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Case Studies in Environmental Medicine

29

Reproductive and Developmental Hazards

Environmental ALERT . . .

- ☑ *Approximately 8% of all couples are infertile.*
- ☑ *It is estimated that 15% to 20% of all recognized pregnancies end in spontaneous abortions.*
- ☑ *Of the 3 million infants born during the 1980s, approximately 7% were low birth weight, 5% were preterm, 2% to 3% had major congenital anomalies, and an unknown number have developmental or functional problems in childhood.*
- ☑ *The extent to which environmental or occupational exposures affect these statistics is unknown.*

This monograph is one in a series of self-instructional publications designed to increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients. *See page 39 for more information about continuing medical education credits and continuing education units.*

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Public Health Service
Agency for Toxic Substances and Disease Registry

How to use this issue...

This issue begins with a composite case study that describes realistic encounters with patients. The case study is followed by a pretest. (Answers to the Pretest questions are on pages 13-16.) The monograph ends with a posttest, which can be submitted to the Agency for Toxic Substances and Disease Registry (ATSDR) for continuing medical education (CME) credit or continuing education units (CEU). See page 39 for further instructions on how to receive these credits.

The objectives of this monograph on reproductive and developmental hazards are to help you

- ❑ **Describe the factors that may adversely affect reproduction and fetal development**
- ❑ **Identify adverse reproductive and developmental outcomes that may be caused by environmental or occupational exposures**
- ❑ **Identify evaluation and treatment protocols for adverse reproductive and developmental outcomes**
- ❑ **List sources of information on reproductive and developmental hazards**

Contents

This issue is prepared with the assistance of those who share a common concern for physician education, public health, and the environment, including the following organizations: American Academy of Clinical Toxicology, American Academy of Family Physicians, American Academy of Pediatrics, American College of Emergency Physicians, American College of Occupational and Environmental Medicine, American Medical Association, Association of State and Territorial Health Officials, and the Society of Teachers of Family Medicine. Final responsibility for the contents and views expressed in this monograph resides with ATSDR.

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Case Study

From an article in your local newspaper, you learn that an underground waste solvent storage tank at a local semiconductor manufacturing plant is leaking toxic chemicals. According to the plant manager, the tank, which contains mostly 1,1,1-trichloroethane (TCA), is located about 2000 feet from a well that supplies drinking water to a nearby residential area. The article also mentions that at the time the leak was discovered, the concentration of TCA in the well was 1700 ppb. The well was immediately removed from service. The newspaper article states that as reporters interviewed residents for the story, they were told about five cases of spontaneous abortion and four cases of cardiac defects in the area.

Two weeks later, TCA levels in the well reached 8800 ppb, and minor amounts of 1,1-dichloroethylene (DCE) were found. Eighteen of your patients received water from the contaminated well, and several of them, including a 30-year-old pregnant patient, have requested consultations with you. After listening to their concerns, you contact the Agency for Toxic Substances and Disease Registry (ATSDR) to request assistance. In the health consultation provided, ATSDR concludes that the levels are far above levels established to protect public health; however, no human epidemiologic studies have been reported that adequately address reproductive effects caused by TCA or DCE. Data from animal studies do not suggest adverse reproductive or developmental outcomes from ingestion of these chemicals.

ATSDR decides to conduct a Public Health Assessment for this site. While collecting information for the health assessment, ATSDR finds that birth certificates for the county do not reveal an excess of adverse pregnancy outcomes in the water-service area compared with the rest of the county. However, because only 20% of all birth defects are typically reported on birth certificates, the agency advises that birth certificate studies alone cannot rule out an increase of birth defects; furthermore, vital records do not provide data on spontaneous abortions.

Currently, ATSDR is developing a protocol for an epidemiologic study to determine whether an association exists between exposure to the contaminated well water and congenital anomalies and spontaneous abortions. Pending the outcome of the epidemiologic study, you must communicate the risk of adverse reproductive and developmental effects due to toxic exposures. How will you address the following questions from your patient who is pregnant and her neighbors?

(a) *Can adverse reproductive effects such as spontaneous abortion and birth defects be caused by drinking and using contaminated well water?*

(b) *I am 3 months pregnant. How will this exposure affect my pregnancy?*

(c) *Can I breast-feed if I have been drinking the contaminated water?*

(d) *My wife is having trouble getting pregnant; could this chemical exposure be responsible?*

(e) *We are planning to become pregnant; is it safe to do so?*

(f) *What is the health consultation provided by ATSDR? What is a public health assessment?*

Answers to the Pretest questions are on pages 13-16.

The Magnitude of the Problem

- **About one in twelve couples of reproductive age in the United States is infertile.**
- **At least 40% of all conceptions are lost before the 28th week of gestation.**

Several adverse reproductive effects can result from exposure of men and women to biologic, chemical, or physical hazards. Damage to the male or female germ cells can reduce fertility, and exposure before or during gestation can cause early pregnancy loss (clinically manifested as menstrual irregularity or infertility), spontaneous abortion, preterm or low-birth-weight neonates, birth defects, abnormal growth and development, and carcinogenesis (manifested as childhood cancer). Accurate data on reproductive and developmental effects are limited by the intrinsic difficulty of diagnosis and the lack of a national data collection system. Nevertheless, some estimates of adverse reproductive and developmental outcomes in the United States have been made.

About one in twelve couples of reproductive age in the United States is infertile. (A couple is deemed infertile if conception has not occurred after 1 year of unprotected sexual intercourse.) At least 40% of all conceptions are lost before the 28th week of gestation. About 2% to 3% of all newborns (approximately 3 million during the 1980s) have major congenital anomalies, 7% are low birth weight, 5% are preterm, and an undetermined number have developmental or functional problems in childhood. The causes of most of these adverse outcomes are unknown. If even a small percentage of these effects is attributable to environmental or occupational exposures, the number of families affected is large.

Chemical Agents and Adverse Outcomes

- **Many chemical agents are suspected of causing adverse reproductive or developmental effects; however, strong evidence exists for only a few.**
- **Folic acid supplements administered during the periconceptual period may prevent fetal CNS anomalies.**

To cause reproductive or developmental harm, toxicants must be absorbed into the bloodstream and pass from the blood to the reproductive organs or through the placenta to the fetus. Many chemical hazards react with the first tissues they contact—eyes, nose, throat, lungs, or skin—and rarely enter the bloodstream. Hence, these substances are unlikely to affect reproduction or fetal development. The following are examples of substances that are unlikely to enter the bloodstream in significant amounts, except when ingested.

ammonia	potassium hydroxide
asbestos	silica
chlorine	sodium hydroxide
fiberglass	sodium hypochlorite (bleach)
hydrochloric acid	sulfuric acid
nitric acid	

Much of what we know about chemical exposures and their effects on reproduction and fetal development is from research using experimental animals. Effects of an absorbed toxicant may vary among the animal species and even among different strains of the same species. Extrapolating positive findings from animal studies

to humans involves great uncertainty, and negative animal studies do not necessarily mean a compound poses no risk to humans. Differences in species response can be due to genetic variability, to differences in absorption and metabolism (including activation of the toxicant), or to different types of interactions within cells and tissues. Thalidomide, which has no detectable effect on mouse embryos but caused limb deformities in humans and higher primates, illustrates the variability of response among species.

Most human data are from exposures that occurred in the workplace, but in many cases, the data are inconclusive or difficult to interpret. Strong positive associations between a hazard and reproductive or developmental effects have been found for only a few substances including lead, mercury, certain organic chemicals (e.g., ethanol and ethylene oxide), and ionizing radiation. Certain biologic agents (e.g., rubella and mumps) are also strongly associated with adverse reproductive or developmental outcomes. Tobacco smoke has been reported to reduce fertility in both males and females.

Table 1 lists some environmental or occupational agents suspected to cause decreased female reproductive capacity or adverse developmental effects in the fetus. Some therapeutic agents reported to affect female reproductive capacity include steroids, alkylating agents, methotrexate, levodopa, quinacrine, appetite suppressants, opioids, antipsychotics (e.g., phenothiazines), antidepressants (e.g., imipramine, amitriptyline, and monoamine oxidase inhibitors), serotonin, sympathomimetic amines (e.g., epinephrine, norepinephrine, amphetamines), and reserpine.

Antifolate agents have been associated with macroscopic malformations in the fetus, especially central nervous system anomalies. Malformations have included spina bifida, hydrocephaly, anencephaly, and meningoencephalocele. To reduce the risk of having a pregnancy affected with neural tube defects (NTDs), the United States Public Health Service recommends that all women of reproductive age consume 0.4 milligrams (mg) of folic acid per day. Principal dietary sources of this vitamin include green, leafy vegetables, broccoli, spinach, mushrooms, liver, nuts, dried beans, peas, egg yolk, and whole-wheat bread. A varied diet that includes fresh vegetables and fruits generally provides enough folic acid for the body's needs. However, women who have had a prior NTD-affected pregnancy are at high risk of having a subsequent affected pregancy. In 1991, the Centers for Disease Control and Prevention (CDC) recommended that these high-risk women who are *planning* to become pregnant consult their physicians about taking 4.0 mg of folic acid per day during the periconceptual period (1 month before conception to 3 months after).

