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OCCUPATIONAL EXPOSURES ASSOCIATED WITH MALE REPRODUCTIVE DYSFUNCTION[1]

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INTRODUCTION

Dibromochloropropane (DBCP)-induced sterility in male workers who applied the nematocide has focused scientific, public, and regulatory attention on the potential nontherapeutic chemicals have to affect the human reproductive capacity. Questions are increasingly being asked about the effect of industrial and environmental chemicals on the relatively poor quality of human semen and on what some interpret as a general decline in mean sperm counts (1). Over the past decade, estimates of declining fertility have abounded. In the United States, nearly seven million couples are involuntarily infertile and three million couples contain at least one partner who is sterile; and in 1976, 25% of all married couples with the wife of child-bearing age (15–44 years old) had impaired fecundity (2). Even so, the relationships between occupational and environmental chemicals and reproductive failure remain poorly defined.

Occupational chemical exposure may be thought of as a model for many of the chemicals that contaminate our environment. Exposure levels are generally higher and more closely monitored in the workplace, and individual exposure can be more reliably estimated there. Because health surveillance programs often exist, cause-and-effect relationships may be established more convincingly. Yet many confounding factors complicate this task. Workers are rarely

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exposed to a single agent. Our total environment, including the work environment, is a multi-chemical world that makes it difficult to single out one reproductive toxin. Occupational settings provide the potential for both acute and chronic chemical exposure, with their resultant particular effects. This chapter focuses only on the effects of chronic exposure.

Chemicals, however, are not the only hazards that might affect human reproductive capacity. Physical agents such as altitude (3), temperature, and radiation (ionizing and non-ionizing) may also play a role (4). Elevated workplace temperatures might have not only a direct effect on the male gonads, but may also increase the absorption of toxic substances by increasing lung ventilation and circulatory rates. Absorption of pesticides increases in high-temperature work environments, perhaps because of the effect of the heat itself, because of the tendency of workers to remove protective clothing, or because of a combination of these two factors. Such potentially synergistic relationships between physical and chemical agents in the occupational environment rarely undergo rigorous scientific examination (5). Likewise, personal habits such as smoking (6), consuming alcoholic beverages, taking drugs either therapeutically or recreationally, or eating patterns and diet selection are each suspected to a greater or lesser degree of being confounding factors.

In the past, females have most often been the focus of studies of occupational exposures and reproductive effects, primarily because reproductive endpoints can be more easily determined in women than in men. A woman's menstrual cycle is established at puberty and continues throughout her reproductive life. Estrogens and progestins can be measured, and their effects are reflected in cellular changes in female accessory sex organs and in the regularity of the menstrual cycle. Women are particularly alert to delayed or missed periods, which may indicate spontaneous abortion or pregnancy wastage. Chemical agents may also appear in the secretory fluids of the accessory sex organs; certain ones are concentrated in breast milk. In many cases, the health of a child and the effects associated with nursing provide sensitive indicators of occupational toxicity.

In contrast, males lack an obvious and easily measurable reproductive cycle, and the primary clinical indicator, semen analysis, offers unsure clues to reproductive performance. Because only one sperm is required to fertilize the ovum, it is difficult to establish the probability of a pregnancy based on a reduction in the approximately 30 million sperm usually ejaculated (7). Normal mean semen parameters are 20 million sperm per milliliter of semen; only about 60% of the sperm is motile and about the same proportion is morphologically normal (8). Sperm density fluctuates daily in the same individual, and the predictability of the other variables has not been evaluated. Sperm density is an absolute predictor only when azoospermia is noted. Unless sperm are totally

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immobile, motility is difficult to quantify. And, although some investigators have reported a correlation between sperm morphology and chemical exposure, the link between changes in morphology and altered fertility has not been demonstrated convincingly (9).

Furthermore, no effects on sperm are yet confirmed to be associated with birth defects, and there is no male equivalent to nursing. Impotency is an unsure endpoint and decreased libido seldom causes a man to see a physician or to report to the factory's clinic. Likewise, with the exception of the sperm penetration assay, there are no good laboratory indicators of human sperm functionality [see (10)]. Because the scientist has fewer reliable clinical endpoints for men, the study of male reproductive toxicity is difficult and the drawing of conclusions is tenuous.

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However, progress is being made in developing and evaluating tests to better identify chemical hazards and to estimate human health risks. Wyrobek (11, 12) has suggested that sperm morphology is a stable semen parameter and a reliable predictor of fertility and feels that careful longitudinal studies can reveal the selected changes in sperm morphology that accompany defined chemical exposures. A Y-body test, which scores the frequency of sperm with two florescent spots and is thought to represent sperm with two Y-chromosomes due to meiotic nondisjunction, has been used to evaluate human sperm; unfortunately, it has no direct counterpart in commonly used laboratory animals (13). The interspecies sperm penetration assay has recently been validated as a reliable predictor of fertility (14), and lack of sperm penetrating ability has been associated with chemical exposure (15). Post-testicular events such as sperm maturation, capacitation, acrosome reaction, cervical mucus penetrability, and fertilizing capacity are only occasionally assessed (16). Serum gonadotropins and androgen levels can be monitored, and size and weight of the testes can be easily derived. It is also possible to biopsy the testis, although this clinical procedure is rarely performed in investigations of the effects of industrial chemicals.

