Chapter 4

Evidence for workplace Hazards to Reproductive Function

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Chapter 4

Evidence for workplace Hazards to Reproductive Function

INTRODUCTION

Two elements are required to produce a workplace reproductive hazard. First, a male or female worker, or developing embryo or fetus, must be exposed to a hazardous agent found in the work environment. Second, this exposure must compromise some aspect of male or female reproductive function, or embryonic or fetal growth and development.

This chapter reviews selected chemical, physical, and biological agents that are real or suspected workplace hazards to reproductive functional These agents were chosen for review in consultation with the Advisory Panel for this report. Throughout the text, which is not a full assessment of the hazards of these agents, but rather a sumary of the evidence or lack of evidence for effects of particular agents, the focus is on available human data. These data have been integrated with animal data in order to further define the site and mechanism of action of particular adverse reproductive effects. It is important to note, however, that the identification of an agent as a suspected reproductive or developmental hazard hinges not only on its mechanism of action and evidence of harmful effects in animal and/or human data, but also on the level and kind of exposure the agent presents to humans. It is also important to point out that the National Institute for Occupational Safety and Health (NIOSH) has identified a number of occupational chemicals as reproductive hazards. These chemicals include 1,3-butadiene, carbaryl, carbon disulfide, chloroprene, dinitrotoluene, epichloro - hydrin, ethylene oxide, ethylene thiourea, glycidyl ethers, glycol ethers, monohalomethanes, and polychlorinated biphenyls (PCBS).

IA number of excellent reviews of the effects of chemical and physical hazards on reproductive function have recently been published (2661,69,215,226,260,372,373,4 1I).

EFFECTS OF WORKPLACE CHEMICALS ON REPRODUCTIVE FUNCTION

Of the thousands of chemicals used in the workplace, relatively few have been examined for their effects on reproductive function. A 1982 review of the reproductive hazards of industrial chemicals that explored the effects of 48 compounds (26) found significant gaps in information on reproductive toxicity in either experimental animals or humans for all but one of these chemicals. These gaps in knowledge make estimation of human hazard difficult, and prediction of human risk virtually impossible. Of the 48 chemicals reviewed, only a small number of those known to produce adverse reproductive effects have been classified by both endpoint and mechanism of the effect. Although reproductive toxicity has been suggested for a number of the chemicals that have been studied, many of these finings are in dispute. Moreover, some chemicals have been investigated in one sex, but not in the other. For these reasons, existing knowledge of workplace chemical hazards to reproductive function is incomplete and of uneven quality. A major conclusion of every symposium on the reproductive toxicity of suspected hazards

over the past several years has been the absolute necessity for increased knowledge through additional experimental study.

Discrepancies among results of epidemiological studies of reproductive toxicity appear to arise from four major factors (see chapter 6):*

1. Differences in levels of exposure of the study groups: Exposure levels or biological indicators of exposure are frequently unknown, or not presented in research reports. In some studies, the precise identity of the chemical(s) is either not known or not revealed.
2. Differences in accuracy and sensitivity in detecting reproductive outcomes The ability to detect and measure many of the endpoints of reproductive function (see chapters 5 and 6) varies from laboratory to laboratory and from country to country. For example, one laboratory may use sensitive measures of sperm motility employing video systems while another may employ the older, traditional method of watching sperm under the microscope.
3. Definition of control groups The use of inappropriate controls can skew the findings of a study. For example, an investigator may compare groups composed of small numbers of participants. This can result in a finding of no adverse reproductive effects of occupational exposure. Using control groups that are not well-defined or using historical controls drawn from studies of populations with different sociodemographic characteristics may bias the results in an unpredictable direction.
4. Confounding variables: Failure to control for variables with the potential to modify observed effects can confound the interpretation of results. Control of these confounding variables is essential because lifestyle, ethnic, or disease-related factors may have adverse effects on male or female reproduction or fetal development (see chapter 6).

*The basic overall scarcity of data on the reproductive health effects of many of the substances summarized has led to the inclusion of research findings whose methodology or validity cannot always be determined. Gaps in information and instances of single studies for particular agents are noted where they occur.

It is important to note that a majority, perhaps two-thirds, of the studies on workplace chemical hazards to reproductive function are not conducted in the United States. Most of the epidemiological studies are conducted in the Scandinavian countries and in the Soviet Union, where access to workers and workplace exposure data is less difficult than in the United States. Further, the United States has relatively few large-scale, central data bases from which both occupational and reproductive data can be retrieved. In contrast, Sweden and Finland maintain central data registries that cross-link occupational history, pregnancy data, birth certificates, medical records, and death certificates by means of an individual identification number. Until U.S. scientists have better access to occupational and health data, most conclusions regarding occupational reproductive hazards will necessarily be based in large part on studies conducted in other countries.

Reproductive toxins are classified by: 1) the site(s) or endpoint(s) of adverse effect in the reproductive system, and 2) mechanism(s) of action (see chapter 3). The site of effect defines where the compound acts to interrupt reproduction (e.g., the hypothalamus, pituitary, gonad, accessory organs, placenta, or embryo/fetus). A compound may be a reproductive toxin in the male but not in the female, or the fetus alone may be susceptible. It is important to note that there is no biological basis for assuming that either the embryo/fetus or the female is more susceptible than the male. Only careful experimental studies and reproductive health surveillance of workers exposed to suspected compounds will provide definition of the range of human susceptibility to reproductive toxins

The mechanism of action of a reproductive toxin is important because it defines how the compound produces its adverse reproductive effect (226). The mechanisms of action of reproductive toxins can be classified as direct or indirect. Direct-acting reproductive toxins do not need to be processed in the body to be hazardous. A direct-acting reproductive toxin need only be delivered to its site of action to produce an adverse reproductive effect. An indirect-acting reproductive toxin, by contrast, requires some chemical change in the body before it can produce an adverse reproductive effect (see chapter 3).

Metals

The adverse reproductive effects of lead, mercury, cadmium, arsenic, lithium, antimony, boron, and manganese have been described in both humans and experimental animals. Other metals, such as chromium, copper, nickel, and selenium produce adverse reproductive effects in animals but have not been examined in humans. Only a fraction of the studies assessing the effects of metals on human reproductive function are framed in the context of occupational exposure to a single metal; most workplace exposures are to complex mixtures of several metals and other xenobiotics (a biologically foreign compound).

Many studies are based on workers exposed to metals while employed in metallurgical or smelting industries, These workers are often exposed to a variety of metals, as well as to other substances that may be reproductive toxins (e.g., hydrogen sulfide, sulfur dioxide). Their occupational exposure may also include such confounding exposures as heat, vibration, or dust. It is therefore difficult to attribute specific observed toxic effects in a workplace study to any single hazard, and difficult to define interactions that may increase or diminish the reproductive toxicity of any single agent.

Unlike the case of some chemical exposures, there are biological indicators of metal exposure, such as metal levels in blood, urine, and hair. In fact, the diversity of indicators often makes it difficult to reach a consensus on the toxic level for a particular indicator. For this reason, major research efforts are focused on the identification of sensitive tissues and techniques for monitoring acute and chronic exposure to metals. For some metals, such as methylmercury, there is no agreement among researchers even as to units of measurement; for others, methodology for measurement in biological samples is problematic. In hair analysis, for example, metals adhering to the outer surface of hair must be removed prior to analysis for metal content.

Metals classified by N1OSH as occupational carcinogens include arsenic, beryllium, cadmium, chromium, and inorganic and organic nickel (243). In addition, some metals (e.g., mercury, arsenic) have been found to be mutagenic to human somatic cells. This creates concern for mutagenicity to germ cells; i.e., spermatocytes and oocytes. Other metals (e.g., lead, cadmium) are capable of disrupting the cellular mechanisms involved in mitosis and meiosis, and may, by this mechanism, be toxic to germ cells.

Lead

Lead exists in the environment as a widespread contaminant in both inorganic and organic forms. Approximately 90 percent of the lead entering the atmosphere comes from the combustion of leaded gasolines. Blood levels of lead have been shown to vary directly with the content of lead allowed in gasoline (12).

Lead is found in lead azides, lead salts, tetraethyl lead, tetramethyl lead, metallic lead, tetraethylplumbane, and tetramethylplumbane. Workers who are exposed to lead include smelters, battery manufacturers, painters, typesetters, and stained glass artists. Workers may also be exposed to lead in the manufacture of paint, ink, ceramics, pottery, ammunition, textiles, and leaded gasoline.

Lead has been recognized as a reproductive hazard since the days of ancient Rome (125). Indeed, it has been suggested that lead in drinking vessels produced enough toxicity to result in the declining population of the upper class. Lead has also been used as a spermicide and as an abortifacient. Provisions for the protection of reproductive health in adults and the health of the developing embryo/fetus in the Occupational Safety and Health Administration's (OSHA) lead standard are discussed in chapter 7.

Male.—A 1975 study reported dose-related disturbances in sperm-related factors in 150 lead workers (194). A number of studies of the effect of lead on various aspects of male reproductive function were published in the 1970s (259)300, 37'!3). One small case control study reported that 3 of 14 men had subnormal sperm counts, one patient had azoospermia, and another had low sperm motility following exposure to tetraethyl lead (379). Another study reported sexual disturbances in 66 men aged 24 to 49 who had been exposed to ethyl benzene containing tetraethyl lead. The major complaints were poor or absent erection, premature ejaculation, and reduced or-

gasm. Semen volume was reduced in 23 of the exposed men. A 1985 study reported no effect of lead exposure on sperm volume or motility compared with controls. Exposure ranged from 1 to 24 years in men aged 27 to 57 (347). A 1983 study of men exposed to lead found lower chromosome stability and lowered secretory function and accessory genital glands, but no difference in sperm number, motility, morphology, or semen volume (395).

There is substantial evidence of excessive rates of abnormal pregnancies among wives of lead workers. An 1860 study of 32 pregnancies in 7 women who were married to lead workers (280) recorded 11 abortions and 1 stillbirth; 8 of the 20 liveborn children died within their first 12 months. A 1985 review of similar data (374) also suggests that paternal exposure to lead alters reproductive outcome in the female. The traditional view that lead exposure leads to male reproductive problems has been supported by studies in the lead-related industries. Additional collection and analysis of data on lead exposure are needed, however, to identify other potential sites of toxicity in the reproductive system.

A 1983 review of the effect of lead on the reproductive capacity of male mammals (209) concludes that the effect of lead on reproductive function may be generally cytotoxic rather than mutagenic. The study also points out that animal data do not support the findings on human fertility. This disparity, which may reflect differences in animal/human metabolism, illustrates the difficulty in extrapolating human effects from animal studies.

Female.—Female exposure to lead has been associated with amenorrhea and other menstrual disorders, infertility, spontaneous abortion, stillbirth, and neonatal deaths (122,207,273,304,305) for more than a century and lead was at one time used to induce abortion (122). Although exposure to lead in earlier times was probably greater than it is today (46), occupational lead exposure of men and women still appears to pose a threat to normal reproductive function.

A recent review of the effects of various forms of lead on female reproduction in experimental animals noted decreased fertility, delayed vaginal opening, ovarian atrophy, and altered ovarian cyclicity (225). The sites of action include the hypothalamus, pituitary, ovaries, and uterus.

Pregnancy. -Exposure to a mixture of metals, including lead, has been associated with an increased rate of spontaneous abortion (264)265). Exposure to lead is reported to be detrimental to implantation and embryonic survival [226) and lead chloride can interfere with implantation (394). It has also been suggested that prenatal exposure to lead can result in spontaneous abortion (146). Reviews of the effects of various forms of lead on the pregnant animals (26,225, 246,394) found no teratogenic effect of tetraethyl lead, tetramethyl lead, and trimethyl lead, when given at doses below those that cause maternal toxicity.

Prenatal exposure to lead, even in small amounts, may have an effect on central nervous system development (255)302). A recent review delineates the specific pre- and post-natal periods during which particular developmental effects of lead exposure occur in the embryo/fetus (179).

Boron

Boron is used for weatherproofing wood and fireproofing fabrics. It is used in manufacturing cements, crockery, porcelain, enamels, glass, leather, carpets, hats, soaps, and artificial gems. It is also used in the manufacture of cosmetics, in printing and dyeing processes, in painting and photography, and for impregnating electric condensers and hardening steel. Boron, in the form of boric acid and berates, is widespread in the environment. Although boron is usually considered a chronic poison, effects are unlikely to be seen at an intake of less than 100 mg of boron per day.

Male.—Soviet studies (which do not describe methodology, selection of control groups, etc.) report oligospermia and decreased libido in men working in factories that produced boric acid (206,348) and in men living in communities with high boron concentrations in well water (190,206). No studies of males are available from the United States.

The major adverse reproductive effect of boron appears to be on the testes, as evidenced from studies in the rat and dog (26). Sodium borate and boric acid given orally (117, 350, or 1,170 ppm in the diet) to rats for up to 2 years caused testicular atrophy and sterility in the high-dosage group. No testicular effects were seen at 117 or 350 ppm. In a similar 2-year study of dogs fed 58, 117, or 350 ppm of boric acid, no changes were seen in histology, or in relative or absolute organ weights. High doses of 1,170 for 38 weeks caused testicular degeneration, spermatogenic arrest, and atrophy of the lining of the seminiferous tubules in the testes. Two of the dogs were put on a control diet for 25 days, after which testicular weights and spermatogenesis were found to be similar to controls, suggesting possible reversibility of the effects (387).

Female.—A three-generation reproduction study was conducted in male and female rats fed diets containing 117, 350, and 1,170 ppm boron equivalents of sodium borate and boric acid. At the highest dose level both male and female rats were sterile; the males had reduced sperm counts, and there was decreased ovulation in females. Reproduction was not affected at the two lower concentrations of boron in the diet (387).

Pregnancy. —The only studies of developmental effects available for boron involved the effects of boric acid on chick embryos (36). Injection of boric acid into chicken eggs causes growth inhibition, interference with feather growth, and several types of malformations. The relevance of these results to humans is not established, and there appear to be no published data on the effect of boron on human pregnancy. There is thus a marked lack of evidence about its reproductive and developmental effects, especially in humans.

Manganese

Manganese is present in more than 20 different compounds, including complexes with acetate, bromide, chloride, phosphate, and sulphate. It is used in the manufacture of steel, dry-cell batteries, glass, ink, ceramics, paints, rubber, and wood preservatives.

Male.—Chronic manganese poisoning in male miners has been reported to produce impotence, decreased libido, delayed ejaculation, and reduced androgen secretion (26,231,282,317). A 1985 study of 85 male workers from a factory producing manganese salts revealed markedly fewer children born to exposed workers than to nonexposed workers (202).

At doses that had no other toxic effects, there are reports of retarded growth of testes and seminal vesicles (131). The testes and accessory glands in experimental animals appear to be particularly sensitive to manganese (26).

Female.—Although one study reports depressed fertility in female rats exposed in utero (200), a recent review found no evidence of detrimental effects on females of exposure to manganese (26).

Pregnancy .-Manganese ***deficiency*** appears to cause developmental effects in a number of species, but there has been little study of the effects of an excess of manganese. Manganese appears to be harmful to the embryo/fetus only at doses that are near or above those toxic to the dam (mouse, rat, hamster, and rabbit). Postnatal development of the rodent, however, may be adversely affected if manganese is transferred from the mother to the newborns during suckling (26,216). Accumulation of manganese in the brain of the newborns may account for biochemical disturbances in the brain, as well as poor weight gain and postnatal survival.

Mercury

Mercury exists in metallic, inorganic, and organic forms, including inorganic mercury salts and organic mercury, both of which may be produced by natural processes. Humans are most likely to be exposed to these two forms of mercury from environmental contamination. The vapor of metallic mercury is the predominant form in occupational exposures. It is estimated that 40,000 U.S. workers are exposed to this form of mercury in manufacturing (e.g., electrical apparatus, mercury vapor lamps, paint, thermometers) and mining (68). inorganic mercury appears capable of producing reproductive toxicity follow-

ing ingestion, inhalation, or absorption through the skin, although the inorganic forms are less well absorbed.

The methylmercury contained in fish and fish products accounts for the balance of human exposure (68). The best documented exposures to methylmercury have not been in the workplace, but in the home, through the ingestion of contaminated fish (see chapter 2) or seed grain.

Male.—Both organic and inorganic mercury can alter spermatogenesis and decrease fertility in experimental animals (26). Altered libido has been observed in men accidentally exposed to mercury vapor. In experimental animals, organic mercury also accumulates in the central nervous system in regions that are involved in the control of reproduction. This suggests that occupational exposures to metallic, inorganic, or organic mercury may disrupt male reproduction at multiple sites.

Female.—Various forms of mercury accumulate in the ovary of experimental animals; inorganic mercury preferentially accumulates in the granulosa cells surrounding oocytes, while metallic mercury accumulates in the corpus Iuteum (225). Accumulation of mercury in the central nervous system is consistent with the menstrual disturbances observed in women following occupational exposure. Monkeys treated with mercury also show alterations in hypothalamic, pituitary, and ovarian function,

Pregnancy. -Inorganic and organic mercury can cross the placenta and gain access to the fetus in both animals and humans. In experimental animals, metallic mercury and inorganic mercury alter fetal growth, increase fetal mortality, and increase the incidence of congenital malformations. Mercury can also produce biochemical changes in the human placenta. Mercury, used historically in the treatment of syphilis, has also been associated with an increase in spontaneous abortions among women treated during pregnancy. The data on organic mercury also show evidence of developmental effects in both humans and experimental animals (69).

All forms of mercury appear to be reproductive toxins. Sites in the reproductive system that are impaired include the hypothalamus, pituitary, and gonad. Effects include chromosome abnormalities, increased rates of spontaneous abortion, low birth weight, congenital malformation, and abnormal development of the nervous system.

Cadmium

Cadmium is used in industry for corrosion protection, as a plastics stabilizer, for electroplating, and in nickel-cadmium batteries, pigments and paints, soldering liquids, semiconductors, photocells, insecticides, and fungicides. Cadmium is set free during welding. Although under some circumstances occupational exposure is the dominant source of exposure, the major source of cadmium intake is usually food (113). Cadmium occurs naturally in zinc-bearing minerals and in phosphate rocks, which are used to make many fertilizers. Cadmium absorption thus occurs from food, water, and air (339), One pack of cigarettes contains 30 micrograms (pg) of cadmium (78), and smoking may contribute to half of the total body cadmium when occupational exposure and exposure via food are low (113).

Some studies have indicated an increased frequency of chromosomal aberrations following exposure to cadmium while others have not (50, 276,327). The chromosomal damage observed in several studies may be attributable to lead exposure, cadmium exposure, or the synergistic effects of exposure to both metals (31,79), Cadmium is classified as an occupational carcinogen, and may therefore alter the integrity of germ cell DNA in workers.

Male.—The testicular toxicity of cadmium has been conclusively demonstrated in experimental animals (26)188,279,292), The effect appears to result from the direct toxicity of cadmium to testicular capillary lining. Human exposure to cadmium fumes or dust is also associated with testicular toxicity, altered libido, and infertility (26).

Female. -Although cadmium has been demonstrated to accumulate in the ovary of experimental animals, there are no reports of alterations in human female pre-implantation reproduction. Women exposed occupationally to cadmium appear to have normal integrated function of the hypothalamus-pituitary mvarian axis (411).

