intake by occupationally exposed women was estimated to be 10 to 20 times higher, mainly by inhalation. The present TLV is 1 mg/m^3 skin (42% chlorine) and 0.5 mg/m^3 skin (54% chlorine). (The usual annotation is TLV-S if penetration of the skin also occurs.)

5.1.1 Health Risks

5.1.1.1 To the Female Reproductive System

No human data are available on risks to reproduction. Allen et al. (1979) studied the effect of oral administration of PCBs on rhesus monkeys: 2.5 or 5.0 mg/kg diet for 4 months (total intake 60 and 120 mg per animal) caused lengthening of the menstrual cycle (+5–7 days) and increased blood loss; the effects were reversible. With administration of 0.5 and 1.0 mg/kg diet (total 8 and 16 mg per animal) no effects were observed.

5.1.1.2 To Pregnancy and Offspring

Wassermann et al. (Israel, 1980) examined PCB concentrations in the blood of 18 nonoccupationally exposed pregnant women who suffered from toxicosis, and of 12 healthy pregnant controls. They amounted to 4.6–676.3 μg/liter and 0.6–33.7 μg/liter

1 see also chapter 19

respectively; in nine of 18 patients the levels exceeded those in the controls. The authors suggested that *toxicosis* might be due to immunosuppression and disturbed endocrine function, corresponding with suggestive evidence of immunosuppression in other studies. Friend and Trainer (Wassermann et al. 1980) measured decreased IGM levels in Yusho patients with chloracne; Hattula and Karlog (Wassermann et al. 1980) reported an increased risk of infections in the respiratory tract. However, this hypothesis has to be confirmed in longitudinal studies; increased PCB levels in blood might be the consequence, and not the cause, of toxicosis. Wassermann et al. (1982) carried out a similar study of 17 nonoccupationally exposed pregnant women with premature delivery (PD) and in ten controls with normal pregnancies (see also Sect. 4.2.1.3). The PCB levels in serum were 1.8–233.0 μg/liter and 0.6–33.7 μg/liter respectively; eight of the 17 had levels higher than the mean + 2 SD of the controls. In the high-PCB-level PD group the percentages of tetra- and pentachlorobiphenyls were lower, while those of hexa- and heptachlorobiphenyls were higher than in the control group; a similar trend existed for the entire PD group as compared with the controls. Of the 17 PD cases, five also had high DDT serum levels; in 11 of 17 PD cases there were high levels of PCBs and DDT, or of PCBs or DDT (see Chap. 4). The authors did not conclude a causal relationship, but this study might serve as a signal for further studies.

Allen et al. (1979) studied the effect of PCBs (Aroclor 1248) on pregnancy and offspring in rhesus monkeys given 2.5 or 5.0 mg/kg diet for 18 months; after 7 months (total amount ingested 105 or 210 mg/animal) fertility and pregnancy outcome were evaluated (Table 8). At 5.0 mg PCB/kg diet the outcome was unfavorable, as compared with 2.5 mg/kg diet; the neonates also had 20% lower birth weights and growth was retarded. Within 2 months the neonates developed PCB poisoning, manifesting as acne, swelling of the eyelids, loss of eyelashes, skin pigmemtation, and edema. In a subsequent study with 0.5 or 1 mg/kg diet (total 8 or 16 mg per animal) birth weight was still slightly low, and pigmentation developed during the lactation period, but further development appeared to be normal. A no-effect level was not established. Spencer (1982) fed pregnant and decidualized, i. e., pseudopregnant rats with Aroclor 1254, at 25 to 900 ppm in the diet. At 25 ppm the uterine protein content began to decrease in the pseudopregnant rats, more so at higher dose levels; the uterine glycogen and ovarian protein content also decreased at 25–50 ppm, and more significantly from 100–150 ppm onwards. Similar exposure-effect relationships were observed in the pregnant rats. There was no effect on

Table 8. Effect of PCBs on breeding performance of female rhesus monkeys (Allen et al. 1979)

	After 7 months' diet		1 Year after exposure	
	Dosage (mg/kg diet)			
	2.5	5.0	2.5	5
Total number	8	8	8	7
Total impregnated	8	6	8	7
Absorption/resorption	3	4	1	1
Stillbirths	0	1	0	1
Normal births	5	1	7	5

the number of implantations or on the number of conceptuses at day 12, but the fetal survival rate decreased from 25 ppm onward, significantly from 300 ppm onward. The average birth weight decreased significantly ($P < 0.05$) from 100 ppm onwards. A dietary content of 25 ppm with a daily intake of 20 g food per day at an assumed body weight of 200 g means a daily intake of about 2.5 mg/kg body wt. per day. An effect threshold could not be derived from this study, but it is apparently < 2.5 mg/kg body wt. per day.

5.1.1.3 Through Lactation

In Japan Yakushiji et al. (1978) and Yoshida and Nakamura (1979) measured the PCB concentrations in the milk of a 36-year-old woman occupationally exposed to PCBs; the concentrations were 10 to 20 times higher than those in nonexposed females. Within 9 months after delivery 170 mg PCB had been excreted, in 16 months about 200 mg. The PCB concentration in blood decreased during lactation with a biological half-life of about 8 months. This corresponded to an intake of 45 μg/kg per day by the infant; therefore, one might have expected the development of Yusho disease in the infant who had ingested its mother's milk, as it had been shown that in infants with Yusho disease the intake was about 70 μg/kg/day, but this did not occur.

Kuwabara et al. (1978) measured PCB levels in the blood of women occupationally exposed for 4–19 years and in the blood of their children aged 0–13 years. Table 9 shows that PCB levels in the blood of occupationally exposed women and their children were even higher than those in Yusho patients; the blood levels in children increased with the length of the lactation period. Very probably the intake through lactation could be considered relatively much more important than transplacental passage (also observed by Masuda et al. 1978). Kodama and Ota (Japan, 1980) observed a PCB level in blood of infants four times higher than that in mothers after a long lactation period. None of these children showed any signs of PCB poisoning.

Atkinson (Canada, 1979) reported that between 1971 and 1974 the average level of PCBs in breast milk (in Ontario) was 40 μg/kg, decreasing to 20 μg/kg in 1978. There was no evidence of PCB poisoning among infants in Canada and the United States. Miller et al. (Israel, 1979) reported high levels in the breast milk of 15 women, averaging 74 μg/liter (up to 172 μg/liter) 3 to 5 months after delivery; no data on the health of the infants were presented. Baluja et al. (1982) measured an average of 250 μg/liter (190–320) in 20 Spanish mothers (Madrid). It is not known whether the high levels in Spain should be regarded as true levels, or whether they were due to the analytical technique. Wickizer et al. (USA, 1981) examined breast-milk samples from 1057 nursing mothers in Michigan.

Table 9. PCB concentrations in blood (μg/liter) of occupationally exposed women, their children, Yusho patients, and nonexposed women (Kuwabara et al. 1978)

	PCB-exposed women	Children of PCB-exposed mothers	Yusho patients	Nonoccupationally exposed women
	$n = 20$	$n = 39$	$n = 12$	$n = 28$
Range	8.3 – 84.5	0.8 – 93.2	1.8 – 8.6	0.8 – 5.7
Average ± SD	36.8 ± 21.5	14.3 ± 18.1	4.2 ± 1.9	2.6 ± 1.2

All samples contained residues of PCB, from trace amounts up to 5.1 mg/kg (on a fat basis), mean 1.5 mg/kg; 49.5% had 1–2 mg/kg, 17.4% had 2–3 mg/kg, and 6.4% had >3 mg/kg. The fat content of milk was 34.8 g/liter; consequently a mean of 1.5 mg PCB/kg fat corresponds to 52.5 μg PCB/liter breast milk. The 'median' infant would consume approximately 9.4 mg PCB in the first 8 months of life, of which approximately 8 mg would be retained.

Allen et al. (1979, see Sect. 5.1.1.2) observed PCB poisoning in rhesus young: the level in breast milk was 154–397 μg/liter.

5.1.2 Discussion and Conclusions

In occupational exposure to PCBs the intake may be 10 to 20 times that for nonoccupationally exposed subjects. Most information on occupational health risks has to be extrapolated from studies in environmentally exposed (via ingestion) women or from animal studies.

In rhesus monkeys, whose biotransformation is similar to that of man, menstrual disturbances have been observed at a total intake of 60 mg/per animal, but not at 16 mg/per animal.

In two studies of nonoccupationally exposed women an adverse effect on pregnancy (toxicosis and premature delivery) was suggested, related to a high PCB concentration in blood; however, these studies certainly need further confirmation. In animal experiments a dose-dependent adverse effect on the offspring was observed; a no-effect level was not established.

Health risks to the offspring are probably greatest during lactation. Although the intake may be on the same order of magnitude as for subjects with Yusho disease, no health effects in infants of occupationally exposed women have been reported. Wickizer et al. (1981) established that in about 50% of Michigan women the FDA tolerance limit for cow's milk (1.5 mg/kg, fat-weight basis) was exceeded. They recommended that nursing mothers who have had potentially high exposure to PCBs, for example, those occupationally exposed, should submit their breast milk for testing; PCB levels >2.3 mg/kg (fat-basis) might be considered elevated. A long duration of breast-feeding in particular might raise some concern. A panel under chairmanship of B. W. Weil convened in 1981 (Editorial, 1981); it concluded that Michigan mothers should not hesitate to breast-feed their infants unless they had had unusual exposure as a result of employment. The panel also recommended that such women have their breast milk tested. Animal studies emphasized the importance of lactation as a matter of concern.

5.2 Polybromobiphenyls

In the period 1973–1974 a large-scale contamination of human foods occurred in Michigan after accidental contamination of cattle feed with PBBs. No data are available about health effects on occupationally exposed women.

Allen et al. (1979) exposed seven female rhesus monkeys to 0.3 mg PBB/kg diet for 6 months (total 12 mg per animal); the menstrual cycle was lengthened. After breeding with nonexposed males, one of seven embryos was resorbed, and one pregnancy ended

in a stillbirth; the birth weight of live-born neonates was below normal and growth was retarded. MacCormack et al. (1981) observed similar results in rats.

Brilliant et al. (1978) measured PBBs in the breast milk of 99 lactating women living in the contaminated area in Michigan: the maximum was 1.2 mg/kg fat, the median <0.1 mg/kg fat. No health effects on their infants were reported.

Weil et al. (1981) examined the effect of PBBs on infants and young children born in Michigan between September 1, 1973 and December 31, 1975; in this period PBB contamination of the farmer population should have been the highest. Of the exposed (in utero and/or during lactation), 33 children were examined and compared with 20 controls; the mean ages were 37.2 and 38.7 months respectively. Of the exposed, 42% had been breast-fed for an average of 14.8 weeks; of the controls, 85% for an average of 29.6 weeks. Parents reported an average of 9.4 symptoms for the exposed infants as compared with 6.9 for controls. The exposed presented more respiratory disease, more urinary tract infection, more fever of unknown origin, and increased clumsiness. However, this did not correspond with the results of physical examination: 13 of 33 exposed infants and five of 20 controls had no abnormal conditions. No specific finding was more common in the exposed than in the controls. Although more parents of controls reported loss of appetite and slow weight gain for their infants, actual measurements of body weight did not show any difference. There was no significant difference in overall psychological performance. However, when the exposed children were ranked according to PBB level of body fat, a negative correlation was observed for four of five development scales. The PBB levels in fat for 27 infants ranged from 0.010 to 20.96 mg/kg, and in their mothers' blood from 1 to 845 μg/liter; all control mothers had PBB <1 μg/liter blood.

The authors offered several explanations for the discrepancies between the historical and the objective evidence about the health of the exposed children: (a) there may have been a difference in parental perception, perhaps due to anxiety and overinterpretation of minor complaints; (b) there may have been decreased immunity (however, no positive indication existed that this might be the case); (c) the methods might not have been sensitive enough to pick up differences, or not appropriate to establish such differences; (d) the exposed children might have been more symptomatic, but were recovering from the effects of PBB by the time the study was carried out.

The parents were not occupationally exposed, but their intake was increased by consumption of contaminated milk or meat. In occupational exposure the intake by fetus or infant may be higher. Additional studies, particularly of cognitive development, appear to be necessary.

The available data are too limited to allow any reliable conclusions on extra health risks for occupationally exposed women and/or their offspring. The reported evidence of effects on cognitive development are a matter of concern. There is a need for further study, particularly of health risks to infants nursed by occupationally exposed mothers.

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6 Plastic Monomers

Macromolecular plastics are built from monomolecular compounds — monomers. From the multitude of monomers five compounds will be discussed, for which evidence suggestive of adverse effects on women and/or offspring has been reported. This limitation to five compounds in no way suggests that exposure to monomers not discussed does not carry any extra risk for women and/or offspring, but rather that no data were available for others.

6.1 Vinyl Chloride

Downs et al. (1977) critically reviewed the available literature on vinyl chloride (VCM). Only those data are discussed which suggest adverse effects on the offspring of occupationally exposed women or on the offspring of parents exposed to VCM in the ambient environment. In the last case, it is not possible to distinguish between effects through exposure of father or mother. Evidence suggestive of adverse effects on offspring due to occupational exposure of the father is not discussed.

Edmonds et al. (USA, 1975) studied the incidence of congenital abnormalities of the central nervous system (mainly anencephaly and spina bifida) from 1970 to 1974 in three cities in which PVC plants were situated; the state of Ohio served as control. The data were obtained from hospitals which participated in the Birth Defects Monitoring Program (BDMP). The incidence of neonates with abnormalities was higher in the three towns than in the state as a whole. In Painesville one hospital had registered 15 cases; live births directly before and after each case served as controls. No case parents, but two control fathers had been working in the PVC factory at the time of birth; significantly fewer case mothers than control mothers worked within 10 miles of the factory. Therefore, evidence for a relationship with VCM exposure did not exist. Edmonds carried out another study (1977) of the incidence of congenital abnormalities of the central nervous system (CNS) in 17 areas with PVC plants and with at least one BDMP hospital; controls were always drawn from the whole state. Again, no relationship between supposed ambient exposure to VCM and the incidence of congenital abnormalities of the CNS was observed. However, if the investigator had compared towns with PVC plants and towns without such plants the design would have been more sensitive.

Infante (USA, 1976) and Infante et al. (USA 1976a, 1976b) studied the incidence of congenital abnormalities in three cities with PVC plants (Painesville, Ashtabula, Avon Lake), and compared this with the incidence in the whole area, in the whole state (Ohio), and in ten cities of comparable size for the period 1970–1973. The data, as regrouped by

Downs et al. (1977), are presented in Table 10. The study by Infante et al. focused on the relative risks (RR) in the three cities as compared with the entire state: for live-born and stillborn neonates the RR for congenital abnormalities of the central nervous system was 2.97 (observed 25, expected 8.42). Downs et al. (1977), however, compared the incidences in each of the three cities with those in surrounding cities without PVC plants; in this way possible differences in life style, ambient factors, and other confounders were minimized to a large extent. A significantly increased incidence was observed in Painesville, and in two control cities (Geneva, North Ridgeville).

Conclusions. The available data do not provide any evidence of an increased risk of congenital abnormalities in the offspring of parents who live in towns with PVC plants, and consequently with possible low-level ambient exposure to VCM. No data are available on health risks to offspring of occupationally exposed women.

6.2 Styrene

Zlobina et al. (USSR, 1975) studied the effects of low-level occupational exposure to styrene on the female reproductive system. In women exposed to high concentrations of styrene (and simultaneously to other chemicals) evidence had previously been reported suggestive of adverse effects on menstruation and on pregnancy. The 110 exposed women studied by Zlobina et al., worked in a polystyrene production plant; exposure was below 5 mg/m^3 and the temperature was 37 °–38 °C for about 50% of the time. Women from the personnel department and women who cared for children served as 231 controls; they were reported to be of the same socioeconomic level as the exposed women. The data are summarized in Table 11. No information is presented on age and obstetric history, and the health effects were not defined; the incidence of toxicosis appeared to be excessively high in both the exposed and the controls. Zlobina et al. (1975) also exposed female rats to 1.0 ± 0.2 or 5.0 ± 0.4 mg styrene/m^3 for 4 months (24 h

Table 10. Incidence of congenital abnormalities in 13 cities in relationship to possible ambient exposure to VCM (Downs et al. 1977)

Area	Number of neonates with congenital abnormalities per 1000 live births	Number of live births	*P*
Ohio state	10.14	719 287	
Ashtabula (PVC plant) and two surrounding cities	17.4 16.1	1 900 1 429	<0.90
Painesville (PVC plant) and five surrounding cities	18.1 5.7	1 381 7 762	<0.001
Avon Lake (PVC plant) and three surrounding cities	20.3 12.1	738 12 330	<0.10

Table 11. Incidence of effects on menstruation and pregnancy in women occupationally exposed to styrene (Zlobina et al. 1975)

	E	C
	$n=110$	$n=231$
Diseased uterus and adnexa	12.7%	4.7%
Disturbed menstruation	29.7%	9.1%
	$n=67$	$n=70$
Toxicosis (first half of pregnancy)	49.2%	18.5%
Toxicosis (second half of pregnancy) and nephropathy	10.4%	1.4%

E, exposed; C, controls

per day?); the estrous cycle and estrus proper were lengthened in the animals exposed to the higher concentration.

Hemminki et al. (Finland, 1980) reported an increased incidence of abortion (RR 1.5–2.5, $P<0.01$) in female workers exposed to styrene as compared with the general population; however the RR was based upon only six cases (for further details, see Chap. 15). Holmberg (Finland, 1977) carried out a case-control study based upon the Finnish registry of congenital abnormalities of the central nervous system: 43 cases were reported between June 1, 1976 and March 1, 1977; infants born in the same district directly prior to the cases reported served as controls. Two of the 43 case mothers and none of the control mothers had worked in the reinforced plastics industry (exposure to about 200 mg styrene/m^3, as well as to polyester resin, organic peroxides, and acetone). The prevalence of anencephaly and hydrocephalus in Finland was 0.5 per 1000 live births. During the study period about 400 women (250 considered fertile) worked in the reinforced plastics industry; there were about 65 live births per 1000 women per year in Finland, i. e., per 250 women, 16 births per year are expected. The expected number of births was 12 in 9 months. When among these 12 births two congenital CNS abnormalities occur, this might suggest a more than 300-fold (however, not yet statistically significant) increase in risk. The author also discovered a third case: in the 7th month of pregnancy a 20-year-old woman gave birth to an anencephalic neonate. On six different occasions during her pregnancy she had been exposed to styrene, polyester resin, and organic peroxides while her husband was renovating the kitchen with reinforced plastic; however, diabetes could also have constributed to the anomaly.

More recently, Härkonen and Holmberg (Finland, 1982) assessed the obstetric histories of women occupationally exposed to styrene. They compared 67 women working in the reinforced plastics industry and exposed to styrene with 67 age-matched controls working in textile and food production without obvious chemical exposure; the women ranged in age from 19 to 40 years (mean 30 ± 6 and 31.5 respectively), and the duration of exposure to styrene was 0.5–10 years (mean 4.5 ± 2.6). Interviews were held during 1979 and 1980. The obstetric histories were divided according to the period before and the period during exposure to styrene (302 person-years of exposure). Prior to styrene exposure the number of women with pregnancies, births, spontaneous

abortions, and induced abortions did not differ in the two groups. The expected number of births for the styrene exposure period was 20.9; four took place in the exposed group and 14 in the reference group. The number of births in the exposed group was significantly different from the expected number ($P < 0.001$) and from that in the controls ($P < 0.01$). The number of spontaneous abortions did not differ, but eight and four induced abortions were reported for the respective groups. From other studies it could be assumed that the average exposure level was about 66 ppm (277 mg styrene/m^3). The lower number of births in the exposed group could be explained partly by the increased number of induced abortions; moreover, consumption of tobacco and alcohol during pregnancy was less favorable in this group. No effects on menstruation were observed.

Conclusions. There is no conclusive evidence that exposure to styrene has an adverse effect on menstruation. One study suggested an increased risk of abortion (six cases), two others, of congenital abnormalities (two or three cases); however, a recent study did not reveal any effect on the incidence of spontaneous abortion.

6.3 Caprolactam

Petrov (USSR, 1977) compared absenteeism due to sickness among young women exposed to carbon disulfide (group I, $n = 1422$, see Chap. 3) or with that among women exposed to caprolactam and dinyl (group II, $n = 5430$), with that among nonexposed females (group III, $n = 2575$). No data on age distribution, level of education, or marital status were presented; exposure to caprolactam was below the USSR MAC (10 mg/m^3). Most sickness absenteeism occurred among women 20–39 years of age (due perhaps to pregnancy, illness of children, and/or household activities). Group II experienced fewer vascular disturbances than did groups I and III, possibly due to a hypotensive effect of caprolactam. Twice as many skin diseases occurred in group II as in group I. Groups I and II experienced more complicated pregnancies — e. g., abortions, toxicosis — than group III. This study presents too little information to permit any reliable conclusion.

Martynova et al. (USSR, 1972) examined 300 women exposed to caprolactam between 1955 and 1969; before 1964 the exposure level many times exceeded 10 mg caprolactam/m^3; between and 1966 the level decreased to about 10 mg/m^3. Among 300 exposed women (76.5% below 40 years of age) the prevalence of decreased menstruation was 2.5 times higher than among 600 nonexposed controls; the prevalence increased with duration of exposure (58.8% > 5 years), or perhaps with age — the study did not make this clear. Nadezdhina and Talankina (USSR, 1971) studied the prevalence of disturbed menstruation in 170 women (82% < 30 years of age) exposed to caprolactam; exposure to benzene, cyclohexanon, cyclohexane, cyclohexanon oxime, and trichloroethylene might also have occurred. There were 101 women (72% < 30 years of age) who served as controls. At first the MAC for various chemicals was exceeded in up to 50% of samples, later in only 5%. Disturbed menstruation was reported for 37% and 13% and painful menstruation for 19.4% and 8% of exposed and controls respectively. Lengthening of the desquamative phase from 3–4 to 5–6 days was more frequent among the exposed. In the groups with highest exposure the prevalence of signs and symptoms increased. Timoshenko and Petrov (USSR, 1977) compared the prevalence of disturbed menstruation among 321 women exposed to CS_2 (see Chap. 3), 218 exposed to about 10

mg caprolactam/m^3, and 385 nonexposed controls; ages ranged from 20 to 40 years, duration of exposure averaged 3 years. The regularity of the cycles was not affected, but 11.8% of those exposed to CS_2, 55% of those exposed to caprolactam, and 1.8% of controls had profuse menstruation; decreased bleeding was also more frequent in both exposed groups. The frequency of abortions was similar: 21% (caprolactam) and 19% (controls).