The study of occupational reproductive toxicology involves both the biological and the epidemiological sciences, and as a result the difficulties in designing a truly successful study are many (17). Surveillance of human reproductive capacity involves both prospective and retrospective studies, but they generally lack statistical power because of the unsure endpoints available and the generally low number of men observed (18, 19). Pregnancy loss and spontaneous abortion may also be important indicators of abnormal sperm function and have been included in surveillance programs (20, 21). The obvious need for better data collection on exposures and reproductive endpoints, as well as for greater coordination of these data and their analyses, has been discussed elsewhere (22–28).

OCCUPATIONAL EXPOSURE

While a large number and wide variety of therapeutic agents have been reported to affect male reproductive capacity based on laboratory and clinical reports (29), the list of industrial chemicals thought to affect the human male is much shorter. Because this is an area of increasing scientific interest and importance, various investigators have summarized existing knowledge and have offered their own lists of about a dozen potentially harmful industrial chemicals each (30, 31–33). However, except for length, agreement among these lists is far from perfect.

For some of these listed agents the mechanism of action is obvious, while for others the molecular interactions that account for their toxicity are generally unrecognized. Many are cytotoxic and generally toxic, and some also share carcinogenic, mutagenic, and/or teratogenic properties. Yet the reproductive hazard of greatest concern is probably the chemical that does not share mutagenic or carcinogenic potential, is not generally cytotoxic, acts by disrupting biological processes unique to the reproductive process, and is subtle in its onset.

This review focuses on those industrial chemicals thought to affect human male reproductive capacity for which published data are available (Table 1). Reports in the literature that associate industrial chemicals with male reproductive dysfunction are evaluated, laboratory approaches used in an attempt to identify hazards are examined, and the clinical signs indicating infertility are noted.

Agents with Confirmed Adverse Effects

For the following agents, whose adverse reproductive effects have been confirmed, there is a strong scientific concensus regarding a cause-and-effect relationship. Either a number of studies have shown toxicity or the effect of the chemical is predictable based on its known biological activity.

CARBON DISULFIDE Carbon disulfide (CS_2) is a solvent used primarily in the production of viscose rayon, and chronic exposure is associated with apparent nervous system toxicity. European studies of the reproductive effects of occupational exposure reveal multiple statistically significant effects on endpoints of spermatogenesis (34, 35), on levels of serum FSH and LH (35–37), and on libido (34–36). These effects have been found to persist in 66% of the workers subject to follow-up examinations (35). However, dose-response relationships have not been statistically established for any of the parameters.

In a US study of low CS_2 exposure over considerably shorter periods of time (measured in months rather than years), Meyer (38) failed to demonstrate significant differences in semen parameters when exposed men were compared

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Table 1 Occupational exposures associated with male reproductive dysfunction[a]

Agents with confirmed adverse effects	Agents with inconclusive effects	Agents with no observed adverse effects
Carbon disulfide	Anesthetic gases	Epichlorohydrin
Dibromochloropropane (DBCP)	Arsenic	Glycerine
Lead	Benzene	p-TBBA
Oral contraceptives	Boron	PBB
	Cadmium	PCB
	Carbaryl	
	Chlordecone	
	Chloroprene	
	DNT and TDA	
	Ethylene dibromide	
	Manganese	
	Mercury	
	Pesticides	
	PCP	
	Radiation-ionizing	
	Radiation-nonionizing	
	Solvents	
	TCDD (dioxin)	
	Vinyl chloride	

[a]Classification based upon analysis of currently available literature. Refer to text for specific comments.

to controls. Yet Romanian (34, 35), Italian (36), and Finnish (37) experiences seem to support the inclusion of CS_2 on any list of male reproductive hazards because of its multiple effects. The data also suggest that levels of occupational exposure should be well controlled.

DIBROMOCHLOROPROPANE Dibromochloropropane (DBCP) originally was registered as a soil fumigant used to control nematodes. In 1979, the Environmental Protection Agency (EPA) banned the sale, distribution, and movement of DBCP in commerce, two years after suspending most end-use products. This was the first regulatory action taken by a US agency based on reproductive toxicity, and the literature is replete with references. The US Public Health Service reported that DBCP is mutagenic and "may reasonably be anticipated to be a human carcinogen" (39).

Whorton et al (40) were the first to describe the reproductive effects of DBCP. They reported azoospermia and oligospermia, as well as increased serum levels of FSH and LH, in 14 of 25 men working in a pesticide factory. No other major abnormalities were detected, and testosterone levels were normal. Although exposure levels could not be quantified, the observed effects appeared to be related to duration of DBCP exposure. In recent years, reports of

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DBCP testicular toxicity have been published by investigators throughout the world (41–48).

Glass et al (49) reported studies of male DBCP applicators and determined that the effects of the agent are limited to individuals in certain situations, such as applicators involved in irrigation set-up work and in the calibration of equipment. Once released from those situations, the sperm counts of these individuals return to normal. Statistical reanalysis of these data by Kahn & Whorton (50) showed that all applicator groups had reduced sperm counts in a dose-related manner and that reversibility was not a certainty. Glass (51) responded to these criticisms.