Pregnancy. -Cadmium impairs implantation and produces placental necrosis in experimental animals. Similar effects on placental vasculature have been reported in women exposed to cadmium. In addition, occupational and environmental exposure to cadmium have been associated with decreased birth weight (69,411). Congenital malformations have been observed in experimental animals following cadmium exposure. However, it is not known whether human exposure is associated with a higher frequency of congenital malformations.

Arsenic

Arsenic occurs in industry largely as a by-product of copper and lead smelting. It occurs naturally in trace amounts in soil, minerals, and some foods. Compounds containing arsenic are used in pesticides, glass, ceramics, paints, dyes, wood preservatives, and leather processing. An estimated 545,000 workers in the United States are potentially exposed to arsenic in metal smelting and in the manufacture and application of pesticides (112).

Male.—Evidence of an adverse effect of arsenic on male reproductive function is inconclusive (316). Workers exposed to arsenic at a smelter in northern Sweden were found to have an increased frequency of chromosomal aberrations when compared with healthy males from a nearby city. Among the affected smelter workers, the groups with higher exposure to arsenic had a greater frequency of chromosomal aberrations. The data also suggested an interaction between smoking and arsenic exposure, although smoking status was not controlled in the analysis (263). An increased frequency of chromosomal aberrations was found in the white blood cells of wine growers exposed to arsenic pesticides (263) and in patients with psoriasis treated with arsenic (53).

Recent studies list several effects of arsenic on reproductive function in mice and pigs, including testicular toxicity, altered sexual behavior, and impaired sperm quality and fertility (26). Effects are seen only at higher levels and the decreases in fertility are probably secondary to abnormal sexual behavior.

Female.—Studies of the effect of arsenic on the female have largely been limited to its carcinogenic potential. No effects on the fertility of female mice in multigeneration studies at doses ranging from 0.025 to 215 mg/kg of diet have been observed (26). Although arsenic has an effect on post-fertilization events, it apparently has no direct effect on the mature reproductive system (226).

Pregnancy.—A 1982 study examined the rate of spontaneous abortion in a Scandinavian community where a metallurgic industry was located (144). The industry produced mostly zinc and cobalt and emitted sulfur dioxide, hydrogen sulfide, arsenic, and to a lesser extent, cadmium and mercury into the environment. Twenty-five percent of the community's men were employed at the metals plant. The wives of workers in the metallurgic industry had a higher rate of spontaneous abortion (11.5) than wives of all industrial workers (9.3 percent). This study also demonstrated that specific male and female occupations may provide increased risk of adverse pregnancy outcome.

Several other studies of female workers in the metallurgy industry in Finland, who were exposed to arsenic as well as sulfur, zinc, cobalt, and copper, were based on women who were members of the Metal workers Union between 1973 and 1976 (141). The rate of spontaneous abortion was found to be higher among the 35,000 metal workers (13.8 percent) than in the general population of Finnish women (10.3 percent). Parity was not factored into the data analysis. A 1983 update of this study that included membership up to 1979 (146) reported no difference in the rate of spontaneous abortion for pregnancies before or after union membership (7.1 percent). Spontaneous abortions were more frequent among smelters (21 percent) than among other union members, but the numbers of workers studied was small (n= 7).

Inorganic arsenic in the pentavalent (arsenate) or trivalent (arsenite) form is fetotoxic and teratogenic to rodents (154,155,156,245). Of the two forms, arsenate has been the most extensively studied, and at doses equally toxic to the mother

produces the highest malformation rate. Arsenite is more toxic than arsenate, however, and thus is teratogenic at lower doses. The inorganic arsenical produce a broad spectrum of developmental toxic effects, ranging from inhibition of fetal growth and prenatal death to gross skeletal malformation, including neural tube defects such as exencephaly (brain outside of the cranial cavity). A single intraperitoneal injection of sodium arsenate at 45 mg/kg body weight of pregnant mice on day 8 of gestation resulted in a 65-percent incidence of exencephaly (245). Higher doses (60 or 75 mg/kg/body weight) produced significant maternal toxicity. Sodium arsenate and sodium arsenite are considerably less toxic and teratogenic when given orally than when given by intraperitoneal injection. In the case of arsenite, doses required to produce fetotoxicity and maternal toxicity are similar. Organoarsenicals (e.g., methylated arsenical such as sodium cacodylate) are significantly less toxic to the rodent embryo than are inorganic arsenic compounds **(155).**

Antimony

Salts of the trivalent and pentavalent forms of antimony, which have been used for centuries as drugs, have more recently been used as parasiticides (30). Metallic antimony is used in some alloys and inorganic salts are used as pigments, abrasives, and flame retardants.

There is little evidence that antimony acts as a reproductive toxin in either humans or animals. Although radioactive antimony is released from nuclear industries, it does not appear to be a teratogen, probably due to its inability to cross the placental barrier. Antimony can be passed to offspring via the milk of the exposed mother (123).

A Russian study found that women working in an antimony metallurgy plant had a higher incidence of premature births, spontaneous abortion, and other, unnamed reproductive system disorders. Their infants did not gain weight as rapidly as infants of nonexposed women (34). Further experimental data will be required before antimony is judged to be toxic or nontoxic to the reproductive system.

Agricultural Chemicals

Agricultural chemicals include compounds used as insecticides, herbicides, and fungicides. Certain of these chemicals (i.e., dibromochloropropane (DBCP), Kepone (chlordecone), and 2,2-bis [p+hloro-phenyll 1,1,1 -trichloroethane (DDT) are no longer used in the United States, in part because of adverse reproductive effects in animals or humans. Nonetheless, these chemicals are important to consider because of: 1) their similarity to chemicals still in use; 2) their long-term effects on workers who were exposed to them during their production and use; 3) their possible persistence in the environment; and 4) their sites and mechanisms of action, which have undergone detailed investigation and can provide useful insights into reproductive toxicity.

Exposure to agricultural chemicals can occur throughout the manufacturing process of these products as well as during their distribution, sales, and final application. Few agricultural chemicals are well-studied, In some cases there has been only one animal or human reproductive investigation of a given chemical. In most cases only one or a small number of reproductive variables have been studied for each compound. The reproductive outcomes that have been studied are usually in males. There is a notable lack of data on the effects of exposure of women workers to agricultural chemicals in the English literature, although several studies conducted in eastern Europe and Russia suggest the potential reproductive toxicity of these substances.

Although agricultural chemicals have been shown to have a variety of reproductive effects, published studies do not provide good evidence of individual human exposure levels to a given chemical. Several studies have utilized aggregate, rather than individual, data. Although this approach is appropriate for early studies designed to identify reproductive hazards, it may not be useful for deriving definitive conclusions about effect or causality. unfortunately, individual exposure levels are difficult to secure in the agricultural chemical field because of a lack of industrial hygiene data and inadequate long-term exposure records. It is even more difficult to gauge exposure in circumstances where exposure

Photo credit: Pemina Meisels

Further study is needed of the unknown reproductive and developmental chemicals that are similar to DDT and DBCP, which have been banned in the United States.

occurs outside the production. site; for example, to the pesticide applicator. Despite these difficulties, evaluation of animal and human data implicates selected agricultural chemicals as reproductive toxins and suggests the need for further animal studies of the reproductive effects of these economically important compounds.

Carbaryl

workers may be exposed to carbaryl (1-Napthyl methyl carbamate), a broad-spectrum insecticide, during both its manufacture and its widespread application. It is readily absorbed through the skin. The potential for exposure during the manufacturing process is probably greatest among workers bagging the product (404).

Male.—Animal studies have demonstrated that carbaryl is distributed to the testis, seminal vesicles, and prostate after absorption. Suggestive data link carbaryl exposure and male infertility, although a definitive relationship has not yet been established. Chronic feeding of carbaryl to experimental animals impairs spermatogenesis and fertility and produces testicular atrophy. In 1979, carbaryl-exposed workers were compared with nonexposed workers with respect to sperm count and blood levels of reproductive hormones. No abnormalities in blood or semen could be related to carbaryl. A borderline decrease in sperm count was observed among carbaryl-exposed workers (393). A reexamination of the same cohort of carbaryl-exposed workers 2 years later identified an excess of morphologically abnormal sperm compared with the sperm of nonexposed, newly hired employees (404).

Female.–There has been little study of the ef - feet of carbaryl on the female reproductive system in humans or experimental animals. ***Other*** cholinesterase inhibitors have been demonstrated to alter reproductive function in experimental animals and are associated with reproductive abnormalities in exposed populations. Women exposed to cholinesterase inhibitors in agricultural chemical production or application have an increased incidence of menstrual cycle disturbances and secondary infertility. Data from acute poisoning suggest a direct effect on the ovary.

Pregnancy.- carbaryl has been demonstrated to be a structural teratogen in experimental animals. However, the doses required are close to those that are lethal to the maternal organism. Its effects on the human embryo/fetus are unknown.

Dibromochloropropane

Dibromochloropropane (DBCP), a nematocide, was widely used in agriculture in the United States and abroad from the mid-1950s until 1977. In 1977, the discovery of adverse reproductive effects in humans led to a partial ban on its production in the United States. Prior to the ban, DBCP was used on a variety of crops, including cotton, soybeans, fruits, nuts, vegetables, and ornamental plants. Since 1981, the sole U.S. use of DBCP has been on Hawaiian pineapple plantations, The pineapple industry won a reprieve after promising to reduce worker exposure to the chemical. In 1985, the Environmental Protection

[2]Choline esters transmit information between nerve cells. Cholinesterase metabolizes choline esters to maintain proper levels of the choline esters in the body. Cholinesterase inhibitors prevent the metabolism of choline esters and thus permit abnormal levels of the esters to accumulate in the body.

Agency (EPA) mandated that remaining uses of DBCP in Hawaii be phased out by 1987. DBCP has been found in drinking-water wells on oahu and Maui (380,383). (See chapters 2 and 7 for further detail on DBCP.)

Male.—Interest in the adverse human reproductive effects of DBCP arose in the late 1970s when DBCP production workers in a northern California chemical plant complained of their inability to father children. Initial studies (391) confirmed semen and hormonal abnormalities in 11 of the 25 men who had not had vasectomies, and found a direct relationship between sperm count and duration of DBCP exposure in the others. When divided into groups by duration of exposure, 9 of 11 men with the longest exposure (an average 8 years) were azoospermic and two had sharply reduced sperm counts with reduced motility and increase in abnormal forms. Subsequent studies of 154 DBCP-exposed and 42 nonexposed workers in this plant confirmed the original findings of testicular toxicity (235,316,392).

Animal studies confirm the specific toxic effect on the testes. In the 1960s, prior to the observations of the effects on male pesticide-manufacturing workers, a comprehensive, multispecies study demonstrated the testicular toxicity of DBCP (353). In this study, testicular atrophy in rats was noted even at the lowest of three dose levels. Later studies confirmed these effects in rats and rabbits (52,296)297).

Eventual recovery of spermatogenesis following DBCP-induced testicular toxicity has been documented in some but not all of the exposed men. In Israel, 4 years after DBCP exposure, 17 healthy children were born. However, the sex ratio in this group was highly abnormal, Only 6 of the 17 (35 percent) were males (the ratio is normally 105 males for every 100 females). A subgroup of men who had recovered from azoospermia and oligospermia showed an even more skewed sex ratio of 2 males in 12 live births (16.6 percent).

Female.—DBCP has been shown to alter ovarian function and decrease fertility in female animals (297). Although females have been less thoroughly studied than males, females appear to be less sensitive to the toxicity of DBCP. Its effect on human female reproductive function is not known.

Pregnancy.—There is some evidence of fetal weight reduction in rats (310).

DBCP is clearly a testicular toxin in men and experimental animals. The extent of damage is proportional to the extent of exposure. The effects of DBCP on female reproduction and pregnancy in animals and humans require further investigation.

DDT

DDT (2,2 -bis(p-chloro-pheny l)l,l,l-trichloroethane) is a pesticide in common use around the world. It reached its peak agricultural use in the United States in 1959, but U.S. use was halted in 1972 in response to concern about the pesticide's wide-ranging effects on the ecosystem. Because DDT accumulates in fatty tissue, its presence persists in the body for many years. Major concern about the reproductive toxicity of DDT arose because it mimics the effects of estrogen, a normal sex steroid in males and females.

Most of the animal studies that have been conducted on the effects of DDT have been multigeneration reproduction studies on the rat, mouse, rabbit, and dog. Chronic exposure to DDT impaired fertility in female rats and caused reduced weight gain and survival of the offspring. In the dog, administration of DDT caused early onset of estrous but all other fertility parameters were normal. with a 14-month regimen, male dogs experienced diminished libido and females had delayed estrous, infertility, and increased infant and maternal mortality.

Rabbits exposed to DDT exhibit premature delivery, increased fetal resorption) and decreased intrauterine growth but show no evidence of teratogenic effects (260).

The effects of DDT on avian eggshells (DDT decreases eggshell thickness) are a direct reflection of its estrogenic properties. DDT can also increase the metabolism and excretion of estrogen. This is thought to partially explain the lack of calcium metabolism and soft egg shells in birds of prey (281).

In a comprehensive study of the health effects of DDT exposure of migrant farm workers, menstrual irregularities were the most frequent complaint of women seen in health clinics (63).

In addition to its adverse effects on the adult reproductive system, DDT exposure alters the development of the reproductive system. Human prenatal exposure to DDT has been suggested to be associated with polycystic ovary disease, Other systems of the developing organism may also be susceptible to adverse effects following prenatal exposure to this estrogen.

DDT has been found as a contaminant in human breast milk in persons exposed both occupationally and otherwise. However, no association has yet been found between milk concentrations and human health effects of DDT (397).

Mutagenic properties of DDT were studied in Brazil in 23 DDT-production workers and 35 nonexposed persons. Exposure levels were quantified by measurement of plasma levels of DDT and its metabolic products, This study showed a higher frequency of white blood cells with chromosomal abnormalities among workers with high blood DDT levels than among those with low blood DDT levels (294).

Kepone IChlordecone]

Kepone is a chlorinated hydrocarbon insecticide and fungicide that mimics the action of estrogen and is chemically related to Mirex, Endrin, Dieldrin, Heptachlor, chlorophenothane, and DDT. Kepone was manufactured and used in the United States until 1975, Its use was banned in 1977. Kepone was used most commonly as a pesticide against fire ants and in ant and cockroach traps.

Male.—Reported effects of Kepone on male fertility include reduced sperm count and motility and decreased spermatogenesis as judged by testicular biopsy in 13 of 23 exposed Kepone production workers (349). Abnormal sperm morphology has also been reported in Kepone production workers (56). Animals exposed to Kepone exhibit adverse effects on the testes at doses as low as 10 ppm in the diet over a prolonged period (2 years) (96).

Female.—Female rats and mice fed Kepone in the diet exhibit constant estrus with some damage to the ovaries (134,157). No human studies are available.

Pregnancy.—Kepone has been shown to alter embryonic development in animals but at levels that are also toxic to the dam (67). Female offspring that survive prenatal or neonatal treatment suffer reduced reproductive capacity (102,120, 121). There is evidence that Kepone can concentrate in breast milk in humans (124,159). No data on developmental effects in humans are available.

2,4,5-T, Dioxin, and Agent Orange

2,4,5-T (2)4,5 -trichlorophenoxy acetic acid) is a chlorinated herbicide that was used widely in the United States from 1948 until 1970 in large-scale farming, family gardens, forest management, and weed control along roadsides and railroad rights-of-way. The observation of birth defects in animals exposed to 2,4,5-T led the U.S. Department of Agriculture to suspend many uses in 1970. In 1979, EPA banned the use of 2)4,5-T except for range land and rice fields.

In 1957, dioxin was identified as a contaminant of the synthesis leading to 2,4,5-T. Dioxin (2,3,7,8-tetrachlorodibenzo-pdioxin, or TCDD) also occurs as a contaminant in the manufacture of 2,4,5-trichlorophenol (TCP), which, in turn, is used in the synthesis of 2,4,5-T and 2-(2,4,5 -trichlorophenoxy) proprionic acid, also known as Silvex. Dioxin, then, is an unwanted, unavoidable contaminant in the manufacture of these other chemicals. It is not a product in itself.

NIOSH reported in 1984 that it was not possible to provide an accurate estimate of the number of U.S. workers then at risk of exposure to dioxin (370). Occupational exposure to dioxin may occur:

- during production of TCP;
- in decontamination of worksites from prior production or use of TCP, 2,4,5-T, or Silvex;
- from waste materials, such as reclaimed oil, contaminated with dioxin;
- from cleanup after fires in transformers containing polychlorinated aromatics; or
- from dioxin-wontaminated dust or soil particles that can remain airborne or accumulate on indoor or outdoor work surfaces,

Agent Orange was the most widely used of several herbicides sprayed by U.S. military forces

for defoliation and crop destruction between 1962 and 1971 during the Vietnam War. Most of the spraying was done between 1967 and 1969 from fixed-wing aircraft, as part of "Operation Ranch Hand." Agent Orange was a 50/50 mixture of 2,4-D (to be discussed) and 2,4,5-T (114).

Public concern over possible reproductive effects of Agent Orange has been extreme for three reasons. First, between 2.4 and 2.8 million American military personnel served in Vietnam, and an unknown large number of Vietnamese soldiers and civilians lived or fought in sprayed areas. Second, anecdotal reports persist of birth defects attributed to exposure to Agent Orange or its constituents. Third, Agent Orange contains 2,4,5-T, which is contaminated during manufacture by dioxin (114).

Males. -Definitive adverse reproductive effects of occupational exposure to 2)4,5-T or dioxin on adult reproductive function have not been documented. To date, studies of exposed and nonexposed groups of workers have found no differences in semen characteristics, male potency and libido, infertility, and spontaneous abortion (201, 331)342).

A study of U.S. Air Force personnel who worked with Agent Orange in Vietnam found an excess of minor birth defects, such as birthmarks, among their offspring compared with the offspring of nonexposed personnel. No difference in incidence of more severe birth defects was observed between the exposed and nonexposed groups. In this study, the Air Force Ranch Hand Study, data were obtained from parental history and were not verified through medical records (130)201). A study based on the experiences of parents of babies born in metropolitan Atlanta from 1968 to 1980 contained no evidence to indicate that Vietnam veterans have been at greater risk than other men for fathering babies with birth defects, when all types of serious structural birth defects are combined (97).

Although concern about the effects of dioxin on the offspring of exposed males has overshadowed concern about the direct reproductive toxicology of dioxin, there is little or no evidence to suggest that dioxin alters fertility or sexual function in human males (355).

Female.—Female reproduction in animals appears to be sensitive to dioxin. At doses of 1 @kg/day for 13 weeks there were changes in estrous cyclicity and corpora lutea formation (184). There is also evidence of altered steroid metabolism and/or production in nonhuman primates exposed to dioxin (27).

2,4-D

2,4-D (2,4dichlorophenoxyacetic acid) is an herbicide commonly used in agriculture and forestry. It is closely related to 2)4,5-T in chemical structure. A 1984 case report from Arkansas described multiple malformations, including facial, digital, and limb defects and severe mental retardation, in a child born to parents who had both been heavily exposed to 2)4-D while spraying trees (59). Exposure of the parents was prolonged and at high levels and occurred both through respiratory and cutaneous routes. Exposure to the mother occurred 7 hours per day, 6 days per week from 6 months before conception to 5 weeks after her last menstrual period, when pregnancy was confirmed. A study of rats exposed prenatally on days 6 to 15 of gestation, reported subcutaneous edema, wavy ribs, delayed ossification, and lumbar ribs (319).