Martynova et al. (1972) also examined the effect of exposure to caprolactam on the course of pregnancy and delivery in 136 exposed and 150 nonexposed women 20–39 years of age. The following prevalences were determined for exposed and controls respectively: toxicosis in 28.7% and 17.3%; premature birth in 6.6% and 2.0%; hypotonic uterus in 14.7% and 8.0%; postpartum bleeding in 33.8% and 18.0%; asphyxia neonatorum in 12.5% and 4.7%, complicated extraction in 15.4% and 4.7%. The development of infants did not vary. Livke et al. (USSR, 1971) examined the same groups as were studied by Nadezhina and Talankina (1971): the prevalence of complicated pregnancy was 30.5% for exposed women and 9.9% for controls. ($P < 0.01$); the delivery was complicated in 10.0% and 3.9% respectively ($P < 0.05$).

Conclusions. The various epidemiologic studies provide little information: insufficient data are presented on age, obstetric history, level of education, and specific conditions of exposure; health effects are poorly defined; and in many cases there was combined exposure to many chemicals. Three studies reported menstrual disturbances; two studies, adverse effects on pregnancy and delivery. Although not conclusive, they may serve as an indication of an increased health risk.

6.4 Acrylates

Chobot (USSR, 1979) examined 1044 women (< 40 years of age) from a polyacrylic fiber plant and 440 nonexposed women from the same area (no data were reported on age distribution, obstetric history, life style, or occupation). Occupational exposure to *nitrilacrylic acid* and *the methylethyl ether of acrylic acid* (no data on exposure level; duration of exposure > 14 years) was reported to affect menstruation. Decreased menstruation was reported for 10.0% of the exposed and 4.9% of the controls ($P < 0.05$), profuse menstruation for 5.3% and 2.9% respectively ($P < 0.05$); the incidence increased with duration of exposure (confounding by age was not examined). The data presented provide too few details to permit a conclusion.

6.5 Formaldehyde

Exposure to formaldehyde occurs in occupations, in the ambient environment, and at home. In recent years exposure in (mobile) homes and in offices in which formaldehyde emanated from ureum formaldehyde condensation resins has received much attention; formaldehyde may emanate from adhesives in wood-chip board. Moreover, exposure occurs in health care facilities, where formaldehyde (formalin) is applied as a desinfectant, and where a relatively large number of women are employed (see Chap. 13).

Olsen and Døssing (Denmark, 1982) studied the effects of exposure to formaldehyde on 66 women employed in mobile day-care centers in which wood-chip board was used

for indoor paneling; 34 nonexposed women served as controls. The formaldehyde concentration in air averaged 0.43 (0.24–0.55) mg/m^3 and 0.08 (0.05–0.11) mg/m^3 for the exposed and controls respectively. A self-assessment questionnaire was used. In the exposed group about 40% complained of menstrual irregularity (controls, 0%), in addition to irritation of eyes and airways, unnatural tiredness, and headache.

Shumilina (USSR, 1975) examined 446 women exposed to 4.5 mg formaldehyde/m^3 (apparently emanating from resins used in producing crease-resistant fabric) in the textile industry and 200 nonexposed women. She also reported a higher prevalence of menstrual disturbances; in addition there was an increase in toxicosis and anemia in pregnancy and the birth weight of neonates was below normal. However, the data reported were deficient in details.

From the few data available on women occupationally exposed to formaldehyde no firm conclusion can yet be drawn; further study of effects on the female reproductive system and on pregnancy appears to be necessary.

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7 Carbon Monoxide

The affinity of carbon monoxide (CO) for hemoglobin (Hb) is about 200 times greater than its affinity for oxygen (O_2); consequently, carboxyhemoglobin (COHb) is produced instead of O_2-Hb. The percentage of Hb present as COHb is a measure of exposure and of health risk (oxygen deficiency). Occupational exposure to CO particularly affects those functions which require high O_2 consumption: the cardiovascular system, the nervous system, and fetal development.

No data are available which suggest any sex-dependent difference in susceptibility, or any effect on the female reproductive system; CO is not excreted in breast milk. Smoking may increase COHb by 4%–10%. The TLV for CO is 55 mg/m^3 (50 ppm); the short-term exposure limit (STEL) is 440 mg/m^3 (400 ppm).

7.1 Health Risks to Pregnancy and Offspring

No data are available on occupationally exposed women who do not smoke. Therefore, one can only extrapolate indirectly from other data.

The human body produces endogenous CO by metabolism of heme (about 0.4 ml CO/h); this leads to a background COHb of 0.2%–0.5%. The endogenous production increases in pregnancy by a factor of about 2 (0.9 ml/h). Because pregnant women usually have a low amount of physical activity at work (alveolar ventilation of about $\leq$12 liters/min), COHb will probably not exceed 4% in exposure to 15–30 mg CO/m^3 for 8 h in nonsmokers; in exposure to 55 mg CO/m^3 for 8 h COHb may increase up to 6.4%–7.6%, at an alveolar ventilation of 6–18 liters/min.

The NRC (1977) concluded that in pregnant women who smoke the ratio between fetal and maternal COHb levels is 0.6–1.2, i.e., CO readily crosses the placenta.

Based upon theoretical calculations, it can be concluded (NRC 1977) that in respect of O_2 supply, fetal tissues are in a more unfavorable position than maternal tissues.

All data available on the effect of CO on human pregnancy and offspring derive from studies of pregnant smokers, so it is not possible to distinguish clearly between effects due to CO and those due to other constituents of smoke (see also Chaps. 4 on nicotine and 10 on cadmium). Where smoking habits were similar, no difference in COHb levels was observed between men and women (Wallace et al. 1974). Possible health risks with occupational exposure have to be extrapolated from women who smoke (COHb > 4%) and/or women living at high altitudes (hypoxia).

The NRC (1977), the US-DHEW (1979), Abel (1980), and Rylander and Vesterlund (1981) reviewed the adverse health effects of smoking on pregnancy and offspring. It was found that birth weight is below normal (average about 150 g). The percentage of

neonates weighing less than 2500 g increases with the number of cigarettes smoked by the mother per day. According to Abel (1980) average birth weight for white female children in the United States decreases as the number of cigarettes smoked by the mother increases: nonsmoker, 3399 g; 1–10 cigarettes per day, 3272 g; 11–20, 3185 g; more than 20 per day, 3128 g. Luke et al. (1981) also reported a decrease in head circumference, independent of lower birth weight. There was an increased incidence of abortion (RR about 2) and of perinatal death (RR about 2); stillbirth is probably related to an increased risk of solutio placentae, and not to decreased birth weight. An increased placenta coefficient (ratio of placenta weight to birth weight) was reported; the placenta weight itself does not increase. There was an increased incidence of congenital cardiac abnormalities (RR about 1.5), and shorter pregnancies, though the latter is insufficient to explain below-normal birth weight.

Because lower birth weight and increased perinatal death occur in pregnancies of both mothers who smoke and those living at increased altitudes, it has been concluded indirectly that uptake of CO plays a causative role (hypoxia) in the first group.

Data on exposure of pregnant animals to CO have been reviewed by Rylander and Vesterlund (1981) and the US-DHEW (1979). With exposure to 55–110 mg CO/m^3 adverse effects such as fetal resorbtion, increased liquid content of brain tissue, perinatal death, and lower birth weight have been observed. They may indirectly suggest a risk of adverse effect from occupational exposure to CO at the TLV of 55 mg/m^3.

7.2 Discussion and Conclusions

The findings in women who smoke and in those living at increased altitudes are a matter of concern with regard to occupational exposure of pregnant women to CO (COHb up to 8%–10%): this exposure might lead to lower birth weight or increased risk of abortion or perinatal death. The no-effect threshold is not known. At exposure to 55 mg CO/m^3 for 8 h COHb may increase by 7% to 8% in the course of a working day in women who do not smoke; the present TLV may not fully protect against adverse effects on the offspring. Reducing exposure to 25–30 mg CO/m^3 for 8 h at work will minimize risks to pregnancy and offspring. Further studies are needed of occupationally exposed female nonsmokers.

It should be noted that exposure to *dichloromethane* (*methylene chloride*) causes biotransformation into CO; in exposure for more than 2–3 h, CO production becomes the decisive factor. However, at the present TLV of 100 ppm (360 mg/m^3) COHb probably does not exceed 4%–5%; although an increased risk cannot be excluded, the risk is probably small.

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8 Metals: General Orientation

Occupational exposure to metals is widespread. Intake is predominantly by inhalation, but sometimes, to a relatively large extent, by secondary and primary ingestion as well. Workers are also exposed away from their work through food, water, beverages, ambient air, and smoking. Biological monitoring is often of great importance, because it may make it possible to estimate total exposure.

Because various metals — and various compounds of the same element — may differ greatly in toxicokinetics and toxicodynamics, no rule of thumb on health risks can be given.

A few general aspects are discussed in this section, and some metals for which only a few data are available are reviewed. For most metals there are no relevant data. Lead, cadmium, and mercury will be reviewed separately in Chaps. 9, 10, and 11.

8.1 Toxicokinetics

Transplacental passage may differ considerably for various metals (and compounds). According to Luckey and Venugopal (1977), those metals similar in structure to essential metals may readily cross the placental barrier. Accumulation in the placenta may affect its structure and function, with a possible health risk for the offspring (see Chap. 10, cadmium).

Uptake by the gastrointestinal tract is usually higher in neonates than in adults, at least in animal studies (Jugo 1977), and more so in cases of nutritional deficiency of proteins, calcium, or iron. Moreover, transfer through the blood-brain barrier usually occurs more readily in fetuses and infants than in adults.

Excretion takes place in faces and/or urine and in breast milk. According to Jugo (1977), excretion may be less in young animals than in adults because of a stronger binding to organic ligands; this may result in lower levels of "diffusiable metals."

8.2 Health Risks in the Metal Industry

Hemminki et al. (1980) studied the incidence of spontaneous abortion in 35 000 women working in the Finnish metal-industry (members of the Union of Metal Workers, membership about 95%). The data are for the period 1973–1975; the total Finnish population served as reference. The ratio of spontaneous abortions to 100 births was higher ($P < 0.001$) for metal workers than for all Finnish women, but the rate of spontaneous abortions per 100 pregnancies did not differ. Increased rate and/or ratio

per branch was observed only in electronics. The authors also compared the frequency of abortion (standardized for age) before and during union membership: both rate and ratio increased ($P < 0.001$ and $P < 0.01$ respectively) after start of work for almost all age groups, again, particularly for women occupied in the production of radio and television sets; soldering fumes may have contributed (see also Chap. 9, lead). The data are presented in Table 12. The authors suggested that induced chromosomal aberrations in the embryo may have been the cause of the increased incidence of spontaneous abortions; however, this was not examined. This study certainly serves as a signal for further research, but does not allow definite conclusions. The possible influence of parity was not studied, nor was it known whether the workers has been exposed before joining the union. Moreover, other chemical may have been present, e. g., resinflux (colophonium) in soldering.

8.3 Conclusions

Metals (and their compounds) differ greatly in the health risks they present to the female reproductive system, pregnancy, and offspring. Particularly suggestive evidence in certain branches of the metal industry (e. g. electronis) raises concern. There is need for further studies, with great emphasis upon assessment of specific exposures (type of metal and compounds, other chemicals, intensity, duration).

There is still a serious lack of knowledge on the health risks to reproduction from occupational exposure to many metals and metal compounds.

Table 12. Spontaneous abortions among Finish metal workers 1973–1975 (Hemminki et al. 1980)

Branch of employment	Number of spontaneous abortions	Rate per 100 pregnancies	Ratio to 100 births
Electronics	58	9.22	16.48**
Mainly in radio and television production	24	12.44*	20.87*
Manufacturing of machinery	46	6.70	12.40
Manufacturing of other metal objects	25	8.20	13.09
Shipbuilding	23	7.32	14.20
Manufacturing of household machinery	11	9.91	15.94
Manufacturing of iron and steel	9	10.00	17.65
Manufacturing of transport equipment	6	5.56	8.00
Manufacturing of precious-metal objects	4	15.38	33.33
Mining	3	12.00	25.00
Others	10	6.21	9.90
All Union members	195	7.82	13.79**
All Finnish women	24 107	7.34	10.34

* $P < 0.01$, ** $P < 0.001$

8.4 Metals on Which Little Information Is Available

Friberg et al. (1979) systematically reviewed evidence of the effects of various metals on reproduction.

8.4.1 Arsenic

Exposure to inorganic arsenic (As) may occur in various metallurgical industries (often as a contaminant of ore) and in the production and use of arsenic compounds. Exposure may also occur in the ambient environment through air pollution (e. g., impurity in coal), pesticide residues in tobacco, or geochemical pollution of drinking water and food. Seafood in particular may contain organic arsenic. The toxicokinetics and toxicodynamics of inorganic and organic arsenic compounds differ broadly. Reviews have been presented by the NRC (1977), Fowler (1977), and the WHO (1981). The TLV is 200 μg As/m^3 for inorganic arsenic and soluble compounds.

Tsuchiya (Japan, 1977) investigated the health of inhabitants of a village near an already closed mine; drinking water usually contained < 50 μg As/liter (maximum 125 μg/liter), and vegetables ≤ 50 mg/kg. The author reported an increased prevalence of abnormal electromyograms in women in comparison with men; however, the data presented also allow a contradictory conclusion. No data have been published on health risks in jobs with predominantly female workers. No adverse effects on the female reproductive system have been reported.

Transplacental transfer of arsenic takes place: according to Kadowaki (Japan, 1960; quoted by Fowler et al. 1979), arsenic concentrations in fetal tissues and in newborns increase with age; the levels in bone, liver, skin, and brain in full term neonates were two to four times higher than in 7-month, stillborn fetuses. In studies of 101 women (Kagey et al. USA, 1977; quoted by the WHO 1981) cord blood levels were about as high as maternal blood levels.

Pershagen et al. (1977) reported evidence of increased mortality among children because of congenital malformation among the general population living near a metal smelter in northern Sweden. In various subsequent studies, Nordström et al. (1979 b) found that, among 291 neonates of women who had worked in this plant during pregnancy, 17 (5.8%) had congenital malformations; for women who had not worked during pregnancy the rate was 2.2% ($P < 0.005$). Five of six neonates with multiple abnormalities were of mothers who had continued to work during pregnancy. Similar results were obtained when the women were restricted to those born between 1930 and 1959: among women exposed before, during, or after pregnancy there were respectively 3.22%, 5.14%, and 2.17% neonates with congenital abnormalities, and 0.00%, 1.98%, and 0.00% with multiple abnormalities; prevalence was highest among those exposed during pregnancy.

Nordström et al. (1978a, b, 1979a) observed an increasing rate of abortion (7.6% to 11.0%) with decreasing distance (> 30 km to only a few) between the home and the smelter (no age correction), particularly in primiparae (5.1% to 10.1%). They also reported a lower birth weight for neonates of mothers employed in the smelter, compared with those not employed and living at < 10 km from the plant. The birth weight was lower ($P < 0.001$) when the mother worked in the factory than in the

laboratory; however, female office workers also had neonates with low birth weight; smoking habits and socioeconomic status were not taken into account. Birth weight and rate of spontaneous abortion in relation to duration of employment and to distance of home from the plant was analyzed in the cases of 612 female workers born between 1930 and 1959. The average birth weight again was lower, particularly at parity >2 ($P<0.001$), compared with nonemployed. The highest incidence of abortion occurred in those employed before pregnancy and those who lived less than 10 km from the plant (17.0%), and in those who continued to work during pregnancy (13.9%). The incidence was reported to increase with exposure intensity (estimated, not measured). In the smelter workers were also exposed to lead (Chap. 9), copper, and SO_2.

Animal experiments confirm the teratogenic/embryotoxic potential of arsenic, at least at high dose levels. Mammary excretion is probably limited; a few data on arsenic concentrations in human breast milk are available (3 μg As/liter, WHO 1981).

The limited data suggest an increased health risk to reproduction and offspring; however, there was exposure to other chemicals as well. No individual assessment of exposure was carried out. A threshold dose for arsenic is not known; further confirmation is certainly needed. In view of the fact that much lower occupational exposure limits (e. g., the OSHA 1981: 10 μg As/m^3 as ceiling per 15 min) have recently been proposed, the risks to reproduction and offspring — if they are real — will be reduced, perhaps becoming negligible. Studies are still needed to confirm the suggestive evidence reviewed above.

8.4.2 Antimony

Balayeva (USSR, 1967, quoted by Zeuthen Heidam 1978) examined menstruation and pregnancy in 318 women exposed to antimony (Sb), antimony oxide, and antimony pentasulfide; 115 women served as controls. She reported a nonsignificant increase in disturbed menstrual function and significantly lower birth weight. No data were presented on age, obstetric history, smoking habits, or levels of exposure, and those presented do not allow any firm conclusion.

8.4.3 Chromium

Chromium (Cr) crosses the placenta, particulary as chromium III in the glucose tolerance factor. There is no evidence of increased risk to reproduction and offspring in occupational exposure to chromium VI. In animal studies high dose levels induced congenital malformation. (See also NRC 1974.)

8.4.4 Copper

The distribution of Copper (Cu) in body tissues is similar for men and women (Vuori et al. 1978). During pregnancy or use of oral contraceptives the serum copper level may increase by a factor of 2, because the synthesis of ceruloplasmin is affected.

8.4.5 Manganese

Reviews of manganese (Mn) have been presented by the NRC (1973) and Piscator (1979). The WHO (1980) recommended a health-based occupational exposure limit, similar for male and female workers.

Manganese is an essential element. Manganese deficiency in animals causes increased risk of abortion, congenital malformation, perinatal death, and a disturbed estrus cycle. Administration of manganese increases fertility in cattle.

According to Piscator (1979), manganese concentrations in tissues of fetuses, neonates, and nonoccupationally exposed adults do not differ; only the manganese level in fetal bone was reported to be increased. Transplacental passage apparently takes place.

Manganese has been demonstrated in human breast milk, but no epidemiological studies have been found of effects on reproduction and offspring in occupationally exposed women.

The relevant animal data on manganese exposure may be summarized as follows:

1. Manganese crosses the blood-brain barrier, particularly in iron deficiency, and more so in the fetus than in the mother.
2. Iron deficiency during pregnancy may increase the risk of anemia in the offspring.
3. Feeding pregnant and lactating rats with 1004 mg Mn/kg diet did not increase the incidence of congenital malformation; at higher dose levels adverse effects on the offspring were observed (Kaloyanova et al. 1967, quoted by the IARC 1976). Administration of *Maneb*–manganous ethylenebis-dithiocarbamate)—700 mg/kg body wt., twice a week for $4\frac{1}{2}$ months increased the risk of stillbirth and incomplete development of the skull.

The data available do not suggest any extra health risks for women and/or offspring at the present TLV for manganese and its compounds (5 mg Mn/m^3 ceiling), Mn fumes (1 mg Mn/m^3), or manganese cyclopentadienyl tricarbonyl (0.1 mg/ Mn/m^3-skin).

8.4.6 Nickel

Recently Sunderman et al. (1983) reviewed the available evidence of nickel (Ni) embryotoxicity and teratogenicity. Evidence of embryotoxicity has been established in several animal species after administration of many nickel compounds. Teratogenic effects have been observed after administration of soluble nickel compounds in chickens, mice, and hamsters, but not in rats; nickel carbonyl [$Ni(CO)_4$] appears to be the most potent teratogen. Nickel compounds also induce internal bleeding in the fetus (not observed in adult animals). Ni^{2+} traverses the placental barrier and accumulates in the fetus.

Nickel concentrations in human cord-blood serum are approximately equal to those in blood of the mothers, but relatively high concentrations have been observed in enamel and dentine of teeth from human fetuses. In human embryos (10–16 weeks) an average of 3.6 mg Ni/kg (dry weight) was found, which is 2.2 times higher than the serum level (1.6 mg Ni/kg) at 20–28 weeks; also, in kidneys at 22–25 weeks the level was higher than in full-term infants. This suggests that Nickel concentrations are highest during early prenatal devleopment.

There is practically no clinical or epidemiological evidence of embryotoxic or teratogenic effects of nickel on humans. In the ribs and kidneys of one malformed infant respective concentrations of 27 and 5 mg Ni/kg (dry weight) were found at death, 12 days after delivery; this corresponds to 5 and 3 times the median level in 18 control infants who died of various causes during the first year of life. It is not known whether the mother in this case had been occupationally exposed to nickel.

These data do not permit firm conclusions in regard to reproductive hazards for female workers exposed to approximately the present TLV of nickel metal (1 mg Ni/m^3) or soluble nickel compounds (0.1 mg Ni/m^3). In view of the evidence available, further study is needed to firmly establish the absence of adverse effects on the offspring in cases of occupational exposure.

8.4.7 Selenium

This essential metal selenium (Se) interacts with other metals, such as mercury. Irregular menstruation and amenorrhea have been reported in occupationally exposed women (Nagai 1959, quoted by the NRC 1976). Se traverses the placenta and is excreted through breast milk. In 72 samples of breast milk Smith et al. (USA, 1982) measured 16.3 $\pm$4.9 µg Se/liter, higher than in proprietary formula milk. Butler et al. (USA, 1982) observed decreased whole blood and plasma levels in nonoccupationally exposed pregnant women, whereas erythrocyte and plasma glutathione peroxidase activity increased with the progress of pregnancy. In a few animal experiments adverse fetal effects have been observed; however, exposure to sodium selenate decreased the risk of adverse fetal effects from exposure to cadmium or arsenic. Selenium poisoning has been reported in the offspring of animals grazing on seleniferous soils, due to hypoplasia of male and female reproductive organs. A report that intake of selenium-contaminated food among the general population had caused congenital malformations was regarded as questionable by NRC (1976). No conclusion can be drawn from the available data on the risk of reproductive effects in women occupationally exposed to levels of selenium approximating the present TLV of 0.2 mg Se/m^3.