In studies of Y-chromosome nondisjunction, DBCP-exposed workers had a higher average YFF frequency compared to nonexposed individuals (13). An agent that increases Y-chromosomal nondisjunction (the frequency of YFF sperm) might be anticipated to result in increased pregnancy wastage.

International efforts have also been directed toward determining the reversibility of DBCP's effects (52–54). Wheater (55), responding to an inquiry in the *Journal of the American Medical Association,* rightly suggested that the DBCP effect appears reversible and that the more severe and potentially long-lasting reproductive effects, such as decreased testicular size, are probably restricted to production workers [see (43–45)] since farm workers and applicators are exposed only sporadically to diluted material.

Effects in chemical workers surveyed in Michigan were consistent with the known testicular effects of DBCP and again demonstrated the reversibility of the effect over time (47). Whorton & Milby (56) reexamined 21 men with DBCP-reduced sperm count after termination of exposure in 1977. When initially examined, 12 of the men were azoospermic and nine were oligospermic. Almost all of the oligospermic men improved considerably, while none of the 12 azoospermic men recovered.

Lipshultz et al (57) reported the gonadotoxic effects of DBCP on the largest group of workers to date. Semen analyses, serum hormonal determinations (LH, FSH, and testosterone), and genital examinations were completed on 228 workers at two chemical production sites. Their dose-response model suggested significant changes in sperm density after more than 100 adjusted hours of exposure. Broadening the focus of DBCP studies, Kharrazai et al (58) looked for effects on wives of DBCP-exposed field applicators and found an apparent increased risk of spontaneous abortion, although the health of the liveborn infants seemed unaffected.

A four-year reassessment of 20 Israeli workers with DBCP-induced testicular dysfunction, as well of the outcome of the pregnancies that accompanied their recovery process, demonstrated that the reversibility of the gonadotoxic effects was related to previous exposure time and was most likely to occur in patients with normal FSH levels (54). A delayed toxic effect of DBCP on

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Sertoli and Leydig cell function was suggested to explain the lack of recovery. Pregnancies occurring after recovery from DBCP-induced spermatogenic impairment apparently are not associated with an increased risk of fetal congenital malformation.

Of all environmental agents, DBCP presents the clearest picture relating occupational exposure to testicular toxicity and human reproductive dysfunction [see (58a)]. Exposure levels have been estimated and dose-response relationships investigated. Studies have also focused on recovery from both mild and severe testicular effects. Thus, DBCP offers a valuable data base for assessing the reliability of laboratory test methods to predict the toxicity of similarly acting chemicals and for correlating human reproductive endpoints with chemically induced dusfunction and subsequent recovery.

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LEAD Lead exists in the environment in both inorganic and organic forms. People working as smelters, with batteries, as artisans such as stained-glass workers (59), and as painters may absorb inorganic lead. However, because organic or tetraethyl lead (TEL) is used as an additive to gasoline, it is the most common form of lead found in the environment. Although the literature includes two early reports showing reduced libido and increased impotency among TEL workers [see (30)], a study of US TEL workers found no detectable health differences between them and a group of matched controls (60).

Evidence of the deleterious effects of lead on human reproduction dates back to ancient Rome, where Gilfillan has suggested that lead in drinking vessels produced sufficient toxicity among the upper classes to result in declining populations (61). In addition, lead also has long been known as a spermicidal agent and an abortifacient (62).

Although most of the literature dealing with the effects of lead on reproduction relates to women and children (63), there is clear evidence that lead is also a male reproductive toxin. Lancranjan et al (63a) reported finding dose-related disturbances of spermatogenic endpoints, including asthenospermia, hypospermia, and teratospermia among the 150 lead workers studied. However, gonadotropin levels were unaffected. The results of their study suggest that lead may act directly on spermiogenesis.

Even more research has been directed toward the effects of lead on chromosomes. Thomas & Brogan (62) cite ten international studies that report an increased incidence of chromosomal damage in workers exposed to lead (e.g. 64–67) and six studies that fail to establish such an association (e.g. 68, 69). Interestingly, DeKnudt et al (64) examined the chromosomes of workers exposed to lead, zinc, and cadmium and found aberrations only among the lead workers. In addition, Nordenson et al (67) noted that, although the sperm effect for the groups in their study correlated in a dose-dependent manner with blood

lead levels, individual blood lead levels were poor predictors of chromosome damage.

The evidence is convincing that lead affects spermatogenesis, results in abnormal sperm morphology, and is associated with infertility. Lead also appears to have a genotoxic potential. Thus, every effort should be made to reduce occupational and environmental lead exposure.

ORAL-CONTRACEPTIVE FORMULATION Although this review could include the occupational hazards associated with a variety of therapeutic agents with known reproductive effects, it discusses only a single example because few well-designed studies are available. Harrington et al (70–71a) have described an investigation in a Puerto Rico factory that formulated oral contraceptives using synthetic estrogens and progestins. During a twelve-month period, 25 (20%) of the male employees experienced symptoms associated with hyperestrogenism. All of the affected males had gynecomastia, and three also reported a history of decreased libido or impotence. Elevated plasma ethinyl estradiol levels accounted for the effects observed. Hyperestrogenism among men, women, and children resulting from the adults' exposure to diethylstilbestrol (DES) and other estrogens while working in pharmaceutical plants has been a worldwide concern [see (70, 72, 73)]. Diaminostilbene, an optical brightener structurally similar to DES, has also been implicated as a male reproductive toxin. In 1981, the National Institute of Occupational Safety and Health (NIOSH) investigated a report of sexual impotence among male workers employed in the manufacture of diaminostilbene [see (74)]. This investigation indicated that more than one-third of the men in the affected area had a history of probable or possible impotency. The toxic effects of the oral contraceptives observed are predictable based on the pharmacological actions of the drugs involved.