Table 1. Agents associated with adverse female reproductive capacity or developmental effects in human and animal studies*

Agent	Human Outcomes	Strength of Association in Humans†	Animal Outcomes	Strength of Association in Animals†
Anesthetic gases¶	Reduced fertility, spontaneous abortion	1,3	Birth defects	1,3
Arsenic	Spontaneous abortion, low birth weight	1	Birth defects, fetal loss	2
Benzo(a)pyrene	None	NA§	Birth defects	1
Cadmium	None	NA	Fetal loss, birth defects	2
Carbon disulfide	Menstrual disorders, spontaneous abortion	1	Birth defects	1
Carbon monoxide	Low birth weight, fetal death (high doses)	1	Birth defects neonatal mortality	2
Chlordecone	None	NA	Fetal loss	2,3
Chloroform	None	NA	Fetal loss	1
Chloroprene	None	NA	Birth defects	2,3
Ethylene glycol ethers	Spontaneous abortion	1	Birth defects	2
Ethylene oxide	Spontaneous abortion	1	Fetal loss	1
Formamides	None	NA	Fetal loss, birth defects	2
Inorganic mercury ¶	Menstrual disorders, spontaneous abortion	1	Fetal loss, birth defects	1
Lead ¶	Spontaneous abortion, prematurity, neurologic dysfunction in child	2	Birth defects, fetal loss	2
Organic mercury	CNS malformation, cerebral palsy	2	Birth defects, fetal loss	2
Physical stress	Prematurity	2	None	NA
Polybrominated biphenyls (PBBs)	None	NA	Fetal loss	2
Polychlorinated biphenyls (PCBs)	Neonatal PCB syndrome (low birth weight, hyperpigmentation, eye abnormalities)	2	Low birth weight, fetal loss	2
Radiation, ionizing	Menstrual disorders, CNS defects, skeletal & eye anomalies, mental retardation, childhood cancer	2	Fetal loss, birth defects	2
Selenium	Spontaneous abortion	3	Low birth weight, birth defects	2
Tellurium	None	NA	Birth defects	2
2,4-Dichlorophenoxyacetic acid (2,4-D)	Skeletal defects	4	Birth defects	1
2,4,5-Trichlorophenoxyacetic acid (2,4,5-T)	Skeletal defects	4	Birth defects	1
Video display terminals	Spontaneous abortion	4	Birth defects	1
Vinyl chloride ¶	CNS defects	1	Birth defects	1,4
Xylene	Menstrual disorders, fetal loss	1	Fetal loss, birth defects	1

* Major studies of the reproductive health effects of exposure to dioxin are currently in progress.

† 1 = limited positive data. 3 = limited negative data.
2 = strong positive data. 4 = strong negative data.

§ Not applicable because no adverse outcomes were observed.

¶ Symbol used to designate agents that may have male-mediated effects.

Toxicology of Reproductive Function

Germ Cell Development

Female. Oogonia develop in the female during fetal life when they undergo the first meiotic division. As a result, a woman is born with a full complement of oocytes. Through natural processes, the number of oocytes decreases from a maximum of about 7 million in the 5th gestational month to about 400,000 at puberty. Only 300 to 500 of the oocytes remaining at puberty will mature during a woman's reproductive life span.

- **Females are born with a full complement of oocytes. In contrast, spermatozoa are in continual development in males after puberty.**
- **Because reproductive regeneration does not occur in females, the ramifications of oocyte damage are significant.**
- **Chemical exposures to males can cause adverse pregnancy outcomes by several mechanisms.**

The oocytes rest in the ovary until ovulation occurs, which for some oocytes may be 45 years or more after formation. At the start of the menstrual cycle, a group of small primary follicles begins to develop, each containing an oocyte. Release of pituitary follicle-stimulating hormone (FSH) supports the selection and growth of a dominant follicle; the remaining follicles degenerate. The growing follicle produces estrogen, which causes proliferation of endometrial tissue. When a critical blood concentration of estrogen is reached, the anterior pituitary releases a mid-cycle burst of hormones (FSH and luteinizing hormone [LH]), causing the follicle to rupture and ovulation to occur. The remaining cells of the ruptured follicle form the corpus luteum.

Fertilization can occur within 12 hours after ovulation. In the absence of fertilization, the corpus luteum degenerates. The consequent decrease in ovarian steroids produces ischemia and sloughing of the endometrium, resulting in menstruation. If fertilized, the ovum completes a second meiotic division, forming a zygote that undergoes several rapid cell divisions to become a blastocyst. The blastocyst implants in the endometrium approximately 5 days after fertilization.

Because many opportunities for exposures exist throughout a woman's life and there is no mechanism for reproductive regeneration, the potential for damage to the oocytes is significant. Researchers are elucidating the mechanisms by which oocyte damage or loss occurs; however, no studies have documented an association between exposure to industrial chemicals and oocyte damage or loss, which can cause infertility or premature menopause.

Male. In contrast to oocyte formation, spermatozoa are in continual production in stem cells after puberty. In humans, spermatozoa mature in an average cycle length of 74 days.

At precise intervals, primitive spermatogonia in the testes proceed from the basement membrane to the lumen of the seminiferous tubule where they undergo mitotic and meiotic cell divisions. Each germ cell duplicates itself (meiosis I), and each resulting diploid cell

(46 chromosomes) divides into two haploid cells with 23 chromosomes each (meiosis II). Haploid cells then undergo spermiogenesis, developing a head, midpiece, and tail. The head consists of the sperm nucleus and the acrosome that contains the enzymes necessary for egg penetration.

After leaving the testes, sperm acquire motility and fertilizing capacity during transit through the epididymis and vas deferens. Sperm transport is dependent on the production of seminal fluid by the seminal vesicles. Sertoli cells in the testes play an important role in initiating spermatogenesis, synthesizing essential proteins, and providing nurturance. Supporting Leydig cells manufacture and secrete testosterone, which helps to maintain spermatogenesis and is essential for sexual interest and activity.

Exposure to ionizing radiation (alpha, beta, and gamma radiation; X rays), heat, or certain chemicals (Table 2) has been documented to cause male infertility and decreased libido. Destruction of the basic stem-cell spermatogonia usually causes permanent infertility; damage during subsequent stages of the maturation process is potentially reversible. Chemical exposure to the male can cause adverse pregnancy outcomes not only by damaging the sperm, which can produce an abnormal zygote, but possibly also by transmission of toxic agents in seminal fluid. In addition, contaminated skin and clothing of the male is a potential source of toxicant exposure to the pregnant woman.

Endocrine Function

- **Reproductive function in both men and women depends on the endocrine cycle, which is sensitive to physical and chemical agents.**

Reproductive function in men and women depends on the functioning of the neuroendocrine system. For men, FSH from the pituitary and testosterone from the Leydig cells of the testes act upon the Sertoli cells to initiate spermatogenesis. Pituitary LH induces high intratesticular concentrations of testosterone. For women, reproductive function requires pituitary LH and FSH, ovarian and adrenal estrogen, and progesterone.

Endocrine functioning in both men and women can be interrupted by agents with steroid-like activity or by neurologic effects induced by stress. Disorders of circadian rhythm, as can occur with some types of rotating work schedules, can also affect the endocrine cycle. The clinical results may be menstrual disorders in women and disorders of libido in both sexes.

Table 2. Exposures associated with male reproductive dysfunction

Agent	Human Outcomes	Strength of Association in Humans*	Animal Outcomes	Strength of Association in Animals*
Boron	Decreased sperm count	1	Testicular damage	2
Benzene	None	NA†	Decreased sperm motility, testicular damage	1
Benzo(a)pyrene	None	NA	Testicular damage	1
Cadmium	Reduced fertility	1	Testicular damage	2
Carbon disulfide	Decreased sperm count, decreased sperm motility	2,3	Testicular damage	1
Carbon monoxide	None	NA	Testicular damage	1
Carbon tetrachloride	None	NA	Testicular damage	1
Carbaryl	Abnormal sperm morphology	1	Testicular damage	1
Chlordecone	Decreased sperm count, decreased sperm motility	2	Testicular damage	2
Chloroprene	Decreased sperm motility, abnormal morphology, decreased libido	2	Testicular damage	1
Dibromochloropropane (DBCP)	Decreased sperm count, azoospermia, hormonal changes	2	Testicular damage	2
Dimethyl dichlorovinyl phosphate (DDVP)	None	NA	Decreased sperm count	2
Epichlorohydrin	None	NA	Testicular damage	2,3
Estrogens	Decreased sperm count	2	Decreased sperm count	2
Ethylene oxide	None	NA	Testicular damage	1
Ethylene dibromide (EDB)	Abnormal sperm motility	1	Testicular damage	2,3
Ethylene glycol ethers	Decreased sperm count	1	Testicular damage	2
Heat	Decreased sperm count	2	Decreased sperm count	2
Lead	Decreased sperm count	2	Testicular damage, decreased sperm count, decreased sperm motility, abnormal morphology	2
Manganese	Decreased libido, impotence	1	Testicular damage	1,3
Polybrominated biphenyls (PBBs)	None	NA	Testicular damage	1
Polychlorinated biphenyls (PCBs)	None	NA	Testicular damage	1
Radiation, ionizing	Decreased sperm count	2	Testicular damage	2

* 1 = limited positive data. 3 = limited negative data.
2 = strong positive data. 4 = strong negative data.