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9 Inorganic Lead

In the early twentieth century adverse effects of lead (Pb) on reproduction in, and offspring of, female lead workers were repeatedly reported. Cantarow and Trumper (1944) reviewed the evidence: disturbed menstruation, infertility, abortion, stillbirth, premature delivery, poor postnatal development, and increased infant mortality. The historical data, however, do not allow the establishment of reliable exposure (dose)-effect/response relationships; heavy workloads, poor hygiene, malnutrition, and poverty certainly also played a role. Moreover, no data on lead levels in blood (PbB) or on present-day effect parameters are available.

In this chapter only adverse health effects on women and their offspring reported in the last two decades will be reviewed. When no data are available on occupationally exposed women, those from overexposed general population groups are also taken into account.

The present TLV is 150 μg Pb/m^3; however, the WHO (1980) recently recommended 60 μg/m^3 for men and 40 μg/m^3 for women of fertile age as health-based occupational exposure limits; the maximum acceptable individual PbB level for female workers was stated to be 300 μg Pb/liter, for male workers 400 μg Pb/liter.

9.1 Health Risks

9.1.1 Different for Women than for Men

Table 13 summarizes no-effect levels of lead in blood under long-term, more or less stable conditions of exposure. The data indicate that, particularly in regard to heme synthesis and the nervous system, the health risk is sex and/or age dependent.

9.1.1.1 To Heme Synthesis and Hematopoiesis

In a study of human volunteers Stuik (1974) unexpectedly observed a higher level of protoporphyrin (PP) in erythrocytes in women than in men at similar PbB; this has been confirmed in both nonoccupationally exposed (Wibowo et al. the Netherlands 1977) and occupationally exposed women (Roels et al. Belgium, 1975, 1979, and Alessio et al. Italy 1977). The level of PP/FEP/ZPP starts to increase at lower PbB, and the rate of increase is faster in women than in men. There is also some evidence of a higher urinary excretion of aminolevulinic acid (ALA) and coproporphyrin (CPU) (Roels et al. Belgium, 1979). There is no evidence of an increased risk of anemia; however there are hardly any data on women with PbB > 600–800 μg/liter, and the health significance of this phenomenon

Table 13. No-effect levels of lead in blood (PbB)

Effect	PbB (μg/l)	Sex/age
δ-Aminolevulinic acid dehydratase (ALAD): decrease	< 50–100	
PP }	250–300	Men
FEP } concentration: increase	200–250	Women
ZPP }	150–250	Fetuses, young children
Hemoglobin: decrease	500–600	
Peripheral nervous system		
Conduction velocity: decrease	400–500	
Muscle weakness, paralysis	800	
Central nervous system		
"Minor brain dysfunction" (MBD)	~500	
Encephalopathy	> 800	Adults (m and f)
	> 600	Young children
Symptoms	> 500	
Poor development of CNS; MBD	> 300	Fetuses, young children
Disturbance of renal function	> 600	
Chromosomal aberrations	> 300–600(?)	

PP, protoporphyrin; FEP, free-erythrocyte porphyrin; ZPP, zinc protoporphyrin

as such is not established. Hemesynthesis also takes place at the cellular level in various organs, because heme is essential to many enzyme systems. Silbergeld and Lamon (1980) therefore suggested consequences for neurotoxicity because ALA as such is neurotoxic; therefore, one might expect an increased susceptibility of the female nervous system (see following section). The susceptibility of hemesynthesis in women is probably not due to a relative iron deficiency in women, but is perhaps related to different endocrine status (Wibowo and Zielhuis 1981).

9.1.1.2 To the Nervous System

Adverse effects on the nervous system of adult workers may occur at PbB > 400–500 μg/liter (peripheral nervous system) and at PbB > 500–600 μg/liter (central nervous system) (see Table 13). Seppaläinen (Finland, 1974) tentatively suggested an increased susceptibility of the peripheral nervous system (nerve conduction velocity) in female workers. Yamada et al. (Japan, 1981) compared symptoms of perceived health impairment in female and male workers: at PbB > 200 μg/liter women felt fatigued nine to ten times as frequently as men ($P > 0.01$). In both studies the evidence is still weak and cannot be considered conclusive.

9.1.2 Reported for Women Only

There is an abundance of studies of male workers, but there are only a few of female workers. Moreover, jobs in which mainly or exclusively women are exposed to lead probably do not exist, though soldering of electronic material is often done by women (see next section and Chap. 8).

Forni et al. (Italy, 1980) examined the chromosomes in 18 women occupationally exposed to lead (PbB = 240–590 μg/liter), and in 12 nonexposed controls (PbB = 220–370 μg/liter); a higher prevalence of chromatid and chromosomal anomalies was found in the exposed group. Similar data have also been reported for exposed men. However, it is still questionable whether lead exposure actually carries a risk of chromosomal effects, in view of contradictory evidence (Gerber et al. 1980, Forni 1980).

9.1.3 To the Female Reproductive System

Panova (1972, Bulgaria examined 140 women, 20–30 years of age, exposed to ≤ 7 μg Pb/m^3 for 1 to 2 months in a printing plant (Pb level in urine > 110 μg/liter in 34%; ALA level in urine > 8 mg/liter in 53%); 100 nonexposed women served as controls. By means of a vaginal smear the menstrual cycles were classified as normal, anovulatory, or cycles with disturbed luteinization. For 37% of the exposed and 22% of the controls disturbed cycles were reported; there was some evidence of a dose-effect relationship. However, inconsistencies in the data (e. g., inhalation of lead in air ≤ 7 μg/m^3 is not expected to cause increased ALA in urine; the ALA level in urine is too high in view of the moderately increased lead excretion) do not permit firm conclusions. Panova (1975, available as summary) and Panova and Ivanova (1975, available as summary) reported similar health effects in 90 women involved in the production of television sets (soldering; exposure to lead and to tin), and in 84 women involved in the production of telephone equipment. Although the data reported from Bulgaria are not very informative, they cannot be discarded; evidence of effects on the reproductive systems of women exposed to solder fumes was also reported from Finland (Chap. 8). However, even if this type of job carries a health risk, it is not known whether overexposure to lead as such is causative. There certainly is need for further study of women involved in the production of electronic/electrotechnical equipment.

9.1.4 To Pregnancy and Offspring

9.1.4.1 Placental Transfer

Lead concentrations in maternal blood (PbB-m) and in neonatal umbilical blood (PbB-n) are closely related; PbB-n is usually somewhat lower than PbB-m. Placental transfer increases with the length of pregnancy. Lead has been measured in the fetus from week 12–14 onward; the fetal body burden increases during pregnancy, particularly in fetal bone. Khera et al. (United Kingdom, 1980) measured lead concentrations in the placenta of occupationally exposed women and found that the average concentration increased with duration of exposure: two women, exposed < 1 year 290 μg Pb/kg; six, exposed 1–3 years, 350 μg Pb/kg; 13 women, 4–6 years, 400 μg Pb/kg; 14 women, > 6 years, 480 μg Pb/kg; nonexposed women, 290 μg/kg. A relation with intensity of exposure was also suggested. The concentrations in the placenta reported for nonexposed controls were much higher than those in other studies, perhaps owing to the analytical method. Karp and Robertson (USA, 1977) observed that accumulation of lead in the placenta might affect various enzyme activities. In 474 nonoccupationally exposed women in Belgium

Lauwerys et al. (1978), Buchet et al. (1978), and Roels et al. (1978) measured PbB-m at usually <200 µg Pb/liter; PbB-n, usually <150 µg Pb/liter; Pb in placenta: median 50 µg Pb/kg (wet weight). Although there were urban-rural differences in PbB-m and PbB-n the lead in placenta was similar. This study also provided indications that increased mobilization of lead might have occurred during pregnancy.

Alexander and Delves (United Kingdom, 1981) measured PbB in the course of pregnancy in 184 nonoccupationally exposed women: the concentration decreased. This could not be explained by increased blood volume alone; transplacental passage or increased urinary excretion might also have played a role. In this study no relation was found with the outcome of pregnancy (perinatal death, congenital malformations). Huel and Boudene (France, 1981) observed no relationship between the lead concentration in hair of mothers and neonates; the level in mothers' hair decreased with increasing gestational age of the fetuses.

9.1.4.2 Birth Weight, Abortion, Congenital Malformation

For 2 years in Scotland, Wilson (1956, quoted by Rom 1976) followed the course of pregnancy in 72 nonoccupationally exposed women living in an area with soft, lead-solvent drinking water (>50 µg Pb/liter). The excretion of coproporphyrin in urine was increased in 31% of women (35 pregnancies) who did not take any preventive measure but in only 1% of women (40 pregnancies) who consumed as little water as possible and drank large quantities of milk. In the first group four complications occurred (stillbirth, congenital abnormalities, premature delivery). The PbB ranged from 310 to 720 µg Pb/liter.

Fahim et al. (1976) examined the course of pregnancy in 253 women living in the "lead-belt" area (Missouri, USA) and in 249 controls. The authors reported an increased incidence of premature delivery (13%) and of early rupture of membranes (17%) in the first group compared with 3% and 0.4% respectively in the controls. However, it is questionable whether these events should be ascribed to lead, because the PbB-m and PbB-n levels were similar in both groups, albeit somewhat higher in the women with complicated pregnancies; the reported PbB-n levels were very much lower than the PbB-m levels, which does not correspond to most data in the literature; moreover, the first group also had increased exposure to cadmium (no quantitative data available). Contrary to what was concluded in the reviews by Bridbord (1978, 1980), this study does not provide conclusive evidence of adverse effects of lead on the outcome of pregnancy in nonoccupationally exposed women.

In recent years a few case studies of women with high PbB and/or lead poisoning during pregnancy have been published. Pearl and Boxt (USA 1980) observed a neonate with evidence of congenital lead poisoning: lead lines and delayed development of bone, low birth weight, and PbB-n, 790 µg/liter. The mother had nonoccupational lead poisoning (PbB-m, 790 µg/liter). Qazi et al. (Rumania, 1980) examined an infant whose mother had lead poisoning (PbB, 860 µg/liter; Pb in amniotic fluid, 900 µg/liter; PbB-n 600 µg/liter). At 6 weeks and at 3 months the infant showed an increased prevalence of chromosomal and chromatid anomalies, with normalization after 3 months. Bridbord (1980) mentioned the birth of a probably normal infant (at delivery PbB-m and PbB-n were 330 µg/liter) of a mother who had been occupationally exposed until 7 weeks before delivery (PbB up to 570 µg/liter).

Bryce-Smith et al. (United Kingdom, 1977) measured lead and cadmium concentrations in ribs ($n=26$) and vertebrae ($n=42$) of stillborn neonates: the lead levels were five-ten times and the cadmium levels ten times higher than those in live-born infants who died at 6 weeks to 10 months (see Chap. 10). Wibberley et al. (United Kingdom 1977) observed higher levels of lead in the placentas of perinatally deceased neonates than in the placentas of normal infants: in lethal congenital abnormalities ($n=13$), 1490 ± 570 µg Pb/kg (wet weight): in stillbirths ($n=9$), 1450 ± 500 µg Pb/kg; in first-week deaths ($n=14$), 1730 ± 570 µg Pb/kg; in normal births ($n=24$), 930 ± 640 µg Pb/kg. However, the authors quite rightly pointed out that the high placenta lead levels were not necessarily causative; both lead levels and abnormalities might have been the consequences of underlying disease; moreover, the normal levels were very high in comparison with other literature data. Subsequently Khera et al. (United Kingdom, 1980; same group as Wibberley et al.) measured lead concentrations in mothers' blood (PbB-m) and in umbilical blood (PbB-n), and in placenta, liver, ribs, and skull of stillborn neonates whose mothers had worked in a pottery plant. The lead levels in the placenta (wet weight) were: for 20 stillbirths, 450 ± 320 µg Pb/kg; for eight children of mothers not exposed for the last 2 years, 290 ± 90 µg Pb/kg; for nine live births with congenital malformations, 320 ± 40 µg Pb/kg; for ten with fetal pathology, 430 ± 190 µg Pb/kg; for those with normal placentas, 120 µg Pb/kg (much lower than in Wibberley et al. 1977). In 11 stillborn neonates of occupationally exposed mothers the mean lead concentration in the kidney was 480 ± 130 µg Pb/kg; in the liver 420 ± 300 µg Pb/kg; in the ribs 2010 ± 970 µg Pb/kg; in the skull 1280 ± 660 µg Pb/kg. In ten cases of cot death (<18 weeks) the concentration in the rib was significantly lower: 720 ± 460 µg Pb/kg. Although the authors, again, did not conclude that occupational lead exposure had been the cause of stillbirth, they nevertheless considered these findings a cause of concern; they advised against exposing pregnant women to lead.

Barry (1981) measured lead levels in tissues of 72 neonates and 49 infants (age <1 year). The levels in 14 stillborn neonates were not higher, but lower than in 15 live-born infants who died within 12 days. This study did not provide evidence that lead exposure caused stillbirth or perinatal death, at least not among the nonoccupationally exposed population.

The Swedish studies of arsenic by Nordström et al. (1978a, 1978b, 1979a, 1979b) have been discussed in Chap. 8. Exposure to arsenic, lead, and SO_2 might have contributed to the incidence of abortion and of congenital malformations. However, on the basis of the data presented a causative role of exposure to lead and/or arsenic can only be suggested; further studies are needed, with due emphasis on individual indices of exposure (e. g., lead in blood, arsenic in urine). Yamada et al. (Japan, 1981) reported an increased incidence of abortions in six of 15 female painters with lead in urine ≥ 60 µg/liter as compared with the incidence in nine of 59 painters with lead in urine <60 µg/liter; however, in this case as well, exposure to other chemicals might have taken place.

Wide (1983) studied the effect of lead on early fetal development in mice (1 mg lead chloride i. v. in the tail vein); lead caused inhibition of implantation, probably by interfering with ovarian steroid hormone stimulation of the endometrium. The author stressed the need to pay more attention to the possible adverse effect of lead on the fertility of exposed subjects, because the animal studies suggest adverse effects on preimplantation and implantation, i. e., a phase during which the woman is not even aware of being pregnant. However, the dose was high; PbB increased up to almost 3000 µg/liter.

9.1.4.3 Central Nervous System

There is a general consensus that the central nervous system of young children in particular, and presumably also of the unborn fetus, is more susceptible to lead than that of adults (see Table 13); there is no consensus about the adverse-effect threshold. McCabe (1979) mentioned the following factors as possibly contributing to this increased susceptibility: increased intestinal absorption, increased susceptibility of heme synthesis, increased risk of calcium deficiency, increased permeability of the blood-brain barrier, and an increased susceptibility of the developing nervous system as such. Encephalopathy usually has a more acute character in children than in adults. Most important is the risk of irreversible neurobehavioral effects. Rutter (1980) critically reviewed the literature on exposure-effect relationships and concluded that at PbB >600 μg/liter the risk is probably increased; that some studies strongly suggest that this may already take place at PbB of 400–600 μg/liter; and that, while there is no conclusive evidence with regard to the risk at PbB of 200–400 μg/liter, an increased risk cannot be excluded. Conclusive follow-up studies have not been carried out; confounding variables cannot easily be excluded.

Animal studies provide supporting evidence. Rice et al. (1979) administered 500 μg lead acetate/kg body wt. to *Macaca fascicularis* ($n=4$, four controls) from birth onward; PbB increased to 500–600 μg/liter at 200 days, and stabilized thereafter at 200–300 μg/liter. At the age of 2 to 3 years the animals showed no signs of manifest lead intoxication, but the exposed differed slightly from the controls in behavior.

9.1.4.4 Heme Synthesis

Not only are adult women more susceptible than men with respect to effects on heme synthesis; the same applies to infants and young children compared with adults. It is probably true as well for unborn offspring. This may be relevant for the increased risk to the nervous system (see Sect. 9.1.1.1).

9.1.5 Through Lactation

Lead is excreted in breast milk; the lead concentration in milk is on the same order of magnitude as that in blood plasma (i. e., about 10% of the concentration in whole blood): in the United States the average is 12 μg/liter, in Japan ≤ 12 μg/liter (Tsuchiya 1979). Larsson et al. (Sweden, 1981) analyzed breast milk samples from 18 women at 3 months postpartum, and of 23 other women at 6 months postpartum (all women 21–35 years of age). No difference in lead levels was found between the groups: the median was 2 μg Pb/kg fresh weight (range 0.5–9.0 μg/kg). In New Zealand the level was <10 μg Pb/liter (quoted by Larsson et al.). Haschke and Steffan (Austria, 1981) found no significant difference between 13 samples of pooled breast milk (50.2 ± 22.5 μg/liter) and formula milk or cow's milk. Chatranon et al. (Thailand, 1978) measured the lead concentrations in 164 samples of breast milk during the lactation period: at day 1 the average was 115 μg/liter, at day 8–14 71 μg/liter, at 3–5 months 67 μg/liter; the levels in Thailand and Austria are much higher than those reported in the United States, Japan, and Sweden, perhaps owing to differences in analytical techniques.

The extra intake through breast milk of women who have been occupationally exposed during pregnancy, and who are still exposed during lactation, increases the load to the infant, already born with an increased lead body burden. Moreover, as shown by Alexander et al. (United Kingdom, 1973), intestinal resorption is increased in the young. This is supported by animal studies, in which it was also shown that milk feeding increased uptake (Jugo 1977). Ziegler et al. (USA, 1978) performed 89 lead-balance studies in 12 healthy children, aged 14–746 days. The urinary and fecal excretion of lead increased with the daily oral intake; the former was about 1/19 of the latter. The net gastrointestinal absorption averaged 26% of intake – at >5 μg/kg per day as high as 41.5%. Intestinal absorption increased in cases of calcium deficiency. All data point to a relatively higher uptake of lead in infants than in adults.

9.2 Discussion and Conclusions

Heme synthesis is more susceptible to lead in women than in men: the increase of protoporphyrin levels in red blood cells starts at lower levels of PbB, and the rate of increase is greater. This is supported by animal studies. Because there are only a few data on occupationally exposed women, the threshold PbB level for anemia is not known; in view of the increased susceptibility of heme synthesis in women, and even more so in young children, it is expected that this effect may occur at PbB levels below 600 μg/liter.

There is evidence (still insufficiently confirmed) that occupational exposure to lead may cause menstrual disturbance, e. g., in women involved in the production of electrotechnical equipment (exposure to soldering fumes?). Further studies are needed.

There is also insufficiently confirmed evidence of increased risk of complicated pregnancies (abortion, stillbirth, malformations) in women who do not themselves have manifest lead intoxication. Further studies are needed.

There is general consensus that the developing nervous system (during pregnancy and lactation) is more susceptible to lead than the developed nervous system. The threshold PbB level is probably between 200 and 400 μg Pb/liter but there is no consensus on the level; at 300 μg Pb/liter the risk cannot be excluded.

The WHO (1980) recommended that in women of fertile age the individual PbB level should not exceed 300 μg/liter (for men 400 μg/liter), and that lead in workroom air should not exceed 40–60 μg respirable Pb/m^3-TWA respectively; i. e., lower levels for female workers than for male workers. In exposure to the present TLV of 150 μg Pb/m^3 PbB levels as high as 700–800 μg Pb/liter may be expected in pregnant or lactating women, as well as in fetuses or infants. At this level of exposure there is probably an increased health risk to fetus and neonate.

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10 Cadmium

There are hardly any data on occupational exposure of women to cadmium (Cd). Because cadmium has severely contaminated the general environment (particularly in Japan), data from women with nonoccupational exposure were also taken into account. Smoking cigarettes also contributes to the total daily intake. The present TLV is 50 μg Cd/m^3-TWA; the WHO (1980) recommended 10 μg respirable Cd/m^3-TWA.

10.1 Health Risks

10.1.1 Different for Women than for Men

Among nonoccupationally exposed Japanese subjects 0–80 years of age the cadmium concentration in the renal cortex is usually higher in women than in men; similar findings have been reported from Sweden (Tsuchiya 1978). Suzuki and Taguchi (Japan, 1970) examined the cadmium in urine (CdU) concentration in 28 men, 18–44 years old, and 49 women, 16–49 years old, all of them nonoccupationally exposed; the average CdU concentration was 1.52 μg Cd/g creatinine in men and 2.44 μg Cd/g creatinine in women; age and smoking habits could not explain this difference. Roels et al. (Belgium, 1982) studied seven male and seven female workers, all nonsmokers, from an electric condensor factory. Biological parameters of exposure were measured three times during 1 year; the concentration in air was probably below 10 μg Cd/m^3. The levels of cadmium in blood (CdB) — 1.7 μg Cd/liter for men and 2.2 μg Cd/liter for women — did not differ significantly, but the CdU levels (0.50 ± 0.08 and 1.72 μg Cd/g creatinine respectively) differed significantly ($P < 0.01$), if taken over the whole year. In three male-female pairs, also matched for duration of exposure and type of work, and sampled over a period of 4–6 h, the excretion/4 h was again about two times higher in women than in men (mean 0.27 and 0.12 μg Cd/4 respectively). Although the authors point out the possibility that with higher exposure e. g., 50 μg Cd/m^3 the CdU in male and female workers could differ by a different factor, animal studies also indicate a similar difference at higher dose levels. These findings strongly suggest a greater retention of cadmium in the renal cortex of women than of men with similar amounts of external exposure, and consequently an increased health risk. Adamsson et al. (1979) established a higher rate of intestinal absorption in subjects with a poor iron status; this might explain — at least in part — the above-mentioned difference in uptake. Animal experiments support this human evidence (Tsuchiya 1978; Taguchi et al. 1981).