Agents with Inconclusive Effects

The following agents are those whose reproductive effects are inconclusive. Clinical studies of them have been performed or case studies reported, but the data lack the strength necessary to be convincing. Often their effects are chromosomal aberrations whose ultimate effect on male reproduction is unclear. The literature reviewed does not conclusively support the effects suggested in textbooks and reviews that may list a particular substance as harmful.

ANESTHETIC GASES A 1967 report from Russia was one of the first to register concern about human health risks associated with the operating room environment. Vaisman [see (75)] noted a wide range of health complaints, including such adverse pregnancy outcomes as spontaneous abortion, premature delivery, and congenital malformations, among 21 of 31 reported pregnan-

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cies. Worldwide interest ensued, with initial reports focusing on the exposure of female nurses from Denmark (76), the United States (77–79), and Great Britain (80).

Among males occupationally exposed to anesthetic gases, infertility has been reported (76, 81). Their wives are reported to have an increased rate of spontaneous abortions (76, 81, 82), and among their children there apparently are greater numbers of congenital malformations (81, 83–88), low birth weights (81, 84), and a higher rate of female births (84, 89).

Wyrobek et al (90) analyzed semen samples from 46 male anesthesiologists who worked for at least one year in hospital operating rooms reventilated with modern gas-scavenging devices and observed no significant differences in the number and morphology of the sperm between the exposed group and controls. The outcome remaincd the same when the analysis was limited to men having no confounding factors such as varicocele, recent illness, medication, heavy smoking, or frequent sauna use. It is interesting to note, however, that the men who had one or more confounding factors (excluding anesthetic gases) showed significantly higher percentages of sperm abnormalities than did the group of men without such factors.

The study of the relationship between occupational exposure to anesthetic gases and reproductive toxicity is different from the study of exposure to other agents for two reasons. First, because of the educational level, socioeconomic status, and training of the veterinarians (91), dentists (82), and physicians exposed (80, 81, 83, 84), their responses to questionnaires appear to reflect an increased concern with and cognizance of health-related issues. This point is supported by the study results of Knill-Jones et al (86), who suspected bias in respondents reporting minor congenital abnormalities because there was no consistency in the type of abnormality reported and no increase in reports of major abnormalities. Second, the number of people exposed to anesthetics is large and is organized into professional associations that have sponsored large-scale epidemiological surveys (81–83). This is not true for any of the other occupational groups examined in this review.

Finally, although a causal relationship between anesthetic gases and male reproductive dysfunction has not been clearly established, it is obvious that waste gas concentrations should be maintained at a minimum and that other contributing factors should also be carefully controlled (88).

ARSENIC This literature review identified only one major research effort devoted exclusively to the study of arsenic and its noncarcinogenic effects on human males (91a, 91b). The preliminary report (91a) described the detection of significantly higher numbers of chromosomal aberrations among nine Swedish smelter workers than among a control group. The follow-up report (91b) found similar results among the total cohort of 39 arsenic-exposed workers.

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The researchers were very careful to point out that because of very large individual variations and the fact that the correlation between the frequency of all aberrations and arsenic exposure was not very good, it is nearly impossible to conclude that arsenic damages DNA structure. Arsenic appears to inhibit the repair of DNA damaged by the synergism of arsenic and smoking and/or by other agents such as lead and selenium. Arsenic is a known human carcinogen, but its effect, if any, on male reproduction remains unclear.

BENZENE Reports published in the early 1970s supported the concern that exposure to high concentrations of benzene used as a solvent can cause chromosomal aberrations in male workers [see (92)]. A 1980 review of occupational benzene exposure reported that the results of tests showing weak toxic effects on the reproductive organs of male animals have prompted additional research supported by the American Petroleum Institute and the Chemical Manufacturers Association (93). The results of those studies are not yet available.

BORON In the mid-1970s, Soviet scientists reported infertility associated with oligospermia and decreased libido among men working in factories in which boric acid is produced and among those living in communities where boron concentrations in artesian well water are high [see (94)]. In the US, much less concern surrounds the possible health hazards associated with boron compounds because laboratory tests suggest that inorganic boron compounds are not highly toxic (95).

CADMIUM Despite the fact that the effects of cadmium on male reproduction have been studied throughout the world for two decades, the results are inconclusive and even confusing [see (96)]. Epidemiological and case study data suggest an association between the occupational inhalation of cadmium dusts and fumes and prostate cancer [see (97)]. Autopsy reports indicate no spermatids or sperm in the testes of a small group of men engaged in the manufacture of copper-cadmium alloy (98). There is one self-report of impotence in an alkaline storage battery worker (99), but no significant differences in urinary excretion of steroids were observed among the total of ten battery workers compared with a control group of lead-exposed workers. In addition, chromosomal aberrations have been associated with workers manufacturing cadmium pigments (100).