† Not applicable because no adverse outcomes were observed.

Developmental Biology

- **The major organ systems of the human embryo develop during the third to ninth week of gestation.**
- **It is uncertain whether a threshold exists for all teratogens.**

Soon after the blastocyst implants in the endometrium, trophoblastic cells rapidly proliferate, invading the uterine decidua and its vasculature. Placental circulation, which provides nutrient transport, is established by about the 17th day after ovulation. Substances that are of low molecular weight, lipophilic, and nonionized at physiologic pH readily diffuse across the placenta. The embryonic stage of development begins about the third week after ovulation. During the ensuing six weeks, the major organ systems of the embryo (i.e., cardiovascular, central nervous system, genitourinary, respiratory, endocrine, and immune system) form in a precisely timed sequence. Dramatic growth and maturation then continues during the remaining fetal period, until birth, when the average fetus weighs about 3000 to 3600 grams (about 6.6 to 8.0 pounds).

Exposures during weeks 1 and 2 after conception (i.e., the period of rapid division of the zygote, implantation, and formation of the bilaminar embryo) may cause early pregnancy loss by interfering with tubal transport or implantation. Heavy metals such as lead or copper have been found to inhibit implantation in experimental animals by interfering with uterine hormone-binding mechanisms.

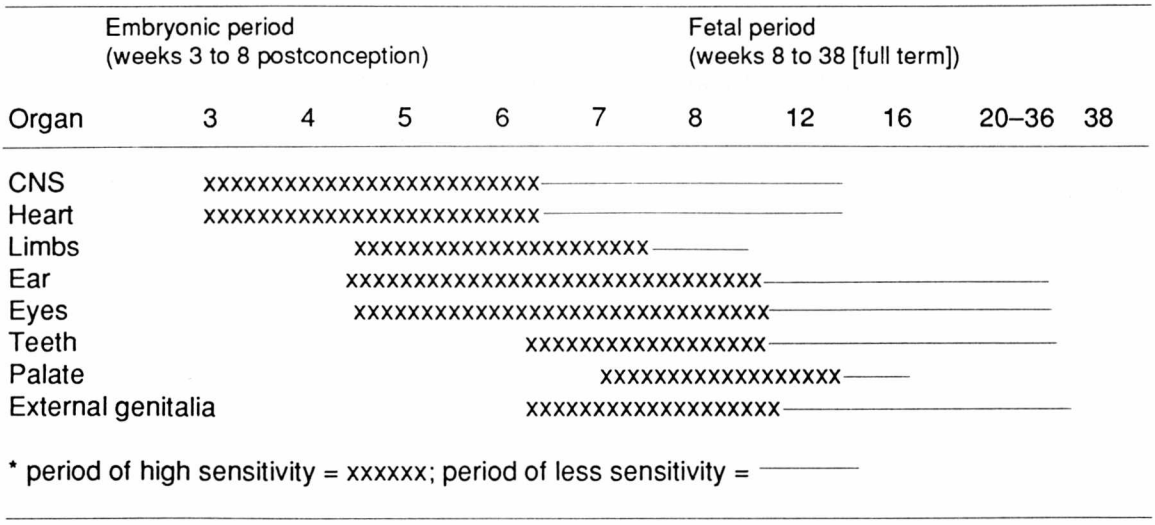
Teratogenic effects usually occur during the critical periods of organogenesis. Different agents given at the same critical period can cause the same anomaly, and the same agent administered at different periods of organogenesis may cause different anomalies. An insult delivered just before or during the early stages of the development of a particular organ is most likely to render the organ abnormal. (See Table 3 for a list of agents and conditions that are teratogenic in humans.) Thalidomide taken by humans between the 27th and 29th day of pregnancy caused limb deformities.

Table 3. Known or suspected human teratogens

Chemicals/Drugs	Radiation
Aminopterin	Atomic weapons
Androgenic hormones	Radioiodine
Antithyroid drugs	Radiotherapy
Busulfan	
Chlorobiphenyls	**Infectious agents**
Coumarin anticoagulants	Cytomegalovirus
Cyclophosphamide	Hepatitis B virus
Diethylstilbestrol	Herpes simplex virus
Diphenylhydantoin	Rubella virus
Lithium	Treponema pallidum (syphilis)
Mercury, organic	Toxoplasma gondii
Methimazole	Varicella virus (chicken pox)
13-cis-Retinoic acid	Venezuelan equine encephalitis virus
Tetracyclines	
Trimethadione	

Thus, the timing of an exposure often determines its effect. In the first 2 weeks after conception, when organogenesis has not yet begun, the most probable effect of significant exposure is severe damage and death of the embryo; that is, immediate postconception exposures do not usually result in specific birth defects. The period from 3 to 9 weeks postconception is a critical time when classic birth defects can be induced (Figure 1). Growth deficits, minor morphologic abnormalities, and postnatal functional abnormalities typically occur after 9 weeks of gestation. Carcinogens potentially can exert an effect at any stage in development.

Figure 1. Periods of sensitivity* for major organ systems



Adapted from Hays DP, Pagliaro LA. Human teratogens. In: Pagliaro LA, Pagliaro AM, eds. Problems in pediatric drug therapy. Hamilton, IL: Drug Intelligence Publications, 1987.

Some chemical toxicants cause severe effects on the embryo and have no effect on the pregnant woman; others affect the embryo only at maternally toxic doses. Traditional theory contends that a threshold exists for defects of organogenesis because the embryo can usually repair damage caused by low levels of exposure. Exposure must occur above the threshold to cause damage. However, recent studies of the fetal metabolism of xenobiotics suggest that a threshold may not exist for all substances; for example, no threshold has been defined for carcinogens.

A toxic agent may affect the embryo even when exposure occurred to the mother or father before conception. In some cases, damage to genetic material in the ovary or sperm (mutagenesis) results in pregnancy loss or inheritable defects in offspring. In other cases, exposure before conception affects the development of the fetus because the toxicant persists in the maternal body. For example, polychlorinated biphenyl (PCB) compounds are stored in adipose tissue for a significant period of time, and lead may be stored in bone

for years. Toxicants generally reach a steady state between the storage depot and the blood, but the stresses of pregnancy may cause the toxicant level in the bloodstream to increase. The fetus may be exposed to these body stores through maternal circulation.

Toxicants can also be passed to the infant through breast feeding. Transfer of chemicals into breast milk occurs primarily by passive diffusion. Table 4 lists the milk-to-maternal plasma ratios for several toxicants; substances with ratios greater than one tend to be highly lipophilic and nonpolar molecules. High maternal exposures, such as those caused by the ingestion of PCB-contaminated rice oil in Japan in 1968, have led to disease in infants, either through exposure in utero or through breast feeding. Chemical exposures by routes other than maternal ingestion have not been reported to produce adverse health effects in breast-fed infants.

Table 4. Milk-to-maternal plasma ratios in exposed women

Chemical	Milk/Plasma Ratio
Mercury, inorganic and organic	0.9
Lead	≤ 1.0
Tetrachloroethylene	3.0
Polybrominated biphenyls (PBBs)	3.0
Polychlorinated biphenyls (PCBs)	4.0–10.0
Dieldrin	6.0
o,p-Dichlorodiphenyltrichloroethane (DDT) residues	6.0–7.0

Adapted from Wolff MS. Occupationally derived chemicals in breast milk. Am J Ind Med 1983;4:259-281.

Management

- **Infertility secondary to chemical exposure may be reversible in males because of continuous sperm production.**
- **The effects of chemical exposures on female fertility are unknown in most cases.**

Male infertility secondary to occupational exposure may be reversible because of the capacity of the male to regenerate sperm. In men chronically exposed to 1,2-dibromo-3-chloropropane (DBCP), recovery occurred in those with oligospermia (a subnormal concentration of spermatozoa in the semen), although it required as long as 18 months in some cases. However, in men exposed to doses of DBCP that caused azoospermia (absence of living spermatozoa in the semen), long-term sterility resulted. In addition to changes in sperm counts in DBCP-exposed workers, testicular biopsy revealed atrophy of the seminiferous epithelium or tubular hyalinization with few germ cells, and in some tubules only Sertoli cells persisted. These histopathologic changes were associated with elevated LH and FSH plasma levels and decreased testosterone levels. Follow-up studies of DBCP-exposed workers showed recovery was directly linked to FSH levels (i.e., greater recovery occurred in men whose FSH levels were normal). Data from patients treated with high-dose therapeutic radiation suggest that even azoospermia can be reversed in some cases, but recovery may take 4 to 5 years. (Acute exposure to lower doses of radiation [~15 rads] affects spermatogenesis only transiently.)