10.1.2 Reported for Women Only

In Belgium Roels et al. (1981) and Lauwerys et al. (1982) studied healthy women over 60 years of age living in a cadmium-polluted area (Liege, $n=60$) and in two nonpolluted areas (Brussels, $n=45$, Charleroi, $n=70$ respectively). The subjects had not been occupationally exposed, and lived under similar conditions in homes for retired persons. The first group showed a higher cadmium body burden on the average, as reflected by increased CdU (77 ng/h in polluted area, 30 ng/h in nonpolluted area; the CdB medians were 1.3 and 1.0 μg/liter respectively); moreover, parameters of renal function showed the same trend. A significant relation ($P<0.001$–0.005) was found between CdU and the excretion of proteins, amino acids, β_2-microglobulin, and albumin for the total population, and for the first two effect parameters within each locality. Men were not examined; therefore, it cannot be established whether this reflected a sex-dependent difference in susceptibility. The authors also examined the mortality data (standardized for age, 1969–1976) for all causes and for renal urinary tract diseases, comparing only data from Liege and Charleroi. The SMR for total mortality did not differ, but the combined specific mortality was significantly increased in Liege over Charleroi, particularly for age over 60 years, mainly due to a different mortality for nephritis plus nephrosis in both women and men. The data suggest an increased susceptibility to Cd in elderly subjects (perhaps particularly in old women), because there was evidence of impaired renal function even at much lower CdU levels than those established for adult workers.

No studies have been published on occupational exposure to cadmium in jobs carried out mainly or exclusively by women.

10.1.3 To the Female Reproductive System

Reviews of health effects on women never mention evidence of an adverse effect on menstruation. The USSR study reviewed in the following section even stated explicitly that intensive exposure for 2–16 years had not caused disturbed menstruation.

10.1.4 To Pregnancy and Offspring

Only one study of occupationally exposed women provided data. Tsetkova (USSR, 1970) examined 106 women, 18–48 years of age, who had been exposed to cadmium for 2–16 years in three plants; 20 women served as controls. The data are presented in Table 14. Exposure to cadmium was intensive up to as much as 35 mg/m^3; the exposure was terminated after "the first months" of pregnancy. Number and length of pregnancies were not affected, but the author concluded that exposure to cadmium caused below-normal birth weight. However, the study design shows several deficiencies: no data on parity and on smoking habits is presented; the SD was about ten times larger in the chemical factory and in the controls than in the two other groups; there was simultaneous exposure to other chemicals; no data were presented on individual CdU or CdB levels. If exposure had actually been as high as 35 mg Cd/m^3, the mothers might

Table 14. Effect of occupational exposure to cadmium on birth weight (Tsetkova 1970)

Plant	Exposure	No. of women	Number born		Average weight (g)	Av. weight, boys (g)	Av. weight, girls (g)
			Boys	Girls			
Accumulators	1–25 mg Cd/m^3	61	13	14	3351* ± 33	3217* ± 36	2938* ± 32
Zinc	0.02–25 mg Cd/m^3	21	17	10	3351* ± 31	3388* ± 28	3196* ± 31
Chemicals	0.16–35 mg Cd/m^3	24	8	5	3203 ±230	3115 ±245	3340 ±316
Controls		20	11	9	3630 ±120	3700 ±120	3544 ±820

* $P<0.01$, compared with controls

have been expected to have kidney disease. The data therefore do not allow any firm conclusions.

It has often been shown that cadmium crosses the placenta, even in nonoccupationally exposed women, although transfer of cadmium is less than transfer of lead or mercury; the cadmium level in cord blood is also much lower than in maternal blood. The CdB concentration in mothers (CdB-m) who smoked was about twice that in mothers who did not, but CdB-n (cord blood) did not differ (Lauwerys et al. 1978; Buchet et al. 1978; Roels et al. Belgium, 1978; see Sect. 9.1.4.1). In another study CdB-m in mothers who smoked was even five times that in those who did not, but here, as well, CdB-n was similar (Hubermont et al. Belgium, 1978). The research group also measured the cadmium concentration in the placentas of 474 women; it averaged 10 μg Cd/kg (wet weight), i. e., ten times the CdB-m. Cadmium is apparently deposited in the placenta to a much larger extent than lead or mercury. The average cadmium levels in the placenta of mothers who smoked and those who did not were 18 and 10.5 μg/kg (wet weight) respectively. In the Netherlands, van Hattum and De Voogt (1981) measured 66 ± 33 μg/kg ($n=40$) and 51 ± 20 μg/kg ($n=31$) respectively (dry weight).

Copius Peereboom et al. (1979, the Netherlands) measured averages of 82 (41–158) μg/kg ($n=10$) and 48 (25–91) μg/kg ($n=10$) respectively (dry weight), total amount 7.1 (3.5–13.7) μg and 4.1 (1.8–7.7) μg. In the placentas of mothers who smoked, the following structural changes were observed: decreased volume density of small vessels, decreased diameter of vessels; electronmicroscopical thickening of the basal membrane of the syncytium; development of a two- to five-layer structure of the basal membrane of some blood vessels (van der Velde et al. 1983). These changes corresponded to structural effects observed in the placentas of rats treated with cadmium. Copius Peereboom-Stegeman et al. (1983) also reported data from a new study of placentas of 20 mothers who smoked 20–60 cigarettes per day during pregnancy and of placentas of 20 mothers of the same age, parity, height, and weight who did not smoke, all living in Amsterdam. More pronounced differences in placenta structure were observed in this study than in the study by Copius Peereboom et al. Contrary to expectation, the cadmium concentrations in placentas of the mothers who smoked excessively were similar to those in mothers who did not smoke: 53 ± 20 μg/kg and 48 ± 22 μg/kg (dry weight) respectively; the CdB-m concentration was two times higher, averaging 3.67 μg/liter ($n=13$) and 1.81 μg/liter ($n=17$) respectively. The authors formed the following hypothesis: assuming a limited capacity of the placenta to deposit cadmium, in case of high exposure (20–60 cigarettes daily; CdB = 3.67 μg/liter) the placenta might become

saturated, allowing increased transplacental passage. In this study the placenta weight was not lower, but — as is common for neonates of mothers who smoke — the birth weight was 80 g lower. Based on the data reviewed, lower birth weights of newborns of mothers who smoke might possibly be due to cadmium exposure and not (only) to carbon monoxide exposure (see Chap. 7).

A few studies have measured cadmium concentrations in tissues of stillborn neonates. Cumbrowski and Auermann (German Democratic Republic, 1980) examined three; cadmium was found in most organs, with the highest concentration 25 μg/kg (wet weight?) in liver and kidney. In 26 ribs and 42 vertebrae of stillborn neonates Bryce-Smith et al. (United Kingdom, 1977) measured 5.2 and 2.2 mg/kg (wet weight) respectively; the corresponding amount in bone samples from 24- to 75-year-old adults was only 0.03–0.95 mg/kg. Bryce-Smith et al. considered exposure to cadmium one of the factors contributing to stillbirth; however, the increased cadmium levels may have been the consequence and not the cause of a disease (see Sect. 9.1.4.2.). Huel and Boudene (France, 1981) measured the cadmium content of hair (CdH) in mothers and newborns at delivery. There was a positive correlation between CdH-m and CdH-n ($r = 0.48$, $P < 0.001$, $n = 103$), and CdH-n was inversely related to birth weight.

Supportive evidence from animal studies, reviewed by Friberg et al. (1979), Jugo (1977), Kostial et al. (1979), the CEC (1978), Copius Peereboom and Copius Peereboom-Stegemann (1981), Carmichael et al. (1982) and Parizek (1983), can be summarized as follows.

Intestinal absorption is greater in young animals than in adults; in case of iron, calcium, or protein deficiencies retention is increased, particularly in young animals. In studies of monkeys given ≤ 3 μg Cd/kg per day for 18 months no effects on the offspring were observed; when pregnant rats were exposed for 21 days to 200, 400, or 600 μg Cd/m^3 retarded growth of the neonates was observed only at the highest level of exposure. Congenital malformations were observed only at high dosages.

In pregnant rats receiving daily s. c. injections of 200 μg $CdCl_2$/kg during days 0–19 of pregnancy the following structural effects were observed at day 19: decreased volume density of maternal and fetal vessels and increased volume density of the trophoblastic layer and the mesoderm. These findings corresponded well with those observed in human subjects by the same research group.

Similar effects (hemorrhages) have been observed in the testes and nonovulating ovaries of prepubertal rats and of rats in persistent estrus in single parenteral dose studies. The selective toxic syndrome (convulsions, lung edema, and renal necrosis in the mother rats) observed in cadmium-treated rats towards the end of pregnancy was strictly pregnancy dependent. There was vascular damage due to cadmium itself and not to metallothionein, and it could be prevented by administration of zinc or selenium (Parizek, 1983); a poor nutritional status (deficiency of zinc, calcium, or proteins) may increase the risk in exposure to cadmium.

10.1.5 Through Lactation

Schulte-Löbbert and Bohn (Federal Republic of Germany, 1977) measured 3–35 μg Cd/liter, in breast milk of five women, which is reasonably comparable to other data in the literature. The highest levels were observed during the first 3 days after delivery;

subsequently, the level decreased to about 10 μg/liter. If the analytical methods applied are assumed to be precise, and the cadmium level in blood is assumed to be 1–3 μg/liter, the levels in milk appear unexpectedly high. Larsson et al. (Sweden, 1981) measured cadmium levels in breast milk at 3 and 6 months postpartum: the mean was 0.1 μg Cd/kg ($n=41$); no difference was observed between the two periods. These levels were much lower than the older data reported above. Further studies are needed, measuring the concentrations in both milk and blood. There are no data on occupationally exposed women.

10.2 Discussion and Conclusions

It is very probable that the retention of cadmium in the renal cortex is higher for women than for men under similar conditions of exposure, even at levels far below the present TLV. This evidence strongly suggests that at similar levels of occupational exposure the health risks to kidney function may be greater in women than in men. Moreover, there are indications of an increased risk of renal function impairment, and even mortality, in elderly women due to kidney disease (factor ~ 3), at CdB and CdU levels far below those recommended by the WHO (1980).

Only one study has been published on occupationally exposed pregnant women, suggesting below-normal birth weight of the offspring. However, the results do not permit valid conclusions. Much research has been carried out on transplacental transfer, particularly in comparisons of women who smoke with those who do not. The placenta retains cadmium, and only a relatively small amount is transferred to the fetus. Structural effects have been observed in placentas of mothers who smoke, comparable to those in cadmium-treated pregnant rats. Although it is known that the birth weight of neonates of mothers who smoke is about 150 g lower than that of neonates of mothers who do not, this cannot yet be explained conclusively as the result of either hypoxia (see Chap. 7) or cadmium-induced structural changes in the placenta, or even of other factors. Because, in occupational exposure to cadmium dust, secondary or primary ingestion may lead to relatively high intestinal intake, an extra health risk for mother and offspring may be expected in pregnant women with deficient nutrition. Animal experiments (high dose) indicate the possibility of adverse effects on ovaries and on pregnancy, presumably mediated through direct effects of cadmium on the vascular system. The findings in women who smoke and in animals provide reason for concern, because they indirectly suggest that occupational exposure to 50 μg Cd/m^3 or even to 10 μg Cd/m^3, might lead to structural changes in the placenta.

If a ratio of 10 between the cadmium concentration in breast milk and that in maternal blood proves to be true, lactation may considerably increase cadmium uptake by the infant. The neonate of an occupationally exposed mother may already have an increased body burden at birth. Moreover, gastrointestinal absorption is relatively high. However, the high cadmium levels reported have not been confirmed in recent studies. Animal studies do not provide evidence of an important effect on offspring through lactation.

The present TLV (1982) is 50 μg Cd/m^3. The evidence of increased accumulation in women's kidneys points strongly to a sex-dependent risk of impairment of renal function: the risk is very probably greater for female workers.

The WHO (1980) recommended 10 μg respirable Cd/m^3 (TWA) as the health-based occupational exposure limit, with individual maximums of CdB at 5 μg/liter and CdU at 5 μg/g creatinine. This recommendation applied both to male and female workers. However, new data suggest structural effects on the placenta in women who smoke 20–60 cigarettes per day; whether this adversely affects offspring has not yet been determined. Consumption of 30 cigarettes per day corresponds to an extra respiratory intake of 3–6 μg/day. If one assumes 65% deposition in the airways and 50% pulmonary absorption, smoking 30 cigarettes per day corresponds to an extra uptake of $0.65 \times 0.5 \times 5$ (3–6) = 1.6 μg/day. In exposure to 50 μg respirable Cd/m^3, 8 h/day, an uptake of 50 (μg/m^3) × 8 (m^3/8 h) × $0.65 \times 0.5 = 130$ μg/day may be expected. If the evidence of structural effects on the placenta in women who smoke is proved to be due to cadmium, the adverse effect level is below 1.6 μg/day; this is far below the 130 μg/day calculated for exposure to 50 μg Cd/m^3, 8 h/day, and even below 26 μg/day in occupational exposure to 10 μg/m^3.

These indirect data are certainly a matter of concern about extra risks in occupationally exposed women, because adverse effects on the offspring cannot be excluded, even below the occupational exposure limit of 10 μg/m^3 recommended by the WHO (1980).

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11 Mercury

The health risks in occupational exposure to mercury (Hg) and its compounds may differ greatly between various groups:
1. *Metallic mercury* (Hg°), particularly Hg° vapor
2. Inorganic *mercury*$^{1+}$ and *mercury*$^{2+}$ *salts*
3. *Organic methyl* (or *ethyl*)-*mercury*$^{2+}$, (short-chain) compounds
4. Organic mercury (long-chain) compounds, mainly *phenyl* ($PhHg^+$) and *alkoxy-alkyl* ($AAHG^+$) compounds.

For this review groups 1, 2, and 4 are covered together, because, to a large extent, their relevant toxicokinetic and toxicodynamic properties are similar, whereas those of the organic short-chain Hg^{2+} compounds differ essentially from the other three.

Inorganic Hg° is oxidized to $Hg^{1+} \rightarrow Hg^{2+}$ ions; groups 2 and 4 also release Hg^{1+} or Hg^{2+} ions. The Hg^{2+} ion appears to be the actual toxic agent. The main effector organs are the nervous system and the kidneys. However, in group 3 the methyl/ethyl mercury groups act as such, with the main effector organ the central nervous system.

Reviews have been presented by, among others, Friberg and Vostal (1972), Berlin (1979), the WHO (1976, 1980), and Reuhl and Chang (1979).

Studies of workers have been carried out, mainly of those exposed to Hg° vapor (1). Data on short-chain organic compounds (3) are derived almost exclusively from the environmentally exposed (oral ingestion) general population.

11.1 Metallic Mercury, Mercury Salts, and Long-chain Organic Mercury Compounds

11.1.1 Health Risks

11.1.1.1 Different for Women than for Men

According to Goncharuk (USSR, 1977) sickness absenteeism of female workers exposed to Hg° vapor was reported to be higher than that of male workers, mainly due to diseases of the gallbladder and kidneys; the number of spells increased with duration of exposure. However, detailed data were not presented.

11.1.1.2 Reported for Women Only

Some jobs with exposure to Hg° may employ relatively more women than men: there are more women as laboratory or dental assistants, in hospitals, and in the electrotechnical industry. However, no studies on female workers have been reported.

11.1.1.3 To the Female Reproductive System

Goncharuk (1977) examined 196 women 18–45 years of age, exposed to as much as 100 μg Hg°/m^3; 204 women (office, sales department, canteen) with similar age distribution served as controls. He reported increased prevalence of painful and/or diminished menstruation, 44.7% and 18.6% respectively ($P < 0.01$), particularly in cases of exposure for more than 3 years; however, confounding of age with duration of exposure was not investigated; individual measures of exposure to Hg° (e. g., mercury levels in urine or in air) were not presented.

11.1.1.4 To Pregnancy and Offspring

Mercury crosses the placenta. In almost 500 nonoccupationally exposed Belgian women Lauwerys et al. (1978), Buchet et al. (1978), Roels et al. (1978), and Hubermont et al. (1978) (see also Chaps. 9 and 10) observed that the concentrations of mercury in maternal blood (HgB-m) and in cord blood (HgB-n) were about similar. Several studies mention highly variable mercury concentrations in the placenta: 2.3–71.5 mg/kg; all data refer to total mercury concentrations.

Goncharuk (1977) reported adverse effects on pregnancy in 168 exposed women compared with 178 controls: imminent abortion (8.8% and 1.9% respectively, $P < 0.01$); abortion (16.7% and 5.0%, $P < 0.001$); toxicosis (34.9% and 1.9%, $P < 0.001$), premature delivery (6.0% and 1.1%, $P < 0.05$), abnormal position of fetus (2.3% and 0.4%, $P < 0.05$). However, age and obstetric history were not accounted for.

Mishonova et al. (USSR, 1980) examined 349 women exposed to Hg° vapor and 250 controls, all between the ages of 17 and 42 years; no data on age distribution or obstetric history were presented. No difference in length of gestation was observed, but the duration of delivery was reported to be longer for those in the exposed group, more so with increasing duration of exposure (or age?); blood loss was estimated to be three times that in controls, particularly in cases of long-term exposure; birth weight averaged 3400 g and 3500 g respectively; 13% of neonates of women exposed for more than 3 years weighed less than 3000 g (in contrast to a 2-cm increase in body length). Structural and biochemical effects in the placenta were reported; in exposed women there was a decrease in capillary surface and thickness of the trophoblastic layer (more so with longer duration of exposure) and increased activity of lactate dehydrogenase, succinate dehydrogenase, cytochromoxidase, and alkalic phosphatase. These findings were reported to occur at < 10 μg Hg°/m^3. No data on individual indices of exposure were presented. The authors concluded that pregnant women exposed to Hg° should receive special supervision. Because of insufficient data on such matter as age, smoking, obstetric history, and defined effects no firm conclusion can be drawn.

Friberg and Vostal (1972) quoted an observation from 1928 that mercury had been measured in the fetus of a syphilitic woman who had received dermal treatment with mercury salts.

Animal experimentation has shown that Hg° passes through various membranes more readily than do mercury ions; however, the transfer of both is less than that of the short-chain organic mercury compounds (Gatti et al. 1979). After administration of high doses of $PhHg^{+}$ compounds to hamsters and mice, adverse effects on the offspring were observed; oral dosage of mercury (Hg^{2+}) salts had similar results at 8 mg Hg^{2+}/kg body

wt., but not at 4 mg Hg^{2+}/kg. Exposure of female rats to 0.1 mg Hg°/m^3 during pregnancy did not affect the mortality of the offspring, but exposure for either 7 weeks before mating or 3 weeks before and throughout pregnancy increased neonatal mortality during the first 60 days after birth (Baranski 1982).

11.1.1.5 Through Lactation

After i. v. injection of mice with $HgCl_2$ the mammary mercury level increased; this suggests the possibility of mammary excretion (Friberg and Vostal 1972) (see also Sect. 11.2).

11.1.2 Discussion and Conclusions

The WHO (1980) recommended extra protection of female workers exposed to metallic mercury because of suggestive evidence of an increased risk to pregnancy and offspring. Because Hg° passes through membranes more readily than do Hg^{2+} ions no extra protection was recommended for exposure to inorganic salts and long-chain organic mercury compounds.

The few studies discussed present some evidence of an increased risk to menstruation, pregnancy, and offspring, although the data cannot yet be regarded as conclusive. It is not possible to suggest a threshold dose. An increased health risk to pregnancy and offspring in exposure of females to the present TLV of 50 μg Hg/m^3, TWA, (all forms of mercury compounds and Hg° except organic short-chain compounds) cannot be excluded.

11.2 Short-chain Organic Mercury Compounds

11.2.1 Health Risks

No evidence is available that women as such respond differently than men, and there is no evidence of an adverse effect on the female reproductive system. However, there may be severe adverse effects on the offspring during pregnancy and lactation.

The available data are derived mainly from two large epidemics of methyl-mercury poisoning: in Japan (1950^{s}–1960^{s}, contaminated fish, Minamata disease) and in Iraq (1971–1972, contaminated grain). The greatest risk probably lies in the last trimester of pregnancy. The offspring may become severely affected even when the mother is considered to be healthy. Delivery as such is not usually complicated; sometimes the skull is malformed. The main risk is retarded development of the central nervous system, which may become manifest either as severe brain malformation at birth or only as slight mental retardation after months, or any grade in between. With moderate exposure signs and symptoms may develop even during infancy, weeks or months after birth: apathy, retarded movement, absence of response to visual stimuli, disturbed coordination in suckling and swallowing, convulsions. The signs increase in severity with dose — spastic or flaccid paralysis, severely disturbed coordination, mental retardation, sialorrhea, sometimes blindness (Iraq), disturbed hearing and speech, retarded

growth — ultimately resulting in debility; in perhaps a minority of cases are behavioral or intellectual deficiencies detected, and only in specific studies. Complete recovery has never been documented.

Exposure in Japan was 35–100 μg Hg/kg body wt. per day for many months or years, in Iraq up to 200 μg Hg/kg body wt. per day for a shorter period. The concentrations of mercury in blood (HgB) and hair (HgH), but not in urine (HgU), either as total or as organic mercury, provide the best estimate of exposure.

Alkyl mercury compounds pass through the placenta, much more readily than do the other mercury compounds; accumulation is even greater in the fetus than in the pregnant mother; the mercury concentration is often 20%–30% higher in cord blood than in maternal blood.

Mercury is excreted in breast milk. Baluja et al. (Spain, 1982) measured total mercury concentration in the breast milk of 20 lactating women at 9.5 ± 5.5 μg Hg/liter (skew distribution). They mentioned lower levels from Sweden (0.9 and 0.8–1.6 μg Hg/liter), but higher levels from the Minmata area (healthy women 63 μg Hg/liter), and even 500–540 μg Hg/liter in another area in Japan; in Tokyo 2.2 μg Hg/liter has been reported. Although total mercury has been measured, the source of uptake was probably largely methyl mercury. Because various studies have not been comparable in analytical precision and accuracy, at least a part of the range reported may be due to the analytical technique. Total mercury concentration in milk is reported to be about 5% of that in blood; organic mercury concentration in milk is 20%. The level of total HgB in nonexposed subjects is usually < 10 μg/liter, but in a case of poisoning by short-chain organic mercury compounds, HgB may increase up to several mg/liter, most of it as organic mercury. The biological half-life of total HgB averages 66 days, but shortens during lactation (average 42 days). The neonate of an exposed mother is born with an increased body (brain) burden, and lactation adds an extra load: if the milk contains ≥ 2 μg Hg/liter (20% of 10 μg/liter), intake of 600 ml milk corresponds to ≥ 1.2 μg Hg per day, i.e., 0.4 μg/kg per day.