Cadmium is used in electroplating, in plastics manufacturing, in battery production, and in paint mixing. The Occupational Safety and Health Administration (OSHA) has estimated that 360,000 workers are exposed currently, and this number is expected to increase. Better scientific surveillance of cadmium

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workers and more carefully designed protocols are necessary to define clearly cadmium's reproductive effects.

CARBARYL Carbaryl (Sevin) is one of the least acutely toxic of the carbamate insecticides. Whorton et al (101) and Wyrobek et al (102) used virtually the same cohort of exposed men to study the effects of carbaryl exposure on fertility by checking for infertile marriages and by measuring sperm counts and serum gonadotropins. Both groups have reported no significant differences between the cohort and a control group for any of the endpoints, although the carbaryl-exposed group included nearly three times as many oligospermic men as the control group. Because sperm counts are known to be statistically less sensitive to small changes, Wyrobek et al (102) analyzed sperm morphology and determined a non–dose related, significant elevation in sperm head abnormalities compared to controls, a condition that may not be reversible. Both studies had low participation rates, relied on self-reports of exposure levels, and used less-than-ideal control groups for comparisons. In a recent article discussing methods for evaluating the effects of environmental chemicals on human sperm production, Wyrobek et al (33) list carbaryl as an agent suggestive of adverse effects.

CHLORDECONE Chlordecone (Kepone) is a chlorinated hydrocarbon insecticide that was produced in the US, added to other chemicals in West Germany, and then exported to Central and South America, where it was used to control banana borer weevils. From March 1974 through July 1975, the Life Science Products Company of Hopewell, Virginia, was the sole producer of Kepone and, because it is no longer produced, the exposures of the employees at that time have served as the basis for all published reports about the reproductive toxicity of Kepone (104–106).

The Center for Disease Control became aware of Kepone toxicity in 1975, but the scientific community was not alerted until a report by Cannon et al in 1978 (104) described a previously unrecognized clinical illness characterized by neurological symptoms (Kepone shakes) and oligospermia, with abnormal and immobile sperm predominating. Kepone appears to be a direct-acting male reproductive toxin. None of the reports attempt to analyze the data in terms of a dose-response relationship between Kepone levels in serum or fat and the degree of oligospermia, and none of the reports associate sterility with the altered semen parameters. However, the excretion of stored Kepone was hastened in 13 patients who received cholestyramine, an anion-exchange resin, in a controlled clinical trial (105). The researchers chose sperm counts as a dependent variable because neurological signs were more difficult to quantify and found that the number of mobile sperm increased as blood Kepone concentrations decreased in 12 of 13 patients.

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CHLOROPRENE Chloroprene is a pungent, colorless liquid used in the manufacture of synthetic rubber. Although it has been reported to affect male reproductive capacity (107–110), all reports quote the same obscure original Russian study (111). In summarizing that study, Sanotskii (109) writes, "Examinations of chloroprene workers revealed functional disturbances in spermatogenesis after six to ten years of work in chloroprene production, and morphological disturbances after 11 years or more. The questionnaire showed that cases of spontaneous abortion in the wives of chloroprene workers occurred more than three times as frequently as in the control group." Because of the inadequacy of the data, it is impossible to draw reliable conclusions regarding the male reproductive toxicity of chloroprene.

DINITROTOLUENE AND TOLUENE DIAMINE A 1980 preliminary survey by NIOSH of the Olin Corporation plant in Kentucky detailed reduced sperm counts and higher miscarriage rates among 21 workers exposed to dinitrotoluene (DNT) and toluene diamine (TDA) (112). Olin disputed the report (113) and commissioned another. Subsequently, Hamill et al (114) found no differences between the 84 men in the exposed group and the 119 nonexposed workers in measures of sperm count, sperm morphology, FSH levels, testicular volume, reproductive histories, and urogenital function. These results, from Olin's Louisiana plant, differ considerably from those reported in Kentucky; thus, DNT and TDA should remain on the list of agents with inconclusive effects on male reproduction.

ETHYLENE DIBROMIDE The use of ethylene dibromide (EDB) as a fumigant recently has received widespread public attention, even though its major, although declining, use is with lead as an anti-knock compound in leaded gasoline. Wong et al (115) assessed the reproductive performance of male workers in four plants exposed to EDB and in one plant found a statistically significant, non-dose related decrease in the expected number of children born to workers' wives. These investigators properly point out the drawbacks associated with their use of national fertility tables. A randomly chosen, in-plant control group would have been a more representative population; testing of such a group would be more likely to detect a decrease in fertility. Semen analysis of 44 occupationally exposed men in Florida, New Jersey, and Texas found no significant differences between the sperm counts of these men and two large statistical comparison groups (116). Ter Haar (117) concludes that neither sperm counts (116, 117) nor the incidence of live births among the workers' wives (115) indicates decreased fertility among exposed males. The data are meager, however, and the small number of workers with potential exposure (only about 1,000 worldwide) (117) is insufficient to draw firm conclusions about the reproductive toxicity of EDB.

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MANGANESE Workers can be exposed to manganese in the steel-manufacturing, chemical, and manganese-mining industries. Although specific studies of the reproductive effects of manganese are not available, reports of manganese poisoning among miners have included reproductive effects. Of fifteen manganese-poisoned Chilean miners, all of whom exhibited psychomotor and neurological disturbances, 27% experienced disturbances of libido and 20% had difficulty ejaculating (117a). This and similar reports [see (30)] were published decades ago. Manganese appears to be a rather weak reproductive toxin that, in cases of severe poisoning, affects both sexual desire and the ability to perform.