Volume, standardized count, motility, and morphology analysis should be performed on two semen samples to make a diagnosis of male infertility. Normal values for semen analysis are listed in Table 5. No clear guidelines are available on how much of a change in semen parameters constitutes significant improvement. Although 20 million sperm per milliliter (mL) of semen is traditionally accepted as a minimal sperm count, conception can occur with counts below this value, and some men who have higher counts may still be infertile. An improvement in the sperm count from 5 million to 40 million per mL is clinically significant, but a change from 10 million to 15 million per mL is probably not. Consultation with a fertility expert may be helpful.

Table 5. Normal values for semen analysis

Volume	2–6 mL
Sperm concentration	20–250 (10^6/mL)
Sperm motility	> 50 %
Sperm vitality	≥ 50 %
Normal forms	≥ 60 %

If abnormal values for semen analyses are found, and no other cause for the abnormalities is obvious, exposures should be eliminated using engineering controls and protective equipment, changing the patient's job, or substituting less toxic materials. If removal from exposure is used as a diagnostic test, removal should continue as long as 18 months before the trial is concluded. (Semen analyses should be performed every 2 to 3 months to monitor improvement in sperm parameters.) If biomarkers are available to monitor body burden of a toxicant, as with lead, the 18-month period should be measured from the time the biomarker indicates that the body burden of the toxicant has returned to the normal range.

Even if a trial involving removal from exposure has been undertaken, it is important to remember that infertility may be a problem of the couple, rather than due solely to the man or the woman. For example, a submaximal sperm count in association with abnormalities of cervical mucus can lead to infertility, when neither condition alone would prevent conception. If the fertility evaluation suggests that infertility is due to a cumulative effect of the couple and the man is exposed to an identified toxicant, a trial of removal from exposure may still be appropriate while measures to correct the other disorders are carried out.

Occasionally, male infertility is due to both a medical condition and an identifiable occupational or environmental cause. The therapeutic approach in these cases should be one that recognizes both aspects of the problem. For example, if a varicocele (a condition manifested by abnormal dilation of the veins of the spermatic cord, which is a frequent cause of oligospermia) coexists with exposure to

lead, elimination of the lead exposure could be tried along with consideration of corrective surgery.

Chemical exposures associated with infertility have thus far been linked primarily to effects on the male. Potentially comparable effects on females have not been elucidated because parameters that affect female reproductive capacity cannot be easily measured. Chemical exposures should be strictly controlled or eliminated for all females of reproductive age. At the very least, pregnant females who have had exposures to organic solvents or lead should receive ultrasound monitoring and cervical checks if they have engaged in strenuous work and are at risk for preterm delivery.

Regulation of Reproductive Hazards

- **Regulatory standards may not be protective of reproductive health.**

The most direct approach to reducing environmental or work-related adverse reproductive outcomes is by controlling contamination in the environment and by limiting exposure to toxic substances in the workplace. Various statutes regulate exposure to reproductive toxicants encountered in the workplace, and a variety of regulatory agencies are responsible for enforcing these statutes. No single agency has complete regulatory responsibility for reproductive and developmental toxicants.

The most comprehensive federal statute governing health and safety in the workplace is the Occupational Safety and Health Act of 1970. The Occupational Safety and Health Administration (OSHA) is empowered to promulgate permissible exposure limits (PELs) for toxic substances in the workplace, including those posing risks to the reproductive health of workers. However, only a handful of the thousands of chemicals currently in use are regulated because of their potential to produce adverse reproductive effects. Many substances that threaten to damage reproduction may do so at exposure durations or levels lower than the PELs set to protect against other effects.

The Toxic Substances Control Act (TSCA) and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) mandate EPA to require the testing of products for toxicity and to limit the commercial use of toxic substances in the environment and workplace. Regulation of a substance under TSCA or FIFRA could theoretically result in a ban of the product. Reproductive toxicity, however, has seldom been the major consideration in the decision to ban a substance.

Answering the Questions

Clinicians are frequently questioned about potential risks to the reproductive health of men and women exposed to chemical toxicants and about the causes of adverse pregnancy outcomes. These questions most often come from persons exposed in the workplace; however, many communities have hazardous substances in air, water, and soil. The number of people potentially affected by environmental exposures is relatively large, and these persons are probably more susceptible to toxicants than healthy workers. Yet, most references on the medical evaluation of adverse pregnancy outcomes or infertility fail to mention the role of environmental toxic exposures.

Clinicians have been given little guidance in answering patients' questions concerning adverse reproductive and developmental outcomes. Most of the information available is from animal studies, and no consensus exists on extrapolating from experimental animal data to human risk. Nevertheless, much can be done with the information published; reasonable and informed decisions can be made.

The most commonly asked questions regarding the reproductive and developmental effects of exposures are the questions in the Pretest on page 1. These questions are answered below in the context of exposure to TCA and DCE, as presented in the case study, but additional information is given regarding exposures to other substances as well.

a) "Can adverse reproductive effects such as spontaneous abortion and birth defects be caused by drinking and using contaminated water?"

It is unlikely that the adverse reproductive and developmental effects stated in the case study were caused by exposure to TCA or DCE, either by drinking or using contaminated water or by exposures to these substances at work. In general, if a link between an adverse reproductive outcome and an environmental exposure is strongly suspected and the exposure can be stopped, the parents can be reassured that future pregnancies will not be at increased risk. If no clear cause is obvious, but exposure to a potential toxicant exists, the management of future pregnancies becomes a concern.

Etiologic questions may be extremely difficult to answer in a legal context. Typically, data are insufficient to link specific exposures to specific outcomes. Nevertheless, the same rules used to evaluate any suspected environmentally or occupationally caused diseases apply. Other known causes of the abnormality must be excluded and the nature, timing, and degree of exposure must be estimated to determine whether the dose is comparable to the dose associated with the particular adverse effect.

Parents who have suffered adverse reproductive or developmental outcomes require sensitive counseling because they may be concerned about the child's health, their own health, the presence of undetected genetic problems, and risks in future pregnancies. An environmental and occupational history should be obtained, and evaluation should proceed as medically indicated. (See *Case Studies in Environmental Medicine: Taking an Exposure History,* ATSDR, 1993.)

b) "I am 3 months pregnant; how will this exposure affect my pregnancy?"

Many substances have been linked to increased rates of spontaneous abortion. TCA and DCE are not among these chemicals. If the literature or other sources reveal that an exposure has been associated with an increased risk of a birth defect, you can discuss this with the patient in the context of the timing of the exposure and background rates of adverse pregnancy outcomes in general. For example, the overall rate of a particular severe defect (without exposure) is 1 in 200 births. If a chemical exposure raises the risk of a *specific* defect from 1 in 2000 births to 3 in 2000 births (or 0.3 in 200 births), it would have a relative risk of 3 for that defect. The overall risk of the defect is then increased from 1 per 200 (without exposure) to 1.3 per 200 (with exposure). For many people, understanding this relative risk may be reassuring. An increased risk of early fetal loss or of giving birth to a small-for-age baby is not an indication for therapeutic abortion.

However, for some exposures, the risk of adverse outcomes may be considerable. In cases in which the risk is high, some persons may choose to terminate the pregnancy. For example, acute exposure to ionizing radiation of greater that 30 rads at any stage of gestation is associated with a high probability of congenital abnormalities. Another situation in which the relative risk is high is an acute poisoning (e.g., carbon monoxide poisoning) that results in severe anoxia of the mother, which can have severe consequences for the fetus.

Ultimately, the decision to maintain or terminate a pregnancy rests with the patient. What is considered a significant risk that warrants pregnancy termination depends on a complex set of patient values—individual, cultural, and social. It is the responsibility of health professionals to ensure that the patient's decision is as well informed as possible, in terms of both the risks and alternatives. When the relative risks are high, you may wish to refer your patient to a genetic counsellor for more help in making this decision.

c) "Is there danger to breast feeding if I have been drinking contaminated water?"

After the child is born, its growth and development can be affected by exposure to substances brought home on the clothes of family members or used in the home, and those excreted in breast milk. Obstetricians and pediatricians justifiably encourage breast feeding, which provides IgA, amino acids, and fats that are essential for the developing infant, and considerable psychologic advantages to both mother and child. Only in rare cases are the advantages of breast feeding outweighed by the transmission of toxic chemicals.

The dose of the chemical to which a breast-feeding infant is exposed depends on the biologic fate of the substance in the mother. Toxicants that are fat soluble may reach high levels in the breast milk, which may be the major route of excretion, even though maternal exposure has stopped. By contrast, many organic solvents, although fat soluble, are also excreted through the lung, liver, and kidneys, generally decreasing maternal body burden soon after exposure has stopped.