Polyhalogenated BiphenyIs

Polybrominated biphenyls (PBB) and polychlorinated biphenyls (PCB) belong to a class of chemicals known as halogenated aromatic hydrocarbons. They have been a valuable resource in industry because of their chemical stability, low volatility, and nonflammability (210). Yet these same properties cause the persistence of these chemicals in the environment. They are a potential reproductive health concern to humans and animals because once absorbed they are metabolized poorly, excreted slowly, and accumulate in fatty tissue (309). Since 1979, all manufacture, processing, and distribution of these chemicals has been banned in the United States, in part out of concern for reproductive toxicity (244).

There is a dearth of information concerning the reproductive effects of PBB and PCB, and existing information is derived largely from incidence of food contamination rather than workplace ex -

posure. Both PBB and PCB are known to cross the placenta, although not readily. Levels of these agents, which are extremely fat-soluble, have been found in breast milk at up to 100 times maternal blood levels. Lower birth weights and dermatological effects of PCB and PCB-like chemicals were observed in offspring of women exposed in a cooking-oil contamination accident in Japan, but no persistent morphological or behavioral effects have been documented. There have been no reports of congenital malformations associated with PBB.

Polybrominated Biphenyls

Polybrominated biphenyls (PBB) were developed for use as a flame retardant in thermoplastic products (309). In 1973, PBB was inadvertently mixed into cattle feed in Michigan, which led to widespread contamination of the food chain (176). Measurement of PBB in breast milk suggested that the chemical had been widely disseminated across the State (47), a finding later confirmed in a larger study (398). Farmworkers exhibited higher PBB levels than the general population (397), but there were few objective findings related to male reproductive effects (316). Most of the information on the health effects of PBB has been generated from this Michigan incident.

Male.—To date, only one human study has examined the effects of PBB on human spermatogenesis. Research efforts generated in 1979 by findings of a clinical field study of PBB-exposed men who complained of loss of libido (ıI) analyzed the semen quality of farmers and individuals who had consumed food from PBB-contaminated farms and PBB workers who might have inhaled or ingested the chemical (309). The results showed no difference in sperm counts, motility, and morphology in these men compared with a control group of male university students. Men with possible confounding factors (e.g., varicocele; marijuana use) were eliminated. However, because the collection of sperm did not occur until 4 years after the contamination incident, an earlier transient effect of PBB on spermatogenesis could have been reversed. No other studies have been conducted to explore the effect of PBBs on human male reproduction (26).

Although testicular damage and abnormalities in sperm function have been reported in cows and monkeys, these effects appear to be secondary to the general toxicity of this compound (26). Polybrominated biphenyls are also potential inducers of the hepatic mixed function oxidase system, which might alter testosterone pharmacoki - netics and indirectly impair testicular function.

Female.—Disrupted menstrual cyclicity and a 7 percent weight loss were observed in monkeys fed 0,3 ppm PBB; no other signs of toxicity were observed (4). Perinatal exposure to PBB increased liver metabolism of estrogens in offspring of rats. The effect of estrogen on uterine weight and uterine RNA content was also decreased (41).

Pregnancy.—A 1983 analysis of blood, placenta, and umbilical-cord blood samples, as well as tissue and milk samples, from women giving birth found that cord blood and the placenta contained one-tenth the maternal serum concentration of PBB (103), In a 1984 study (165), cord blood contained one-sixth the maternal serum concentration of PBB.

The high fat volubility of PBB allows it to accumulate in maternal breast milk. Detectable levels of PBB were found in 96 percent of the 53 samples randomly collected from nursing mothers in Michigan's lower peninsula (47). In another study, breast milk levels of PBB in women living on PBB-contaminated farms were more than 100 times greater than their blood levels, and reached approximately 80 percent of the PBB level in their body fat tissue (103). In a 1984 study, breast milk levels of PBB were twice those of maternal blood (165).

A number of studies have been conducted to assess the possible effect of PBB exposure on the developmental abilities of young children (318, 320,386). The studies examined children in Michigan who were exposed to PBB in utero, in early infancy, or both. A number of these children were breastfed by mothers who ingested PBB-contaminated foods. The first investigation of this kind, in 1981, failed to identify any effects of PBB on physical health and growth when 33 children born on PBB<ontaminated farms were compared with 20 unexposed controls. Psychological devel-

opment tests were also negative. However, on several of the McCarthy Scales of Children's Abilities an inverse relationship was shown between body-fat PBB level and performance. The mean age of the children was 37.2 months (386).

Developing fetal and newborn animals are readily exposed to PBB by transplacental and milk transfer from the exposed mother (25,88). Placental transfer of PBB has been shown in the cow, rat, and guinea pig.

PBB administration to pregnant rats causes lower body weight, increased mortality, and liver carcinomas in the offspring (132). Feeding PBB to pregnant pigs causes toxicosis in the dams and abnormalities in the thyroid and liver of the offspring. The major route of exposure of the offspring appears to be via the mother's milk. PBB can also cross the placenta in the pig (388).

Polychlorinated Biphenyls

Polychlorinated biphenyls (PCB) are a family of synthetic compounds introduced in industry in 1929. Until the 1970s, these chemicals were manufactured and used in coolant fluid in electrical transformers, hydraulic fluids, lubricants, plasticizers, coatings, sealants, and pesticide extenders. Mixtures of PCB may be oily, viscous liquids, or sticky resins.

PCB may enter the workplace or ambient environment through the careless disposal of industrial fluids, the leakage of nonclosed systems, and electric transformer fires. PCB has been found in samples of air, soil, water, and fish. Since the 1979 EPA ban on manufacturing, processing, and distribution of PCB, occupational and environmental exposure has been reduced (210). The principal hazard today rests with transformers and capacitors put in use before the ban and still containing PCB fluid. Estimates of the number of PCB-containing transformers range from 20)000 to 150,000 (65). PCB-laden transformers pose a potential hazard to utility workers, appliance service workers, and fire fighters (21o).

Males.—There are no reports of studies designed to evaluate the effect of PCB on human male reproduction (26,316). Postnatal exposure to PCBS depresses mating ability and fertility in adult male rats (311). Male reproductive function appears to be somewhat resistant to the effects of PCB (26].

Females.—Women exposed to high levels of PCB have been reported to experience altered menstrual cycles (384). Chronic exposure to 5 ppm in female mice and monkeys causes prolongation of the estrous cycle. Ovulatory failure has also been observed in exposed female monkeys (26,28). Daily exposure of rats to 30 mg/kg Aroclor 1254 for 1 month produced prolongation of the estrous cycle, decreased sexual receptivity, vaginal bleeding during pregnancy, decreased litter size, and delay in the time to parturition (45).

After 18 months of consuming 2.5 to 5.0 ppm PCB, female rhesus monkeys were placed on a control diet for 1 year. Infants born to these mothers showed signs of PCB toxicity similar to those of siblings born during PCB intoxication. This illustrates the tremendous residual ability of PCB in the female (2). The reproductive effects of PCBS in mammals include longer estrous cycles, decreased implantation sites, and increased stillbirths in a variety of species, including rats, mice, rabbits, monkeys, dogs, and mink (178).

Pregnancy.—Several studies indicate pregnancy abnormalities in women exposed to high levels of PCBS following the ingestion of contaminated rice oil (26). A recent study reports that pregnant women with Yusho (rice oil disease) deliver babies with fetal PCB syndrome (407). The symptoms include dark brown pigmentation, gingivial hyperplasia, shorter gestation length, and lower birth weight. The study's authors suggest a possible alteration in calcium metabolism similar to that seen in the fragile egg-shell formation exhibited by DDT-exposed birds,

Women exposed to PCB 3 to 4 years prior to conception have high levels of placental monoxygenases, enzymes that are capable of metabolizing many environmental pollutants to reactive products that may be toxic to the fetus (400). These findings suggest that PCB stored in maternal adipose tissue could have a persistent effect on placental metabolism in subsequent pregnancies. An inverse correlation between PCB exposure and fetal head circumference and birth weight has also been reported (108).

A number of abnormalities of pregnancy have been associated with PCBS in animals (26). The effects include disruption in implantation and prolonged gestation. PCB does not appear to be teratogenic or fetotoxic when given after implantation. Behavioral effects have been noted in mice exposed prenatally to PCBS. Neonatal exposure to PCB through the milk has been shown to impair the fertility of male and female offspring (26). An interesting interaction between dioxin and PCB has been reported in which PCB potentates the dioxin-dependent cleft palate formation in mice tenfold (37). This suggests that exposure to complex mixtures in the occupational environment may be more harmful than exposure to individual compounds.

Both PCBS and PBBs appear to be reproductive toxins in both male and female; fetal toxicity may also occur. Because PCBS and PBBs are metabolized very slowly, exposure may exert adverse effects even when it is far removed in time from reproduction.

Organic Solvents

Organic solvents such as carbon disulfide, carbon tetrachloride, styrene, xylene, toluene, and benzene are widely used in manufacturing and in the chemical industry. A new, major source of potential occupational solvent exposure is the electronics industry, where these chemicals are used to clean and fabricate electronic components. Despite the potential daily exposure of an estimated 10 million workers to organic solvents, few studies have examined the reproductive effects of these chemicals. Many solvents are mutagenic and carcinogenic in experimental animals, and some have been identified as human carcinogens. Carbon disulfide has been identified as an occupational reproductive hazard by NIOSH (244).

Accurate biological indicators of most solvent exposures, such as urine or blood levels, unlike those for some metal or pesticide exposures, can only be obtained soon after exposure because of the rapid metabolism and clearance of the chemicals. Many of the workers studied were exposed to multiple solvents and often to other chemicals. Little is known about the synergistic effects of multiple exposures that include industrial alcohols.

Studies on the neurotoxicology of solvents suggest the existence of a synergistic relationship between alcohol use and solvent exposure, yet no studies on the reproductive hazards of solvents have factored alcohol use into the results. Nor have other confounding variables been taken into account in analysis of the data. Most of the reported results are therefore based on crude estimates of actual exposure.

Male.—It is likely that solvents affect male fertility and semen quality. Single studies of carbon disulfide and derivatives of toluene have reported deleterious changes in semen quality, levels of serum FSH and LH, and testicular size (1,133,316). Wives of workers exposed to carbon disulfide have an increased rate of spontaneous abortion (141), and wives of painters exposed to aromatic solvents were found to be more likely to have children with congenital malformations. The effects of benzene, carbon tetrachloride, styrene, tri - chlorethylene, and xylene on male fertility in humans have not been investigated.

Some information on male reproductive effects of solvents is available from animal studies. Carbon tetrachloride produces testicular atrophy in mice and rats (172,321) Trichlorethylene has recently been examined for male reproductive effects in animals (410). No structural changes were observed, but reproductive behavior was altered. Male rodents may be more suspectible ***to ex***posure to carbon tetrachloride than females (26). There have been no studies of the effect of benzene on male fertility except for one dominant lethal study (26). Carbon tetrachloride is carcinogenic in several animal species, increasing concern for germ cell mutations. No eff&ts on fertility and no dominant lethal effects were observed in one study of the effect of styrene on male mice. The effects of xylene have not been studied.

Female.—Adverse reproductive effects have also been observed in women workers exposed to organic solvents. Irregular menstrual flow has been associated with carbon disulfide exposure (55,93). A recent study of women workers found no association between styrene exposure and menstrual disturbances, refuting the findings of an earlier study (208). An increase in the incidence of spontaneous abortion has been associated with carbon disulfide exposure (144), and inconsist-

ently associated with styrene exposure (141). Three studies have reported increased incidence of toxemia in solvent-exposed women (carbon disulfide, styrene, and mixed solvents) (55). Menstrual disturbances and heavy bleeding have been observed in women exposed to benzene, and women appear to be more susceptible to benzene exposure than men **(160).**

A 1975 report noted adverse effects on the estrous cycle of female rats (16) exposed to benzene; confirmation is needed from other studies. Effects of carbon tetrachloride on estrous cycles in rodents have been inconclusive because the relationship of the general toxic effect on liver function to gonadal function is unclear. No work has been done to ascertain whether there are similar effects on males (26). Inhalation exposure of the rat to styrene appears to alter gonadotrophin function and estrous cycles; the levels of exposure, however, are just below those which cause overt toxicity (26,163)412). No data are available for toluene and xylene.

Pregnancy. -Several studies have suggested that children of solvent-exposed workers are more likely to have congenital malformations and tumors; three studies have implicated solvent exposure in malformations of the nervous system. One study suggests the existence of a fetal solvent syndrome similar in nature to the fetal alcohol syndrome; because the structure and metabolism of many industrial alcohols are similar to those of ethanol, such a solvent syndrome is considered plausible (151)152)192,274)354). Studies are needed on exposure during pregnancy to confirm or deny this effect. Benzene crosses the placenta and is present in fetal blood in amounts equal to or greater than levels in maternal blood (84). No data are available for carbon tetrachloride.

Benzene and carbon tetrachloride may alter ovarian function in experimental animals (16,26). Consistent findings on benzene's effects during pregnancy in the mouse, rat, and rabbit include embryolethal and teratogenic effects such as reduced body weight and skeletal variants in the offspring at doses that are not toxic to the dams (26,158,247,385). The industrial solvent 2-ethoxy - ethanol is a behavioral teratogen in rodents; human effects have not been defined (356).

Anesthetic Agents

At room temperature, anesthetic agents are either gases or volatile liquids. Traces of anesthetics present a potential occupational health hazard when these gases and vapors leak from the anesthetic breathing circuit. An estimated 214)000 medical personnel, including surgeons, anesthesiologists, nurse anesthetists, operating room nurses and technicians, dentists, laboratory personnel, and veterinarians are regularly exposed to anesthetic agents (362).

The most widely used anesthetic gas is nitrous oxide (375). Other commonly used agents include fluorinated hydrocarbons (halothane, enflurane, and methoxyflurane) and cyclopropane. The fluorinated hydrocarbons replaced diethyl ether and chloroform, which were used commonly as anesthetics until 1950 (362). While dentists tend to administer nitrous oxide alone, physicians primarily use nitrous oxide in combination with the halogenated agents, making the effect of any one agent difficult to document (73). Levels of waste anesthetics in ambient air depend on: 1) anesthetic technique, 2) scavenging devices, and 3) ventilation systems (375).

There is concern for two undesirable reproductive outcomes in humans with occupational exposure to anesthetic agents: 1) an increase in the frequency of spontaneous abortion, and 2) an increase in congenital malformations (147,162,316). The various epidemiologic investigations are difficult to compare and to validate because they lack information on the actual chemical agents used and quantification of exposure. Most of the studies define "exposure" by occupation—for example, operating-room nurse, dentist, or anesthesiologist—and/or by number of years spent working with anesthetic agents. Further, few studies have discussed the sorts of scavenging devices or ventilation systems, or lack thereof, operating within the workplace.

General methodological problems characterize many of the studies (89,109,147)162)377)3 78). Pitfalls include retrospective design and the use of poorly designed postal questionnaires, the primary source of data for most studies. A common criticism is the degree of candor of the questionnaires: they were often considered to be '(loaded"

so as to encourage a bias in reporting. For example, one study (9) entitled its questionnaire, "Effects of Waste Anesthetics on Health." With the exception of two Swedish studies (18)98) that validated their data with information from medical registries, the other studies relied solely on data collected from personal questionnaires. Neither of the Swedish studies revealed positive findings.

Male.–Infertility has been reported among men exposed to anesthetic gases; however, analysis of sperm number and morphology reveals no differences. Although experimental animals exposed to anesthetic gases appear to have normal reproductive function, alterations in sperm morphology have been observed in some studies (195). Reversible effects on spermatogenesis were reported when male rats inhaled nitrous oxide (260).

Female.—Although anesthetic agents have acute effects on the integrated control of the hypotha - lamic-pituitary-ovarian axis in women, the effect appears transient. Studies of exposure to halothane and nitrous oxide have been inconsistent with respect to fertility effects in females and embryolethality and fetotoxicity effects on the embryo/fetus. Nitrous oxide does not destroy oocytes in rodents (147).

Pregnancy .—Although studies are somewhat inconsistent, exposure to anesthetic gases has been correlated with increased rates of spontaneous abortion (147,346). Women working as dental operatory chairside assistants show increased rates of spontaneous abortion compared with wives of operating room personnel and wives of dentists (147). Experimental animals exposed to various anesthetic agents (227) demonstrate delayed development. Analysis of infant outcome in cases of either maternal or paternal exposure has been inconsistent with respect to congenital malformations in humans (147).

Epichlorohydrin

Epichlorohydrin, which is a liquid at room temperature, is a highly reactive compound used as an intermediate in the manufacture of a broad spectrum of chemicals, including agricultural chemicals, insecticides, coatings, adhesives, plasticizers, textile chemicals, and pharmaceuticals. An estimated 85)000 workers face potential exposure to epichlorohydrin (365).

Evidence suggests that epichlorohydrin is a potential human mutagen. Human somatic-cell chromosomal changes have been reported, both in vitro and in vivo (193,285,338).

Male.—In a study of testicular function in two cohorts of workers at two plants where epichlorohydrin was produced (236), semen of 128 of 216 eligible workers was compared with that of a 90-member control group. No differences were found between sperm count distributions in exposed workers and the control group. Further, no relationship was found between sperm count and either the duration or intensity of exposure to epichlorohydrin.

A 1980 study examined the fertility status of 64 men employed in the glycerin department of a Texas industrial chemical plant (376). Epichlorohydrin was one of three carbon compounds produced. The other two were allyl chloride and 1,3-dichloropropene. All of these are structurally related to DBCP, a pesticide known to cause sterility in male workers. Employees were divided into three subgroups on the basis of their work areas: 1) epichlorohydrin and allyl chloride, 2) allyl chloride and 1,3-dichloropropene, and 3) epichlorohydrin, allyl chloride and 1,3-dichloropropene. Employees were also classified by strength of exposure (a subjective measure) and duration of employment. No associations were shown between lowered fertility and exposure to epichlorohydrin, allyl chloride, or l,3dichloropropene when the 64 exposed and 63 unexposed employees were compared. Further, there were no differences between the three groups in measures of fertility (e.g., sperm count, percent viable sperm, sperm motility). A 1982 review found no studies that show an association between epichlorohydrin and human male sexual function (26).

The antifertility effects of epichlorohydrin on the male rat are welldocumented. Reversible infertility in the absence of histologic damage to the gonads was first shown in male rats given epichlorohydrin orally at 15 mg/kg body weight for 12 days (26). Higher doses caused damage to the testes which resulted in permanent sterility. Exposure of male rats to 50 ppm epichlorohydrin by inhalation for 10 weeks resulted in infertility that was reversed 2 weeks after removal from exposure (170). At a lower exposure level of 25 ppm, fertility was impaired but not abolished in

male rats. An exposure level of 5 ppm epichlorohydrin in air had no effect on fertility in male rats. In male rabbits exposed to 5, 25, or 50 ppm epichlorohydrin in air, no effect on fertility could be seen.

Female.—Among female rats inhaling 5, 25, or 50 ppm epichlorohydrin for 10 weeks prior to mating, no adverse effects were noted on the estrous cycle, pregnancy rate, or number and viability of the offspring (170). No studies of humans are available.