METHYLMERCURY Chronic exposure to methylmercury results in severe central nervous system damage, particularly to the fetus. These effects were identified in the 1970s in Minamata, Japan, where pregnant women consumed fish contaminated with methylmercury. There also is some weak evidence that dental personnel suffer minor genetic damage as a result of mercury exposure (118).

Two case reports involving a total of nine men have outlined such reproductive effects of methylmercury as hypospermia, decreased libido, and impotence (119, 120), symptoms that persisted for at least five years. McFarland & Reigel (120) noted these chronic effects among six men who were exposed only briefly. A dose-related decrease in libido and significantly higher incidences of hypospermia, asthenospermia, and teratospermia have also been noted in 50 chronically exposed men who did not exhibit signs of poisoning (119).

As a possible reproductive toxin, methylmercury presents a unique methodological problem. First, because its primary effect is on the nervous system, symptoms may be classified as psychological in origin and remain unreported. When symptoms are reported, McFarland et al note that the physician often associates them with the depression that commonly occurs in methylmercury poisoning. Second, few males are occupationally exposed to methylmercury.

PESTICIDES Spurred by the discovery of the toxic potential of DBCP, researchers have widened their search for additional reproductive toxins among the pesticides. Reports have been made of residual levels of DDE and BHC isomers in the semen (121), hexachlorobenzene in the fat, and DDT in the testicles and fat (122) of a randomly drawn sample of 50 fertile and infertile men.

Among occupationally exposed men, there are reports of disturbed spermatogenesis and increased chromosomal breakage (especially of the Y chromosome) (123) as well as impotence (124). In both of those reports, however, the number of workers was very small (five and four respectively). Moreover, the workers recovered potency after discontinuing exposure and

receiving hormone therapy. A recent report cites no differences in the total number of pregnancies, sex ratios, spontaneous abortions, and birth defects in a sample of 314 agricultural pilots and 178 sibling families (125). Obviously, much more research is needed in this area before any conclusions about the reproductive consequences of pesticide accumulation can be determined.

PENTACHLOROPHENOL Pentachlorophenol (PCP), a widely used wood preservative, has been found in the semen of exposed workers [see (126)], and a significantly increased incidence of chromosomal aberrations in their peripheral lymphocytes has been documented (127). Although reproductive dysfunction has not been reported, these findings suggest a higher priority for future investigations of this chemical.

RADIATION: IONIZING Ionizing radiation has recognized cytotoxic and carcinogenic effects, and careful attempts have been made to establish clinical and occupational exposure levels that provide an adequate margin of safety. However, in recent years, exposure levels once thought to be safe have been questioned. The effects of ionizing radiation on male reproduction are much easier to predict than is the threshold for such effects. The clinical effects of ionizing radiation on the testes and other male reproductive endpoints have been well studied (128–130). The effects of chronic occupational exposure include significant decreases in serum gonadotropins (131) and significant changes in semen parameters (132). The effects of ionizing radiation on spermatogenesis are usually reversible and recovery of fertility has been observed within a few years (133–135).

RADIATION: NONIONIZING In contrast to ionizing radiation, the biological effects of microwaves are much less apparent. Yet, the level of human exposure continues to increase annually, as does scientific and regulatory concern. The most obvious effects of nonionizing radiation observed in laboratory studies are those associated with thermal effects. Analyzing the human risk associated with nonthermal effects is of greater priority but is also more difficult. The 1975 report of a group of 31 men who experienced decreased libido and decreased semen parameters after long-term occupational exposure to microwaves from an unspecified source appears to be one of the only studies available on this subject (136).

SOLVENTS (HYDROCARBONS AND GLYCOL ETHERS) A provocative study of the possible role of the father's occupation in the risk of malignant diseases among his offspring found a significant excess of fathers employed in hydrocarbon-related occupations in a group of 386 Quebec children who died before the age of five (137). One possibility suggested to explain this effect is a direct

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effect of some hydrocarbon contained in petroleum and oil on spermatogenesis that transmits the carcinogenic defect to the child. Of course, direct exposure is a more easily accepted possibility, assuming the association reported also shares a cause-and-effect relationship.

Other researchers have focused their concern on measuring spermatogenesis among workers exposed to the group of chemical solvents known as glycol ethers. Cook et al (138) reported no significant gross abnormalities or clinically meaningful differences in fertility indices among 15 of 97 men studied who submitted semen samples. The small number of participants and the fact that men in the exposed group had smaller testicles makes drawing realistic conclusions about this study impossible. Glycol ethers deserve further attention because they have been associated with male reproductive toxicity in laboratory animals [see (139)].

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2,3,6,8-TETRACHLORODIBENZO-p-DIOXIN 2,3,6,8-Tetrachlorodibenzo-p-dioxin (dioxin, TCDD) is a toxic contaminant of trichlorophenol synthesis, of hexachlorophene manufacturing, and of the herbicide 2,4,5-trichlorophenoxy-acid (2,4,5-T). The acute effects of TCDD are associated primarily with the skin and the liver.