Animal experiments support the human evidence. The fetal body burden increases with daily intake by the mother animal, duration of exposure, and length of gestation. The concentration in fetal brain is often about twice as high as that in the brain of the mother animal. The developing nervous system is more susceptible than the developed nervous system at similar mercury levels. Congenital malformations (mainly palatoschisis, exencephaly, encephalocele, and hydrocephalus) occur in rats at dosages > 7 μg/kg body wt. per day; one administration only of 1.3 mg/kg body wt. to a pregnant rat may cause behavioral effects in the offspring.

11.2.2 Discussion and Conclusions

The developing brain in utero and in the neonate accumulates organic mercury more than the brain of the mother; moreover, it is more susceptible than the developed brain. Therefore, the fetus may be affected, even when the mother is asymptomatic. It has been estimated that with long-term intake of 3–7 μg Hg/kg body wt. per day a small percentage of adults develop slight neurologic effects. Adverse effects in the offspring may occur even when the intake of the mother does not exceed 3 μg Hg/kg per day. This corresponds to an equivalent concentration in workroom air of 26 $\mu g/m^3$ (3 μg/kg × 70

kg × 8 m^3). The TLV is 10 μg Hg/m^3 (TWA); at this level an increased health risk to offspring cannot be excluded. The WHO (1980) recommended a health-based occupational exposure limit of 10 μg Hg/m^3 (TWA) for men, with a maximal total individual HgB of 100 μg Hg/l; it recommended that women of fertile age not be exposed at all.

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12 Operating Room Personnel

In 1967 Vaisman (USSR) published the results of a small study of female anesthetists: of 31 pregnancies, 18 ended in abortion. The author suggested that the working conditions (e. g., long and irregular working hours, mental stressors, abnormal climatic conditions) might be the cause of this unexpectedly high incidence of abortions. This study was followed by many epidemiological studies of operating room (OR) personnel, and by animal experiments, with emphasis upon effects on reproduction in long-term exposure to anesthetic gases. Some studies provided suggestive evidence of an increased risk for renal disease and cancer. Wives of male anesthetists have also been reported to carry an increased risk of abortion and congenital malformation; in this chapter, however, only risks to female OR workers are reviewed.

Recent critical reviews (Vessey 1978; Vessey and Nunn 1980; Spence and Knill-Jones 1978; Ferstandig 1978) and some recent studies will be discussed. The epidemiological studies vary greatly in design, number of subjects, criteria for health and disease, and quality of exposure data. According to Rejger (the Netherlands, 1980) in ORs without ventilation the concentration of *nitrous oxide* (N_2O) may range from 30 to 7000 ppm, and that of *halothane* from 1 to 1680 ppm. Exposure may depend on the type of job performed: anesthetists are exposed to the highest concentration, but paramedical staff are usually exposed for more hours per day. According to a questionnaire completed by over 200 Dutch anesthetists (Rejger 1980) the average duration of exposure per week to N_2O was 36 h, to halothane 29 h; only a minority of anesthetists were exposed to *enflurane* for an average of 11 h per week and/or to other anesthetics for the same average duration.

Biological monitoring studies have measured 0.8 ppm halothane present in exhaled air at 16 h after exposure (Whitcher et al. USA, 1971); 0.5–15.2 mg halothane/ml serum at 20 h after exposure (Gostomzyk et al. Federal Republic of Germany 1973); N_2O in both blood (average 18 ± 6 µg/liter) and end-tidal air (average 8 ± 1 µg/liter) at 21 h after exposure for 4 h (Korttila et al. Finland, 1978); and up to 1.37 mg halothane/liter in the blood of anesthetists at the end of administration of this anesthetic (Davies 1976, quoted by Rejger 1980). Because anesthetic gases accumulate in the body, frequency, intensity, and duration (h per day) of exposure determine the internal dose to the effector organs. The available information on exposure provides hardly any consistent insight into the relationship between external exposure and biological indices of internal exposure; this is an important topic for further study.

12.1 Health Risks

12.1.1 Different for Women than for Men

12.1.1.1 Renal Diseases

The American Society of Anesthesiologists (ASA) sponsored an extensive survey on "Effects of waste anesthetics on health" (Cohen et al. 1974), based on questionnaires sent to 49 585 subjects working in the OR and 23 911 hospital workers not exposed to anesthetics. The subjects included members of the ASA, the American Association of Nurse Anesthetists (AANA), the American Association of Operating Room Nurses (AORN), and the American Association of Operating Room Technicians (AORT). Members of the American Academy of Pediatrics (AAP) and the American Nurses Association (ANA) served as controls. The response of the female members was: ANA 42% ($n=6560$), AORN/T 55% ($n=12\,272$), AANA 59% ($n=7136$), AAP 72% ($n=639$) and ASA 76% ($n=1059$). The data are summarized in Table 15. This study indicated an increased relative risk (RR) for renal diseases in exposed women, which was not observed in men. In a large-scale study of male dentists and female dental assistants exposed mainly to N_2O, Cohen et al. (USA, 1980) observed an increased RR for both men and women, albeit somewhat higher for women (RR = 1.2–1.7) than for men (RR = 1.2).

12.1.1.2 Cancer

Corbett et al. (USA, 1973), in a questionnaire survey on the incidence of cancer death, observed an RR of 4 ($P=0.031$) for 525 nurse anesthetists (active members of the AANA) in Michigan, compared with the general female population of that state; this was not observed in men. Because only active members were questioned, the RR may have been overestimated. Moreover, the data on the general population referred to cancer death and not to morbidity. The period between manifestation of cancer and start of

Table 15. Renal diseases in hospital personnel exposed to anesthetics and in controls (Cohen et al. 1974)

Exposed	Renal disease % (*n*)	Nonexposed	Renal disease % (*n*)	RR	*P*
Women		Women			
ASA	2.4 (908)	AAP	1.9 (506)	1.3	0.28
AANA	3.1 (5216)	ANA	2.3 (4550)	1.4	0.01
AORN/T	2.9 (9960)	ANA	2.3 (4550)	1.2	0.05
Men		Men			
ASA	4.2 (5743)	AAP	4.6 (2334)	0.9	0.76
AANA	4.3 (1604)	ANA	1.1 (86)	4.0	0.07
AORN/T	2.6 (761)	ANA	1.1 (86)	2.4	0.19

ASA, American Society of Anesthesiologists; AANA, American Association of Nurse Anesthetists; AORN/T, American Association of Operating Room Nurses/Technicians; AAP, American Academy of Pediatrics; ANA, American Nurses' Association; RR, relative risk

occupational exposure varied from 0 to 40 years; the relationship with duration of exposure was not studied. In total, 35 cases of cancer were reported over the period from 1935 to 1971, two of these before exposure began; surprisingly, however, ten of these occurred in one year (1971). These considerations make the conclusions of the authors questionable. In the above mentioned ASA study Cohen et al. (USA, 1974) also reported an increased RR (Table 16). No increased RR was observed for men; for women the RR was significantly increased, however only for leukemia and lymphoma ($P = 0.05$): 11 of 384 cases in the exposed group, one of 104 in the nonexposed group. Cohen et al. (1980) observed a not significantly increased RR (1.1–1.5) in both men and women exposed in dental practice.

These studies do not provide conclusive evidence of an increased risk of cancer for women compared with men.

12.1.2 Reported for Women Only

Both female and male OR personnel are exposed to anesthetics, and studies referring only to women have not been found.

12.1.3 To the Female Reproductive System

Knill-Jones et al. (United Kingdom, 1972) reported an increased RR of 1.5–2 ($P < 0.001$) for infertility of unknown cause in female anesthetists compared with other female physicians (Table 17). This single study provides suggestive evidence of an increased risk for infertility in female anesthetists, but the infertility cannot be ascribed to exposure to anesthetic gases as such.

Table 16. Cancer in hospital personnel exposed to anesthetics and in controls (Cohen et al. 1974)

Exposed	Cancer % (*n*)	Nonexposed	Cancer % (*n*)	RR	*P*
Women		Women			
ASA	3 (1008)	AAP	1.6 (566)	1.9	0.05
AANA	2.6 (6507)	ANA	1.8 (5400)	1.4	<0.01
AORN/T	2.3 (11843)	ANA	1.8 (5400)	1.2	0.07
Men		Men			
ASA	0.7 (6233)	APA	0.7 (2495)	1	0.49
AANA	1.5 (1858)	ANA	0.0 (109)	?	0.13
AORN/T	0.3 (851)	ANA	0.0 (109)	?	0.27

Abbreviations as for Table 15

Table 17. Infertility reported by female anesthetists and nonexposed female physicians (Knill-Jones et al. 1972)

Cause of infertility	Female anesthetists % ($n=563$)	Female physicians % ($n=826$)	RR	P
Known	4	4	1	
Unknown	12	6	2	<0.001
Total	16	10	1.6	

12.1.4 To Pregnancy and Offspring

12.1.4.1 Abortion

Askrog and Harvald (Denmark, 1970) made a study of pregnancy complications among female OR nurses and anesthetists who were exposed before and/or during pregnancy and among those who were not exposed until after pregnancy. Among the exposed nurses, 38 of 229 pregnancies (17%) ended in abortion; among exposed anesthetists seven of 26 (24%). In contrast, for nonexposed nurses the figure was ten of 85 (12%) and for nonexposed anesthetists, none of eight (0%). Because no independent control group was studied, and because the number of subjects was small, and age, parity, and various other job factors were not taken into account, the results may serve only as a signal for further study. Cohen et al. (USA, 1971) compared the prevalence of abortion among exposed OR nurses and anesthetists with that among nonexposed nurses and anesthesists. Among exposed OR nurses ten of 36 pregnancies ended in abortion, among nonexposed nurses three of 34 (RR = 3.3, $P=0.045$); among anesthetists the data were 14 of 37 and six of 54 (RR = 3.4, $P=0.0035$) respectively. Moreover, for the exposed groups the abortion occurred an average of 2 weeks earlier than for the controls; according to the authors, this pointed to an effect of embryotoxic agents. Although the mean age of the exposed nurses and anesthetists was 3.4 and 2.9 years higher respectively than that of the controls, this could not explain the increased RR; data on parity were not presented.

Knill-Jones et al. (United Kingdom, 1972) compared the course of pregnancy in female anesthetists working (exposed) during pregnancy with that in anesthetists not working during pregnancy (not exposed) and in female physicians, no anesthetists; 134 of 737 (18%) pregnancies in the exposed group, 46 of 336 (13.7%) in the nonexposed, and 315 of 2150 (14.7%) in the physicians' group ended in abortion (RR for exposed/physicians was 1.2, $P=0.025$). The response was about 80% in all groups. No data on age at the time of pregnancy were presented.

Rosenberg and Kirves (Finland, 1973) submitted a questionnaire to four groups of nurses; the response was 70%–75%. The data are summarized in Table 18. Group II was also exposed to anesthetic gases during cleaning activities, but total exposure was less than in group I; groups I and II also had the highest exposure to ionizing radiation. In I and II the differences between the percentages of abortive pregnancies before and during employment were inverse (there was no internal consistency). No relation was observed with the intensity of exposure to halothane. This study did not suggest any increased risk of abortion for women exposed to anesthetics.

In the ASA study, Cohen et al. (USA, 1974) also examined the abortion rate after standardization for age and smoking habits (Table 19): there was an increased RR in the exposed groups. Moreover, there was an increased risk (after standardization for age and smoking) in those who worked during pregnancy compared with those who did not within each organization studied: RR-ASA = 1.1 (P (one-sided) = 0.35), RR-AAN A = 1.2 (P = 0.06), RR-AORN/T = 1.3 (P < 0.01). This is suggestive of an increased risk of abortion, at least within the AORN/T, particularly because the exposed and nonexposed (during pregnancy) groups in each organization were more comparable than the members of different organizations. No difference was observed in the average length of pregnancy at the time of abortion. In this large-scale study the percentage of abortive pregnancies was always higher among women working in the OR. However, the authors pointed out that the increased RR might also have been due to other work factors, such as other chemicals, or stress.

Knill-Jones et al. (1975) studied the abortion rate among the wives of 5569 male physicians (70.1% of those who received a questionnaire) who worked in the OR; they also recorded data on occupational exposure of the wives themselves to anesthetic gases. The percentage of abortive pregnancies of exposed wives of men who also worked in the OR was 15.5% (81 of 523 pregnancies), 1.5 times higher than that among nonexposed women married to nonexposed men (10.9%, or 795 of 7296 pregnancies). After standardization for age and smoking habits the abortions in the second group amounted to 5.5%–9.2% (depending upon parity), as compared with 14.5%–14.9% (RR = 1.6–2.7)

Table 18. Spontaneous abortion among four groups of nurses (Rosenberg and Kirves 1973)

	Group			
	I Anesthesia nurses (n = 58)	II Scrub nurses (n = 24)	III Casualty dept. nurses (n = 75)	IV Intensive-care nurses (n = 43)
Abortion prior to employment, % (n)	21.5 (14)	10.3 (29)	12.6 (40)	12.4 (16)
Abortion during employment, % (n)	15 (80)	21.5 (177)	8.3 (96)	16.7 (54)
Average pregnancy week of abortion	11.1 ± 1.4	9.3 ± 0.8	13.1 ± 1.1	10.4 ± 1.1
Average age (years)	29.4	29.6	30.4	28.4

Table 19. Abortion rate in ASA study (Cohen et al. 1974)

Exposed group	Abortion % (n)	Nonexposed group	Abortion % (n)	RR	P (one-sided)
ASA	17.1 (468)	AAP	8.9 (308)	2	< 0.01
AANA	17.0 (1826)	ANA	15.1 (1948)	1.1	0.07
AORN/T	19.5 (2781)	ANA	15.1 (1948)	1.3	< 0.01

Abbreviations as for Table 15

among exposed partners. A portion of the data may already have been included in the previously mentioned study (1972); the findings corresponded.

Pharoah et al. (United Kingdom, 1977) observed no difference in frequency of abortion in 670 pregnancies of female anesthetists compared with that in 6377 pregnancies of nonexposed female physicians (both 13.8%). However, the term "anesthetist" referred only to the period of conception, which did not necessarily imply long-term exposure, and age was not taken into account. Also in the United Kingdom, Tomlin (1979) published the results of a questionnaire (a part of the data had already been covered by Knill-Jones et al. 1972 and 1975) with a response of 92.4%; many respondents were still in training (young age). He compared 102 pregnancies of 60 female anesthetists which had taken place before the women practiced their profession or at least one year after ending this practice (group I) with 32 pregnancies which occurred during the women's activity as anesthetists (group II): RR II/I = 3.5 ($P < 0.05$). No correction was made for age and parity and the number of observed pregnancies was small.

Rejger (1980) sent a questionnaire to Dutch anesthetists; the abortion rate was highest after women started their training (eight of 40: 20%; however, four in one subject), whereas no abortion had occurred before the training started (0 of 20). Again, the number of subjects surveyed was small.

Cohen et al. (USA, 1980) conducted a large-scale questionnaire survey among 138 278 predominantly male dentists and predominantly female dental assistants, with response about 70%. The groups were divided into users of inhalation anesthetics (I; 80% only N_2O) and users of only local anesthetics (II); the groups were also divided into "light" (< 8 h per week) and "heavy" (> 8 h per week) users. Correction for age and smoking habits was made, and the data are summarized in Table 20. An exposure-response relationship is suggested, and an increased RR (1.5–1.7) was observed among wives of male dentists. The use of N_2O in combination with other anesthetic gases had the highest RR.

In Belgium Lauwerys et al. (1981) compared the abortion rate among female members of the Belgian Associations of Anesthetists and of OR nurses with that among female members of the Belgian Associations of Dermatologists and of Occupational Physicians, as well as among intensive-care or general duty nurses. The response was between 41% and 55%. In the women who worked in the OR 22 of 259 pregnancies (8%) ended in abortion, as against 63 of 1056 (6%, RR = 1.3) in the controls. Exposure to ionizing

Table 20. Percentage of abortive pregnancies among dental assistants using anesthetic gases (Cohen et al. 1980)

Female dental assistants — use of anesthetic gas	Abortion % (*n*)	RR	*P*
Nonusers	8.1 (3184)		
Light users	14.2 (407)	1.7	<0.01
Heavy users	19.1 (400)	2.3	<0.01
Users of N_2O	16.0 (701)	2	<0.01
Users of combination of N_2O and other anesthetics	24.6 (93)	3	<0.01

radiation and use of oral contraceptives was highest among OR personnel. Differences in life-styles and in other work conditions were not accounted for.

Recently, Axelsson and Rylander (Sweden, 1982) published data on the spontaneous abortion rate among female personnel in one hospital: a cohort was composed of all female personnel (with the exception of physicians), born in 1930 or later, who had worked continuously for at least 3 months between Jan. 1, 1970 and June 30, 1979 in departments where it was judged that exposure to anesthetic gases could have taken place. Nonexposed persons to serve as controls were selected from personnel registers of the medical wards where such regular exposure did not take place. A short questionnaire covering pregnancies and their outcome was mailed; a second, more detailed questionnaire was mailed to those who reported that they had experienced an abortion or had born a child. The information on miscarriages was compared with data from hospital records. The response rates were high (85% and 84%, questionnaire I; 92% and 90%, II — exposed and controls respectively). Among the exposed women with high, low, or no exposure, 21.8%, 21.2%, and 9.8% respectively were 30 years of age or older. The miscarriage rates were 15.8%, 3.8%, and 9.1% respectively (total 655 pregnancies, 66 (10%) miscarriages, verified from hospital records). The highest miscarriage rate was found among women who smoked more than 10 cigarettes a day (smoking habits were similar in all three groups ($P < 0.05$). No relation was observed with "stress," heavy work, X-ray exposure, or medication. No difference in abortion rate was observed between women exposed (high and low) to anesthetic gases and those nonexposed when age and smoking were taken into account ($P = 0.6$).

Among the 51 who did not respond the authors found a total of 113 pregnancies in the hospital records; the observed number of miscarriages was higher than expected from the questionnaire data, and all occurred in the nonexposed nonrespondents. When the data of the nonrespondents were added to those of the respondents, no statistically significant difference was observed between the high-exposure group and the controls. The authors could not demonstrate a statistically significant difference in miscarriage rate between exposed and nonexposed women. The discrepancy between this result and those of several other studies was considered to be due possibly to relatively small numbers and low exposure intensity. However, the methods of study have often been important as well: in this study correction for age and smoking habits was made, and the data on the nonrespondents were also taken into account. If these corrections had not been made the study would have suggested a significantly increased abortion risk for women from the "high"-exposure group compared with nonexposed women ($P = 0.042$).

It may be concluded that several studies provide evidence suggestive of an increased risk of abortion for women occupationally exposed to anesthetic gases. However, in only one study was an exposure-response relationship weakly suggested, albeit without quantitative data on actual exposure. Moreover, biased lack of response, smoking habits, age, etc., may have produced biased data. Even when there is evidence of an increased rate of abortion, this cannot be confidently ascribed to exposure to anesthetic gases alone.

12.1.4.2 Congenital Malformations

Askrog and Harvald (1970) did not observe congenital malformations in the offspring of eight and 26 pregnancies respectively in female anesthetists exposed before and after

start of exposure; among nurse anesthetists the respective data were none of 85 and one of 229. This limited negative study, however, does not exclude an increased RR. Knill-Jones et al. (1972) reported 39 neonates with congenital malformations among 599 live-born infants (6.5%) of working female anesthetists (I), seven of 284 (2.5%) of nonworking anesthesists (II), and 89 of 1817 (4.9%) of female physicians-nonanesthetists (III); RR I/II $=2.6$ ($P<0.02$), RR I/III $=1.3$ ($P<0.05$). No data were presented on age, smoking habits, and parity. Rosenberg and Kirves (1973) did not observe any case of malformation in their small-scale study. However, Corbett et al. (USA, 1974) observed 71 cases among 434 neonates (16.4%) of nurse anesthetists (AANA) in Michigan who worked during pregnancy, and only 15 among 261 neonates (5.7%) of those not working (RR $=2.8$, $P<0.005$). The RRs according to type of congenital malformation were: skin RR $=4$ ($P<0.05$); hemangioma RR $=7$ ($P<0.05$), musculo skeletal system RR $=5.4$ ($P<0.005$), inguinal hernia RR $=4$ ($P<0.05$). In the large-scale ASA study Cohen et al. (1974) also observed an increased precentage of congenital malformations in the offspring of nurse anesthetists (AANA): RR-AANA/ANA $=1.25$ ($P=0.03$), and suggestive evidence among exposed female anesthetists: RR-ASA/AAP $=2$ ($P=0.07$), but not in AORN/T/ANA $=1.0$ ($P=0.47$). The study by Corbett et al. (1974) covered only a part of the membership of AANA. In the total study by Cohen et al. (1974) an increased risk was again observed: RR $=1.6$ ($P<0.01$); however, one study indicated an increased risk of cardiovascular, the other of musculoskeletal malformations. In a second study Knill-Jones et al. (1975) observed major malformations in seven (1.6%), minor in 14 (3.2%), of 438 neonates of exposed female physicians. The numbers among 6442 neonates of nonexposed controls were 68 (1.1%) and 152 (2.4%) respectively ($P<0.05$; corrected for age and smoking habits). According to Pharoah et al. (1977) eight (12.8%) neonates of female anesthetists had cardiovascular malformations, compared with 26 (3.6%) nonexposed controls (RR $=3.8$, $P<0.05$); no difference was observed for other malformations. Tomlin (1979), however, did not observe a difference in his small-scale study (RR $=1.1$, $P<0.05$); no correction was made for age. In Belgium Lauwerys et al. (1981) also observed no increased risk. In the Swedish study by Axelsson et al. (1982) five children were born with malformations among 114 (4.4%) whose mothers worked in high-exposure areas, and only nine of 434 (2.1%) among the nonexposed controls; and there were no malformations in children of mothers working in the low-exposure areas.

The data of the large-scale study on dental practice (Cohen et al. 1980) are presented in Table 21. Only in the case of "light" users of anesthetic gases was the risk increased in the

Table 21. Percentage of congenital malformations among children born to dental assistants in the United States (Cohen et al. 1980)

Female dental assistants — use of anesthetic gas	Congenital malformations % (n)		P
Nonusers	3.6	(2882)	
Light users	5.7	(341)	<0.05
Heavy users	5.2	(316)	n. s.
Users of only N_2O	5.5	(579)	<0.05
Users of N_2O in combination with other anesthetic gases	7.7	(68)	n. s.

offspring of dental assistants, particularly when they were exposed to N_2O in combination with other anesthetic gases (n. s.)