Pregnancy.—Although epichlorohydrin appears to have no specific adverse effects on the outcome of pregnancy in animals, there has been little study of possible effects. In pregnant rabbits inhaling epichlorohydrin at 2.5,25,50, or 100 ppm, no effects were observed in the absence of maternal toxicity (26). No significant effects were reported at up to 25 ppm for 7 hours/day on days 6 to 16 of gestation on pregnancy outcome in rabbits. No data are available for humans.

Ethylene Dibromide [EDB]

Ethylene dibromide is used chiefly as an antiknock additive in leaded gasoline. It was also used as a pesticide from 1948 to 1984, primarily as a preplanning soil fumigant against nematodes, but also to fumigate fruits, vegetables, grain, and grain-milling machinery. Pesticidal use of EDB is now limited to fumigation of citrus and tropical fruits for export and, until 1986, certain beehive equipment. EDB continues to be used as an intermediate in the synthesis of dyes and pharmaceuticals, and as a solvent for resins, gums, and waxes. It is used less frequently in fire extinguishers and as a catalyst in the synthesis of organic chemicals.

In 1983, an estimated 56)000 (66) to 108)000 (359) workers in the United States were potentially exposed to EDB during its production and use. Because most pesticidal use of EDB was halted in late 1984, these figures are now likely to be overestimates of current exposure. An additional 875,000 workers are potentially exposed to low concentrations of EDB while working with leaded gasoline. This use of EDB is declining as the demand for leaded fuel decreases (359).

A colorless, nonflammable liquid, EDB is absorbed into the body by skin contact and inhalation. It binds with many of the constituents of living cells, reacts chemically with and alters DNA, and can accumulate in body tissues overtime with repeated exposures. Since it is similar in structure to DBCP, its potential mutagenic, carcinogenic, and male infertility effects have been investigated. Both continual and repeated intermittent exposures constitute a hazard to genetic mechanisms via accumulation of EDB in tissues (359). NIOSH recommends warning workers about the reproductive toxicity of EDB (244).

Male.—A 1979 study monitored fertility in wives of male workers in four plants who were exposed to EDB at levels up to 5 ppm (401). At three of the plants there was no evidence of fertility changes and at one there was a suggestion of lower fertility. Recent evaluation of workers exposed to EDB during its production suggests that exposure to levels below 5 ppm impairs spermatogenesis (350).

Adverse effects of EDB on the male gonads have been demonstrated in the rat and the bull. Atrophy of the testes and secondary sex organs occurred in rats inhaling 89 ppm EDB for 10 weeks (26). At this level of exposure, however, 20 percent of the animals died. At lower concentrations of EDB that were not significantly toxic (19 or 39 ppm), no specific effects on the gonads of male rats were seen. Calves and bulls were shown to be much more susceptible to a selective toxic action of EDB on the gonads. Daily oral doses of EDB averaging 2 mg/kg/body weight/day resulted in semen and sperm abnormalities and damage to the testes, which occurred in the absence of other signs of toxicity (26).

Female.—There are insufficient data to comment on the potential for adverse reproductive effects in women exposed to EDB. Chickens appear to be relatively sensitive to EDB as evidenced by impaired follicle growth and egg size. However, in one study, rat estrous cycles were affected only at doses that were lethal to 20 percent of the animals (26).

Pregnancy.-The effect of inhalation exposure of EDB during pregnancy was studied in rats and mice. In one series of experiments, pregnant rats and mice inhaled EDB at 20, 32, 38, or 80 ppm on days 6 to 15 of pregnancy (26). There was no apparent effect of EDB treatment on the incidence of major congenital malformations in the fetuses of rats or mice. Fetotoxicity was observed at doses that caused maternal toxicity. In one group of pregnant rats inhaling 32 ppm EDB, an increase in the incidence of minor congenital defects was observed in conjunction with slight maternal toxicity. In a 1983 study, rats were exposed to EDB at levels of 0.43, 6.67, or 66.67 ppm in air during pregnancy (333). Maternal toxicity was evident at the two higher dose levels, and the offspring showed signs of postnatal neurobehavioral impairment. No effects on the mother or fetus were evident from exposure to 0.43 ppm of EDB in air. EDB administered by daily intraperitoneal injection at 55 mg/kg body weight to pregnant rats on days 1 to 15 of gestation produced signs of maternal toxicity (significant change in maternal organ weights) but no evidence of fetotoxicity or tera - togenicity (137).

EDB is a potent animal carcinogen and testicular toxin, Evidence indicates that human males are more susceptible than animals. Because data on fertility are equivocal, in late 1983 NIOSH began a cytogenetic and semen study of the effects of occupational exposure to EDB. Fifty workers exposed to EDB in the fumigation of fruit are under study, as are 50 nonexposed sugar refinery and plantation workers. Blood and sperm samples are being analyzed, and each participant has contributed a questionnaire covering demographic data, occupational history, and medical history (270).

Ethylene Oxide {EtO]

Ethylene oxide, a colorless gas, is a major industrial chemical ranked 26th in U.S. production of chemicals. The vast majority of EtO is found in chemical plants, where it is produced and used in the production of ethylene glycol for automotive antifreeze, polyester fibers and films, and detergents (368). EtO is also used in sterilizing equipment and supplies used in hospitals and health-care facilities, as a fumigant in the manufacture of medical products and foodstuffs, and in libraries and museums (107).

Because EtO is highly explosive and chemically reactive, the processing equipment containing it in chemical plants generally consists of tightly closed and highly automated systems. Such equipment is often located outdoors, and workers spend most of their shift in and around control rooms, away from the equipment. The greatest potential for worker exposure in these settings occurs during the loading or unloading of transport tanks, product-sampling procedures, and equipment maintenance and repair (368).

In contrast to chemical-manufacturing plants, health-care and medical-products industries use a very small portion of total EtO production, but workers in these industries face potentially high levels of occupational exposure to the chemical (368). Workers in hospitals and health care facilities are believed to be both the largest single group of workers exposed to EtO, and the group exposed to the highest levels of EtO (see table 4-1). Estimates of the number of workers exposed to EtO from all sources range from 100,000 (126) to 140,000 (271), including 75,000 health care workers employed in sterilization areas.

Exposure to EtO during sterilization of medical equipment is quite variable within a given hospital or health care facility, and also varies greatly from one hospital or health care facility to another. Some institutions may have several sterilization cycles per day, involving a number of different sterilization units. In other institutions, there may be only one sterilizer unit that is run infrequently. Other variables affecting exposure include:

- the nature and installation of the sterilization equipment,
- design and layout of the room housing the sterilizer,
- the nature and frequency of equipment maintenance activities,
- sterilizer operating practices, and
- the type and functional capacity of ventilation systems.

Exposures of sterilizer personnel to EtO consequently vary widely; some sterilizer personnel are exposed daily, and others may be exposed intermittently or infrequently (107).

Table 4-1.-Estimated Ethylene Oxide Fumigation Use and Potential Operator

Site	Ethylene oxide of operators (pounds x 10,000/year)	Estimated number
Manufacturing and production of sterile medical disposable	3.3-5.7	3,000-4,000
Hospitals (1976 figures)	822-1,000	11,000-26,000
Medical clinics	111	1,150
Dental clinics	65.5	400
Doctors, private	37	750
Dentists, private	7.3	80
Veterinarians, private and clinic (estimated)	0.1	NA[a]
Museums	0.7	15
Libraries and archives	1.9	40
Research laboratories:		
Animal breeding	50	25-30
Drug and medical device	550-900	NA[a]
Microbiological and cancer	*5-25*	NA[a]
USDA[b] high-containment research labs	4.3	10-15
USDA[b] APHIS[c] quarantine operations,	0.7	200-300
Railroad cars	2	5-1o
Beehives	1-2	30
Spices	750	60
Black walnuts	3.2	10
Cosmetics	24	25
Dairy packaging	32	30

aNA—pJ~t available.
bUSDA—United States Department of Agriculture.
cAPHIS—Animal and plant Health Inspection Service.

SOURCE: "Occupational Exposure to EtO, Final Standard," *Federal Register* 49(122):25734, June 22, 1904.

Major emissions of EtO into workroom air occur during discharge of EtO into floor drains, following opening of the door of the sterilization equipment after completion of a cycle, and during exchange of gas cylinders. Additional exposure may result from off-gassing of EtO from sterilized articles during aeration, leaks in the sterilizer system, and releases during maintenance of equipment. All of these variables hinder the determination of precise worker-exposure levels (107).

EtO is a recognized mutagen and has a genotoxic mode of action. At very low dose levels, (TWA of 1 to 10 ppm), mutagenic effects were observed (107). Changes in genetic material and aerations in DNA repair occur at average EtO exposure concentrations of 1 ppm. Effects observed in humans include unscheduled DNA synthesis, and deficiencies in DNA repair, sister chromatid exchange, and chromosomal aberrations, including quadriradials, a relatively rare aberration. These data demonstrate clearly the genetic toxicity of EtO in somatic cells and signal the potential of this chemical to damage germ cell DNA.

Male.—EtO has produced testicular damage and impaired fertility in rodents inhaling a toxic concentration (26). Guinea pigs inhaling 357 ppm EtO for 25 weeks showed general growth depression and testicular degeneration. Decreased fertility and dominant lethal effects were found in rats following a single 4-hour exposure to 1,000 ppm EtO in air. Exposure of male rats to 10, 33, or 100 ppm EtO in air for 12 weeks had no effects on fertility indices (336). A single intravenous injection of EtO at 25, 50, or 100 mglkg body weight in male mice did not result in dominant lethal mutations when the animals were subsequently mated with untreated females (26).

Female.-A study of hospital workers using sterilization equipment revealed an increase in the spontaneous abortion rate that was correlated with exposure to EtO (143). Although some misclassification of the pregnancies according to exposure may have been possible, the data suggest a toxic effect of ethylene oxide on human reproduction (143).

Pregnancy. —Exposure of pregnant rats to 10, 33, or 100 ppm in air on days 6 to 15 of gestation resulted in fetotoxicity at the highest dose level, but no evidence of embryolethality or teratogenicity (335). Similar findings of fetotoxicity were reported in pregnant rats and rabbits inhaling 150 ppm EtO (138). The fertility of female rats exposed to 10, 33, or 100 ppm EtO in air, beginning 12 weeks before mating and continuing throughout pregnancy and lactation, was not affected although there were significantly fewer offspring born per litter in animals exposed to 100 ppm (335). Maternal toxicity did not result from the treatment, and survival and growth of offspring during the postnatal period were not adversely affected, even while the nursing mothers were exposed to EtO.

Formaldehyde

Formaldehyde is a colorless, flammable gas with a pungent odor. Formaldehyde may be used either in a water-based solution (i.e., formalin) or in solid form. In 1983, the United States used more than 7.5 billion pounds of formaldehyde in some 60 different industrial and laboratory applications (399). For example, formaldehyde and its derivatives are used: to give wet strength to paper; in transforming raw animal skin and fur into tanned leather; to harden and protect the gelatin surface of film and photographic papers; in textile processing; in the manufacture of particle board, plywood, and foam insulation; and as a preservative of biological material.

During a 1972-74 survey, MOSH estimated that 1.6 million workers were exposed to formaldehyde. Of these workers, about 57,000 were exposed to formaldehyde for 4 or more hours per day. Nearly one-third of workers, some 507,200, were engaged in medical and other health services (367).

Formaldehyde is ubiquitous in the human environment and is a normal metabolize in human biochemistry. It is contained in cigarette smoke, car exhaust fumes, and in ambient air, even in remote areas. Formaldehyde can be found in a large variety of consumer products, ranging from permanent-press fabrics to cosmetics. The most common sources of exposure for the nonsmoking general population are particle board, plywood, and urea formaldehyde foam insulation. When new, these emit formaldehyde and can cause the levels in indoor air to become relatively high.

Male.—A 1984 study reported that formaldehyde exposure in men had no effect on sperm count or morphology (381). The human subjects in this study were 11 hospital autopsy service workers and 11 matched controls. Sperm counts were lower (but not significantly) in exposed men than controls, however, indicating the need for a larger study from which more definite conclusions can be drawn.

Data regarding the reproductive toxicity of formaldehyde in animals are limited. In male rats chronically exposed to formaldehyde at two doses (0.1 mgfliter in water, 0.4 ppm in air), no effects on fertility were seen (26). In a dominant lethal study treatment of male mice with single intraperitoneal injections of formaldehyde at 16 to 40 mg/kg body weight produced no effects on pregnancy rate or dominant lethal effects (25).

Female.—A study of 446 Soviet workers exposed to urea formaldehyde resins in a fabric plant found menstrual disorders in 47.5 percent of exposed fabric finishers and inspectors. By contrast, only 18.6 percent of the 200 industrial saleswomen in a comparison group were found to have such disorders. Dysmenorrhea was the most common disorder reported. No test for statistical significance was performed, but the highest frequency of menstrual disorders occurred among the youngest women, and among the fabric finishers who experienced the greatest exposure. Formaldehyde concentrations ranged from less than 0.05 ppm to 3.7 ppm, depending on the area of production (329). A 1980 study found that gynecological disorders accounted for only 2.3 percent of all disorders in 13,000 cases of unfitness for work at a plywood factory where women were exposed to formaldehyde (15). Another 1980 study reported no increase in miscarriages among women exposed to formaldehyde in the home

Table 4-2.—Workplace and Ambient Exposure to Formaldehyde

Exposed population	Number of individuals exposed
Industrial workers:	
Abrasives manufacturers	7,000
Particle board manufacturers	4,000
Resins manufacturers	6,025
Apparel manufacturers	777,000
High school biology students	3,834,000
Beginning medical students	16,000
Residents of new mobile homes	4,200,000
Residents of urban areas, exposed to ambient air	162,000,000

[a]Only a small sample of the various categories of workplace and ambient exposure is given.

SOURCE: Adapted from B. Hileman, "Formaldehyde: Assessing the Risk, " *Environ. Sci. Technol. 16(7)*:216 *A-221A, 1964.*

(119). All of these studies are flawed by the fact that exposures were not measured. The study of Soviet workers appears to have confounding factors that prevent formaldehyde per se from being implicated as a reproductive hazard. There are no adequate studies of the effects of formaldehyde on female animal fertility or pregnancy.

Pregnancy.—In the Soviet study, anemia was the most frequent pregnancy complication in women exposed to formaldehyde (329). Although not analyzed for significance, this pregnancy complication was reported twice as often by the exposed group as by the unexposed group.

No difference in the frequency of spontaneous abortion was found in a comparison of pregnant women who sterilized medical instruments with formaldehyde and pregnant women not exposed to formaldehyde (143), Frequencies were based on total number of pregnancies, and rates were adjusted for age, parity, decade of pregnancy, smoking, and alcohol and coffee consumption. Of the children born to mothers exposed to formaldehyde, 17 percent weighed 2,500 to 2,990 grams. Only 11 percent of the babies born to unexposed women were in this borderline-low weight category. Whether variables know to affect birth weight were controlled is not known.

Pregnant mice given formaldehyde orally at doses up to 185 mg/kg body weight/day on days 6 to 15 of gestation showed no adverse effects other than maternal toxicity. Dogs who were fed diets containing 125 or 375 ppm of formaldehyde (corresponding to doses of 3.1 or 9.4 mg/kg/day) from days 4 to 56 after mating (26) showed no evidence of embryolethality or teratogenicity, although fetal weights were slightly reduced in comparison with untreated control animals. Postnatal development of pups from formaldehyde-treated mothers appeared to be normal, and the pups were reported to have subsequently produced normal litters. A more recent study showed no effect of formaldehyde on embryos when hamster dams were exposed on day 8, 9, 10, or 11 of gestation (278).

Rubber

The production of rubber involves an estimated 500 or more chemicals, including acrylonitrile, aromatic amines, 1,3-butadiene, carbon black, chloroprene, epichlorohydrin, mineral oils, nitrosoampounds, styrene and other solvents, and vinyl chloride. The reproductive toxicity of all of the individual chemicals involved, as well as various combinations of them, is poorly understood, although some are identified as reproductive toxins. The range of possible reproductive hazards caused by exposures in the rubber industry has not been comprehensively studied.

Researchers have not attempted to separate or to measure chemical exposures, although efforts have been made to identify specific work areas where greater exposures probably occur. Although accurate individual exposure estimates are difficult to make in an environment such as a rubber plant, evidence from reproductive as well as other studies suggests that the level of harm from chemical exposure may vary greatly throughout the plant, making such determinations important.

Information on reproductive and developmental effects is available for several of the chemicals involved in the production of rubber-hloroprene, 1-3 butadiene, and ethylene thiourea.

Chloroprene is a colorless liquid that is slightly soluble in water. It is used as a chemical intermediate in rubber manufacturing. Chloroprene at room temperature apparently dimerizes to several different compounds. It has been demonstrated that these reaction products are often more toxic than chloroprene, which may explain the inconclusive results obtained by several investigators. Since dimerization is likely to occur in industrial settings, the reproductive toxicity of the dimers may need to be explored in order to enhance understanding of the reproductive effects associated with chemical exposure in rubber plants,

I,a-butadiene is a gas, readily soluble in organic solvents, used in the manufacture of rubber, latexes, and resins. Although there are no data showing human reproductive effects of 1,3-butadiene, NIOSH recommended in 1984 that 1,3-butadiene be regarded as a potential occupational human reproductive hazard. The NIOSH recommendation was based on long-term animal studies that demonstrate maternal and fetal toxicity, teratogenicity, and testicular and ovarian atrophy (371).

Ethylene thiourea is a rubber accelerator, used to speed the curing process in the manufacture of rubber. It is available as a powder, or as a powder suspended in oil, which retards the dispersion of ethylene thiourea dust in the air. NIOSH recommended in 1978 that ethylene thiourea be handled as if it were a human teratogen. Based on data derived from animal studies, NIOSH found that ethylene thiourea poses a risk of teratogenesis, particularly to the central nervous system, that is greater than has been generally recognized. An estimated 3,500 workers in the rubber industry have potential occupational exposure to ethylene thiourea (365). A 1976 study of employees formerly exposed to ethylene thiourea (exposure ended in 1972), identified no increase in specific congenital anomalies such as hip dislocation, malformed trachea and esophagus, cleft palate, and heart disease among the offspring of exposed workers compared with those of nonexposed workers (332).

Male.—A Russian study found reduced sperm motility in workers after 6 years exposure to chloroprene and changes in morphology after 11 years (26)312). Few details of the study are given, so it is impossible to access the significance of the result. A threefold increase in the abortion rate in the wives of rubber workers was also reported. A NIOSH (1977) document reports sexual impotency with both loss of libido and sexual dynamics following exposure to high levels of chloroprene.

Female.—Menstrual disorders have been associated with chloroprene exposure (47 percent in exposed v. 10 percent in controls) (26). A 1976 study reported 6.1 percent sterility in chloroprene workers v. 2 percent in controls (312). Females appear to be less susceptible to gonadal toxicity than males (26,312). Fertility is not affected by chloroprene exposure in animals where the purity of the substance is known.

Pregnancy.—In 1983, two investigations focused on rates of spontaneous abortion and congenital malformations among women exposed to chemicals in the rubber industry. In one report (213), the rate of spontaneous abortion did not differ between pregnancies occurring during employment and those occurring before or after employment, after adjusting for differences in age. A casewontrol study of spontaneous abortion in the footwear department (a high-exposure area) of one plant indicated a tenfold increase in risk of spontaneous abortion for women exposed to rubber chemicals compared with unexposed women working in a nearby area of the plant. A second report (19) found an increase in pregnancy complications, including miscarriages and threatened abortions, among tire builders.