In July, 1976, an unfortunate explosion discharged products containing TCDD over an area of 700 acres in Seveso, Italy. The immediate health effect was chloracne, but concern about reproductive effects arose. Follow-up studies two years after the incident showed that the number of pregnancies, the incidence of spontaneous abortions, the rate of chromosomal aberrations, and the number of birth defects remained within expected rates for that area of Italy (140, 141). Similar results were obtained in an interviewer–administered questionnaire survey of a group of Michigan wives of men potentially exposed to dioxins as well as wives of in-plant controls (142). In addition, a recent comparison of 204 men exposed to TCDD in herbicide manufacturing and 163 not exposed to TCDD revealed no significant differences between the groups in pregnancies, live births, infant deaths, miscarriages, birth defects, and still-births (143). An unpublished study of railroad workers involved in cleaning up a dioxin spill found a 40% decrease in sperm count and plasma testosterone [see (144)], yet none of the data thus far have been able to confirm the reproductive effects of paternal exposure.

A group of major chemical-manufacturing companies recently settled a class-action lawsuit litigated on behalf of Vietnam veterans exposed to TCDD in the defoliant Agent Orange. A report that children fathered by veterans with symptoms of Agent Orange toxicity show twice the incidence of congenital anomalies as do children fathered by men without symptoms may have prompted that decision [see (144)]. However, Agent Orange exposure was not quantified, nor were other comparisons of the symptomatic and asymptomatic

men published. Thus, the effects of paternal exposure to TCDD on reproductive function and the incidence of spontaneous abortions or stillbirths are unresolved, as is the more general question of the possibility that paternal exposure to chemicals can account for congenital abnormalities.

VINYL CHLORIDE Vinyl chloride monomer (VCM), used in the manufacture or polymerization of polyvinylchloride (PVC), is a known human carcinogen that has been associated with an increased incidence of angiosarcoma, a rare liver tumor. Beginning in 1975, there were reports of increased incidences of chromosomal aberrations among small numbers of PVC manufacturers [see (4, 145, 146)]. As research in this area expanded, larger numbers of PVC workers were examined, and increased chromosomal abnormalities were related to the duration and extent of exposure (147).

Follow-up studies of workers who reduced their exposure showed concomitant decreases in chromosomal abnormalities (148, 149), and a Czech study (150) detected no chromosomal aberrations among men working in an environment where the VCM maximum allowable concentration (MAC) was 1 ppm. Comparisons of measurements of conventional chromosomal abberations with sister-chromatid exchanges demonstrated the former to be more sensitive in detecting changes (151, 152). However, differences among the various studies cited in the composition of the populations under study make direct comparisons difficult. Hatch et al (153) have proposed study guidelines that might solve some of the difficulties in drawing conclusions from inadequate study designs.

Wives of VCM-exposed workers have been reported to have a significant excess of fetal loss (154–157). However, these results must be assessed against the weakness inherent in interviews with fathers (157).

Among the symptoms experienced by men exposed to VCM in the workplace, impotence and loss of libido have been reported [see (30)]. However, there have been no reports of infertile men, and the true impact of chromosomal aberrations on male fertility cannot be assessed.

Agents With No Observed Adverse Effects

This category, agents with no observed adverse reproductive effects, is reserved for chemicals sometimes mentioned as affecting human male reproduction about which there are little or no published data. Also included in this category are chemicals that have been studied and that fail to show a toxic effect.

EPICHLOROHYDRIN Epichlorohydrin (ECH) is a colorless liquid used in the manufacture of insecticides and many other products. It is an alkylating agent and is a suspected human carcinogen. Milby et al (158) have reported the results of an industry-supported study of the sperm counts of men from two

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ECH production plants in which no significant differences among any of the groups were found, even after a variety of analyses. However, this study does not allow firm conclusions about ECH's toxic potential because the control group of "chemical plant workers unexposed to any agents known to be toxic to the testes" was inadequate at best, its participation rates were low, it did not examine such confounding factors as age or smoking, and, although it conducted a medical history and physical examination of "each of the participants," the only data analyzed were number of years worked and sperm density.

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GLYCERINE The manufacture of glycerine may result in exposure to allyl chloride, epichlorohydrin (see above), and 1,3-dichloropropene, agents that are structurally similar to DBCP (see above). This similarity to DBCP has prompted a fertility study of male manufacturers of glycerine (159). No statistically significant differences were demonstrated among the exposed and the control groups when serum gonadotropins, semen variables, and testicle size were analyzed. Thus, it appears that the manufacture of glycerine poses no obvious threat to male reproductive capacity.

PARA-TERTIARY BUTYL BENZOIC ACID Para-tertiary butyl benzoic acid (p-TBBA) is an organic acid used in cutting oil and in paint that has adverse testicular effects in animals. Prompted by the results of animal studies, Whorton et al (160) studied the testicular function of 90 men occupationally exposed to p-TBBA. They concluded that the levels of p-TBBA exposure experienced at the selected chemical plant had no apparent clinical or epidemiological effect on sperm count, gonadotropin level, and fathering children. The design used in this study is based on studies of DBCP and serves as a prototype for similar investigations.