This review provides weak evidence of an increased risk of congenital malformations; some (usually small) studies were negative, but no exposure response-relationship was established.

12.1.4.3 Lower Birth Weight

Rosenberg and Kirves (1973), Pharoah et al. (1977) and Tomlin (1979) reported evidence of lower birth weight for neonates of anesthetists or nurse anesthetists. Data on age, parity, and smoking habits were not always taken into account.

12.1.4.4 Deviant Sex Ratio

Askrog and Harvald (1970) and Tomlin (1979) observed a preponderence of female neonates, but Lauwerys et al. (1981) of male. Knill-Jones et al. (1972) and Cohen et al. (1974) did not observe any deviation of the sex ratio.

12.1.4.5 Perinatal Death

Neither Askrog and Harvald (1970) nor Knill-Jones et al. (1972, 1975) observed any increased perinatal mortality in the offspring of female OR personnel. A nonsignificantly increased RR = 1.7 was reported by Pharoah et al. (1977).

12.1.5 Through Lactation

No data on adverse effects through lactation have been reported, but because anesthetic gases are liposoluble, excretion in breast milk may be expected.

12.2 Discussion and Conclusions

The data reported are sometime contradictory, even when one takes into account only reasonably well designed studies. Deficiencies in design, such as absence of standardization for age, parity, and smoking habits of the mother, have already been mentioned. The questionnaire method may provide biased data, as has been shown by Axelsson and Rylander (1982). Moreover, most studies do not report quantitative and qualitative data on exposure (type of anesthetic gas, intensity, duration, combinations), which may also have differed between various groups of OR personnel. Almost no data are reported on other work conditions.

Animal experiments with exposure to anesthetic gases indicate that the threshold exposure for hepato-, nephro-, and neorotoxicity may be lower than that for induction of abortion or congenital malformations. Data on mutagenicity are inconclusive.

There is no conclusive evidence of any increased risk for renal diseases or cancer among female OR personnel.

One study reported an RR of 1.5–2 for infertility, but further study is needed.

There is suggestive evidence of an increased risk of abortion; only one study suggested an exposure-response relationship, whereas — although they looked for it — other authors did not observe this. This indicates that other occupational factors may also have played a role.

The large-scale studies particularly provide evidence suggestive of an increased risk of congenital malformation. A few studies provide weak evidence of below-normal birth weight.

The data on deviation of the sex ratio and perinatal mortality do not provide any conclusive evidence of an effect.

The evidence of an increased risk of adverse effects on pregnancy and/or offspring cannot conclusively be ascribed to exposure to anesthetic gases; other work conditions, such as mental stress, irregular and/or long working hours, climate, exposure to X-rays, and exposure to other chemicals, may also play a causative role. The total evidence is suggestive of an increased risk of women for adverse effects, particularly on pregnancy and/or offspring, but the specific cause has not been conclusively established.

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13 Health Care Personnel

Exposure to other chemicals than anesthetics might also carry health risks for women in the health care profession and/or their offspring, as well as for operating room personnel (Chap. 12). Many women are employed in health care, in some countries forming a large majority. No studies have been found indicating any sex-dependent difference in health risks to organ systems not related to reproduction. The same applies to risks to the female reproductive system and through lactation.

13.1 Health Risks

13.1.1 Reported for Women Only

13.1.1.1 Mutagenicity

Falck et al. (Finland, 1979) examined female nurses who handled *cytostatic* drugs, suspecting that exposure might carry a cancer risk. The authors studied urine samples of seven exposed and 32 nonexposed nurses and ten treated patients. The nurses did not smoke and did not follow a special diet. Two samples were taken, on a Thursday afternoon and on a Monday morning after a work-free weekend; this permitted an internal comparison. Usually, combinations of *cyclophosphamide* and *vincristine* were administered, sometimes with *doxorubicin*, *bleomycin*, *dacarbazine* and *lomustine* as well. All patients and most of the exposed nurses produced urine which had mutagenic activities, although three-to-five-times higher activity was observed in patients than in nurses. The urine sampled on Monday morning showed a lower ($P < 0.01$) activity than that on Thursday afternoon. No mutagenicity was present in the urine of the controls. The authors quoted a study by Wall and Clausen (1975), who showed an increased incidence of urogenital cancers in patients treated with cyclosphamide; they suggested that the exposed nurses might also run an increased cancer risk. In a study of male and female Dutch nurses handling cytostatic drugs, an increased mutagenic activity in urine could not be confirmed (Leenaars 1981); however, the number of subjects examined was small.

Norppa et al. (Finland, 1980) examined the prevalence of sister chromatid exchange (SCE) in lymphocytes; the data are summarized in Table 22. The slightly higher prevalence of SCE in exposed nurses is on the same order of magnitude as that found in a study by Husgafvel-Pursianinen et al. (1980, quoted by Norppa et al. 1980). Waksvik et al. (to be published, quoted by Norppa et al. 1980) observed an increased prevalence of both SCE and chromosomal abnormalities in nurses who handled cytostatic drugs.

Table 22. Prevalence of sister chromatid exchange (SCE) in nurses handling cytostatic drugs, patients, and controls (Norppa et al. 1980)

	Number of subjects	SCE/cell	*P*	
Patients (A)	4	36.8±0.6	<0.001	compared with B, C, and D
Nurses handling cytostatic drugs (B)	20	9.4±0.3	<0.1 <0.01	compared with C compared with D
Nurses not handling cytostatic drugs (C)	10	8.7±0.2	<0.1	compared with D
Hospital office personnel (D)	10	8.1±0.3		

Leenaars (1981) carried out animal studies: in rats treated with cyclophosphamide or doxorubicin the urinary mutagenic activity was increased 8.1- and 3.1-fold respectively.

13.1.1.2 Immunity

Lassila et al. (Finland, 1980) examined the blood of ten nurses handling cytostatic drugs, and of a matched control group working in the department of radiotherapy and oncology; nurses who smoked and/or used oral contraceptives were excluded. No difference was observed in the number of leukocytes, lymphocytes, or E-rosette-forming cells. However, the response to phytohemagglutinin (PHA), concanavalin A, and a purified protein derived from tuberculin was increased in the exposed nurses, although not statistically significant. The authors concluded that handling cytostatic drugs probably did not carry any health risk.

13.1.1.3 Skin Diseases

In Poland, Rudzki and Wladzinsky (1978) and Rudzki alone (1979) examined cases of dermatitis in men and women working in health care professions. Occupational eczema was observed in 24 of 59 female nurses, mainly due to desinfectants (mostly formaldehyde; see also Chap. 5) and antibiotics (mostly half-synthetic penicillins). Among 43 physicians 12 had contact eczema, six due to rubber gloves, three to disinfectants, two to chromium catgut, one to nickel speculum, and one to formaldehyde; among 25 dentists 12 had skin disease, mainly due to mercury and formaldehyde (the sex of the physicians and dentists is not reported, but, presumably, most of them were women). In Warsaw, health care personnel took third place among the groups most at risk; however, this may be an overestimation, because health care personnel in a dermatology department probably seek treatment more readily than other workers. Hegyi and Kotulova (Czechoslovakia, 1979) described two case histories of nurses sensitized to ampicillin.

This review shows some evidence of extra health risks for men and women working in health care, but none of a sex-dependent difference in susceptibility.

13.1.2 To Pregnancy and Offspring

13.1.2.1 Abortion

In a nation-wide study in Finland based upon official registries (1973–1975), Hemminki et al. (1980)[1] observed an increased risk of spontaneous abortion (507 cases) in nurses: 6.5 per 100 pregnancies ($P < 0.001$) and 8.3 per 100 births, compared with women in the general population, 11 731 cases, 5.4 per 100 pregnancies, 8.3 per 100 births.

Strandberg et al. (Sweden, 1978) examined the course of pregnancy in 56 women employed in hospital laboratories: 32 had been pregnant, for a total of 71 times. Eight of 24 pregnancies during employment ended in abortion, whereas only nine of 47 pregnancies ended in abortion when the women were not employed (RR = 1.7, $P < 0.05$, one-sided). However, age and smoking habits were not taken into account. The authors themselves did not conclude an increased risk of abortion among hospital laboratory workers because of the small number examined and the low level of significance. Both studies provided weak evidence of increased risk, but further confirmation is necessary; moreover, the relationship with exposure to chemicals was not studied.

13.1.2.2 Congenital Malformations

Halling (Sweden, 1977) studied the incidence of congenital malformation in the offspring of health care personnel who handled *hexachlorophene*, present in the detergents pHisoHex (3%) and Sanitval (0.5%). Of 65 live-born neonates 12 had malformations (five major); in addition there was one case of intrauterine death. Another group, employed in the same hospital but not handling hexachlorophene, served as control; only one case was observed among 68 neonates. The groups did not differ in age, health, or use of drugs. Hexachlorophene could be detected in blood serum of those who used soap containing hexachlorophene. According to the authors, animal experiments had shown that hexachlorophene crosses the placenta. It should be noted that Sanitval was contaminated with dioxin (see Chap. 4) and/or furanes, which may be teratogenic. In a subsequent study Halling (1979) examined a larger group of women who worked in four hospitals. The women washed their hands 10–60 times a day with soap containing 1% hexachlorophene. Women not handling this soap and also employed in the hospitals served as controls; they did not differ in age, smoking habits, alcohol consumption, health, or use of drugs. Neonates with congenital malformations amounted to 15% in the exposed group, 3.4% in the controls, and 3% in the general population. The studies were disputed by Kallen (1978) because of a selection bias; the cases were selected as malformations and not as neonates of mothers who had handled hexachlorophene. Moreover, among the general population the incidence was 6% to 7% (major plus minor), and not 3% (major only). The Swedish Board of Health Experts also considered Halling's data unreliable.

A large study was undertaken in Sweden by Baltzar et al. (1979a, 1979b), in which 31 hospitals participated. Data were gathered on 1500 pregnancies in the period 1965–1975. The Medical Birth Register and the Swedish Register of Congenital Malformations provided the controls; age and parity were taken into account. No increased risk of congenital malformation was observed. The authors also examined the

1 see also chapter 19

pregnancy data for all Swedish medical personnel during 1973–1975: $n = 29\,806$, i. e., 9.3% of all Swedish pregnancies. Only in 1973 was the RR increased (152 observed, 118 expected, RR = 1.29, $P < 0.005$), particularly among nurses and scrub nurses. No explanation for this could be suggested. These studies neither confirm nor exclude an increased risk.

13.2 Discussion and Conclusions

There is evidence of an increased risk of skin disease due to disinfectants and antibiotics. There is suggestive evidence of an increased risk of mutagenicity (chromosomal aberrations) in those handling cytostatic drugs. No increased risk of a disturbed immune response has yet been demonstrated, and it is not known whether there is a sex-dependent difference in the risks mentioned.

Increased risk of abortion has been reported in two studies of nurses and/or female workers in hospital laboratories, but the evidence is not conclusive and further studies are needed (see also Chap. 15). Weak evidence of an increased risk of congenital malformation in those handling hexachlorophene could not be confirmed in a large-scale study.

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14 Pharmaceutical Industry

The pharmaceutical industry produces chemicals which are biologically active in humans; consequently, workers occupationally exposed to drugs and intermediates may also be affected. In this chapter a few studies are reviewed which suggest increased health risks due to exposure to drugs, particularly hormones. In other studies, however, reported health effects could not be ascribed to specific drugs. No studies have been found on effects not related to reproduction mainly or exclusively in female workers; the same is true of studies on health risks through lactation.

14.1 Health Risks

14.1.1 Different for Women than for Men

Thomas and Decoufle (USA, 1979) studied the proportional mortality ratio (PMR) in several groups of workers in a large pharmaceutical plant; the general population served as control. The PMR for malign tumors was increased for all men (PMR = 1.24, $n = 66$, $P < 0.05$) and for all women (PMR = 1.26, $n = 139$, $P < 0.05$). The cause-specific PMRs were: breast cancer, 1.8 ($n = 22$, $P < 0.05$); lung cancer — women — production, 2.4 ($n = 7$, $P < 0.05$); lung cancer — men — production, 1.3 ($n = 19$, $P > 0.05$); leukemia — women — production 3.5 ($n = 4$, $P > 0.05$); leukemia — men — production, 0.5 ($n = 1$). No data were given on specific exposures because the workers were handling many chemicals , they also changed their place of work often. Differences in PMRs between women and men may be due partly to different exposure (women were employed more in the packaging departments, men more in the production departments). No conclusion can be drawn about sex-dependent differences in susceptibility to carcinogens.

14.1.2 To the Female Reproductive System

14.1.2.1 Hyperestrogenism

Pacynski et al. (Poland, 1971) reported hyperestrogenism in nine women and one man working in a plant which produced *stilbestrol*. No controls were studied. Adverse effects were also observed in the offspring of these ten, but it could not be established whether that might be due to transplacental transfer or to intake at home of dust adhering to the clothes of the parents. Further confirmation is needed.

14.1.2.2 Menstruation

Agapanova et al. (USSR, 1973) reported an increased risk of disturbed ovarian function and menstruation in 18 of 34 women, aged 20–47 years, who were exposed to *androgens;* exposure to intermediates had a less pronounced effect. Suggestive evidence of decreased fertility was also reported. No controls were studied. The data were not statistically tested and are not very informative.

Harrington et al. (Puerto Rico, 1978) examined 30 women and 25 men employed in a plant which produced the oral contraceptives *mestranol* and *norethindrone* (exposure to about 9 and 40 $\mu g/m^3$ respectively). The menstrual patterns of the last 12 months prior to the study were compared with those of 60 controls (women who visited a gynecology clinic), matched according to age and socioeconomic status. The RR was 4.26 (95% confidence interval 1.61–11.26). However, the design can be disputed: no data were reported on use of oral contraceptives; women who left employment for health reasons were not studied; and the control women may have formed a selected group (no data were presented on the reason for their visits, but they may have been healthy women who came for semi-annual checkups). The RR may therefore have been underestimated. Although this study suggests an increased risk, further confirmation is required.

14.1.2.3 Vaginal Diseases

By means of a questionnaire and gynecological examination, Carnevale et al. (Italy, 1977) studied the prevalence of gynecological diseases in 43 women who worked in a plant producing *antibiotics.* Disturbed menstruation was observed in 44.2% and various vaginal symptoms in 40%–50%. The latter were thought to be due to exposure to antibiotics, which might have changed the normal vaginal flora. However, the design can be disputed as no controls were examined and the difference in prevalence between various departments was not studied, although exposure was mentioned as differing widely. The authors reported other studies which indicated a 20%–40% prevalence of vaginitis in women exposed to antibiotics, but not through their occupation. The evidence needs to be confirmed by further studies.

14.1.3 To Pregnancy and Offspring

Agaponova et al (1973) reported that among women exposed to *androgens* four 12 pregnancies had ended in abortion. Hansson et al. (Sweden, 1980) conducted a cohort of female laboratory workers from three pharmaceutical plants; other female personnel served as controls. The information was gathered from interviews, questionnaires, union registers on births, and registers of congenital malformations. The incidence of abortion (from 1973 onward) in the entire female work force did not differ from that in the general population (RR = 1.8; $P = 0.053$); the data are summarized in Table 23. The incidence of major congenital malformation in particular (from 1965 onward) was increased; the RR for abortion was borderline. According to the authors, the laboratory workers were younger than the controls: this might mean that the RR was underestimated. Smoking habits were not accounted for, although they probably were known. Three cases of solutio placenta occurred, two in laboratory workers who did not smoke and one in a

Table 23. Incidences of abortion, stillbirth, and congenital malformation among female laboratory workers from three pharmaceutical plants (Hansson et al. 1980)

	Total	Laboratory personnel	Other personnel	RR	*P*
Abortion per number of pregnancies, % (*n*)	12 (405)	18 (78)	10 (327)	1.8	0.053
Stillbirths per number of births, % (*n*)	1.8 (400)	6 (103)	0.3 (297)	2.0	0.0014
Major malformation per number of births, % (*n*)	1 (400)	6 (103)	0.7 (297)	9	0.0046
Minor malformation per number of births, %, (*n*)	2.2 (400)	3 (103)	2.2 (297)	1.5	0.42

control who smoked 10 cigarettes a day. The data do not permit the evaluation of a possible influence of socioeconomic status. It was not possible to relate the reported incidence of malformation to specific agents, because there was exposure to a multitude of chemicals. The data do not provide conclusive evidence, but may serve as a signal. Moreover, similar health risks have been reported for women working in non-pharmaceutical laboratories (Chap. 15). Hemminki et al. (1980) also reported an increased risk of abortion (RR = 2–3, $P < 0.05$; only five cases) among women working in the Finnish pharmaceutical industry. Moreover, during the years 1959 to 1975 an odds ratio of 3.22 ($P < 0.05$) was observed for childhood cancer in the offspring of female pharmacists; however, the number of cases was only 12 (Hemminki et al. 1981).

14.2 Discussion and Conclusions

There is evidence that occupational exposure to hormones may adversely affect the endocrine balance in female workers; this may be manifested as disturbed ovarian function, disturbed menstruation, and hyperestrogenism. There is also evidence of an increased risk of congenital malformation and perhaps of abortion and childhood cancer, but this needs to be confirmed by further studies. There is weak evidence of a relationship between exposure to antibiotics and the prevalence of vaginal diseases. Harrington (1982) dicussed some methodological problems in studying the health effects of exposure to synthetic estrogens: it is very difficult to assess effects on libido, or frigidity; minor effects on the breasts are not easily quantified; menstrual history is notoriously prone to error; and measurement of estrogen levels in biological specimens should also be carried out.

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15 Chemical Industry/Laboratories

Studies of workers in the chemical industry and/or chemical laboratories which do not specify exposure are discussed in this chapter. Studies of women employed in specific branches are reported in other chapters: metal industry (8), exposure to solvents (2), exposure to pesticides (4), health care (12 and 13), pharmaceutical industry (14), rubber industry (16), beauticians (17).

No studies have been found of sex-dependent differences in susceptibility not relevant for reproductive functions, or mainly or exclusively in female workers.

15.1 Health Risks

15.1.1 To the Female Reproductive System

Reichardt (German Democratic Republic, 1972) did not observe any difference in the age at which menopause started in women employed in the chemical industry compared with that in the general population. Aleksieva (Bulgaria, 1979) did not find any increased risk of cervical cancer. Disturbed menstrual cycle has been reported for Bulgarian women exposed to *ethylene* and *ethylene oxide;* concomitant exposure to unsaturated hydrocarbons might, however, have been a confounding factor (Ecetoc 1982).

15.1.2 To Pregnancy and Offspring

15.1.2.1 Abortion

Strandberg et al. (Sweden, 1978) asked 56 women employed at a country hospital laboratory for details of their pregnancies: 32 women had 71 pregnancies; eight of 24 "exposed" pregnancies ended in abortion as opposed to nine of 47 "nonexposed" pregnancies. To account for possible confounding factors such as smoking, family history, and age, stratification by a multivariate confounder score was applied. There seemed to be an increased risk for spontaneous abortion in women exposed to laboratory work during pregnancy: RR (Mantel-Haentzel) = 1.9.

The ECETOC (1982) mentioned data from the USSR which suggested effects on reproduction from the manufacture of ethylene oxide: there was a tendency to immature and premature termination of pregnancies, even at exposure levels ≤ 1.1 mg/m^3. However, in experiments with animals exposed to 66 mg/m^3 no effect was observed. The ECETOC concluded that at current exposure levels adverse effects on reproduction in man are unlikely.

Hemminki et al. (Finland, 1980) examined the prevalence of abortion as registered by the Union of Workers in the Chemical Industry (about 9000 female numbers). A similar study of the metal industry has been reviewed in Chap. 8. The register reported only hospitalized cases; the general population served as control. The data are summarized in Table 24. The prevalence was higher in various branches of the chemical industry; this applied to all age categories, and particularly to women 15–19 years old. Although these studies do not permit a definite conclusion, they do indicate the need for further research.

15.1.2.2 Congenital Malformations

Erickson et al. (USA, 1978) analyzed 989 interviews with parents of babies born with congenital defects in the Atlanta area; four mothers had worked as "craftsmen" in the printing industry before (not after) their babies were conceived. Of their four babies, three had either omphalocele or gastroschisis (O/G). Of the 989 mothers interviewed 74 had babies with O/G; the frequency of printing craftsmen among mothers of babies with O/G was 37 times the frequency among mothers of babies with other defects ($\chi^2 = 17.6$). Mothers of healthy babies were not interviewed. Meirik et al. (Sweden, 1979) analyzed the data of the Medical Birth Register for women employed in chemical laboratories between April 1, 1972 and December 31, 1977; the data are summarized in Table 25. No

Table 24. Prevalence of abortion in female workers in various branches of the chemical industry in Finland (Hemminki et al. 1980)

	Number of abortions	Number of abortions per 100 pregnancies	Number of abortions per 100 live births
General population	15482	5.52	7.98
Union of workers in the chemical industry	52	8.54[b]	15.57[c]
Plastics industry	21	8.94[a]	17.80[c]
Styrene production	6	15.00[b]	31.59[c]
Viscose-rayon industry	9	11.25	22.50[c]
Chemical laundries	17	10.14	16.67[a]
Pharmaceutical industry	5	10.20	22.72[a]

[a] $P<0.05$; [b] $P<0.01$; [c] $P<0.001$

Table 25. Incidence of congenital malformation in female chemical-laboratory workers (Meirik et al. 1979)

Malformation	Children of laboratory workers ($n=245$)	RR	P	Children of nonlaboratory workers ($n=65$)	RR	P
Major	11 (4)[a]	3.8	<0.01	3 (1)	3	n. s.
Minor	18 (13)	1.4	n. s.	3 (3)	1	n. s.
Total	29 (17)	1.6	<0.01	6 (4)	1.5	n. s.

[a] Expected number (general population) after correction for age and parity

excess perinatal mortality was observed, but the incidence of major congenital malformation was higher than that in the general population (RR = 3.8, $P < 0.01$); no significantly increased risk was observed in women not employed in laboratories. The authors could not suggest a cause for the increased risk.