Exposure to pure chloroprene up to 25 ppm has no effect in animals. Following exposure to chloroprene where purity was in question, teratogenicity and embryo death were noted at concentrations as low as 1 ppm, suggesting that impurities or reaction products are responsible. Many of the chemicals used in the rubber industry are teratogenic in the chick embryo assay (186,187). Those with the highest teratogenic potential were the highly aromatic oils and tricresylphosphate.

Vinyl Halides

Vinyl halides are in widespread industrial use, especially in the manufacture of plastics. These chemicals are easily polymerized with acrylonitrile, vinyl acetate, and styrene to form pliable, lightweight plastics or resins. The best studied and most widely used vinyl halide is vinyl chloride, which may occur as a monomer or polymer, called polyvinyl chloride (PVC). Polyvinyl chloride occurs in a wide variety of commercial products, including clothing, upholstery, flooring, wire insulation, food containers, and phonograph records. Other vinyl halides of industrial importance are vinylidene chloride, vinyl bromide, vinyl fluoride, and vinylidene fluoride. Exposure to the vinyl chloride monomer, generally in the polymerization industry, is considered the most hazardous of vinyl halide exposures (171).

Studies of vinyl chloride provide exposure levels, at least on an industry-wide basis. However, the extent and type of exposure vary widely, according to the production facility and process utilized, Discrepancies among results may occur because of differences in exposure levels across studies and in the differences of exposures to other agents, such as organic solvents, during the production of vinyl chloride.

Male.—There is some evidence that vinyl chloride may cause sexual dysfunction in men **(26).** A study of pregnancy outcome among wives of 95 workers showed increased fetal loss following their husbands' exposure to vinyl chloride monomer. The greatest increase occurred in pregnancy outcome associated with husbands under age 30 (161).

The absence of dominant lethal effects in male rats and mice inhaling vinyl chloride has been demonstrated by high dose short-term exposure (30,000 ppm for 5 days), and lower dose subchronic exposures (5,000 ppm for 10 weeks or 1,000 ppm for 5 days). However, reduced mating performance and fertility have been observed in male rats inhaling 250 or 1,000 ppm for 11 weeks. Pregnant rats, rabbits, and mice exposed to vinyl chloride at concentrations up to 2,500 ppm have exhibited maternal toxicity and some embryolethality and fetotoxicity (26,149,169).

Pregnancy. -Vinyl chloride has also been associated with increased rates of fetal death following paternal exposure (161), and possibly associated with malformations of the fetal central nervous system following environmental exposure of both parents. Studies of female exposure have been limited and tend to focus on environmental rather than workplace exposure and to utilize aggregate rather than individual data.

Residents of Gainesville, Ohio, the site of two PVC plants, showed a significant increase in central nervous system (CNS) malformation. Scientists from the Centers for Disease Control used Birth Defects Monitoring Program (BDMP) data to compare CNS malformations rates in Gainesville and a similar Pennsylvania community housing a PVC plant with rates for both States (91). The study found no increase in CNS malformations in the Pennsylvania community, but did find an increase in the Gainesville area, primarily in anencephaly and spina bifida. A small, follow-up, case-ontrol study (cases =15; controls =30) failed to show an association with vinyl chloride exposure.

BDMP data were also used to identify the rate of CNS defects in Kanawha County, West Virginia, which houses a polyvinyl chloride facility, as being higher than the national rate. In a follow-up, case control study, 46 cases with CNS defects were matched with 2 normal controls each. The study found no evidence that higher CNS rates in Kanawha County were related to parental exposure to vinyl chloride monomer (90).

Pregnant rats, rabbits, and mice have been exposed to vinyl chloride at concentrations of up to 2,500 ppm in air. A 1981 study reported that maternal toxicity, but not fetotoxicity or teratogenicity, resulted from exposure of pregnant mice to 50 ppm and exposure of pregnant rats and rabbits to 2,500 ppm vinyl chloride in air (169). Maternal toxicity, embryolethality, and fetotoxicity developed in pregnant mice exposed to 500 ppm vinyl chloride in air, Embryolethality in the rat was increased by inhalation of 1,500 ppm vinyl chloride early in pregnancy (days 1 to 9 of gestation) (26).

The mutagenicity of vinyl chloride raises concern for the integrity of germ cell DNA in exposed individuals. There is insufficient evidence to reach conclusions about fertility effects in animal reproduction.

Table 4.3.-Workplace Vinyl Halide Exposures

Chemical	Estimated number of workers potentially exposed	
	Definite[a]	Probable[b]
Vinyl chloride	27,000	2,200,000
Vinyl bromide	360	26,000
Vinylidene chloride	6,500	58,000
Vinylidene fluoride	1,900	32,000
Vinyl fluoride	NA[c]	NA[c]

[a]Definite estimates are extrapolated from actual observations of the use of the specific chemical or the use of a trade name product known to contain the chemical.
[b]Probable estimates include additional extrapolations from observations of trade name products suspected of containing the chemical because of generic for. mutations.
[c]NA—not available,

SOURCE: U.S. Department of Health, Education, and Welfare, National Institute for Occupational Safety and Health, "Vinyl Halides Carcinogenicity," NIOSH/OSHA Current Intelligence Bulletin 28, DHEW (N IOSH) Pub. No. 79-102, Sept. 21, 1978.

Hormones

Synthetic hormones have a wide variety of uses, ranging from supplements in animal feeds to human pharmaceuticals (e.g., oral contraceptives, cancer therapeutic agents). Occupational exposure to synthetic hormones occurs chiefly during their production in pharmaceutical plants. The principal exposure of workers is usually to the synthetic estrogens ethinyl estradiol and

diethylstilbestrol (DES) or to synthetic progestogens. Sources of exposure are via the air and direct contact, especially when hygienic or prophylactic measures are neglected. In the United States, an estimated 3,000 persons are exposed to ethinyl estradiol in the work environment (140).

There have been few studies of the reproductive effects of workplace exposure to synthetic hormones. Despite their small number, however, studies of these and other hormones in clinical settings provide a broad data base for evaluation and identification of site and mechanism of action. The literature is limited to data on observations in factories producing oral contraceptives and synthetic estrogens. These studies are noteworthy for their: 1) efforts to measure workplace exposure levels of the hormones, 2) measurement of exogenous hormones in the worker's bloodstream as exposure indicators, and 3) focus on exposure of both male and female workers.

Certain methodological problems (e.g., difficulty in measuring the clinical effects of exposure) complicate studies of this type. Effects are both subjective (e.g., complaints of loss of libido), and difficult to quantitate (e.g., gynecomastia). Clinical examination is not always conclusive; for example, 30 percent of the nonexposed adult male population may present with gynecomastia (139). Uncertainty also exists in identifying the most appropriate indicators of exposure and outcome. Despite these difficulties, adverse reproductive effects reported following occupational exposure to hormones are consistent with the well-defined biological actions of these compounds.

Male.—A 1984 study (237) of 22 hormone-exposed men found an increased incidence of breast swelling, tenderness, and lumps or nodules, and decreased total blood estrogen levels, but no detectable evidence of synthetic estrogens in the blood. These changes are consistent with occupational exposure to and absorption of synthetic estrogens.

Female.—Lower average total blood estrogen levels have been reported in hormoneexposed female workers (237). Again, none of the women had detectable evidence of synthetic hormones in their blood. Among 24 female employees exposed to the synthetic hormones mestranol and norethindrone, 50 percent experienced intermenstrual bleeding, compared with 17 percent of a group of 60 nonexposed women (140).

Pregnancy .-The adverse reproductive effects of the synthetic estrogen diethylstilbestrol (DES) have been welldocumented in pregnant mice, rats, hamsters, rabbits, monkeys, and humans (260). In pregnant mice, daily subcutaneous injections of DES at doses ranging from 0.01 to 10 mglkg body weight/day during gestation caused severe developmental and functional disturbances in both male and female offspring. Females exhibited decreased fertility, sterility, and abnormalities of the genital tract; male offspring showed growth inhibition, sterility, and alterations of the reproductive tract, Similar effects were observed in the offspring of rats and hamsters treated with DES during pregnancy. Abnormalities of the genital tract were reported in female offspring of monkeys given DES orally at doses of 1 mg/day from day 21, 100, or 130 of gestation to delivery. Women exposed to DES in utero have been demonstrated to have abnormalities in the development of the uterus and cervix. In addition, DES is a transplacental carcinogen in women and experimental animals.

High levels of corticosteroid hormones in early fetal life have been associated with developmental toxicity in animals. Hydrocortisone acetate, a synthetic glucocorticoid hormone, has been studied for its ability to induce renal anomalies in the offspring of pregnant rats given an injection of 250 mg/kg body weight during the gestation period of fetal organ development. Polycystic kidney disease may also be induced by injecting newborn rats, rabbits, hamsters, and mice with the hormone because kidney development continues postnatally in these species.

Although workplace exposure to hormones such as DES and hydrocortisone acetate is primarily through inhalation and most laboratory studies have administered the hormones in feed and through injections (77,260), these differences do not obscure the clear reproductive toxicity that follows occupational exposure to hormones.

Undefined Industrial Exposures

A number of studies have examined the effects of particular occupations on workers' reproductive function. These studies do not specify the in-

dividual chemicals to which the workers are exposed, nor do they attempt to quantify exposure.

Agricultural Work.—A 1973 study (408) examined white-blood-cell cultures from 42 pesticide-application workers and 16 nonexposed workers to evaluate chromosomal characteristics. Increases in frequency of chromosomal abnormalities, especially in workers with heavy herbicide exposure, occurred during heavy-spraying seasons.

A 1978 study of five Israeli insecticide workers found impaired spermatogenesis, chromosomal breakage, and Y-chromosome damage. The five men, who were infertile, had been frequently exposed to various chlorinated and phosphate organic insecticides (324).

A series of case reports reported impotence among four of five farm workers exposed to unspecified chemicals. The impotence was not accompanied by a decrease in libido. When contact with the chemicals was stopped and hormone therapy given, the four workers recovered sexual function (101).

Laboratory Work.–A 1977 study (116) found an excess of chromosomal abnormalities in the white blood cells of 73 workers in laboratories and in the printing industry. An increase in chromosomal abnormalities was found in 14 children of 11 women who had worked in laboratories while pregnant.

A study of pregnancy outcome among 32 women working in a Swedish hospital laboratory found an increased risk of spontaneous abortion, which occurred in 17 of 71 pregnancies, when pregnancy occurred in conjunction with laboratory work. This study was conducted on a relatively small population, and confounding variables were not factored into the analysis (341).

A 1979 study (23) of the relationship between delivery outcome and women working in medical professions covered 1,500 women working in hospitals from 1965 to 1975 who gave birth during the period. The hospital workers exhibited increased rates of cesarean deliveries and threatened abortions, and during 1 year of the study, perinatal death.

A 1984 report examined delivery outcomes of 1,161 infants born to Swedish laboratory workers and compared them with the total number (98,354) of births in Sweden in 1976. Although an increase in perinatal deaths and congenital malformations was found among infants of a subset of the laboratory workers, no specific type of laboratory or laboratory worker was found to be associated with these outcomes (97).

Two other Swedish studies have found that laboratory workers are more likely to give birth to infants with congenital malformations of the gastrointestinal tract. A 1979 study (230) looked at perinatal death and malformation rates in 322 deliveries to women working at a Swedish university during their pregnancies. Of these women, 245 were laboratory workers while pregnant. No occupational effect on perinatal deaths was observed, but the study did show an increased rate of congenital malformations among offspring of laboratory workers. Gastrointestinal defects appeared to be especially elevated. A 1982 study of this outcome among pregnant women laboratory workers (99) found that infants with gastrointestinal atresia were more likely than normal infants to have mothers who were laboratory workers.

Oil, Chemical, and Atomic Work.–A 1984 survey of reproductive hazards among 1,280 male oil, chemical, and atomic workers exposed to halogenated hydrocarbons (315) in 7 U.S. plants was conducted by postal questionnaire. Workers in these plants used the chemicals ethylene dichloride, methyl chloride, vinyl chloride monomer, chlordane, epichlorohydrin, and perchlorethylene. Oil, chemical, and atomic workers not exposed to any brominated or chlorinated hydrocarbons served as a comparison group. Subjects were placed, on the basis of occupation, in “higher,” “lower)” or “no-exposure” categories.

The salient finding of this industrial study was an increase in infant deaths among the offspring of exposed male workers. The rate was 2.3 and 4.6 times greater for the “lower” and “higher” exposure workers, respectively, than for the nonexposed workers.

pulp and Paper Work—A study of female employees in the Swedish pulp and paper industry examined congenital anomalies and perinatal survival from 1973 to 1977 (38), Information on all births was gathered from the Swedish Medical

Birth Register. The number of congenital malformations, based on 890 deliveries, was close to the Swedish norm. When pregnancy outcomes were divided into specific job categories of the mother, the highest frequency of birth defects (4.0 percent) and perinatal deaths (1.8 percent) occurred among women in the "converting" section, where paper is refined into various products. Some of these workers were listed as having exposure to ethylene acetate, glues, and various stains.

Textile Work.—Medical records and data from questionnaires in Denmark indicate that female textile workers exposed to textile dyes experienced a fivefold increase in risk of infertility when these data were adjusted for age, education, residence, and parity. The risk of infertility among textile workers was greater than for women working with cutting oils, drydeaning chemicals, lead, cadmium, or mercury. No exposure levels were provided (293).

Several studies have examined the frequency of spontaneous abortion among women in the textile industry, although none of these studies, which are generally part of larger industrial investigations, focuses solely on this industry. In a 1977 Iranian study, the rate of spontaneous abortion (I2 percent) was greater among textile workers than among nonworking women (175). More than 70 percent of the women interviewed were at least 30 years of age and had been employed in one of two local factories for more than 15 years. No specific workplace hazards were cited in the report.

A more recent investigation of spontaneous abortion among women in textile industries yielded similar findings (146). Unlike the Iranian study, this investigation took the husband's occupation into account. Hospital discharge data were employed to obtain information on the study group and their families in the community of Kokkola, Finland. While women in the town worked mainly in the textile industry, men were employed in the metal, leather, and chemical industries. The highest rate of spontaneous abortion in Kokkola (12.2 percent) was recorded among women textile workers. This rate was significantly higher than for women who did not work outside the home (6.3 percent), but only slightly higher than the rate for other economically active women (11.4 percent). A subgroup of women working as seamstresses in the textile factory had a spontaneous abortion rate of 20.4 percent. When the husband's occupation was also considered, women employed in textiles married to men employed at the metallurgical factory had a rate of spontaneous abortion of 16.0 percent. The authors suggest that higher rates of spontaneous abortion among the combined occupations may be due in part to a paternal effect. Although the husbands' jobs in the metallurgic factories were unspecified, possible exposures to arsenic, zinc, cobalt, sulfur dioxide, hydrogen sulfide, and cadmium were suggested.

A Swedish study found an increased rate of spontaneous abortion among both women and wives of men working in rayon textile jobs. The investigators noted that viscose rayon industries use hydrogen sulfide and carbon disulfide. No actual exposure data were provided (144). These studies suggest that occupational exposures during pregnancy in the textile industry are associated with an increased risk for female infertility and spontaneous abortion.

EFFECTS OF WORKPLACE PHYSICAL AGENTS ON REPRODUCTIVE FUNCTION

Workers in every occupational field are exposed to one or more physical agents in their workplace environment. The variety of forces encompassed by the term physical agents incIudes such natural forces as radiation, atmospheric pressure, and electric, magnetic, and gravitational fields. It is essential to recognize the close relationship between physical agents in the occupational environment and these same agents as integral parts of the natural environment. With few exceptions, these physical energies are, in fact, elemental forces that have shaped the evolution of life on earth. The form, behavior, and function—including reproduction-of human, monkey, mouse, rat,

and dog developed under the influences of natural gamma rays, ultraviolet light, gravity, varying barometric pressures, and hot and cold temperatures.

As important as natural physical agents have been from an ecological perspective, they do not become notable agents of biological stress until: 1) above-normal levels are created artificially in industrial and commercial environments, or 2) the background levels become abnormal. The physical factors that have most often been considered as potential occupational hazards include ionizing radiation, optical radiation, radiofrequency/microwave radiation, electric and magnetic fields, atmospheric pressure, hot or cold environments, noise, and vibration.

Certain health effects resulting from occupational exposure to physical forces, such as noise-induced hearing loss, heat stress, and vibration-induced numbness, have been recognized for decades. Unfortunately, very few well-documented studies have been conducted for the specific purpose of evaluating the reproductive effects of exposure to physical forces in the workplace. Data on the adverse effects on reproduction from occupational exposure to physical forces are therefore in most cases either inferential or nonexistent.

Ionizing Radiation

Ionizing radiation is energy that is transmitted in wave or particle form and is capable of causing ionization (ejecting orbital electrons) of atoms or molecules in the irradiated tissue. Alpha particles and beta particles are forms of ionizing radiation that interact directly with irradiated tissues to cause ionization, whereas gamma and X-rays are forms of electromagnetic radiation that generate secondary particles in the irradiated tissues which subsequently lead to ionization. Reactors and high-energy accelerators produce, in addition to gamma and X-rays, protons, neutrons, and other particles that are effective in producing tissue ionization either directly (protons) or indirectly (neutrons).

The critical element for defining the biological effect of ionizing radiation is energy deposition (i.e., absorbed dose), since the different types of ionizing radiation vary in their penetrative powers and number of ions produced. The unit used to quantify the energy deposited in matter by ionizing radiation is the rad, defined as 0,01 joules per kilogram of irradiated material. Since different types of radiation can deposit the same total energy but produce different amounts of damage, a different unit, the rem, is used to quantify the degree of biological damage. Reins are defined as a factor Q times rads, where Q is set equal to 1 for gamma and X-rays, and 20 for alpha particles. Thus, at equivalent energy depositions, the alpha particle will produce 20 times the biological damage of gamma and X-rays. The currently recommended limit for workers exposed to ionizing radiation, set by the Federal Radiation Council (FRC, 1960) and incorporated into regulatory limits by most Federal agencies (e.g., NRC, 1977) is 3 reins/quarter (3 months) for the whole body, or head and trunk, lens of the eyes, gonads, or blood-forming organs. This limit is subject to the further constraint of a cumulative lifetime limit expressed as $5(N - 18)$ rein$_s$) where N is equal to the worker's age in years. Some Federal agencies (e.g., the Departments of Defense and Energy) use a simpler, more restrictive limit of 5 reins/year.

A major source of human exposure to ionizing radiation is natural background radiation. The two sources of this exposure are cosmic radiation produced by collisions of high-energy particles impinging on the earth's atmosphere, and the radioactive elements (radionuclides; e.g., radon, potassium commonly found in soil, brick, concrete, and stone. The total whole-body dose due to natural sources averages about 100 millirems per year; the dose to the lungs from natural sources is about 500 millirems per year; and the average gonadal dose from natural radiation is about 80 millirems per year (250,298). Added to this exposure from background radiation is the dose received from medical use of X-rays, which contributes about 20 millirems per year to gonadal exposure. Other minor sources of nonnatural exposure are atmospheric weapons testing, nuclear powerplant operation, consumer products, and building materials. Tobacco smoking may also result in substantial localized radiation exposures to points within the respiratory tract, possibly reaching 8,000 millirems per year (250).