The acute health effects resulting from a given infant dose of a substance transmitted in breast milk have been defined for only a few substances. Furthermore, chronic effects of low-dose exposures are virtually unknown. These uncertainties make the decision of whether to breast feed a difficult one. The following guidelines for mercury, PCBs, organic solvents, and lead are based on the limited data available, the considerations outlined above, and the availability of a safe alternative.

1. Mercury is the only chemical for which an unequivocal guideline has been set in milk. U.S. Food and Drug Administration (FDA) guidelines set a maximum allowable concentration of mercury in over-the-counter milk at less than 4 micrograms per liter (µg/L).

2. Acute effects of PCBs or related halogenated hydrocarbons on the breast-feeding infant are unlikely at any maternal blood level. Unless the mother has ingested or otherwise has received a considerable dose, breast feeding can be continued in most cases.

3. Maternal exposure to organic solvents should be minimized during breast feeding. Because most organic solvents (including TCA) are excreted relatively rapidly, breast feeding can be resumed several days after an acute maternal exposure. In the interim, milk can be pumped from the breasts (to maintain lactation) and be discarded.

4. The Centers for Disease Control and Prevention (CDC) has set a current action level for blood lead in children of 10 µg/deciliter (dL); above this level, adverse health effects have been reported to occur in children. A woman who has been exposed to lead should consult her physician and have a determination of her blood lead level before breast feeding. (The ratio of the lead concentration in maternal blood (or plasma) to the concentration in maternal milk is approximately 1 [Table 4, page 10].)

d) "My wife is having trouble getting pregnant; could a chemical exposure that I am receiving be responsible?"

A couple is defined as infertile when conception has not been achieved after 1 year of unprotected sexual intercourse. Approximately 10% of all couples are infertile. Male factors are estimated to account for about 40% of this infertility, failure of ovulation for 10% to 15%, tubal factors for up to 30%, and cervical factors for about 5%. In approximately 10% to 20% of infertility cases, the cause is not identified.

Infertility associated with chemical exposures has thus far been linked primarily to effects on the male. This may be partially because semen can be measured and analyzed and thus provides a ready means of assessing reproductive health in men exposed to potential toxicants. No similar parameter is available to determine female reproductive health after chemical exposure. Changes in menstrual patterns may be a biomarker for chemically induced oocyte toxicity and are currently being investigated.

To demonstrate that male infertility is caused by a chemical exposure, the following four criteria must be met:

1. The results of at least two semen analyses must be abnormal (e.g., sperm must be inadequate in number or have abnormal morphology, poor motility, or decreased ability to penetrate the egg).

2. Other causes of infertility must be excluded. An abnormal semen analysis does not necessarily implicate a toxicant as a causative agent. Major causes of male infertility are primary endocrinopathy, prior testicular injury, testicular surgery, mumps, gonadotoxic drugs (e.g., chemotherapy with cytotoxic drugs or estrogens), varicocele, urologic abnormalities (e.g., retrograde ejaculation), ductal obstruction, venereal disease, or vasectomy. These may not cause infertility in all men who are affected by them.

3. Exposure to a toxicant known or suspected of causing infertility must have occurred. Table 2, page 7, lists substances that are known or suspected to cause male infertility in humans or have positive study results in experimental animals. Many agents have not been adequately studied, so clinicians should keep an open mind if the first two criteria have been met and if exposure involves an agent that chemically or structurally resembles an identified reproductive toxicant.

4. Because effects on spermatogenesis are usually reversible, a fourth diagnostic criterion is improvement after removal from exposure. A clear improvement after exposure ceases is compelling diagnostic evidence and may be especially helpful when data about the toxicant in question are limited. However, failure to improve does not demonstrate conclusively that exposure is not the cause because some toxicants affect the spermatogonial stem cells causing long-term or permanent infertility.

e) "We are planning to become pregnant; is it safe to do so?"

Answering this question for patients entails the following three steps:

- Reviewing the information on the exposure (e.g., agent, timing, dose)
- Reviewing the known effects of the exposure and the doses at which effects have been reported to occur
- Applying clinical judgment, taking the individual patient into account

Although current data do not permit a rigid or scientific consensus on guidelines, the following general paradigm is proposed:

1. If the exposure occurs in the home or community environment setting and it is demonstrated that the patient is exposed at doses that cause significant risk, immediate exposure reduction, perhaps even relocation, is required. If the exposure occurs in the occupational setting, decreasing exposure through engineering controls, materials substitution, or job transfer is recommended.

2. Rigorous control of exposure is necessary if significant risk is suspected. (A combination of experimental animal and human data is used to determine if a risk is suspected.)

3. If only minimal exposure to established or suspected agents occurs, simple modifications of the home, community, or workplace environments to reduce or eliminate contact may be feasible.

Suggesting a job transfer can raise difficult social and economic issues. Some employers have a policy regarding transfer during pregnancy, and many will follow the recommendation of a physician regarding job relocation. However, an employer usually is not required to transfer a pregnant worker to a safe job (see *Suggested Reading List,* page 17).

The difference in emphasis between the answers to this question and (b) above is important. The answer to (b) considers medical treatment that has potential morbidity and mortality implications for the patient, whereas this answer affords the opportunity to practice prevention. Preventive actions are more desirable and often require less certainty than other interventions.

f) "What is an ATSDR health consultation? What is an ATSDR public health assessment?"

A health consultation is ATSDR's response to a question or request for information pertaining to a hazardous substance or site. The procedure provides advice on specific public health issues that arise from actual or potential exposure to a hazardous substance. When a rapid response is required, a health consultation is a more limited method of addressing concern about potential adverse health effects than is an ATSDR public health assessment.

A public health assessment is a formal evaluation of relevant environmental data, health outcome data, and community concerns associated with a site where a hazardous substance has been released. In the process of assessing the current or future impact of a release on public health, studies or actions needed to evaluate, mitigate, or prevent human health effects are defined. Written health advisories or other recommendations may be developed and issued.

Suggested Reading List

Barlow SM, Sullivan FM. Reproductive hazards of industrial chemicals. New York: Academic Press, 1982.

Borzelleca JF. Symposium on environmental and occupational health hazards. Clin Lab Med 1984;4:461-7.

Hunt VR. Work and the health of women. Boca Raton, FL: CRC Press, 1982.

LeMasters GK. Occupational exposures and effects on male and female reproduction. In: Rom WN, ed. Environmental and occupational medicine. Boston: Little, Brown and Company, 1992.

Messite J, Bond MB. Reproductive toxicology and occupational exposure. In: Zenz C, ed. Developments in occupational medicine year book. Chicago: Medical Publishers, 1980.

Paul ME, ed. Occupational and environmental reproductive hazards: A guide for clinicians. Baltimore: Williams and Wilkins, 1992.

Rao KS, Schwetz BA. Reproductive toxicity of environmental agents. Annu Rev Public Health 1982;3:1-27.

Rosenberg MJ, Feldman PJ, Marshall EJ. Occupational influence on reproduction: A review of present literature. J Occup Med 1987;29:584-91.

Soderman JV. Handbook of identified carcinogens and noncarcinogens: Carcinogenicity-mutagenicity database (2 vol.). Boca Raton, FL: CRC Press, 1982.

Stein ZA, Hatch MC, eds. Reproductive problems in the workplace. State Art Rev Occup Med 1986;1(3): 361-539.

Vainio H, Sorsa M. Application of cytogenic methods for biological monitoring. Annu Rev Public Health 1983;4:403-7.

Welch LS. Decision making about reproductive hazards. Semin Occup Med 1986;1:97-106.

Wyrobeck AJ, Gordon LA, Burkhart JC, et al. An evaluation of human sperm as indicators of chemically induced alterations of spermatogenic function. Mutat Res 1983;115:73-148.

Zielhuis RR, Stijkel A, Verbeck MM, et al. Health risks to female workers: Occupational exposure to chemical agents. New York: Springer-Verlag, 1984.

Government Publications

American College of Obstetricians and Gynecologists. Guidelines on pregnancy and work. DHEW (NIOSH) Publication No. 78-118, 1977.

Centers for Disease Control and Prevention. Recommendations for the use of folic acid to reduce the number of cases of spina bifida and other neural tube defects. MMWR 1992;41:1-7.

General Accounting Office. Reproductive and developmental toxicants: Regulatory actions provide uncertain protection. Washington, DC: US General Accounting Office, 1991. Publication No. GAO/PEMD-92-3.

Other Sources of Information

Many of the issues in the series *Case Studies in Environmental Medicine* concern individual chemicals; each contains information on the reproductive and developmental effects of that chemical. Members of the Organization of Teratology Information Services (OTIS) and of the Association of Occupational and Environmental Clinics (AOEC) are listed by state in Appendices I and II, respectively.

In addition, risklines (telephone hotlines) or clinics that address reproductive and developmental hazards are available in the United States and Canada. Many of the following organizational resources are listed in *Reproductive Hazards in the Workplace: A Syllabus for Cinicians,* by M. Paul and S. Kurtz, University of Massachusetts, 1990.