Blomqvist et al. (Sweden, 1981) used the same Medical Birth Register to study 890 pregnancies of women employed in the pulp and paper industry between 1973 and 1977. The observed number of malformations was 49 (expected 50) and the number of perinatal deaths eight (11). However, in the subgroup of 162 laboratory workers six cases of major malformation were observed, as against 2.9 expected ($P = 0.07$); moreover, seven major cases occurred in women employed in "converting", as against three expected ($P = 0.03$). Most malformations were cleft lip and atresia ani. Several women were exposed to various *dyes*, *ethyl acetate*, and *glue*. Erickson et al. (Sweden, 1982) performed a case-control study of 201 women who had infants with gastrointestinal (GI) atresia and 402 women with infants without this malformation, but matched for age, parity, and time of year at delivery. The chief obstetrician at each hospital retrieved information on occupation during pregnancy for all cases and for controls with malformed infants; for control cases with normal infants a simple questionnaire was mailed to the mothers. A gross subdivision of occupations was made: (1) housework, (2) "unexposed" occupations, (3) health care, and (4) occupations where chemical exposure is probable (e. g., beauticians, pharmacists, plastics industry) or possible (e. g., laboratory work, unspecified industrial work); 142 complete triplets (one case plus two controls) and 21 pairs (one case plus one control) were available. A third source of information was the 1975 census. The study hypothesis was that there should be an excess of laboratory workers among cases, compared with controls. Among the triplets six had a case laboratory worker but no such control, and two had a control laboratory worker but no such case; among the pairs only one case, but no control laboratory worker, was detected ($P = 0.02$). However, in the case group the percentage of housewives was lower than that in the control group (14% and 25% respectively, within the triplets 13% and 27%; $P = 0.01$). The 1975 census provided information on the occupations of the nonrespondents: among 29 nonresponding cases were 13 housewives, among 25 nonresponding controls, six. There was no difference between the percentage of 193 cases who were housewives and that of 392 controls (24.4% and 27.3%). The difference in laboratory work exposure could harldy be an effect of nonresponse, as none of the 54 nonresponders who had babies were classified as laboratory worker in the 1975 census. The authors therefore concluded a not very great excess risk (RR = about 5) of GI atresia in offspring of laboratory workers. Looking for the occupation of nonrespondents was important, as otherwise an excess risk would have been suggested for any occupation (see also Chap. 12).

In the United States Peters et al. (1981) reported a relationship between the incidence of brain tumors in children aged < 10 years and exposure of the mothers to chemicals (odds ratio = 2.8), particularly to *nitrites* and *N*-nitroso compounds (case-control study, 92 matched pairs). In addition, a relationship was suggested with exposure of the father to *solvents* and paints; the parents of the children with brain tumors had three to ten times more contact with chemicals than did those of the controls. The data were gathered by means of a telephone survey. Gold et al. (1982) emphasized the methodological issues in studies on the relationship between parental occupation and cancer in children, including that of Peters et al. Most studies suffered from

methodological difficulties that prevent definitive conclusions, such as small sample size, no validation of past and present occupational exposure, insufficient information on specific cell types of malignancies; because of this the studies may lead to inconsistent results.

15.1.3 Through Lactation

See the chapters on solvents (2) and pesticides (6).

15.2 Discussions and Conclusions

Various studies discussed in this chapter and others suggest an increased risk of abortion and/or of (major) congenital malformation of offspring among women employed in the chemical industry and/or chemical laboratories. The data reported are limited in detail, in view of the fact that data on actual exposure do exist. It is not possible to conclusively determine causative (groups of) agents, but the studies may serve as a signal for more detailed investigation.

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16 Rubber Industry

Work in the rubber industry involves combined exposure to many chemicals, such as aromatic amines, solvents, plastics monomers, and additives. Several studies on female workers have been published. Some suggest increased health risks due to exposure to specific (groups of) agents, which have been discussed in other chapters: solvents (2), plastics (6); however, synergism with agents not discussed may increase the health risks. Most studies reviewed in this chapter refer to health risks as such, without suggesting specific causes. Chloroprene may also exert adverse effects on the male reproductive system, but this aspect is not discussed here.

16.1 Health Risks

16.1.1 Different for Women than for Men

16.1.1.1 Thioether Excretion

Kilpikari (Finland, 1981) observed higher urinary thioether levels in women than in men who worked under similar conditions; the author suggested a higher dermal penetration and consequently a higher total uptake. The concentrations in mmol/mol creatinine $\pm$ SE in various departments were: conveyer belt, 43 ± 4 (for 19 men) and 71 ± 13 (for two women) — not significant; wedge belt, 44 ± 4 (16) and 89 ± 12 (15), $P < 0.005$; office and canteen, 50 ± 4 (17) and 61 ± 7 (5); controls, 27 ± 2 (62) and 42 ± 2 (18). It should be noted that the levels appeared to be higher not only in women working in the factory, but also in those slightly or not at all exposed. No studies have been found of jobs with mainly or exclusively female workers.

16.1.1.2 Mortality

Monson and Nakano (USA, 1976) compared the standardized mortality ratio (SMR) for 5816 female workers (5501 of them white) in the rubber industry with that of the general United States population; standardization was made for sex, age, and race, but smoking habits were not taken into account. The SMR — all causes — was 78 for women and 65 for white men ("healthy workers effect"). There was suggestive evidence of a higher SMR for bladder cancer in women: SMR for women, 189 (seven cases), SMR for men, 107 (eight cases); the SMR for uterine cancer was 107 (39 cases, 16 of cervical cancer). These SMRs may serve as a signal for further study; the observed numbers of cases were small: for bladder cancer only about 1% of all deaths and about 3% (women) and 5% (men) of

cancer deaths. The authors also looked for specific causes. Two women who had worked in the brake lining department died of mesothelioma or lung cancer (probable exposure to *asbestos*). An excess of uterine cancer (mainly cervical cancer) was observed only in the production department. Bladder cancer in women became manifest at a younger age and after shorter duration of exposure than in men; according to the authors, this might have been due to a higher susceptibility of the female bladder to, for example, *2-naphthylamine;* however, a higher intensity of exposure could not be ruled out. Andjelkovich et al. (USA, 1978) conducted a cohort study of women employed in a rubber manufacturing plant for more than 10 years; the SMR for 1964–1973 (279 deaths) was calculated, taking the general United States population as a control (standardized for sex, age, and race). Of the women, 64% had been employed in production of industrial products and 36% in production of tires, wires, and cables. The SMR — all causes — was 103 for women and 94 for men; an SMR below 100 might have been expected ("healthy workers effect"). Increased cause-specific SMRs for women were: lung cancer, 190 (nine cases), $P = 0.051$; acute myocardial infarction, 125 (68 cases; n. s.); bladder cancer 204 (two cases; n. s.); no deaths of women due to larynx or liver cancer, Hodgkin's disease, leukemia, or suicide were observed, all of which causes had increased SMRs for men. Smoking habits were not known (smoking may be an important cause of lung and bladder cancer and myocardial infarction), although it was suggested that female workers smoked more than male workers. The suggested excess mortality in both United States studies may serve as a signal for further investigation; the studies themselves do not yet permit conclusion of a sex-dependent difference in susceptibility to chemicals used in the rubber industry.

16.1.2 To the Female Reproductive System

Among 5501 white female workers Monson and Nakano (USA, 1976) observed 39 cases of uterine cancer (SMR 107), not related to socioeconomic status.

Beskrovnaia et al. (USSR, 1979) examined the incidence of gynecological diseases in 4996 female workers in the rubber industry and in 766 female workers in the electrotechnical industry, all between 20 and 39 years of age. The rubber industry workers were exposed to 250–350 mg *benzene*/m^3 (see Chap. 2). No data were presented on age categories, life style, parity, or level of education; the difference between number of exposed and number of controls was large. The data are summarized in Table 26. An increased risk of disturbed menstruation, particularly of profuse menstruation, is suggested, increasing with duration of exposure (or age?). The authors did not explain why the prevalences of inflammation of adnexa and of uterine tumors were higher in the controls. The greater prevalence of premature deliveries was suggested to be due to "adaptation to work." The authors also examined the cervical mucosa of 20- to 30-year-old women five times (but not of controls!): in 5% a poor functioning of the corpus luteum was observed (anovulatory cycles). Although the authors suggested that exposure to benzene might play a causative role, there was probably exposure to other chemicals as well. Whether the suggested health risks actually exist has to be confirmed by further research; the reviewed study certainly does not permit any definite conclusion. The fact that with improvement of working conditions (1973–1977) for 1300 women the incidence of disturbed menstruation decreased by a factor of 2, and that of

Table 26. Adverse effects on the reproductive system in female workers exposed to benzene in the rubber industry (Beskrovnaia et al. 1979)

Effect	Exposed < 5 yr		Controls				Exposed > 5 yr		Controls			
	n	%	*n*	%	RR	*P*	*n*	%	*n*	%	RR	*P*
Inflammation	126	8.9	41	12.5			291	8.1	58	10.8		
Uterine tumors	64	4.5	27	8.2			133	3.7	20	3.7		n. s.
Disturbed menstruation	128	9.3	16	5.2	1.8	<0.005	318	11.0	20	4.6	2.4	<0.01
– Amennorrhea – Oligomenorrhea	72	5.2	12	3.9		n. s.	117	4.1	16	3.7		n. s.
– Polymenorrhea	56	4.1	4	1.3	3.1	<0.05	201	6.9	4	0.9	7.7	<0.001
Infertility	42	4.7	7	3.9		n. s.	101	4.5	14	4.1		n. s.
Premature delivery	107	12.6	13	6.6		<0.01	69	3.2	10	3.1		n. s.
Total	1422		327				3574		439			

premature delivery by a factor of 3, might point to a relation with working conditions; however, details were not presented.

Volkova (USSR, 1976) also reported an increased prevalence of disturbed menstruation in 65 female workers (47%; controls 10%) in a plant where polychloroprene latex gloves were manufactured. There was exposure to 3–7 mg *chloroprene*/m^3 in the vulcanizing department, to 5–8 mg/m^3 in the sorting department, and to 1–4 mg/m^3 in the packaging department. Data on age and parity were not reported, so the study provides little information.

Muklametova and Vozovaja (USSR, 1972) suggested a relationship between exposure to benzene (< 10 mg/m^3) and *chlorinated hydrocarbon solvents* (mainly *dichloromethane* and *dichloroethane*, 1.2 to 2.4 times the USSR MAC) and the prevalence of gynecological diseases. They compared 360 women exposed to glues with 616 nonexposed women; 79% were 20–40 years old (there was no comparison of age distribution, parity, or life style). No further details are presented on the prevalence of specified diseases. The data reported give little information.

16.1.3 To Pregnancy and Offspring

Kolosova (USSR, 1974) examined the physical development of 468 neonates of mothers (E) who worked in the rubber industry between 1967 and 1972; 165 neonates of mothers working in the machine shop served as controls (C). Group E was divided into four subgroups: E_1 pressing, E_2 glueing, E_3 laboratory work, E_4 technical staff. No data were presented on age, parity, level of education, or life style (e. g., smoking). There was direct exposure to *chloroprene*, *nitril*, *acrylic acids*, *styrene*, *benzene*, and *ethyl acetate;* the intensity of exposure was not reported. The mothers of group C worked in a department which was in open contact with those of group E. The data are summarized in Table 27. The average length and weight at birth was lower in E_1, E_2, and E_3 compared with E_4 and C ($P < 0.05$). There was no relation to duration of exposure (age?) and the sex-ratio was not affected. The author also mentioned that with the highest exposure level the prevalence of neonates with a weight ≤ 2500 g was increased; however, according to the table the lowest birth weight was about 2500. The data reported were inconclusive and not very informative.

Table 27. Physical development of neonates of women working in the rubber industry, and of controls (Kolosova 1974)

Group	Number of neonates	Average length at birth (cm ± S. E.)	Average weight at birth (g ± S. E.)[a]	With birth weight (%)		
				2505–3200 g	3201–3900 g	3901–4600 g
E_1	86	50.9 ± 0.2	3350 ± 50	39.5	53.7	5.8
E_2	80	51.4 ± 0.2	3520 ± 50	27	48	25
E_3	106	51.2 ± 0.1	3415 ± 40	34	56.7	9.3
E_4	196	51.7 ± 0.1	3545 ± 30	25.4	54.8	19.8
C	165	51.5 ± 0.1	3525 ± 30	25.1	57.9	17

[a] The data suggest that measurement of body weight was approximative

The IARC (1982) quoted a not yet published study by Hemminki et al. (Finland),[1] in which data on hospitalized patients with spontaneous abortions were analyzed in conjunction with membership files of the Union of Rubber and Leather Workers (about 10 000 women), and records of a rubber factory (about 1600 women). The numbers of spontaneous abortions per 100 pregnancies (rate) and per 100 births (ratio) were slightly increased for female union members compared with the total Finnish population. Moreover, the number of age-standardized pregnancies was higher during union membership than before or after. The frequency of spontaneous abortion was higher among those employed for 3–35 months than among those employed for longer periods of time. In the rubber factory the frequency of spontaneous abortion among the female workers was slightly below that of the community population, but higher in those employed for 3–23 months. Because the two studies resulted in conflicting evidence, no conclusions on an increased risk of spontaneous abortion could be drawn by the IARC.

A few animal studies suggest an adverse effect of exposure to *chloroprene* on offspring. A review by Sanotskii (1976) mentioned a study by Salnikova and Fomenko (1973) of rats exposed to 0.6 and 4 mg/m^3 during pregnancy; at the highest concentration fetal death increased ($P<0.001$) and birth weight was lower ($P<0.05$). Salnikova and Fomenko (1975) observed an increased incidence of congenital malformation (cerebral hernia and hydrocephalus) in the offspring of rats exposed for 2 days during pregnancy to 4 mg chloroprene/m^3; the effect threshold was estimated to be 0.15 mg/m^3, which corresponds to one-tenth of the threshold for induction of chronic toxicity in adult animals. The NIOSH (1977), however, quoted a study by Culik et al. (1976), which showed malformation of the sternum in offspring of rats exposed to 0.8, 8.6, or 22.7 ppm, 4 h per day. The number of malformations was small; if the group exposed to 22.7 ppm (~ 100 mg/m^3) is compared with the control group, a P value of 0.056 can be calculated. No effect on fetal death was observed, which does not support the data reported by Salnikova and Fomenko (1973). Length and weight of the offspring was increased at the highest dose level. Both the NIOSH (1977) and Sanotskii (1976) emphasized the adverse effect of chloroprene exposure on male fertility. The effects on the offspring at about 25 ppm (~ 100 mg/m^3), 4 h per day may indicate an increased risk for women at exposure levels exceeding the TLV of 10 ppm.

16.1.4 Through Lactation

Novikov et al. (USSR, 1979) observed a decrease in production of breast milk in 23.8% of 288 lactating women employed in the rubber industry, as against 6.7% of 44 controls. Milk production decreased particularly in those employed in the vulcanization department, by 32.5%, as against 15.8%–21.3% in those working in other departments ($P<0.05$; the number of women was not given). Production decreased with increasing duration of exposure; however, the effects of age and parity were not accounted for. In all milk samples of 71 exposed female workers *benzene* was detected (500–600 µg/liter) at levels 12%–18% higher than those in blood; it was not found in samples from controls. Some babies refused suckling, probably because of poor taste (see also solvents, Chap. 2 and carbon disulfide, Chap. 3). In 22 exposed, lactating women the level of serotonine in

1 see also chapter 19

blood was decreased in comparison with that in 23 nonexposed controls; because serotonine determines the secretion of prolactin, which regulates milk production, the authors suggested that the effect on milk production had an endrocine origin. However, this study did not provide data on exposure intensity, time of exposure in relation to weeks of pregnancy, or to lactation, age, obstetric history, and life style.

Muklametova and Vozovaja (USSR, 1972) measured 0.074 ± 0.046 mg/liter chlorinated hydrocarbon solvents in breast milk, but 17 h after exposure the solvents could not be detected.

The NIOSH (1977) quoted studies by Vanuni (USSR, 1973, 1974) on the protein content of breast milk in four groups of lactating women who were either working in a rubber plant (with exposure to chloroprene) or living at various distances from the plant. The data are presented in Table 28. This study suggests an exposure-response relationship, but there may have been confounding factors: at greater distance from the plant the environment (agriculture), nutrition, and time available for lactation may have been more favorable. In group I the protein concentrations (expressed as percentage of control levels) were decreased: cysteine, 90% ($P < 0.05$); lysine, 66.3% ($P < 0.001$); arginine, 58.8% ($P < 0.001$); valine plus methionine, 75.7% ($P < 0.001$); leucine plus isoleucine, 93% ($P < 0.05$). The mean age of those in the exposed groups was 25.94 ± 0.34 years, the duration of exposure 4.07 ± 0.47 years. According to the author, chloroprene might decrease the production of breast milk.

16.2 Discussion and Conclusions

Many studies reviewed were of poor design, and the evidence is not conclusive. Too easily, specific agents were suggested as playing causative roles; qualitative and quantitative data on exposure (to many agents) usually were not presented. There is a great need for studies on the adverse effects of (combined) exposure to various chemicals used in the rubber industry.

An increased (1.2–2 times) internal exposure to mutagens by female workers in comparison with male workers has been suggested in one study, due perhaps to increased dermal absorption. No health effects were studied. Further research is needed.

Two studies suggest an increased relative mortality for female workers compared with male workers, but the data available do not permit a definite conclusion.

All studies which suggest an increased prevalence of gynecological diseases are deficient in several ways; they may provide weak evidence of an increased risk of

Table 28. Protein content of breast milk in relation to chloroprene exposure (Vanuni 1973, 1974)

Group	*n*	Protein concentration (mg/100 ml)	*P*
I (plant)	30	964 ± 9	< 0.001
II (at 500 m)	30	1049 ± 15	< 0.001
III (at 1500 m)	30	1074 ± 24	< 0.01
IV (at 3000 m)	30	1140 ± 24	< 0.001
Control I	25	1321 ± 22	
Control II	25	1289 ± 17	

menstrual disturbance. The suggested evidence of an increased risk of uterine cancer is not conclusive.

The evidence of increased risks of less-than-normal length and weight at birth, and of malformation and spontaneous abortion is inconclusive. The animal data may indicate a risk in exposure to chloroprene at a TLV of 45 mg/m^3 (10 ppm); further study is needed.

Various chemicals used in the rubber industry also appear in breast milk which some infants refused. No data on the health of the infants have been presented.

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17 Beauticians — Hairdressers

In several countries beauty and/or hairdressing shops employ mainly women. The work may involve exposure to many chemicals, often in combination. Guidotti et al. (1982) presented an extensive list of shampoos, dyes, conditioners, permanent-wave solutions, polish removers, nail polishes, makeups, hair sprays, and artificial nails, each of these in turn containing different chemical compounds. Beauticians/hairdressers may also be exposed both occupationally and as consumers.

17.1 Health Risks

17.1.1 Different for Women than for Men, or Studied Mainly in Women

17.1.1.1 Mutagenicity

Kirkland et al. (United Kingdom, 1978) examined the relationship between exposure to hair dyes and the prevalence of chromosomal abnormalities. They sent a questionnaire to all hairdressing establishments in Central London and Surrey; less than 3% responded. The authors subsequently compared 71 hair dyers with 36 controls (manicurists, receptionists). Data were collected on smoking habits, alcohol consumption, use of drugs, infections, medical history, vaccinations, exposure to X-rays, frequency and duration of application of hair dyes, types of dyes applied, use of protective gloves. Blood was taken for lymphocyte cultures. No difference in the prevalence and type of chromosomal abnormalities was established between the groups, but there was an increased RR for chromatid gaps in female hairdressers (RR = 2.3, $P < 0.02$) and a decreased RR for chromatid breaks in male hairdressers (RR = 0.7, $P < 0.05$). No exposure-response relationship was observed. The authors also compared male and female subjects who dyed their own hair with those who did not. A difference was observed between male consumers ($n = 10$) and nonconsumers ($n = 17$) for gaps (RR = 6.5, $P < 0.01$) and between both groups of women ($n = 16$ and 19) for breaks (RR = 1.7, $P < 0.05$). No relationships existed with smoking habits and use of oral contraceptives, whereas a relationship was established with exposure to X-rays and a few (viral) infections. The authors explained the absence of excess chromosomal abnormalities in occupationally exposed subjects, and the presence in personally exposed subjects as follows: During work the workers used protective gloves, whereas in dying their own hair they applied dyes with bare hands; absorption is probably higher through scalp skin than through palmar skin. However, the authors did not correct for a relationship between occupational and personal exposure, which might have had a confounding effect. In addition, differences in age were not taken into account.

According to Burnett et al. (USA, 1979), the presence of chromosomal gaps and breaks in lymphocytes alone does not indicate a mutagenic effect on male/female gametocytes. They carried out mutagenicity tests on the urine of female subjects who personally used dark-colored hair dyes (Clairol): no effect was observed when comparing the mutagenicity of morning urine (i. e., before application) with that of urine 24 h after application.

17.1.1.2 Cancer

Because several hair dyes proved to be mutagenic in in vitro tests, Garfinkel et al. (USA, 1977) carried out a case-control study. Cases were all female cancer deaths ($n = 3460$) reported in Alameda County, California (1958–1962); controls were 1000 female noncancer deaths from the same computer register, matched for age and race. Among the cancer cases were 24 beauticians, among the controls, four (RR = 1.73, $P = 0.43$); however, among lung cancer cases ($n = 176$) there were six and among controls four beauticians (RR = 8.8; $P = 0.013$, one-sided). The relationship with lung cancer deaths ($n = 176$) was further studied by carefully selecting 176 cancer deaths not due to lung cancer as controls (same race, about the same age at death (± 2 years), about the same time of death: RR = 6.0; $P = 0.062$, one-sided). Although the evidence is suggestive of a relationship between occupational exposure to hair dyes and an increased risk of lung cancer, further confirmation appears to be necessary because smoking habits were not known. Menck et al. (USA, 1977) examined the risk of lung cancer death for female beauticians in comparison with the risk for women otherwise employed. Among 22 792 women who died in Los Angeles between 1972 and 1975, 135 had worked as beauticians; 20 died of lung cancer. The standard incidence ratio (SIR) for lung cancer was about twice ($P < 0.05$) that expected. In a case-control study of 199 lung cancer patients there were six who had been beauticians, compared with six of 187 controls (RR = 0.94). For only two other "female" jobs were increased SIRs observed: waitresses and assemblers. Smoking habits were not taken into account. The SIR is regarded as less sensitive than the SMR. Both studies may serve as a signal for a slightly increased risk, but further confirmation is necessary.