Occupational Exposure to Ionizing Radiation

Some 1.32 million persons are presently occupationally exposed to ionizing radiation each year. About 44 percent of all exposed workers are employed in medicine, 23 percent in industry, 16 percent in government, and 11 percent in the nuclear fuel cycle. Workers in the nuclear fuel cycle accounted for the largest share of the collective dose (37 percent), followed closely by those in medicine (27 percent), and industry (25 percent) (see chapter 7). Comprehensive surveys of the numbers of workers exposed and their doses, age, and sex distributions have been published by EPA (372,373). In general, the exposures are low. However, it is important to remember that ionizing radiation causes dose-related damage to all tissues.

Industrial use of ionizing radiation is now rapidly expanding, both in terms of its application to industrial processes and the type of industry involved. Future developments in the industrial application of ionizing radiation are likely to be focused in the area of radiation processing. Research is being conducted on radiation processing to achieve cross-linking, polymerization, grafting, and free-radical generation in the chemical industry, and in the production of flooring, furniture, textiles, adhesives, paints, membranes, and wood/plastic composites (42).

Preservation and sterilization of foods, spices, cosmetics, and pharmaceuticals by irradiation is also rapidly approaching large-scale commercial application (42)288), These efforts will, of necessity, expand because of the ban on ethylene dibromide for similar uses. The radiation source used in sterilization can be either machine-generated electrons or gamma rays from cobalt-60 or cesium-137 (288). Reduction of microbial load and improvement in food properties occur with applications of about 100)000 to 1 million rads, and sterilization for commercial purposes requires about I million to 5 million rads.

Concern for worker exposures occurring during radiation-processing operations is greater than for other industrial or medical applications. problems can be foreseen due to the experimental nature of the processes, the high doses of radiation employed, the likelihood that radiation processing will be conducted in small establishments with limited resources for protective measures, the lack of employee training regarding the hazards involved, and the absence of regulatory standards and guidelines for controlling exposures. No information currently exists to indicate the magnitude of potential exposure of men and women engaged in these newly emerging occupational tasks (288). This is therefore a research area of major concern because ionizing radiation is known to exert profound effects on the developing embryo/fetus and child and on reproductive function in men and women.

Male.—Ionizing radiation produces dose-related impairment of testicular function. There is some indirect evidence that occupational exposure to radiation is associated with diminished sex drive and decreased sperm viability in men (339). High doses of ionizing radiation clearly have an adverse effect on the gonads of men. Although the effects of relatively low doses of ionizing radiation on male reproductive function (below 5 to 10 rads) are not well understood, sperm production is suppressed by doses of X-irradiation as low as 15 rads (71). Sperm production is transiently eliminated with doses of 50 rads. At high dosages, in the range of 236 to 365 rads, severe spermatozoa damage occurs which persists for many months (75). Radiation doses greater than 400 rads are associated with the complete cessation of testicular function. Although it occurs rarely, recovery of sperm production is possible, even following dosages as high as 400 rads. There are numerous case reports of testicular damage produced by radiation therapy for malignancies (325), but well-documented reports on the effects of occupational exposures are limited.

Testicular gamma and X-irradiation in animals exert profound effects on developing sperm. Numerous studies have been conducted in mice to assess dose-response relationships for induction of sperm abnormalities (48,269). When mice were exposed to testicular X-irradiation, the dose to produce a doubling in the number of abnormal sperm in comparison with controls was determined to be 39 rads (409). A 1983 study determined that the dose of X-irradiation to produce a 50 percent suppression of type A spermatogonia was 30 rads for the mouse and 917 rads for

the human (71). This indicates that human type A spermatogonia are about 3.1 times more sensitive to ionizing radiation than are mouse spermatogonia. Irradiation of the testes also has a mutagenic effect on male germ cells, as evidenced by reduction in post-implantation survival of the offspring of exposed male (313) animals.

Female.—In the female, the reproductive process is susceptible to radiation-induced damage in several ways. Because females are born with a fixed supply of oocytes (egg cells), damaged egg cells cannot be replaced (see chapter 3). Exposure of these cells to ionizing radiation, either during gestation or following birth, can cause reproductive disorders at puberty and during reproductive life. There is evidence that exposure during childhood may lead to disorders of the endocrine system, which subsequently give rise to infertility or failure to undergo normal pubertal development.

Animal studies demonstrate similar effects with a dose-related impairment of reproductive processes. All tissues of the reproductive tract are susceptible to the adverse effects of ionizing radiation but exhibit different dose-response curves, Numerous studies of the effects of ionizing radiation on ovaries, oocytes, and reproduction have been conducted in rodents, primates, and many other species (21). The vast body of data from animal studies reveals wide variations in susceptibility according to species, age, egg-cell stage, and follicle size (22,221). For example, extreme sensitivity of female egg cells to ionizing radiation is seen in postnatal mice and in prenatal squirrel monkeys. Oocytes in women and in adult rhesus monkeys, by contrast, appear to be relatively resistant. In sensitive animals, such as the juvenile mouse, destruction of immature oocytes can result from dosages of less than 6 rads.

Pregnancy .-Exposure of pregnant women to levels of greater than 20 rads leads to birth defects, while lower exposures in the region of 1 to 10 rads are associated with increased mental retardation and childhood leukemia and other cancers in their offspring (218,251). The National Council on Radiation Protection and Measurements (252) recommends that workplace exposure of a fertile woman be controlled to ensure that if she becomes pregnant her fetus will receive a cumulative exposure of no more than 0.5 rads.

Understanding of the teratogenic effects of ionizing radiation on fetal development dates to the explosion of the first nuclear weapon in 1945. Extensive retrospective epidemiological surveys were conducted on individuals exposed to radiation in utero in Hiroshima and Nagasaki (44)277) 343,402,403,405,406). These studies, coupled with earlier case reports, provide clear evidence of severe teratogenic effects, particularly the occurrence of microcephaly (reduced size of the brain), and severe mental retardation.

The effects of exposure on reproductive function are not known for the low-dose range in females although clinical data suggest that reproduction is not impaired. The evidence for harmful effects at high doses is clear, however. High doses can cause sterility and initiate menopause. Some effects of chromosomal abnormalities have been observed in women who were exposed to ionizing radiation prior to pregnancy, but important confounding variables may have biased results, and dosages were unknown.

Nonionizing Radiation

The term nonionizing radiation refers to the region of the electromagnetic spectrum where the energy of the emitted photon is incapable of ionizing atoms or molecules in the irradiated tissue. The lower wavelength limit for nonionizing radiation is considered to be 100 nanometers [rim], which corresponds to ultraviolet light. Succeeding portions of the spectrum correspond to visible light (4oo to 750 nm wavelength), infrared radiation (0.75 micrometers [mm] to 750 nm wavelength), and radiofrequency radiation (1 millimeter [rim] to 10,000 kilometers km] wavelength). As wavelength increases along~ the electromaa-

netic spectrum, wave frequency decreases. Considerable confusion arises from the fact that the anxiety-provoking term "radiation" is applied to X-rays (i.e., ionizing radiation) as well as to microwaves, radio and television transmission signals, and other forms of nonionizing energy. These forms of energy are in fact significantly different with respect to biological activity. All humans are under constant exposure to natural or man-made sources of nonionizing radiation, thereby complicating the design of any population study to assess the health effects of occupational exposure.

Ultraviolet Radiation

Ultraviolet radiation is produced naturally by the sun, and artificially by arcs operating at high temperature. Exposure to ultraviolet radiation in the workplace is associated with incandescent, fluorescent, and discharge-type light sources, as well as with welding and cutting torches, electric arc furnaces, plasma torches, and lasers. In addition, outdoor workers, such as farmers, fishermen, lifeguards, and construction workers receive substantial solar exposures. Ultraviolet radiation can be expected to occur in all occupations involving germicidal lamps, welding arcs, and plasma torches, and in industrial drying and curing processes, printing processes, and chemical manufacturing operations.

Visible Light

Visible light is provided by the sun and by artificial light sources. Industrial exposure to visible light is additionally associated with highly incandescent lights and various types of arc processes. Many sources of high-intensity visible light also produce substantial thermal energy.

Infrared Radiation

All objects emit infrared radiation, which increases as a function of temperature. The sun is a major source of infrared radiation, Occupational exposure occurs either directly from lamps or indirectly from heat sources. The most widely recognized industrial exposures to infrared radiation are from hot furnaces, molten metals or glass, and arc processes.

Laser Radiation

A laser (acronym for "light amplification by stimulated emission of radiation") operates in the infrared, visible, and ultraviolet regions of the electromagnetic spectrum. Lasers are sources of monochromatic optical-frequency waves, whose output can be focused to form extremely high-power beams (127). The source of laser radiation can be a solid, a liquid, or a gas that can be made to fluoresce. Sources in use include ruby, neodymium, helium, neon, argon, krypton, carbon dioxide, and an yttrium-aluminum-garnet combination.

The laser has been of great value in numerous segments of industry, and its applications continue to expand. In the biomedical field, lasers are used in the detection of tumors, to measure circulation and components of blood, and as optical knives to perform delicate surgery. Several methods have recently been developed in which lasers are used to detect air pollutants with great specificity and sensitivity. Lasers are used in metal-working and in the aircraft industry to drill holes, particularly on curved surfaces, with great accuracy and precision. A recent development in laser applications is in communications and information transfer with fiber optics.

The harmful effects of optical radiation appear to be restricted to the surface of the body, especially the skin and eyes. Lasers operating in the visible or near infrared wavelength regions may produce severe retinal burns of the eye, and lasers operating in the infrared region (e.g., carbon dioxide lasers) may produce surface burns on the cornea. Damage is primarily the result of tissue-heating, which causes protein destruction (denaturation) and the typical symptoms associated with burns. An additional biological effect of ultraviolet and infrared radiation, and of lasers, is excitation of intracellular organelles unrelated to tissue-heating (81). The health effects resulting from thermal excitation of cell organelles are

not understood. Ultraviolet radiation is also regarded as a cause of skin cancer. There are no known reproductive effects in humans and lower animals associated with occupational or environmental exposure to optical radiation. In many animals, changes in the ambient levels of light are a powerful modulator of reproductive behavior.

Radiofrequency/Microwave Radiation

The applications of these man-made electromagnetic fields are extremely diverse and rapidly expanding. In terms of potential health effects, two frequency ranges are receiving focused attention. One is the microwave and shortwave frequetlcy range (several MHz to 100 gigahertz (GHz) used by the military and for communications. The other is the extremely low-frequency range (10 to 60 Hz) associated with high-voltage power lines. There is no question that the thermal effects of radiofrequency and microwave radiation are hazardous. There is, however, little agreement as to the potential for health hazard produced by the nonthermal effects of this physical force.

For a human, significant heating will not occur with radiofrequency radiation having a frequency below 15 MHz and a wavelength greater than about 20 m (i.e., television and radio transmission, radiation from power lines). The electromagnetic radiation used in radar is in the microwave frequency range capable of inducing thermal and subthermal biologic effects in humans (234). The American National Standards Institute (ANSI) Committee C95 has recently proposed revised guidelines (8) for safe exposure to radiofrequency electromagnetic fields which acknowledge that prolonged whole-body exposure at intensities above 100 mW/cm^2 are dangerous at frequencies at which significant energy is delivered to the human body. In humans, the radiation absorption efficiency reaches a maximum at a frequency of 77 MHz for a person 1.75 m tall who weighs 70 kg (117). The majority of industrial radiofrequency sources operate from 10 to 40 MHz, whereas a microwave oven operates at 2,450 MHz. Diathermy electromagnetic waves (27.5 Hz) have great penetration into the human body and produce significant heating, while microwaves with frequencies above 10)000 MHz have little penetration (44).

Workplaces designated as hazardous due to the presence of radiofrequency/microwave radiation are generally associated with antenna systems, emitters, generator tubes, and other high-frequency units. The adverse health effects of exposure to radiofrequency/microwave radiation that result in tissue heating are welldocumented (364). The health effects of subthermal doses remain unclear, particularly with respect to low-frequency and weak-field radiation.

Male.—The only form of nonionizing radiation that has been repeatedly associated with damage to male gonads is radiofrequency/microwave radiation. The available evidence is incomplete, however, with respect to dosage and influence of other variables. There is little doubt that radiofrequency/ microwave radiation of sufficient intensity can damage the testes by thermal action. Most studies of occupational exposure to radiofrequency/microwave radiation have involved military personnel. Clinical studies of radar operators in the U.S. Navy showed no adverse effects on male fertility.

Numerous studies have been conducted on testicular and reproductive function in rats and mice exposed to radiofrequency/microwave radiation. Testicular degeneration is clearly associated with microwave dosages sufficient to cause tissue heating (75,203,314). At a dosage of microwave radiation (1.3 GHz) sufficient to cause a net change in body temperature of 1.50 C, no effects were seen on the testes of rats (203). In contrast to the evidence for effects of ionizing radiation, evidence concerning a mutagenic effect for microwave radiation is inconsistent and conflicting (313). Yet impaired male fertility as evidenced by a reduced pregnancy rate in mated females can be achieved with sufficient dosages of microwaves (189). The extent to which thermal effects account for these results is not clearly established.

Female.—Epidemiological studies of microwave workers and military personnel exposed to radar have not provided clear evidence for the development of pathologic damage, reproductive failure in women, or malignancies (233). These negative and in some cases equivocal results may reflect inadequacies in the studies (e.g., inadequate dose information, inappropriate control groups, and lack of recognition of concomitant

exposure to toxic agents). There is thus a need for well-designed and carefully controlled epidemio-Iogical studies of workers and other populations exposed to measured amounts of radiofrequency/microwave radiation. The presently available data suggest that the adverse effects of radiofrequency/microwave exposure are primarily, if not exclusively, the result of tissue-heating. Occupational exposure of women to radiofrequency/microwave radiation at typical power densities would not be expected to produce sufficient internal tissue-heating to harm the fetus or the reproductive organs.

Pregnancy.—The adverse effects of prenatal exposure to radiofrequency/microwave radiation at various frequencies have been extensively studied in rats, mice, chickens, Japanese quail, and insects. Studies have been concerned with morphologic alterations, as well as more subtle neurobehavioral changes. The power levels employed in many of these studies were sufficient to indicate that fetal malformations may have resulted from hyperthermia. At lower power densities, there appears to be a minimum threshold level for induction of fetal abnormalities. Exposures of rats to a power density of 35 mW/cm^2 GHz continuous-wave microwave radiation on gestation days 1 to 6 produced a decrease in implantation sites per litter and decreased fetal weight (254). Exposure to a power density of ***30*** m W/cm^2 on days 6 to 15 of gestation produced a slight increase in fetal malformations. No effects on the offspring were observed when pregnant mice were exposed to power densities of 5 and 21 mW/cm^2.

Negative results have also been obtained with pregnant rats exposed to 915 MHz microwaves at a power level of 10 mW/cm^2 (166), and with pregnant rats exposed to 100 MHz radiation (the frequency region of maximum human absorption) at a power density of 25 mW/cm^2 (198)199). These exposures produce no increase in maternal temperature. It therefore appears that a threshold for induction of teratogenic effects in mice and rats by radiofrequency/microwave radiation may be in the power density region of about 30 mW/cm^2. These results also suggest that the 1982 ANSI exposure standard of 1 mW/cm^2 for frequencies between 30 and 300 MHz will provide adequate protection of pregnant women and the human embryo/fetus. It is important to note, however, that there is a considerable body of disagreement concerning the nonthermal effects of nonionizing radiation. Additional study of these effects will be necessary before acceptable exposure levels can be established.

Ultrasound

Ultrasound is a mechanical vibration of an elastic medium having a frequency range beyond 16,000 to 20,000 Hz, which is above audible frequency for the human ear. Low-frequency ultrasound (18,000 to 30,000 Hz) of high intensity (6 to 7 W/cm^2) is widely used in industry in cleaning baths for metal and fabricated parts; in welding, brazing, and soldering; for electrolytic coating; and for acceleration of chemical reactions. Low-frequency ultrasound is also a compound of the noise produced by jet engines, gas turbines, and powerful pneumatic devices.

High-frequency ultrasound is more readily absorbed by the surrounding medium and does not travel in air. Penetration of human tissue by ultrasound decreases as the frequency increases. High-frequency ultrasound (500 kHz to 5 MHz) of low intensity (0.1 to 10 W/cm^2) is widely used for detection of flaws and structural analysis of matter.

The medical applications of ultrasound have greatly increased in recent years, particularly in obstetrical diagnostic procedures (211). Two types of ultrasound are used with pregnant women. One is pulsed ultrasound, employing frequencies in the 1 to 10 MHz range with output intensities ranging from less than 1 to 10 mW/cm^2. The other is continuous-wave ultrasound, employing frequencies of about 2 MHz with output intensities ranging from less than 1 to 20 mW/cm^2. Continuous-wave ultrasound is used early in pregnancy for placental localization, confirmation of normal or abnormal pregnancy, detection of twins, and in monitoring fetal growth.

Worker exposure to ultrasound, particularly during the loading and unloading of parts of cleaning tanks, may result in damage to peripheral nerves and blood vessels of the fingers, hands, and forearms (306). The adverse effects in humans from high-frequency ultrasound are not clearly understood.

The teratogenic and embryotoxic effects of exposure to ultrasound have not been studied as extensively as those resulting from exposure to radiofrequency/microwave radiation. As with microwaves, when ultrasound exposure has been reported to induce fetal malformations, there is also an increase in maternal temperature (181). When pregnant mice were exposed to 1 MHz ultrasound at power densities up to 1.00 W/cm^2, no statistically significant effects on the fetus could be demonstrated (181). These results suggest that clinical applications of ultrasound diagnostic procedures in pregnant women at typical power levels below mW/cm^2 should not pose an unacceptable risk to the mother or fetus.

Video Display Terminals (VDTS)

Use of VDTS is rapidly expanding as a means to display alphanumeric information in the workplace. An estimated 5 million to 10 million VDTS were in use in the United States by 1980 (249). By 1990, it is projected that 25 million VDTS will be in use (13). The principal applications for VDTS are for data entry, data acquisition, interactive communication, word processing, computer programming, computer-assisted design, and computer-assisted manufacture. The expanding use of VDTS has created an area of special health concern with respect to workplaces and occupations that have been traditionally regarded as hazard-free. The major issue of concern is the potential for chronic worker exposure to radiation emitted by VDTS and its possible health-related consequences.

Most VDTS use cathode ray tubes, and in many respects are similar to television receivers. Cathode ray tubes emit visible radiation (light), but also emit ultraviolet and infrared radiation, and radiofrequency radiation in the 15 to 125 kHz frequency range. Cathode ray tubes also produce internal X-rays, which are effectively fihered by the tube face, thus preventing most emissions. Numerous field surveys and laboratory studies by industry, government, and independent groups have concluded that the emission of all types of radiation by VDTS is well within acceptable limits of exposure (13,249). It should be noted, however, that most VDT emissions are in the radiofrequency range below 300 kHz, where no enforceable emission standards have been established and adverse health effects are not well understood. A limit of 614 V/M or 100 mW/cm^2 for radiofrequencies between 10 kHz and 3 MHz is being recommended by the American Conference of Governmental Industrial Hygienists (5). This level is about 10 times higher than the VDT emissions in the 10 kHz-100 MHz range measured under worst-case conditions in a study by the Center for Devices Radiological Health (249). In the same study, no X-ray emissions could be detected from 91 VDT units operated under normal conditions.