Arizona

Arizona Teratogen Information Service. Arizona Health Sciences Center, Tucson, AZ. Serves Arizona only: (602) 626-6016 or (800) 362-0101 (Arizona only)

California

Hazards Evaluation System and Information Service (HESIS), California Department of Health Services, Berkeley, CA. Serves California only: (510) 540-3014 (collect calls accepted from within California)

Connecticut

Connecticut Pregnancy Exposure Riskline, University of Connecticut Health Center, Farmington, CT. Serves Connecticut only: (203) 674-1465 or (800) 325-5391 (Connecticut only)

Colorado, Montana, Nevada, and Wyoming

Rocky Mountain Poison and Drug Center and the University of Colorado Genetics Unit, Denver, CO. Serves primarily Colorado, Montana, Nevada, and Wyoming: (800) 332-3073 (Colorado only), (800) 525-5042 (Montana only), (800) 446-6179 (Nevada only), (800) 442-2702 (Wyoming only). Out of state: (303) 629-1123; physicians only: (303) 270-8742

Florida

Teratogen Information Service, University of Florida, Gainsville, FL. Serves Florida only: (904) 392-4104

Illinois

Illinois Teratogen Information Service, Illinois Department of Public Health, Chicago, IL. Serves Illinois only: (312) 903-7441 or (800) 252-4847

Massachusetts

Occupational and Environmental Reproductive Hazards Center, University of Massachusetts Medical Center, Worcester, MA. Provides clinical consultation and health provider education regarding reproductive hazards: (508) 856-6162.

Teratogen Information Service, Franciscan Children's Hospital, Boston, MA. Serves primarily Massachusetts but will accept calls from practitioners nationwide: (617) 787-4957 or (800) 322-5014 (Massachusetts only)

Nebraska

Nebraska Teratogen Project, University of Nebraska Medical Center, Omaha, NB. Serves primarily Nebraska but will accept calls from practitioners in surrounding states: (402) 266-2900

New Jersey

Teratogen Information Network, University of Medicine and Dentistry of New Jersey. Serves primarily New Jersey: (609) 757-7812 or (800) 441-0025 (New Jersey only)

Pennsylvania

Pregnancy Healthline, Pennsylvania Hospital, Philadelphia, PA. Serves primarily Pennsylvania: (215) 829-KIDS (829-5437)

Utah

Pregnancy Riskline, Utah Department of Health and University of Utah, Salt Lake City, UT. Serves Montana, Nevada, and Utah: (800) 521-2229 (Montana and Nevada only); (801) 583-2229 or (800) 822-2229 (Utah only)

Vermont

Vermont Pregnancy Risk Information Service, University of Vermont, Burlington, VT. Serves Vermont only: (802) 658-4310 or (800) 531-9800 (Vermont only)

Washington

Seattle Poison Center, Children's Hospital and Medical Center, Seattle, WA. Serves Washington only: (206) 526-2121 or (800) 732-6985 (Washington only)

Canada

A team of physicians and information specialists in the MotherRisk Program at the Hospital for Sick Children, Toronto, Ontario, ([416] 813-6780) will counsel a caller about the safety of an exposure to drugs, chemicals, or radiation during pregnancy or breast feeding. Please be prepared to provide them with the specific name of the product about which you are concerned and the exact dates of the exposure. They will not suggest or prescribe medication by telephone and will not answer questions about advanced maternal age, amniocentesis, chorionic villae sampling, or other pregnancy-related tests. Questions concerning a genetic condition should be directed to the Department of Clinical Genetics at the Hospital for Sick Children ([416] 813-6390).

Computer Databases

Computer databases dedicated to reproductive and developmental hazards

REPROTOX
Contact: Greta Ober
Reproductive Toxicology Center
Columbia Hospital for Women Medical Center
2425 L Street, NW
Washington, DC 20037
(202) 293-5137

TERIS
Contact: Janine E. Polifka, Ph.D.
Teratogen Information System (includes *Shepard's Catalog of Teratogenic Agents*)
Department of Pediatrics, TRIS WJ-10
University of Washington
Seattle, WA 98195

REPRORISK
Contact: Betty Dabney, Ph.D.
Micromedex, Inc.
600 Grant Street
Denver, CO 80203-3527
(303) 831-1400

APPENDIX I

Organization of Teratology Information Services (OTIS)

ARIZONA

Tucson

Arizona Teratogen Information Program (ATIP)
University of Arizona/Department of Pediatrics
Section of Genetics/Dysmorphology
2504 East Elm Street
Tucson, AZ 85716
(602) 795-5675 or in AZ (800) 362-0101 FAX (602) 626-4884
Contacts: Dee Quinn, MS; H. Eugene Hoyme, MD; Lynn Hauck, MS

CALIFORNIA

San Diego

California Teratogen Information Service & Clinical Research Program
University of California, San Diego
Department of Pediatrics
Division of Dysmorphology & Teratology
225 Dickinson Street #8446
San Diego, CA 92103-8446
(619) 294-6084, (800) 532-3749 (CA only), (619) 294-6217 (administrative only) FAX (619) 291-0946
Contacts: Kenneth Loyns Jones, MD; Kathleen Johnson; Christina Chambers; Lyn Dick; Robert Felix

COLORADO

Denver

TIES
The Children's Hospital
B300 Genetics
1056 East 19th Avenue
Denver, CO 80218
(303) 861-6395, (800) 332-2082 (CO only), (800) 525-4871 (Wyoming only) FAX 303-861-3992
Contacts: Karen Prescott, MS; David Manchester, MD; Carol Walton, MS; Cathy Marquez

CONNECTICUT

Farmington

Connecticut Pregnancy Exposure Information Service
Division of Human Genetics Rm L-5072
University of Connecticut Health Center
263 Farmington Avenue
Farmington, CT 06030
(203) 679-1502, (800) 325-5391 (CT only) FAX (203) 679-1531
Contacts: Glenda Lee Spivey, MS; Sally S. Rosengren, MD; Sharon Voyer, MS; Robert Pilarski, MS; Joanne Brochu

DISTRICT OF COLUMBIA

Washington, DC

Reproductive Toxicology Center
2440 M Street NW, Suite 217
Washington, DC 20037-1404
(202) 293-5137 FAX (202) 293-7256
Contacts: Anthony R. Scialli, MD; Armand Lione, PhD; G. Kay Padgett; Christine Colie, MD; Greta D. Ober

FLORIDA

Gainesville

Teratogen Information Service
University of Florida Health Science Center
Box 100296
Gainesville, FL 32610-0296
(904) 392-3050 FAX (904) 392-3051
Contacts: Donna H. Poynor, MM; Charles A Williams, MD

Miami

Florida Teratogen Information Service
University of Miami School of Medicine
Mailman Center PO Box 016820
Miami, FL 33101
(305) 547-6464 FAX (305) 547-3919
Contact: Virginia H. Carver, PhD

Tampa

Teratogen Information Service
University of South Florida
Department of Pediatrics, Box 15-G
12901 Bruce B Downs Boulevard
Tampa, FL 33613
(813) 974-2262 FAX (813) 974-4985
Contacts: James K. Hartsfield, DMD; Boris G. Kousseff, MD; Suzanne R. Sage, RN, MS;
Jaime L. Frias, MD

GEORGIA

Atlanta

Centers for Disease Control and Prevention
Division of Birth Defects and Genetic Diseases
Mail Stop F45
1600 Clifton Road
Atlanta, GA 30333
(404) 488-4967 FAX (404) 488-4643
Contacts: Muin J. Khoury, MD, PhD; José F. Cordero, MD, MPH

ILLINOIS

Chicago

Illinois Teratogen Information Service
Northwestern University
333 East Superior, Suite 1543
Chicago, IL 60611
(312) 908-7441, (800) 252-4847 FAX (312) 908-6643
Contacts: Eugene Pergament, MD, PhD; Amy Risman, MS

INDIANA

Indianapolis

Indiana Teratogen Information Service
Department of Medical Genetics
Indiana University Medical Center
975 West Walnut Street
Indianapolis, IN 46202
(317) 274-1071 FAX (317) 274-2387
Contacts: David D. Weaver, MD; Peg Davee, MS; Lola Cook, MS

IOWA

Iowa City

University of Iowa Prenatal Diagnostic Unit
Department of Obstetrics and Gynecology
University of Iowa
Iowa City, IA 52241
(319) 356-3561 FAX (319) 355-6728
Contacts: Roger Williamson, MD; Katharine Wenstrom, MD; Susan Sipes, MD; Stanley Grant, RN

University of Iowa Teratogen Information Service
Department of Pediatrics/Medical Genetics
University of Iowa Hospitals & Clinics
Iowa City, IA 52242
(319) 356-2674 FAX (319) 356-3347
Contacts: James W. Hanson, MD; Ann Muilenburg, RN, MA