Clemessen (1981) critically reviewed the epidemiological studies on the possible human carcinogenicity of hair dyes, covering cancer of the bladder, the lung, the larynx, and the breast in special studies, and cancer mortality in general statistical surveys done in the United States and the United Kingdom. Some studies reported an increased risk, but others did not confirm it. Clemessen concluded that most samples studied were too small to allow conclusions; moreover, they usually did not take into account duration and/or intensity of exposure, lag time, or the influence of life-style factors such as tobacco consumption. Therefore, according to this author, no evidence has been produced of any carcinogenic effect from hair dyes, either among the occupations or among customers. Recently, in a hypothesis-generating study, Guidotti et al. (1982) analyzed a population-based cancer registry (Los Angeles County, 1972–1978, subjects 20–65 years of age); the age-adjusted expected number was derived by determining the proportion of all organs accounted for according to the tumor in question, all occupations or industries except the occupation/industry of interest, giving the proportional incidence ratio (PIR)[1].

[1] Observed: for occupation or industry of interest; expected: for all other occupations or industries

Female cosmetologists, hairdressers, and manicurists provided eight of 286 cases of multiple myelomas, as against 1.71 expected (PIR = 4.67); for men the PIR was 3.47. A previous study in Washington State (1950–1971) had also indicated an excess rate among male barbers/hairdressers. This observation also needs further confirmation.

17.1.1.3 Impaired Pulmonary Function

In a study of 17 male valunteers (Valic et al. (1974) and Zuskin et al. (1974, available as summary) observed an adverse effect on various parameters of pulmonary function after 2-min exposure to hair sprays (or their components); recovery took place after about 1 h. This led to a study of 95 female hairdressers and 127 saleswomen (controls) in Yugoslavia; the ventilatory capacity was measured before and after work: FEV_1 ($P < 0.01$), $V_{max}50\%$ VC (n.s.), and $V_{max}75\%$ VC (n.s.) were decreased; the relative decrease of V_{max} 50% or 75% was larger than that of FEV_1. The smaller airways appeared to be particularly affected. This study indicated an effect in both male and female hairdressers, but did not suggest any sex-dependent difference in susceptibility. Zuskin and Bouhuys (1978) also exposed seven women and two men (nonsmokers, 20–27 years of age) for 1 min to six hair sprays which differed in the concentrations of *trichlorofluoromethane*, *dichlorodifluoromethane*, *alcohol*, and *perfume;* a placebo spray served as control. Three of the six hair sprays induced bronchoconstriction ($P = 0.005$); all three contained perfume. This suggested a causative role of perfume more than of the other constituents. In another laboratory study of three men and eight women, aged 22–26 years, Zuskin et al. (1981) again observed an effect on the small airways from exposure to hair sprays: eight of 11 subjects responded with a nonsignificant decrease in MEF_{50} and EF_{50}, and a significant increase in VisoV (volume of isoflow).

Mollet et al. (Belgium, 1981) reviewed the overall literature on pulmonary function impairment among hairdressers (epidemiological and experimental). They concluded that the evidence of adverse effects of hair dyes is still controversial; some studies indicate constriction of the small airways. The controversial evidence might be due to the "healthy workers effect," the variable composition of the inhaled products, and the small number of subjects studied. In several studies no distinction was made between male and female subjects. Some studies reported evidence of thesaurosis (or storage disease), probably as a consequence of hyperstimulation of mononuclear phagocytes. The authors also carried out a study of occupationally exposed volunteers (13 men, 17 women) who inhaled a hair lacquer (co-polymer of *vinyl acetate* and *crotonic acid*, *ethanol*, *methoxyethanol*, *lanolin*, *silicon*, *perfume*, and a *propellant* – F_{11}–F_{23}) for 10 s. The data suggested a slight impairment of pulmonary function in hairdressers due to occupational exposure to hair lacquers; short-term (10 s) exposure had no additional effect on pulmonary function.

17.1.1.4 Skin Diseases

Reichenberger (Federal Republic of Germany, 1972) examined 137 female and 21 male hairdressers suffering from skin diseases: 96 had contact eczema (42 in combination with dyshidrosis), 12 hyperhidrosis, two seborrheic dermatitis, 48 dyshidrosis; the remainder had other skin diseases. Sex-different susceptibility was not studied. Landthaler et al. (Federal Republic of Germany, 1981) compared the results of a standard epicutaneous

allergen text on 73 beauticians/hairdressers with the overall data on 3300 patients. The beauticians/hairdressers had a significantly higher prevalence of positive reactions to *p*-phenylenediamine and diacetazotol (Pellidol), and a nonsignificantly higher prevalence of positive reactions to nickel sulfate, cobalt chloride, *p*-aminodiphenylamine and Peru balsam.

17.1.2 To the Female Reproductive System, Pregnancy, and Offspring

No data have been reported, other than inconclusive evidence of an increased risk of breast cancer (See Sect. 17.1.1.2), and no data have been found on health risks to infants during lactation.

17.2 Discussion and Conclusions

At present, the indication of mutagenic effects of hair dyes in humans is still too weak to be regarded as conclusive. No sex-dependent difference in susceptibility to various chemicals has been established. Because in several countries mainly women are employed as beauticians/cosmetologists, the actual incidence of adverse effects may be higher among female than among male workers.

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Valic F, Zuskin E, Skuric Z, Denick M (1974) Effects of aerosols in common use on the ventilatory lung capacity. I. Change of FEV_1 on exposure to hair sprays (in Serbo-Croatian). Acta Med Jugosl 28: 231–246

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Zuskin E, Shuric Z, Valic F (1974) Effects of aerosols in common use on the ventilatory lung capacity. II: Changes in V (max) 50% VC and V (max) 75% VC on exposure to hair sprays (in Serbo-Croatian). Acta Med Jugosl 28: 247–254 (abstract)

Zuskin E, Loke J, Bouhuys A (1981) Helium-oxygen flow-volume curves in detecting acute response to hair sprays. Int Arch Occup Environ Health 49: 41–44

18 General Discussion and Conclusions

18.1 Limitations of the Review

18.1.1 Partial Coverage

This review is based mainly upon epidemiological studies of adverse effects of exposure to chemicals on *female* workers. In some cases data on environmental exposure were also taken into account; in such situations effects of simultaneous exposure of both parents cannot be excluded: genotoxic effects may occur in spermatocytes and/or oöcytes.

Studies of effects on reproduction where *male* workers were exposed were *not* reviewed, although evidence of adverse effects sometimes existed, e. g., in exposure to anesthetics, dibromochloroethane, hydrocarbons, or vinyl chloride. This review, therefore, covers only a part, albeit probably the largest part, of observed adverse effects on offspring due to *maternal* occupational exposure.

18.1.2 Data on Exposure

Several studies, particularly those on work situations (Chaps. 12–17), did not present data on specific chemical exposures. Many studies covered in Chaps. 2–11 presented only qualitative or semiquantitative data. Moreover, combined exposure often prevailed, which did not always reliably indicate the principal causative chemical. In some cases data on women who smoked were used. Therefore, suggested evidence of adverse effects of a specific chemical agent can only be indirect, and actual relationships with exposure to specific chemicals tend to be missed when there are no valid exposure data.

18.1.3 Animal Experiments

Data from animal experiments have been discussed only as *supporting evidence* when data on human subjects were inconclusive. There is also need of a systematic critical review of animal data. However, many animal data refer only to high dosages; study design too often does not permit the derivation of effect thresholds.

Extrapolation from animals to people is always approximative at best, because: (a) intensity of exposure, mode of administration, and the total experimental situation with animals, including nutrition, may differ widely from that in occupational exposure of people; (b) there are species differences in placental structure — e. g., a six-layer placenta

in the horse versus a mono-layer placenta in rats, with humans (three-layer) in between — which may reflect differences in permeability of the placenta, and consequently in the hazard to offspring; and (c) biotransformation in animals (in adults, placenta, fetus) may qualitatively and/or quantitatively differ from that in people.

Many routine animal experiments do not include data on reproductive effects or examine only one, or at best a few, of the numerous end points of reproduction. In the literature for the period 1967–1980, Koëter (1980) found data on 49 chemicals, studied in subchronic tests (3–6 months, oral administration), which covered both general and reproductive toxicity (fertility, course of pregnancy, effects on offspring), not always studied in the same experiment or even in the same laboratory. Studies of only 37 chemicals allowed comparison of effect thresholds: in 35% thresholds for reproductive toxicity were lower than those for general toxicity, in 31% they were similar, and in the remainder they were higher.

18.1.4 Validity of Studies

Most studies on specific agents did not allow the establishment of exposure-effect/response relationships. Many were deficient in design (e. g., lack of control subjects, presence of confounding factors) and/or provided little information (e. g., few details, small number of subjects) and inadequate data on actual exposure. Many studies did not fulfill the minimal set of requirements for epidemiological studies, considered necessary for setting health-based recommended exposure limits (WHO, 1981). However, overall evidence from poorly designed studies, if more or less consistently pointing in the same direction, cannot be disregarded.

18.1.5 Uninformative Studies

Studies which indicate no increase in risk are not always published. However, for most chemicals appearing in lists of TLVs and MAC values probably no studies on reproductive risks in humans have ever been carried out. Therefore, the *majority of chemicals could not be discussed at al* in this review. There still is a vast terra incognita.

18.2 Specific Conclusions

The evidence discussed in Chaps. 2–17 has been categorized according to the *degree of probability* of the occurrence of detrimental effects at exposure levels about equal to the TLVs of 1982. Category I has five parts, and includes agents appearing on the TLV list for 1982.

1. *Category Ia:* Health risks probably or certainly exist at around the TLV level of exposure (see Table 29)
2. *Category Ib:* Suggestive (but not conclusive) evidence of health risk at TLV level (see Table 30)
3. *Category Ic:* Suggestive (but not conclusive) evidence that *no* extra health hazards exist at TLV level; *no* compound could be classified in Ic

Table 29. Agents presenting probable or certain health risks at TLV levels

Agent	Chapter	TLV-1982	Risks				
			Greater to women	Established only for women	To female reproductive system	To pregnancy and/or offspring	To infant during lactation
Inorganic lead	9	150 $\mu g/m^3$	× ×		×	× ×	×
Cadmium	10	50 $\mu g/m^3$	× ×	× ×		×	

×, Suggestive but not conclusive; × ×, probable or certain

4. Category Id: Health risks probably or even rather certainly do *not* exist around the TLV level; *no* agent could be classified in Id

5. Category Ie: Agents for which neither positive nor negative data have been found on one of the five health risks mentioned in Tables 29 and 30; *all agents* not mentioned in Ia and Ib have to be listed in Ie

Several agents have been discussed in the review, e. g., manganese, antimony, chromium, copper, selenium, organophosphate pesticides, vinyl chloride, acrylates; the data are too limited to categorize these in one of the groups Ia-d.

Category II has three parts, and includes agents or work situations not appearing on the TLV lists for 1982.

1. Category IIa: Suggestive (but not conclusive) evidence of health risks at moderate exposure (see Table 31)

2. Category IIb: Suggestive evidence exists, that there is *no* extra health risk; *no* chemicals/work situations could be listed as such

3. Category IIc: Neither positive nor negative data have been found on the five health risks mentioned; *all agents* for which no TLVs have been established and all work situations not listed in IIa come under IIc.

18.3 Overall Conclusions and Recommendations

The classification presented above leads to the following conclusions:

The TLVs for cadmium and inorganic lead have to be lowered; exposure of female workers at the present TLV levels probably carries extra health risk to the female workers themselves and/or to their offspring.

For all chemicals listed in Ib the present TLVs must be reevaluated. Exposure to chemicals listed in IIa raises concern. There is need for epidemiological and experimental animal studies of exposure-effect response relationships, in order to classify these chemicals correctly in Ia (with the consequence of lowering the TLV) or in Id (probably no extra risk exists).

There is an urgent need to study all agents for which neither positive nor negative evidence of extra health risk to female workers or to their offspring is available.

In view of the suggestive evidence of extra health risks for women exposed in various work situations, much epidemiological and experimental research has to be carried out on health risks from exposure to several chemical compounds in combination.

Table 30. Agents presenting possible risk at TLV levels

Agent	Chapter	TLV-1982	Risks				
			Greater to women	Established only for women	To female reproductive system	To pregnancy and/or offspring	To infant during lactation
Carbon disulfide	3	30 mg/m^3			×	×	
Cyclic chlorinated pesticides	4	1 mg/m^3 (DDT)				×	
		0.25 mg/m^3 (dieldrin)				×	
		0.5 mg/m^3 (HCH)				×	
Polychlorobiphenyls	5	0.5–1 mg/m^3				×	×
Formaldehyde	6	1 ppm-C			×		
Styrene	6	215 mg/m^3			×	×	
Caprolactam	6	20 mg/m^3			×	×	
Carbon monoxide	7	55 mg/m^3				×	
Arsenic	8	200 µg/m^3				×	
All forms of mercury except alkyl Hg	11	50 µg/m^3			×	×	
Alkylmercury	11	10 µg/m^3				×	
Dichloromethane	7	360 mg/m^3				×	
Chloroprene	16	45 mg/m^3				×	

Table 31. Agents/work situations presenting possible health risks at moderate levels of exposure

Agent/work situation	Chapter	Risks				
		Greater for women	Established only for women	To female reproductive system	To pregnancy and/or offspring	To infant during lactation
Organic solvents	2			×	×	
Polybromobiphenyls	5				×	×
Operating room personnel	12			×	×	
Health care personnel	13			×	×	
Pharmaceutical industry	14			×	×	
Chemical industry/laboratories	15				×	
Rubber industry	16			×	×	
Beauticians/hairdressers	17	×				

TLVs/MACs should be based on prevention of adverse effects on reproduction due to both paternal and maternal exposure; separate TLVs/MACs should not be established for exposure of men and women.

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19 Appendix: Recent Data

After submission of the manuscript the authors received relevant recent reviews and papers (up to September 1983) on health risks to female workers exposed to chemical agents. A short indicative summary is presented without critical discussion of the data.

19.1 Reviews

19.1.1 Reports, Books

Council on Environmental Quality (1981) Chemical hazards to human reproduction; prepared by Clements Associates Inc. National Technical Information Service, US Dept of Commerce, Springfield, USA; about 200 pp. Data on reproductive risks examined in animals and male and female human subjects; with an extensive bibliography. Recently published as a book. Nibet JCT, Karch NM (1983), Clement Assoc. Inc. Park Ridge New York

Barlow SM, Sullivan FM (1982) Reproductive hazards of industrial chemicals. Academic, London, 610 pp. A systematic survey of reproductive hazards of 50 industrial chemicals of general interest: animal and human data on exposure of men and/or women.

Mattison DR, ed (1983) Reproductive toxicology: Proceedings of Journal Symposium on Reproductive Toxicology, Am J Ind Med 4, nos. 1/2, 396 pp. Compilation of several papers on reproductive biology and toxicology and data from epidemiological studies.

Clarkson ThW, Nordberg GF, Sager PR (1983) Reproductive and developmental toxicity of metals. Plenum Press New York.

19.1.2 Review Papers

Kalter H, Warkany J (1983) Congenital malformations: etiologic factors and their role in prevention. N Engl J Med 308: 424–431 and 491–497

Kameyama Y (1983) Factors in manifestation of developmental abnormalities of the central nervous system by environmental agents. J Toxicol Sci 8: 91–103

19.1.3 Papers on Specific Chemicals/Occupations, Human Data

Angele N, Lavery JP (1982) The relationship of blood lead levels to obstetric outcome. Am J Obstet Gynecol 142: 40–46.

The concentration of lead in blood (PbB) was measured in 635 specimens of cord blood; no relationship was found between the PbB level and premature rupture of fetal membranes, preterm delivery, preeclampsia or meconium staining.

Bercovici B, Wassermann M, Cucos S, Ron M, Wassermann D, Pines A (1983) Serum levels of polychlorinated biphenyls and some organochlorine insecticides in women with recent and former missed abortions. Environ Res 30: 169–174.

PCBs, DDT isomers and metabolites, γ-HCH, dieldrin and hepatachlorepoxide were assessed in the serum of 17 women with recent missed abortions, seven women who had experienced abortions in the past, and seven women with normal pregnancy. The mean PCB level was higher in the first two groups than in the controls.

Copius Peereboom-Stegeman JHJ, van der Velde WJ, Dessing JWM (1983) Influence of cadmium on placental structure. Exotox Environ Safety 7: 79–86.

Description of findings discussed already in Chap. 10.

Eyster JT, Humphrey HEB, Kimbrough RD (1983) Partitioning of polybrominated biphenyls (PBBs) in serum, adipose tissue, breast milk, placenta, cord blood, biliary fluid, and feces. Arch Environ Health 38: 47–53.

A correlation between serum and adipose PBB levels was observed. Pregnant and nonpregnant women and male chemical workers had similar serum-to-adipose concentration ratios, which ranged from 1 : 140 to 1 : 260. Potential exposure to the fetus and newborn was demonstrated. Cord blood contained one-tenth of the concentration in maternal serum. Human milk contained PBBs at 107 to 119 times the quantity found in maternal serum.

Ferstandig LL (1982) Trace concentrations of anesthetic gases. Acta Anaesthesiol Scand [Suppl] 75: 38–43.

A review of recent literature. According to the author the acceptable available evidence requires a negative answer to a causal relationship between exposure and reproductive problems.

Grufferman S, Wang HH, DeLong ER, Kimm SIJS, Delzell ES, Falletta JM (1982) Environmental factors in the etiology of rhabdomyosarcoma in childhood. JNCI 68: 107–113.

In a case-control study childhood rhabdomyosarcoma was associated with — among other causes — exposure to chemicals (RR = 3.7), mothers' age, and low socioeconomic status.

Hemminki K, Niemi ML (1982) Community study of spontaneous abortions: relation to occupation and air pollution by sulfur dioxide, hydrogen sulfide, and carbon disulfide. Int Arch Occup Environ Health 51: 55–63.

Spontaneous abortions were analyzed in a Finnish industrial community. Women employed in rayon textile and paper products jobs had an increased rate of spontaneous abortions; however, in material stratified for age, parity, and socioeconomic class no evidence was found for the association of the level of SO_2 or CS_2 with an increased risk. A nonsignificant relation was observed in exposure to H_2S exceeding 4 $\mu g/m^3$.

Hemminki K, Mutanen P, Saloniemi I, Niemi S-L, Vainio H (1982) Spontaneous abortion in hospital staff engaged in sterilizing instruments with chemical agents. Br Med J 285: 1461–1462.

The study included all the sterilizing staff in Finnish hospitals in 1980. The frequency of spontaneous abortion was increased when women were exposed during pregnancy to ethyleneoxide, but not with exposure to glutaraldehyde or formaldehyde.

Hemminki K, Niemi M-J, Kyyrönen P, Kilpikari I, Vainio H (1983) Spontaneous abortions and reproductive selection mechanisms in the rubber and leather industry in Finland. Br J Ind Med 40: 81–86.

Employees of a rubber factory had slightly fewer spontaneous abortions than the community population. Women employed for 3–23 months in the rubber factory had appreciably higher frequencies of spontaneous abortions than those employed for longer periods. This suggests selection mechanisms with some analogies to the "healthy workers effect."

Kolmodin-Hedman B, Hedström L, Grönqvist B (1982) Menopausal age and spontaneous abortion of women working in a Swedish steelworks. Scand J Soc Med 10: 17–22.

Menstrual irregularity was not found to any higher degree in the industrially exposed groups. A tendency to increased frequency of spontaneous abortion among workers in the metallurgical area was found, but can probably be explained by such factors as age and smoking habits.

Kuhnert PM, Kuhnert BR, Bottoms SF, Erhard P (1982) Cadmium levels in maternal blood, fetal cord blood, and placental tissues of pregnant women who smoke. Am J Obstet Gynecol 142: 1021–1025.

The percentage increase of Cd due to smoking was 32% in the placenta and 59% in maternal blood. The fetuses of pregnant women who smoked apparently received very little additional exposure to Cd.

Kurppa K, Holmberg PC, Hernberg S, Rantala K, Riala R, Nurminen T (1983) Screening for occupational exposure and congenital malformations. Scand J Work Environ Health 9: 89–93.

An analysis of case-control pairs of 289 defects of the central nervous system, 421 orofacial clefts, 200 selected structural malformations of the skeleton, and 137 selected cardiovascular effects showed an association between exposure to organic solvents and defects of the central nervous system in the initial 2-year material, but this was no longer detectable during the following 3-year period.

Mangurten HH, Kaye CI (1982) Neonatal bromism secondary to maternal exposure in a photographic laboratory. J Pediatrics 100: 596–598. Description of a case report.

Saxena MC, Siddiqui MKJ (1983) A comparison of organochlorine insecticide contents in specimens of maternal blood, placenta and umbilical cord blood from stillborn and liveborn cases. J Toxicol Environ Health 11: 71–79.

HCH (α, β and γ), aldrin, *p. p*'DDT, *p. p*'DDD and *p. p*'-DDE were quantified in various biological media. The levels of aldrin and *p. p*'DDT in all the three specimens of stillbirth cases differed from the controls. A correlation was found between maternal blood and placenta for total HCH, γ-HCH, and p. p'DDT, and between maternal blood and umbilical cord blood for aldrin, *p. p*'DDT, and total DDT.

Shiojima S, Hasegawa K, Ishimara N, Ikeda M (1983) Subclinical increases in serum transaminase activities among female workers exposed to toluene at sub-OEL levels. Ind Health 21: 123–126.

The present findings suggest possible hepatotoxicity in female workers.

Stemhagen A, Slade J, Altman R, Bill J (1983) Occupational risk factors and liver cancer. Am J Epidemiol 117: 443–454.

In a case-control study an increased risk of liver cancer was associated with women employed as cleaning-service workers; dose-response trends by level of alcohol consumption were found.

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