POLYBROMINATED BIPHENYLS Polybrominated biphenyls (PBBs) are used as fire retardants in plastics. In 1973–1974, their accidental mixture with cattle feed in Michigan attracted a great deal of public attention because their presence later was detected both in breast milk and in blood serum. Yet Roseman et al (161) reported no effect on spermatogenesis among 52 PBB-exposed men who were studied four years after exposure, and no correlations were observed between serum PBB levels and sperm density or serum testosterone levels. However, because these studies were undertaken some time after the accident, it is not clear whether the lack of an apparent effect reflects recovery.

Interestingly, large surveys of the affected farmers and their customers have shown no relationship between serum PBB levels and the number of subjective symptoms reported (162). Stross (163) has concluded, "Present evidence

suggests that people exposed to PBB have few objective findings at this time, and reactive depression may be responsible for the high prevalence of constitutional symptoms."

POLYCHLORINATED BIPHENYLS Polychlorinated biphenyls (PCBs) have been broadly used in carbonless carbon paper, paints, and as fluids in capacitors and transformers. Because of their extensive use and their capacity to be stored in fat, PCBs are widely found in fish, birds, and animals, including humans. An accidental contamination of rice oil with PCBs and other impurities in 1968 was responsible for a variety of primarily skin ailments in Japanese men and women and their offspring. Its persistence in breast milk has been the focus of many studies, but the male reproductive effects of PCBs are virtually unexamined.

An extensive study of the health of 326 PCB-exposed US capacitor-manufacturing workers included the measurement of sex hormones and explored reproductive histories using a family history questionnaire (164). No abnormal values were reported; in fact, Fischbein et al (164) were surprised by the "striking paucity" of physical abnormalities other than frequent skin problems. However, semen analyses of the 168 males in the study were not performed, so definite conclusions about the reproductive effects of PCBs cannot be drawn.

Male-Mediated Reproductive Effects

The results of studies of men occupationally exposed to anesthetic gases and hydrocarbons have prompted many questions regarding the effect of such exposure on conception and the morphology and physiological functioning of offspring. Soyka et al (165) have reviewed this area, and the research of others points out the difficulty of determining effects. Following a comprehensive study of the pregnancy experiences of the wives of 764 workers in a Swedish copper smelter, Beckman & Nordstrom (166) reported no difference in the number of congenital malformations in offspring but noted a significantly increased rate of fetal death. They believe their results are consistent with the hypothesis that chemical exposure of males resulting in genetic damage will be reflected in an increased rate of fetal loss as the result of dominant lethal mutations.

Hemminki et al (167) recently analyzed spontaneous abortions in an industrialized Finnish community according to the occupation and workplace of both the woman and her husband. The abortion incidence among wives employed in a single factory whose husbands worked at a large metallurgical factory was more than three times higher than among women whose husbands worked elsewhere.

Some scientists have suggested that a seminal defect in the husband may be a

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cause of abortion (168). However, in a retrospective study of 534 pregnancies, Homonnai et al (169) found that the sperm quality of the men whose wives were repeated or habitual aborters was better than in the control group and found no evidence in routine semen analysis that sperm quality was predictive of abortions. These investigators conclude that the cause of the abortions seems to be either a female factor or chromosomal aberration. Kline and coworkers (170) have commented on the power of environmental monitoring of spontaneous abortions and have suggested an important role for such studies in defining reproductive hazards to both men and women.

Fabro (171) has recently summarized paternally induced adverse effects on pregnancy and has discussed the potential mechanisms of these effects.

PRIORITIES FOR THE FUTURE

Too little effort has been directed toward using semen as an indicator of chemical exposure and toward using sperm as a biological indicator of chemical effects. In addition, as a route of exposure, chemicals in semen might have significant effects on sperm motility and function or might act directly or indirectly on the uterus and accessory sex organs to affect fertilization or implantation. Mann (172) has reviewed the literature on the appearance of chemicals in semen, but greatly increased efforts should be undertaken to assess their presence and to document altered biological indicators such as sperm parameters or semen biochemical markers.

The structures and the biological activities of chemicals with either confirmed or suspected adverse effects on male reproduction range broadly, making it difficult to establish priorities for future human studies. Nonetheless, a few warning flags are too obvious to ignore. They indicate that future research should focus on: (*a*) chemicals that are reactive and capable of covalent interactions in biological systems; these chemicals often are cytotoxic and affect spermatogenesis as well; (*b*) chemicals defined as mutagens and/or carcinogens in short-term laboratory tests; (*c*) chemicals demonstrated to cause aneuploidy or other chromosomal aberrations; (*d*) chemicals that affect sperm motility in vitro or are positive in other short-term reproductive screening tests; (*e*) chemicals that share hormonal activity or affect hormone action; and (*f*) chemicals that act directly or indirectly to affect the hypothalamo-pituitary-gonadal axis.

CONCLUSION

Relatively unreliable laboratory tests, clinical endpoints, monitors of exposure, indicators of biological effects, and epidemiological studies each have contributed to the difficulties researchers are experiencing in their attempts to define

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the role of occupational and environmental chemicals in the etiology of male reproductive dysfunction. An increased effort should be undertaken to develop coordinated research to improve our ability to identify reproductive hazards in the laboratory, to detect reproductive dysfunction in exposed populations, to establish causal relationships, and to assess human risk. The current state of the scientific literature in this area documents the need for such a comprehensive effort.

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