KANSAS

Wichita

Prenatal Diagnostic & Genetic Clinic
HCA Wesley Medical Center
550 North Hillside
Wichita, KS 67214
(316) 688-2362
Contacts: Sechin Cho, MD; Paula Floyd, RN, MN; Richard Lutz, MD; Nancy McMaster, RN, MEd

MASSACHUSETTS

Boston

Massachusetts Teratogen Information Service (MTIS)
National Birth Defects Center
30 Warren Street
Boston, MA 02135
(617) 787-4957, (800) 322-5014 (MA only), (617) 787-5834 (office) FAX (617) 787-6936
Contacts: Susan Rosenwasser, MEd; Jane O'Brien, MD; Katryn Miller, MEd; Robin Maltz, MPH; Karen Treat, MS

Embryology Teratology Unit
Warren 801
Massachusetts General Hospital
Fruit Street
Boston, MA 02114
(617) 726-1742 FAX (617) 726-1866
Contacts: Lewis B. Holmes, MD; Ailish M. Hayes, MD; Gerald V. Raymond, MD; Joan M. Stoler, MD

MASSACHUSETTS (continued)

Boston (continued)

TERAS
c/o Dr. Fred Bieber
Department of Pathology
Brigham & Women's Hospital
75 Francis Street
Boston, MA 02115
(617) 732-6507 FAX (617) 732-7513
Contacts: Frederick R. Bieber, PhD; David Genest; George Mutter; Drucilla Roberts; Christopher Crum

Worcester

Occupational and Environmental Reproductive Hazards Center
University of Massachusetts Medical Center
Department of Obstetrics and Gynecology
55 Lake Avenue North
Worcester, MA 01655
(508) 856-6162 FAX (508) 856-2965
Contacts: Maureen Paul, MD, MPH; Jay Himmelstein, MD, MPH; Sabrina Kurtz, MEd; Carol Lewis; Gregory Garran

MISSOURI

Columbia

Columbia Teratogen Information Service
Department of Child Health
Medical Genetics Division
University of Missouri
1 Hospital Drive
Columbia, MO 65212
(314) 882-6991 FAX (314) 882-2742
Contacts: Virginia Proud, MD; Judith Miles, MD; Kathy Morris, MSSW

St. Louis

Genetics and Environmental Information Service (GENIS)
Washington University School of Medicine
Department of Obstetrics, Gynecology, Genetics
216 South Kingshighway
St. Louis, MO 63110
(314) 454-8172 FAX (314) 454-7358
Contacts: Heidi Beaver, MPH; Sheri Babb; Laura Turlington, MS; Cindy Johnson, MS; James P. Crane, MD; Jeffrey M. Dicke; Jane E. Corteville; Diana L. Gray

NEBRASKA

Omaha

Nebraska Teratogen Project
University of Nebraska Medical Center
600 South 42nd Street
Omaha, NE 68198-5430
(402) 559-5071 FAX (402) 559-5737
Contacts: Beth Conover, RN, MS; Bruce Buehler, MD

NEW JERSEY

Camden

New Jersey Pregnancy Risk Information Service
UMDNJ-Robert Wood Johnson Medical School
401 Haddon Avenue
Camden, NJ 08103
(609) 757-7812, (800) 441-0025 (NJ only) FAX (609) 757-9792
Contacts: Michael K. McCormack, PhD; Carol Zuber, MS; Charlotte Furey, BSN

NEW YORK

Rochester

Perinatal Environmental and Drug Consultation Service (PEDECS)
Department of Obstetrics and Gynecology, PO Box 668
University of Rochester Medical Center
601 Elmwood Avenue
Rochester, NY 14642
(716) 275-3638 FAX (716) 244-2209
Contact: Richard K. Miller, PhD

West Seneca

Teratogen Information Service
1200 East and West Road, Building 16
West Seneca, NY 14224
(716) 674-6300 x4812
Contacts: Luther K. Robinson, MD; Sandra Gangell

NORTH DAKOTA

Grand Forks

Division of Medical Genetics, Department of Pediatrics
University of North Dakota School of Medicine
501 Columbia Road
Grand Forks, ND 58203
(701) 777-4277 FAX (701) 777-3894
Contacts: John T. Martsolf, MD; Mary Ebertowski, RN

PENNSYLVANIA

Philadelphia

Pregnancy Healthline
Pennsylvania Hospital
8th and Spruce Streets, 7th floor
Philadelphia, PA 19107
(215) 829-3601 FAX (215) 829-7423
Contacts: Betsy Schick-Boschetto, MSN; Alan E. Donnenfeld, MD; Ronald J. Librizzi, DO

Pittsburgh

Pregnancy Safety Hotline
Department of Reproductive Genetics
School of Nursing, 2nd Floor
Western Pennsylvania Hospital
4800 Friendship Avenue
Pittsburgh, PA 15224
(412) 687-SAFE FAX (412) 578-1125
Contacts: Michael J. Kerr, MS; Kathy A. Bournikos, MS; Karen Filkins, MD; Christann Jackson, MD; Elizabeth Gettig

PENNSYLVANIA (continued)

Pittsburgh

Department of Reproductive Genetics
Magee-Women's Hospital
300 Halket Street
Pittsburgh, PA 15213
(412) 647-4168 FAX (412) 647-4343
Contacts: Sandra G. Marchese, MS; Mona Penles Stadler, MS; Deanna P. Stelle, MS; Luanne Fraer, MS; Amy Niklaus, MS; Faith Callif-Daley, MS; Dolores Pegram, MEd

SOUTH DAKOTA

Vermillion

Teratogen and Birth Defects Information Project
School of Medicine
University of South Dakota
414 East Clark
Vermillion, SD 57069
(800) 962-1642 FAX (605) 677-5124
Contacts: Virginia P. Johnson, MD; Patricia Skorey, MNS, BSN; Carol Strom, MS

TEXAS

Denton

Genetic Screening and Counseling Service
PO Box 2467
Denton, TX 76202-2467
(817) 383-3561 FAX (817) 382-6235
Contacts: Lori Wolfe, MD; Becky Althaus, MS; Donald W. Day, MD; Margaret Drummond-Borg, MD; Judith Martin, MD

UTAH

Salt Lake City

Pregnancy Riskline
44 Medical Drive
Salt Lake City, UT 84113
(801) 583-2229 FAX (801) 584-8488
Contacts: John Carey, MD; Marcia Feldkamp; Lynn Martinez; Marsha Leen-Mitchell

VERMONT

Burlington

Vermont Pregnancy Risk Information Service
Vermont Regional Genetics Center
1 Mill Street, Suite 3-1
Burlington, VT 05401
(802) 658-4310
Contacts: Alan E. Guttmacher, MD; Wendy C. McKinnon, MS

WASHINGTON

Seattle

Central Laboratory for Human Embryology
Department of Pediatrics RD-20, School of Medicine
University of Washington
Seattle, WA 98195
(206) 543-3373 FAX (206) 543-3184
Contacts: Tom Shepard, MD; Alan Fantel, MD; Phil Mirkes

WISCONSIN

LaCrosse

Teratogen Information Service
LaCrosse Regional Genetic Services
PO Box 1326
LaCrosse, WI 54602
(608) 791-6681, (800) 362-9567 (WI, MN, IA, northern IL)
Contact: Janet Williams, MS

Madison

Wisconsin Teratogen Project
Waisman Center Room 347
1500 Highland Avenue
Madison, WI 53705
(608) 262-4719, (800) 442-6692 FAX (608) 263-3496
Contacts: Renata Laxova, MD; Joanne Haun, MS; Catherine Reiser, MD

Milwaukee

Great Lakes Genetics
2323 North Mayfair Road, Suite 410
Milwaukee, WI 53226
(414) 475-7400, (414) 475-7223
Contacts: Lois Magnuson, RN; Jurgen Herrmann, MD; Bonnie-Jo Bates, MD

Eastern Wisconsin Teratogen Service
Medical Genetics Institute, SC
4555 West Schroeder Drive, Suite 180
Milwaukee, WI 53223
(414) 357-6555 FAX (414) 357-9394
Contacts: B. Rafael Elejalde, MD; Maria M. de Elejalde, MS, RN

APPENDIX II

Association of Environmental and Occupational Clinics (AEOC)

CALIFORNIA

San Francisco

Judie Guerriero, RN, MPH
Occupational Health Clinic
San Francisco General Hospital
1001 Potrero Avenue, Building 9, Room 109
San Francisco, CA 94110
(415) 206-5391 FAX (415) 206-8949
Alt. Contact: Patricia Quinlan, MPH

Robert Harrison, MD
Occupational & Environmental Medicine Clinic
University of California at San Francisco
400 Parnassus Avenue A585
San Francisco, CA 94143
(415) 476-1841 FAX (415) 476-6426

COLORADO

Denver

Kathleen Kreiss, MD
National Jewish Center of Immunology and Respiratory Medicine
1400 Jackson Street
Denver, CO 80206
(303) 398-1520 FAX (303) 398-1452
Alt. Contacts: Cecile Rose, MD; Peggy Mroz, MSPH

CONNECTICUT

New Haven

Mark Cullen, MD
Yale Occupational/Environmental Medicine Program
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Posttest and Credits

Continuing education credit is available to health professionals who use this monograph and complete the posttest. The criterion for awarding continuing medical education (CME) credits and continuing education units (CEU) is a posttest score of 70% or better.