Reports of clusters of spontaneous abortions, miscarriages, and birth defects among VDT operators have raised serious concerns over safety. Although at least two of these clusters have been investigated, no association has been confirmed for VDT work and increased risk for adverse reproductive outcome (249). The only documented causal role of VDTS in inducing birth defects or fetal death comes from the fact that VDTS emit ionizing radiation, which has been implicated in birth defects and increased fetal death rates. None of the numerous studies on emissions from VDTS (249) report levels of ionizing radiation that are known to be associated with biological effects of any kind. Since the primary emissions from WTS are below 300 kHz, there is a possibility that low-level nonionizing radiofrequency radiation may be involved in some type of as-yet-unexplained adverse effect on reproduction. Great care should be taken in drawing any such inference, however, since no clear evidence exists to support any such association.

Information regarding the effects of low frequency electromagnetic radiation on reproduction in females is conflicting. Early studies with mice exposed continuously to 60 Hz electric fields (3.5 kV/m, 10 kV/m, and 15 kV/m) over several generations indicated that mortality in the offspring may be higher in certain exposed groups

Photo credit: Pemina Meisels

Reports of reproduction system effects among users of the many video display terminals (VDTS) now in use in the Nation's workplaces have raised questions about the safety of prolonged VDT exposure. Comprehensive studies of these effects are now in progress.

(223). A 1980 study reported no effects on fertility or development of offspring in mice exposed to a 240 kV/m 60 Hz electric field for about 3 months (105). Similarly, in rats exposed for 30 days to a 100 kV/m, 60 Hz electric field, no effect was seen on reproductive performance of the exposed animals, nor were significant adverse effects noted in the offspring (33).

NIOSH has undertaken an extensive study that is designed to help resolve the question of whether VDT use affects reproduction. The 3-year study will involve a cohort of 2,000 VDT-exposed women and 2,oOO nonexposed controls. All women will be employed in nonmanagement positions in a small geographic area. Reproductive, health, and work histories will be obtained by self-administered questionnaires completed at three 9-month intervals. Personal habits such as alcohol, tobacco, and caffeine use will be taken into account, NIOSH intends to perform a follow-up study to evaluate future reproductive outcomes. Specific studies of adverse reproductive effects in men exposed to VDT emissions have not been conducted by NIOSH, nor are any being planned.

Another prospective study of 10,000 office workers has been initiated by Mount Sinai School of Medicine in cooperation with the Service Employees International Union and the 9 to 5 Association of Working Women. The study will be comprised of male and female VDT worker volunteers who will be compared with a group of non-VDT workers. Participants will complete extensive health quesionnaires on a regular basis. Results will be analyzed after 2 years. Follow-up studies are planned to determine whether children of VDT workers suffer an increased incidence of cancer (272). (A discussion of reproductive and other health effects of VDT emissions appears in OTA'S upcoming report, ***Automation and America Offices.)***

Magnetic Fields

Magnetic fields are associated with power transmission lines, electric machinery and appliances, and the Earth's natural electric field. Beyond the near field region, an electric field is always associated with a complementary magnetic field, and vice versa.

The magnetic field strength directly beneath a 60 Hz alternating current (AC) power transmission line ranges from 0.3 to 0.6 G, dropping off to about 0.01 to **0.1 G** 200 feet from the right-of-way center (82). By comparison, the Earth's natural magnetic field strength is 0.6 G, and localized 60 Hz magnetic fields around household appliances (e.g., color television sets, hair dryers) may range from 1 to 25 G. It is generally assumed that the biological effects of magnetic field are attributable to induced body voltage, electric fields, and currents,

Considerable interest has developed in recent years in evaluating the biological activity of low-level, low-frequency (50 to 60 Hz) magnetic fields. Exposure to this type of electromagnetic radiation commonly occurs in the vicinity of extremely low-frequency (ELF) communications antennas, which would result in significant population exposures.

Teratogenic effects in humans have not been associated with exposure to magnetic fields. Several studies in the United States, Sweden, England, and Wales have reported correlations between increased incidence of leukemia and possible exposure to electric and magnetic fields near high-voltage power lines. However, this association was not substantiated by a 1980 study (115). Information regarding effects of low-frequency electromagnetic radiation on reproduction in female laboratory animals is conflicting (105,223,330). Although these data do not permit a firm conclusion, they suggest that occupational exposures to magnetic fields may not constitute a hazard tore-production.

Hyperbaric and Hypobaric Environments

Air pressures in excess of those found at sea level (14.7 pounds/square inch) are considered hyperbaric, and air pressures below that found at sea level are hypobaric. Workers exposed to hyperbaric environments include those engaged in caisson or tunneling operations, where compressed gas is used to exclude water or mud and to provide structural support during construction. Such operations are associated with pressures that can be more than four times that occurring at sea level (363). Underwater diving can be associated with considerable pressure, since each 10-meter increase in sea-water depth is equivalent to an increase of one atmosphere pressure. The primary health effect caused by hyperbaric environments is the tissue damage that results from expansion or contraction of gas spaces found within or adjacent to the body, such as around the teeth, in the sinuses, and within the ear. This type of effect is referred to as barotrauma. Other secondary types of damage caused by hyperbaric environments result from the narcotic action of nitrogen at four atmospheres of pressure or more, oxygen poisoning when its partial pressure exceeds two atmospheres, and the severe effects of rapid decompression.

Hypobaric environments can be of two types, high-altitude and low-altitude. High altitude hypobaric environments occur when pilots and air crews operate aircraft at altitudes in excess of 30,000 feet. In these situations, the greatest hazard is caused by lack of oxygen (hypoxia). Hypoxia also occurs at lower altitudes, as shown by the syndrome of impaired judgment and performance and general feeling of malaise associated with acute mountain sickness (363).

Male. -Only limited data are available on the influence of atmospheric pressure on male reproductive function. one study has described the semen characteristics of nine men exposed to high altitude (14,000 feet) in Peru for 4 weeks (83). A continuous decrease in sperm count was observed throughout the experiment. In addition, increased numbers of sperm abnormalities, decreased motility, and decreased testosterone levels were associated with high altitude. The principal causative factor for these changes may have been reduced ambient oxygen levels.

From the limited data available, it appears that male fertility can be suppressed by both hypobaric and hyperbaric environments (83). A 1968 review cited studies in which brief exposures to high altitude were found to cause impaired spermatogenesis, destruction of germinal epitheliums, and testicular atrophy in several species of animals. These changes are apparently reversible on descent to sea level.

In a 1982 study, mice were exposed to high pressure (50 ATA) at intervals throughout one spermatogenic cycle and then mated with untreated females in order to evaluate effects on sex drive and fertility (20). A significant effect on male fertility resulted, as evidenced by reduced pregnancy rates in mated females. In addition, there was a reduction in live litter size, although no indication of teratogenic effects was obtained, The precise mechanism for the action of high pressure on male fertility could not be identified, especially in view of the fact that no gross morphological abnormalities were seen in the sperm,

Female. -Data concerning the effects of hyperbaric environments on female reproduction are limited to two case reports (40,357); there is thus insufficient scientific evidence to determine whether hyperbaric environments represent a hazard to female reproduction.

Pregnancy.—Atmospheric conditions are known to affect the outcome of pregnancy. Several studies have documented that human birth rates and birth weights are reduced in communities at high altitudes (75).

There is little information available regarding the effects of atmospheric pressure variations on female reproduction. Several studies have been conducted in pregnant dogs and sheep using conditions designed to simulate underwater diving and rapid decompression (258,340). In general, it appears that in the late stages of fetal development, the fetus appears to be less susceptible to decompression sickness than the mother. These studies do not provide an indication of the possible effects of hyperbaric exposures on the embryo/fetus early in pregnancy.

Hot and Cold Environments

The relationship of body heat to the external environment is a function of air temperature, air velocity, moisture content of the air, and radiant temperature. The hazards of working in a hot environment result when an imbalance occurs between metabolic heat production and heat loss from the body to the environment; i.e., heat loss fails to keep pace with heat produced by the body. A rise in body temperature is an indication that the body is storing heat that it cannot dissipate. As a result of the body's inability to adequately dissipate excess heat, four primary illnesses may occur. In order of increasing severity they are referred to as heat rash, heat cramps, heat exhaustion, and heat stroke. Heat stroke is a serious medical condition that can be fatal if not treated immediately. It is recommended (364) that workers should not continue to perform tasks that cause their body temperatures to exceed 380 C.

Maintenance of heat balance in a cold environment requires that the body restrict heat loss and increase heat production. The primary mechanism for limiting heat loss is constriction of the blood vessels (vasoconstriction), particularly in the extremities. This results in a drop in skin temperature and consequently less heat loss to the environment. Under severe conditions, the chilling of the extremities is so great that tissue freezing occurs, which results in frostbite. Work in a cold environment of sufficient duration to result in exhaustion will make the individual more prone to heat loss and the development of severe acute effects of general body hypothermia (364).

Experts have questioned whether women are exposed to work environments that are sufficiently hot to affect reproduction (75). Animal studies indicate that maternal temperature must be raised to at least 38.90 C before effects on the fetus are observed. Teratogenic effects have occurred in humans in conjunction with maternal hyperthermia. Prolonged fever in the mother during the first trimester of pregnancy appears to be a major factor in producing severe central nervous system dysfunction in offspring (70,110, 286). There is no documentation available concerning the specific effects on reproductive function or pregnancy outcome in women exposed to cold environments.

Although hyperthermia is well-known for its antispermatogenic effects in humans, there are no data available on the influence of cold environments on reproductive function in men. Documentation on the suppression of spermatogenesis by heat is largely related to certain medical disorders, such as cryptorchidism (undescended testes) varicocele (enlarged veins in the scrotum), and acute febrile illness (301). There are no case reports or epidemiologic studies of reproductive function in men working in hot environments. One group of experts has concluded that the occurrence of adverse reproductive effects in men from exposure to hot environments is unlikely under normal working conditions (75). Occupational exposure to direct heat, by contrast, may be a leading cause of male infertility.

Application of heat to the scrotum has been promoted as an effective, reversible means of male birth control. In controlled studies with human volunteers, elevation of testicular temperature by 2,50 to 3.00 C for 30 minutes on several alternate days led to depression in sperm count beginning at 3 weeks after exposure and lasting 3 to 5 weeks (299,301). Sperm counts subsequently recovered and in fact increased beyond pre-exposure levels. It is important to note that these transient decrements in sperm count are unlikely to be associated with a decrease in male fertility and should not be used as a contraceptive method.

Noise and Vibration

Noise, generally identified as unwanted sound, is probably the most prevalent of all occupational hazards. Permanent, noise-induced hearing loss has been recognized for several hundred years (5). Noise is classified according to several criteria. wide-band noise refers to sound that covers a large portion of the available frequency spectrums, and is typified by the noise produced by large machinery and jet engines. Narrow-band noises are often associated with a definite pitch, such as that produced by a circular saw or other power-cutting tools. A noise of short duration (less than a second) that rises rapidly to a peak and then falls to below background levels is referred to as impulsive or impact noise. The sounds of a gunshot or a forging hammer are examples of impulsive noise.

Vibration occurs in all segments of industry in which power-driven tools, heavy machinery, and mechanized equipment are utilized. When considering workplace exposure, vibration is usually categorized as either segmental or whole-body vibration. Whole-body vibration is mechanically transmitted to the entire human body through a supporting structure, such as a vehicle seat. Segmental vibration affects localized parts of the body, usually the hands and feet. Hand-operated tools are a common source of segmental vibration.

The harmful effects of segmental vibration appear to be more severe than for whole-body vibration (364). Workers who use vibratory hand tools for prolonged periods may develop Raynaud's phenomenon ("dead hand" or "vibratory white fingers"). This condition is associated with numbness and blanching of the fingers, and can result in loss of muscular control and reduced sensitivity to vibration, pain, and temperature. Numerous additional ailments can be associated with segmental vibration, including changes in bone, nerve degeneration, muscular weakness and atrophy, and Dupuytren's disease, which causes permanent flexion of one or more fingers (364).

Male.—There is no evidence to indicate that occupational exposure to noise is harmful to male reproductive function, nor is there conclusive evidence of adverse effects of vibration on reproductive function in men. one report found sperm abnormalities and decreased fertility among professional drivers, which may have resulted from vibration (75). other factors, however, including elevated intrascrotal temperature from prolonged sitting, may also be implicated.

Female.–Evidence concerning the effects of noise on reproductive function and pregnancy outcome in humans is largely circumstantial and conflicting. No information is available on the effects of occupational exposure to noise. Based on the results of animal studies, it is presumed that vibration may affect the human embryo. There are no specific reports of adverse reproductive effects in the human female resulting from vibration.

Pregnancy.—The most consistently reported reproductive effect of noise in animals is pregnancy-rate reduction (253). In addition, there is evidence that embryolethality and fetolethality are increased by noise exposure. Both positive and negative findings with respect to teratogenesis have been reported. Differences in noise level and variations in spectral and temporal patterns of exposure may all be expected to influence the biologic effect produced. Thus far, it has not been possible to use the results from available animal studies to predict whether similar effects may occur in humans.

There are insufficient data available from animal studies to critically evaluate the reproductive effects of mechanical vibration. In a 1971 study, pregnant mice were exposed at 4% and 7 days gestation to whole-body vibration for 10 minutes at 3 different frequencies (5 Hz, 10 Hz, 20 Hz) (24). Mouse embryos were found to be quite resistant to vibration, although in the 4% day embryos, the incidence of abnormalities was increased in the 20 Hz group.

EFFECTS OF STRESS ON REPRODUCTIVE FUNCTION

Stress, in the workplace as eIsewhere, refers to a type of individual response to an environmental stimulus or condition. The principal sources of stress in the work environment are posture, work on industrial machines, physical exertion, mental stress, environmental factors, and characteristics of the worker (174,220).

Psychological Stress

It has long been suspected that psychological stress may lead to infertility in both men and women. This possibility seems clear from the evidence in animals. The question of a relationship between psychological variables and infertility is complex, and the literature, although extensive, is speculative, anecdotal, and contradictory, Few studies meet adequate methodological standards. Nevertheless, a consideration of the effects of workplace stress on reproductive function must address the question of psychogenic infertility.

Psychological stress can lower testosterone levels (191) and may be associated with decreased sperm counts (35,229). In women, stressful experiences, such as those encountered in wartime, may lead to amenorrhea (182). Clinical evidence of such stress-induced psychological endocrine reactions among patients attending infertility clinics is anecdotal. Hence, although a psychological mechanism associated with infertility is possible, there is little firm evidence of stress-induced infertility, save for some cases of amenorrhea. Knowledge of psychogenic endocrine reactions is extremely limited (33).

Workplace psychological stress may play a role in infertility by means of a behavioral mechanism—through interference with the sexual relationship. In this context, the following sexual problems have been cited: impotence, retarded ejaculation, ejaculation prior to intromission, infrequent intercourse, and vaginismus (extreme aversion to coitus accompanied by painful spasm of the vagina) (94). Detection of behavioral problems induced by psychological stress depends on a number of factors, including the comfort of the clinician in asking, and the comfort of the patient in answering, detailed questions about sexual behavior (54), and how extensive an assessment of sexual function is made (33).

Further study may reveal that the reproductive status of workers facing workplace-induced psychological stress exhibits a distribution that mirrors that of the population at large. Adaptation to psychological stress may not represent the demands of a particular stress, such as job insecurity or long working hours, but rather the manifestations of enduring personality constructs and capabilities (60).

physiological Response to Stress

Stress, from whatever source, stimulates several hormonal responses in both women and men. Prominent among these responses are the secretion of ACTH (adrenocorticotropin, a hormone stimulating the adrenal glands) from the pituitary gland, and neurotransmitters and steroid hormones from the adrenal glands. These hormones serve to adapt the body to stress ranging from the mildly psychological to the intensely physical by affecting the cardiovascular, energy-producing, and immune systems (17).

Plasma levels of the neurotransmitters epineph - rine and norepinephrine are one measure of stress-induced activation of the adrenal glands and nervous system. Until recently, it was difficult to obtain a reliable measure of plasma epinephrine and norepinephrine because of their extremely low concentrations in the blood. The introduction of highly sensitive assays, however, has made it possible to determine their concentrations during stressful situations in humans.

Physical exertion, cold, and heat stress, for example, can cause marked elevations in these hormones. Public speaking may result in a so percent increase in plasma norepinephrine ***and a 100*** percent increase in plasma epinephrine (17).

Proper reproductive function is also heavily dependent on the functional integrity of these three major body systems. As the complex hormonal and biochemical sequelae of workplace stress become better known, it is likely that a more complete understanding of the effects of workplace stress on reproductive function will emerge. At present, the documented effects of repeated or prolonged stress on the cardiovascular, energy-producing, and immune systems should be regarded as factors with the potential to compromise reproductive function.

Physical and Psychological Stress and the Pregnant Worker

The pregnant employee is able, in most cases, to continue productive work until the onset of labor at 40 weeks (168). It is important to note that in a discussion of pregnancy and working, generalizations are made only for normal, uncomplicated pregnancies. Complications of pregnancy (e.g., vaginal bleeding, premature rupture of the membranes) (29) may cause some women to modify certain aspects of their work at specific times during their pregnancies.

Recent research offers reassurance that working during pregnancy is not in itself a risk factor for adverse outcome. Pregnancy outcomes of 7,155 women who worked between 1 and 9 months of pregnancy were compared with outcomes of 4,018 women who were not employed during pregnancy (222). It is significant that no differences were found between the group of working pregnant women and the group of nonworking pregnant women in rates of premature birth, Apgar score, perinatal death rate, birth weight, use of special care nurseries, or prevalence of malformations. These findings indicate that working to term in the absence of contraindications does not impose an added risk on mother or infant. Remaining unanswered is the question of whether any specific occupational groups are at increased risk of adverse pregnancy outcome by virtue of their continued employment during pregnancy.

In a 1982 study comparing pregnant and nonpregnant women and their partners, pregnant women were more likely to report altered states; e.g., “feeling ill” or “feeling overweight .“ Pregnant women, however, reported the fewest impacts of these states on their performance in the workplace as compared with any of the other groups (prospective fathers, and nonexpecting women and men) (214).

Quantifying the relative risks posed by occupational stresses during pregnancy is particularly difficult because of the absence of baseline data for comparison. There has been no scientific study, for example, comparing the pregnant worker’s exertion (mental or physical) during paid employment with that of full-time work in the home. Thus the relative risk to the pregnant worker from workplace stress versus stress in a nonoccupational setting cannot be readily evaluated. A job may entail strenuous activity, such as lifting, which the anatomical changes of pregnancy may make difficult to perform, although women who are accustomed to activities that may be strenuous to others may be able to continue their usual jobs virtually throughout their pregnancies.

The American Medical Association (7) has published guidelines for various job tasks during pregnancy. Table 4-4 shows the period of time during which healthy employees with normal, uncomplicated pregnancies should be able to perform specific tasks without undue difficulty or risk to the pregnancy. All pregnant employees need not stop these activities at the exact time of gestation noted, but the guidelines may be used to help evaluate individual cases. In addressing the issue of the pregnant worker, the American College of obstetricians and Gynecologists makes the following recommendation:

> The normal woman with an uncomplicated pregnancy and a normal fetus in a job that presents no greater potential hazards than those encountered in normal daily life in the community may continue to work without interruption until the onset of labor and may resume working several weeks after an uncomplicated delivery *(6).*

Table 4-4.—Guidelines for Continuation of Various Job Tasks During Pregnancy

Job task	Week of gestation
Secretarial and light clerical	40
Professional and managerial	40
Sitting with light tasks:	
Prolonged (more than 4 hours)	40
Intermittent	40
Standing:	
Prolonged (more than 4 hours)	24
Intermittent:	
More than 30 minutes per hour.	32
Less than 30 minutes per hour	40
Stooping and bending below knee level:	
Repetitive (more than 10 times per hour)	20
Intermittent:	
2 t0 10 times per hour	28
Less than 2 times per hour	40
Climbing:	
Vertical ladders and poles:	
Repetitive (4 or more times per 8-hour shift)	20
Intermittent (less than 4 times per 8-hour shift)	28
Stairs:	
Repetitive (4 or more times per 8-hour shift)	28
Intermittent (less than 4 times per 8-hour shift)	40
Lifting:	
Repetitive:	
Less than 25 lb.	40
25 t0 501b	24
More than 501 b	20
Intermittent:	
Less than 25 1b	40
25 t0 50 1b	40
More than 501 b	30

SOURCE American Medical Association Council on Scientific Affairs, "Effects of Pregnancy on Work Performance," *J. A,M.A. (251):1995-1997, 1984.*

EFFECTS OF WORKPLACE BIOLOGICAL AGENTS ON REPRODUCTIVE FUNCTION

Occupations associated with a risk of an infectious disease fall into two categories: 1) health care occupations, with direct patient contact, laboratory exposure to infective material, or production of biological materials, and 2) nonhealth care occupations, primarily those involving contact with animals or animal products, refuse collection, groundbreaking or earthmoving, individuals in nonmedical settings (e.g., social workers), or travel into areas of endemic disease. Most of the available information about workplace biological hazards to reproductive function concerns workers in the first category.

Among health care workers, the hazards of hospital-acquired, or nosocomia , infectious diseases have long been recognize . Less attention has been given-to such problems among those in outpatient settings; e.g., dentists' and doctors' offices, kidney dialysis centers, laboratories where there is contact with blood, nursing homes, institutions for the retarded, and prisons (118).

Health care personnel are frequently exposed to infectious agents that can cause intrauterine infections, produce teratogenic effects in their offspring, be passed to and infect their offspring, or act as abortifacients. These agents include the viruses rubella, cytomegalovirus, and hepatitis B. Some infectious agents may also infect and impair male reproductive function (e.g., mumps, orchitis).

Rubella

Rubella, or German measles, is a virus that threatens health care workers and certain nonhealth care workers, such as school teachers and day-care workers, who are likely to have contact with children infected with the disease. The major hazard of rubella is infection in pregnant women, with the possibility of congenital rubella syndrome developing in their offspring. Transplacental infection of the fetus in the first trimester produces developmental abnormalities of the heart, eyes, brain, bone, and ears, often without interrupting the pregnancy. Congenital rubella is also associated with developmental abnormalities

of the male reproductive system (291). Intrauterine infection may also result in miscarriages and stillbirths.

The widespread use of rubella vaccine has greatly reduced the incidence of the disease in the United States. In 1984, 959 cases of rubella and 4 cases of congenital rubella syndrome were reported in the United States (243). Thirteen States and the District of Columbia reported no rubella cases, and 284 of 3,137 U.S. counties (91 percent) were free of rubella in 1983 (241). Whether occupational exposure to the production or formulation of rubella vaccine has produced congenital infections is not known.

Depending on the severity of the illness, the costs of caring for an infant with congenital rubella can be substantial. Such costs can include hospitalization for treatment and repair of congenital heart lesions and cataracts, special educational services, and institutionalization for the most severely affected children (275). The existence of even a limited number of cases of congenital rubella syndrome is thus of significant economic consequence. The average lifetime cost for a child with congenital rubella syndrome is estimated to be $221,660 in 1982 dollars (185).

Therapeutic abortion may be a consequence of rubella infection of pregnant women. Limited information suggests that rubella-associated abortions are considerably more common than cases of congenital rubella syndrome. In an outbreak of rubella in Hawaii in 1977, 11 of 12 women who had rubella elected to undergo abortion (224,322).

Rubella vaccine is the most effective means of preventing the disease. It is well tolerated in the work setting and results in minimal absenteeism (118). The authors of a 1984 study (275) declare that the opportunity is at hand to eliminate rubella from the United States by ensuring that susceptible females of childbearing age are vaccinated and by requiring proof of rubella immunity for all children enrolled in schools.

Cytomegalovirus

Cytomegalovirus, a member of the family of herpes viruses, is generally of minor consequence in normal populations, and infection may be asymptomatic. It can have a major impact, however, if contracted during pregnancy. For this reason, the risk of acquiring cytomegalovirus is of serious concern to many female health care workers. Intrauterine infection with transmission to the fetus is one of the most serious consequences of cytomegalovirus infection in women. Offspring of infected mothers may have an enlarged liver, an enlarged spleen, microcephaly (abnormally small head), microphthalmia (abnormally small eyes), and mental or motor retardation.

Infants who are infected with cytomegalovirus shed large quantities of virus into their urine and saliva. Because these infants commonly have no symptoms attributable to cytomegalovirus, the viral infection is likely to go undetected. Nursery and pediatric health care personnel and teachers in day-care centers are frequently exposed to the secretions of infected newborns and older infants. Yet evidence indicates that this occupational contact confers no greater risk than that faced by young women in the community at large. Thus, although female health care workers frequently and unknowingly care for infants shedding cy - tomegalovirus, and exhibit a high degree of concern about this exposure, their incidence of primary infection is not higher than that of other young women (87). Data from experimental animals suggest that the ovary or testis may serve as a reservoir for cytomegalovirus (43,86).

Hepatitis B

Hepatitis B is the most dangerous form of hepatitis, a debilitating liver disease characterized by fever, weakness, loss of appetite, headache, and muscle pain. There are nearly 1 million hepatitis B virus carriers in the United States today, and the cost of hepatitis B infection in this country is estimated to be $1 million per day. Up to 1 percent of those infected with hepatitis B may die of the disease, and 5 to 10 percent of infected persons become chronic carriers of the virus who can remain infectious indefinitely (128). Once infection with hepatitis B occurs, there is no known treatment.

Contact with infected blood or saliva is the essential factor in occupational acquisition of hepatitis B virus. The groups at highest risk for acquiring hepatitis B virus are medical technicians,

operating room staff, phlebotomists, physicians (especially surgeons and pathologists), nurses (particularly intravenous-therapy nurses, and nurses in oncology and dialysis units), dentists and oral surgeons, laboratory and blood-bank technicians, and emergency-room staff. Morticians and their assistants who have routine contact with blood and secretions are also at high risk of hepatitis B infection (242).

Workers may acquire hepatitis B virus via accidental needle punctures, touching the mucous membranes of the nose, rubbing the eyes, and from human bites that penetrate the skin (238). Those routes serve to infect workers of both sexes; there are added consequences if pregnancy ensues.

Transmission from mother to infant during or following birth is an efficient mode of hepatitis B virus transmission; between 10 and 50 percent of infants born to mothers infected with the disease may also become infected (62)308). The risk of postnatal infections can be diminished with the use of hepatitis B immunoglobulin (80,248,308). Although infection is rarely symptomatic in the acute phase, approximately 90 percent of infected infants will become chronic hepatitis B carriers. This presents a double-barreled public health problem: 1) female carriers may subsequently perpetuate the cycle of perinatal transmission, and 2) chronic hepatitis B infection is associated with hepatocellular carcinoma, a form of liver cancer (136).

Other Infectious Agents

Several other infectious agents to which health care personnel may be exposed in the workplace, either in the form of infected patients or contaminated body fluids, may have untoward consequences for pregnant workers, or workers who later become pregnant (389). The principal infectious agents in this group are:

- Herpes simplex virus! which may produce microcephaly (abnormally small head), microphthalmia (abnormally small eyes), and retinal defects in the offspring of infected women. Typical herpes lesions have been noted in newborns of infected mothers, and the virus has been isolated from the placenta. These effects are due to exposure of the neonate to active genital lesions at the time of delivery. Herpes simplex viral infection has recently come under suspicion as a cause of previously unexplained spontaneous abortions (129).
- Congenital syphilis, a bacterial infection, which causes numerous abnormalities in the skin, mucous membranes, skeleton, nervous system, and eyes in infants born to infected women.
- Toxoplasmosis, caused by a protozoan organism, which can cause macro- or microcephaly, microphthalmia, and mental deficiency in babies born to infected mothers.
- Varicella, or chicken pox, caused by the herpes varicella-zoster virus, which can produce skin scars, limb deformities, microphthalmia, cataracts, and mental deficiency in infants exposed in utero during pregnancy.

It is important to note that problem pregnancies caused by infectious agents are relatively rare. The overwhelming majority of women with herpes simplex or herpes zoster infection during pregnancy, for example, give birth to normal babies.

Recombinant DNA

The rapid expansion of the field of biotechnology (360) will increase potential exposures of skilled and unskilled workers to: 1) micro-organisms containing recombinant deoxyribonucleic acid (DNA), and 2) their products. Micro-organisms have for centuries been employed for leavening bread, fermenting beer and wine, and ripening cheese. These traditional applications depend on naturally occurring mutations to provide microbial strains with particularly useful properties. Modern biotechnology, however, takes advantage of recent advances in molecular genetics and cell biology to expand the use of microorganisms. Genetic manipulation of molecules of DNA to form new, recombinant DNA permits the development of novel microorganisms (196).

Under present working conditions, the threat, if any, to reproductive function of occupational exposure to genetically altered microorganisms

appears to be slight. Many micro-organisms currently used in biotechnology are "attenuated, " or debilitated, through genetic manipulation, so that their ability to reproduce outside of carefully controlled culture conditions is severely curtailed. None of the organisms in use today have been shown to cause either infection or disease in workers using the techniques of biotechnology (196).

Any reproductive hazards of occupational exposure to the biologically active products of recombinant microorganisms are not a consequence of recombinant DNA techniques per se. Product hazards in biotechnology are not likely to differ qualitatively from those encountered in other sectors of the pharmaceutical and chemical industries. The fact that the molecules encountered in biotechnology are the products of engineered microorganisms, rather than naturally occurring ones, or of synthetic catalysis, will not alter their reactivity or toxicity. For example, the synthetic manufacturing and packaging of estrogenic hormones has produced excessive breast development, or gynecomastia, in male workers (140). Use of engineered micro-organisms to manufacture these hormones is likely to result in a hazard of similar nature. Exposure to biologically active products constitutes a class of potential hazards throughout the chemical and pharmaceutical industries, and biotechnology applications are not likely to be exempt from such hazards (196).

To the extent that biotechnology uses highly specific techniques to produce particular chemicals, it will decrease the number of currently encountered mixtures of chemicals—sometimes contaminated with toxic compounds—that are common in conventional chemical synthesis. It is noteworthy, too, that recombinant DNA technologies, operating at moderate temperature and pressure, have fewer inherent physical hazards than traditional chemical syntheses (360).

SUMMARY AND CONCLUSIONS

Two elements are required to constitute a workplace hazard to reproductive health. First, a worker (and perhaps a developing embryo/fetus) must be exposed to a chemical, physical, or biological agent. Second, the agent must be toxic to reproductive function or embryonic/fetal development.

Identifying exposed workers, evaluating their level of exposure, and determining their degree of reproductive impairment—if any-continues to be difficult. Studies of experimental animals offer valuable indicators of potential workplace reproductive hazards, but the extrapolability of animal studies to humans is variable.

Although present knowledge is incomplete, concern about workplace chemical hazards to reproductive function has focused on metals (lead, mercury, cadmium, arsenic, antimony, boron, and manganese), agricultural chemicals (carbaryl, DBCP, DDT, chlordecone, 2,4)5-T, dioxin, 2,4-D, PBB, and PCB), organic solvents, anesthetic agents, epichlorohydrin, EDB, EtO, formaldehyde, rubber (1,3 -butadiene, chloroprene, and ethylene thiourea), vinyl halides, hormones, and other undefined industrial exposures, Review of these compounds reveal that there is indeed cause for concern about reproductive hazards resulting from occupational exposures.

Present knowledge is also incomplete for physical factors of potential concern, including nonionizing electromagnetic radiation, atmospheric or ambient pressure (hypobaric and hyperbaric environments), heat, cold, noise, vibration, and stress. Although there is extensive evidence available for the harmful effects of ionizing radiation, the effects of occupational exposure have not been well researched.

Workplace stress refers to: 1) an environmental condition, 2) a worker's response to that condition, or 3) a relationship between the environmental demands and a worker's ability to meet those demands, The elements of occupational stress are posture, work on industrial machines, physical exertion, mental stress, environmental factors, and characteristics of the worker. Aside from imposing physical stressors, workplace

activities may lead to psychological stress. Both physical and psychological stress are thought to be sources of worker infertility, although direct evidence of this phenomenon has proven elusive.

Biological agents—agents of infectious disease—are a potential reproductive hazard to those in health care occupations, either through direct patient contact, through laboratory exposure to infective material, or through exposure to materials on infected individuals. Exposure to the viruses rubella, cytomegalovirus, and hepatitis B is of concern, as is exposure to such infectious agents as herpes simplex virus, congenital syphilis, toxoplasmosis, and varicella through contact with either infected patients or contaminated body fluids.

Most available data only suggest that certain occupations or occupational exposures are associated with adverse effects on male or female reproduction, or fetal development. In some cases it is possible to identify the site and mechanism of reproductive toxicity. In most instances, however, the gaps in information are enormous.

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LIST OF CHEMICAL NAMES

Lead
Also known as, or contained in: lead azides, lead salts, lead tetraethyl, lead tetramethyl, metallic lead, TEL, tetraethylplumbane, TML, and tetramethylplumbane.

Boron
Also known as boric acid, orthoboric acid.

Manganese
Compounds include manganese acetate, borate, bromide, carbonate, carbonyl, chloride, difluoride, dioxide, hypophosphite, iodide, nitrate, oleate, oxalate, oxide, phosphate (dibasic), pyrophosphate, selenide, sesquioxide, silicate, sulphate, sulphide, trifluoride.

Mercury
Also known as hydrargyrum, liquid silver, quicksilver; compounds include mercuric acetate, arsenate, bromide, chloride, chloride (ammoniated), cyanide, bichromate, fluoride, iodate, iodide, nitrate, oxide (red), oxycycanide, subsulphate, sulpate, sulpide, (red), thiocyanate; mercurous acetate, bromide, chlorate, chloride, fluoride, iodide, nitrate, sulphate.

Cadmium
Compounds include cadmium acetate, carbonate, chloride, fluoroborate, fluoride, molybdate, nitrate, oxide, sulphate, sulphide.

Arsenic
Also known as arsen, arsenic black, gray arsenic, metallic arsenic; compounds include arsanilic acid; arsenic pentoxide, sulphide, trioxide; arsine; calcium arsenate; dimethylarsinic acid; lead arsenate; methanearsonic acid (disodium and monosodium salt); potassium arsenate; potassium arsenite; sodium arsenate, arsenite, cacodylate.

Carbaryl
Also knonw as, or contained in l-naphthyl-N-methyl carbamate, I-naphthyl methyl carbamate, nitrosocarbaryl, and Sevin,

Dibromochloropropane
Also known as, or contained in 1,2-dibromo-3-chloropropane, 3-chloro-l)2dibromopropane, Fumazone, Nemazon, and Nemaset.

Kepone (Chlordecone)
Also known as, or contained in Acarin, Kelthane, and Mitigan.

Polybrominated Biphenyls (PBB)
Also known as, or contained in decabromobiphenyl, decabromodiphenyl, hexabromobiphenyl, hexabromodiphenyl, octobromobiphenyl, octabromodiphenyl, and perbromobiphenyl.

Polychlorinated Biphenyls (PCB)
Also known as or contained in askarels, Aroclor, Chlophen, Chlorextol, chlorinated biphenyl, chlorinated diphenyl, chloro-biphenyl, Dykanol, Fenclor, Inerteen, Kanechlo, Noflamol, Phenoclor, polychlorinated biphenyl, polychlorobiphenyl, Pyralene, Pyranol, and Santotherm.

Epichlorohydrin
Also known as, or contained in l+hloro-2,3~poxypropane, 3-chloro-l,2+poxypropane, 3-chIoro-1,2-propylene oxide, (chloromethyl) ethylene oxide, (chloromethyl) oxirane, 2~hloromethyl oxyrane, 3+hloropropene-l,2-oxide, chloropropylene oxide, g-chloropropylene oxide, ECH, ECHH, a%pichlorohydrin, l,2-epoxy-3+hloropropane, 2,3-epoxypropyl chloride, glycerol epichlorohydrin, glycidyI chloride, and SKEKhG.

Ethylene Dibromide
Also known as, or contained in Aadibroom, Bromofume, Celmide, dibromoethane, 1,2-dibromoethane, symdibromoehtane, Dowfume EDB, Dowfume MC-2, Dowfune W-8, Dowfune W-85, Dowfune 40, E-D-BEE, EDB-85, ENT 15, 349, ethylene bromide, Fumo Gas, glycol dibromide, Iscobrome D, Kopfume, Nefis, Pest - master, Postmaster EDB-85, Sanhyuum, Soilbrum-40, Soilbrum-85, Soilfume, and Unifume.

Ethylene oxide
Also known as, or contained in Anprolene, Benvicide, Carboxide, Cry-oxide, dihydrooxirene, dimethylene oxide, epoxyethane, l-2+poxyethane; EO, ETO, oxacy - clopropane, Oxane, oxidoethane, a, B-oxidoethane, Oxiran, Oxirane, Oxyfume, Oxyfume 12, Oxyfume sterilant-20, Pennoxide, Steroxide-12, Steroxide-20, and T-gas,

Formaldehyde
Also known as, or contained in BFV, Fannoform, Formalin, Formalith, formic aldehyde, Formol, ode, HCHO, Ivalon, Karsan, Lysoform, Methanal, methyl aldehyde, methylene oxide, Morbicid, oxomethane, oxymethy - lene, Paraform, and Superlysoform.

Vinyl Chloride
Also known as, or contained in chlorethene, chlorethy - Iene, chloroethene, chloroethylene, ethylene monochloride, monochloroethene, monochloroethylene, Tridene, Trovidur, VC, vinyl C monomer, and VCM.

Carbon tetrachloride
Also known as tetrachloromethan~, Carbona, carbon chloride, carbon tet, methane tetrachloride, perchloromethane, tetrachlorocarbon.

Styrene
Also known as ethenylbenzene, Cinnamene, phenethy - lene, phenylethene, phenylethylene, styrol, styrole, styrolene, vinylbenzene, vinylbenzol.

Xylene
Also known as dimethylbenzene, xylol.

Toluene
Also known as methylbenzene, toluol, methyl benzene.

Benzene
Also known as benzin, benzine, benzol, benzole, benzolene, bicarburet of hydrogen, carbon oil, coal naphtha, cyclohexatriene, motor benzol, phene, phenyl hydride, mineral hnaphtha, pyrobenzol, pyrobenzole.