The Centers for Disease Control and Prevention (CDC) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians, and by the International Association for Continuing Education and Training (IACET) to sponsor continuing education units for other health professionals.

The Agency for Toxic Substances and Disease Registry, in joint sponsorship with CDC, is offering 1 hour of CME credit in category 1 of the Physician's Recognition Award of the American Medical Association and CEU for other health professionals upon completion of this monograph.

In addition, the series *Case Studies in Environmental Medicine* has been reviewed and is acceptable for credit by the following organizations:

The American Academy of Family Physicians (AAFP). This program has been reviewed and is acceptable for 1 prescribed hour by the American Academy of Family Physicians (term of approval: beginning January 1992). For specific information, please consult the AAFP Office of Continuing Medical Education.

The American College of Emergency Physicians (ACEP). Approved by the American College of Emergency Physicians for 1 hour per issue of ACEP Category I credit.

The American Osteopathic Association (AOA). AOA has approved this issue for 1 credit hour of Category 2-B credit.

The American Association of Occupational Heath Nurses (AAOHN). AAOHN has approved this program for 1.0 contact hours. Applicant will receive the assigned code number in the award letter.

The American Board of Industrial Hygiene (ABIH). ABIH has approved this program for 0.5 certification maintenance (CM) point per 3 case studies. The CM approval number is 2817.

To receive continuing education credit (CME or CEU), complete the Posttest on page 40 in the manner shown in the sample question below. **Circle all correct answers.**

Which of the following is known to precipitate migraine headaches?

(a) fatigue
(b) alcohol
c. grapefruit
(d) sunlight
e. sleep

After you have finished the Posttest, please record your answers on the answer sheet on the inside back cover and complete the evaluation on the lower half of that page. Fold, staple, and mail the back cover to Continuing Education Coordinator, Agency for Toxic Substances and Disease Registry, Division of Health Education, E33, 1600 Clifton Road, NE, Atlanta, GA 30333. Your confidential test score will be returned with an indication of where the correct answers can be found in the text. Validation of earned CME credit and CEU will also be forwarded to participants, and their names, if requested, will be placed on the mailing list to receive other issues in the *Case Studies in Environmental Medicine* series.

POSTTEST: REPRODUCTIVE and DEVELOPMENTAL HAZARDS

Circle **all** correct answers and transfer your answers to page 41.

1. Which of the following statements is (are) true?
   a. If an exposure is hazardous to the fetus, the mother will also be ill from the exposure.
   b. In the occupational setting, most exposures to the fetus occur by the mother inhaling hazardous chemicals.
   c. Chemical exposures that occur before, during, or after conception can harm the developing fetus.
   d. Substances at work and in the environment can affect male fertility.
   e. No studies have documented an association between workplace exposures and ooctye damage or loss.
2. Which of the following substances are excreted in breast milk?
   a. lead
   b. fiberglass
   c. ammonia
   d. mercury
   e. polychlorinated biphenyls (PCBs)
3. Which of the following compounds have been strongly associated with infertility in exposed men?
   a. 1,2-dibromo-3-chloropropane (DBCP)
   b. lead
   c. benzene
   d. cadmium
   e. ionizing radiation
4. Which of the following has been strongly associated with spontaneous abortion in exposed women?
   a. lead
   b. 2,4-dichlorophenoxyacetic acid (2,4-D, a component of Agent Orange)
   c. video display terminals
   d. anesthetic gases
   e. carbon disulfide
5. Which of the following statements is (are) true?
   a. To be considered a reproductive hazard, a chemical agent must act prior to conception.
   b. All reproductive and developmental toxicants damage the genetic material in the ovum or sperm.
   c. Risk factors for male fertility need not be considered in the workplace.
   d. A compound stored in bone or fat has no effect on embryonic development.
   e. Exposure to a hazardous substance must occur for at least 5 years to affect female fertility.
6. Which of the following statements is (are) true?
   a. Exposure to ionizing radiation can cause male infertility.
   b. Workplace exposures to teratogens occur most often through ingestion of drinking water.
   c. If exposure to a reproductive toxicant occurs at work, the only solution for a woman planning to become pregnant is a job transfer.
   d. Folic acid supplements in women of reproductive age may help prevent fetal neural tube defects.
   e. Engineering controls in an occupational setting can reduce exposures to reproductive hazards.
7. If your patient is pregnant and has been exposed to lead in her drinking water, you should:
   a. tell her that lead in drinking water cannot affect her pregnancy
   b. determine her blood lead level
   c. discourage breast feeding in any case
   d. recommend that she drink bottled water
   e. immediately begin treatment with a lead chelating agent
8. Which of the following compounds are known or suspected teratogens?
   a. lead
   b. lithium
   c. mercury
   d. chlorobiphenyls or PCBs
   e. 1,2-dibromo-3-chloropropane (DBCP)

CASE STUDIES IN ENVIRONMENTAL MEDICINE: REPRODUCTIVE AND DEVELOPMENTAL HAZARDS

If you wish CME credits or CEU, please indicate your answers to the Posttest questions on page 40 by circling the letters below for the correct answers. Complete the evaluation questionnaire and fill in the information requested on the reverse side. Tear off this page, fold, staple, and mail to Continuing Education Coordinator, Agency for Toxic Substances and Disease Registry, Division of Health Education, E33, 1600 Clifton Road, NE, Atlanta, GA 30333.

1. a b c d e
2. a b c d e
3. a b c d e
4. a b c d e
5. a b c d e
6. a b c d e
7. a b c d e
8. a b c d e

Evaluation Questionnaire

Please complete the following evaluation by putting a check in the appropriate box.

	YES	NO	UNDECIDED
1. As a result of completing this monograph, I will be able to:			
Describe the factors contributing to reproductive and developmental hazards.	❑	❑	❑
Identify adverse reproductive and developmental outcomes that may be caused by environmental or occupational exposures.	❑	❑	❑
Identify evaluation and treatment protocols for adverse reproductive and developmental outcomes.	❑	❑	❑
List sources of information on reproductive and developmental hazards.	❑	❑	❑
2. I am more likely to ask questions about possible environmental exposures as a result of reading this issue.	❑	❑	❑
3. I will recommend this issue to my colleagues.	❑	❑	❑
4. I will keep this issue as a reference.	❑	❑	❑

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Please send me the following *Case Studies in Environmental Medicine*:

- ☐ Arsenic
- ☐ Asbestos
- ☐ Benzene
- ☐ Beryllium
- ☐ Cadmium
- ☐ Carbon Tetrachloride
- ☐ Chlordane
- ☐ Cholinesterase Inhibitors
- ☐ Chromium
- ☐ Cyanide
- ☐ Dioxins
- ☐ Ethylene/Propylene Glycols
- ☐ Gasoline
- ☐ Jet Fuels
- ☐ Lead
- ☐ Mercury
- ☐ Methanol
- ☐ Methylene Chloride
- ☐ Nitrates/Nitrites
- ☐ Pentachlorophenol
- ☐ Polyaromatic Hydrocarbons (PAHs)
- ☐ Polychlorinated Biphenyls (PCBs)
- ☐ Radiation
- ☐ Radon
- ☐ Stoddard Solvent
- ☐ Tetrachloroethylene
- ☐ 1,1,1-Trichloroethane
- ☐ Trichloroethylene
- ☐ Toluene
- ☐ Vinyl Chloride
- ☐ Exposure History
- ☐ Risk Communication
- ☐ Reproductive and Developmental Hazards
- ☐ Skin Lesions

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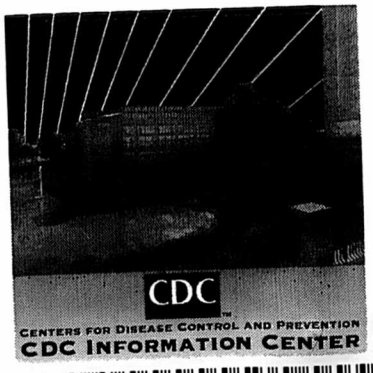

The state of knowledge regarding the treatment of patients potentially exposed to hazardous substances in the environment is constantly evolving and is often uncertain. In this monograph, the Agency for Toxic Substances and Disease Registry (ATSDR) has made diligent effort to ensure the accuracy and currency of the information presented but makes no claim that the document comprehensively addresses all possible situations related to this topic. This monograph is intended as an additional resource for physicians and other health professionals in assessing the condition and managing the treatment of patients potentially exposed to hazardous substances. It is not, however, a substitute for the professional judgment of a health care provider and must be interpreted in conjunction with other sources of authority and in light of specific patient information available to such a professional.

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