

MODULE 8 INDUSTRIAL TOXICOLOGY

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Goals:

1. Understand the basic principles of toxicology.
2. Learn the definition of toxic substances.
3. Identify the factors affecting absorption of toxic substances.
4. Identify the most common hazard exposure routes.
5. Identify the most common types of local effects.

Additional reading material:

Case Studies in Environmental Medicine- Reproductive and Developmental Hazards.

Toxicology is the study of poisons. More specifically, it is the investigation of the adverse effects of chemicals and physical substances on living organisms. The term is reportedly derived from a Greek word, which meant a toxon or bow, inferring to poison-dipped-arrows.

A great number of the poisons in our environment are substances naturally occurring in plant or animal life. These chemicals in their natural or altered state can be or become toxic to humans. The Ebers Papyrus' scrolls (1552 B.C.) are one of the earliest medical recordings of western civilization listing nearly a thousand medical remedies and citing the possible toxic effects of heavy metals. Hippocrates (460 B.C.) identified mercury, lead, antimony, and arsenic as toxic, while Aristotle (350-250 B.C.) described numerous plant, animal and mineral poisons. Throughout history a number of toxic substances have been identified and developed and the art of poisoning has been perfected. Understanding the basic toxicological principles is essential for the practicing physician. If a physician suspects that an illness or clinical findings suggest an occupational or environmental

exposure, an understanding of the absorption, mechanism of action, potency, and elimination of the substance in question will prove invaluable in arriving at the correct diagnosis. Knowing that a substance is toxic does not mean that it will automatically do harm. Toxicity refers to the amount of a substance that will inherently produce adverse effects. According to the National Institute of Occupational Safety and Health (NIOSH) Registry of Toxic Effects of Chemical Substances, the definition of a toxic substance reads in part:

“A toxic substance is one that demonstrates the potential to induce cancer, tumors, or neoplastic effects in man or experimental animals; to induce a permanent transmissible change in the characteristic of an offspring from those of its human or experimental animal parents; to cause the production of physical defects in the developing human or experimental animal embryo; to produce death in animals exposed via the respiratory tract, skin, eye, mouth or other routes in experimental or domestic animals; to produce irritation or sensitization of the skin, eyes or respiratory passages; to diminish mental alertness, reduce motivation or alter behavior in humans; to adversely affect the health of a normal or disabled person of any age or of either sex by producing reversible or irreversible bodily injury or by endangering life or causing death from exposure via the respiratory tract, skin, eye, mouth or any other route in any quantity, concentration, or dose reported for any length of time”.

Toxicology is studied in many different and distinct medical specialties, among which are: Molecular, Reproductive, Genetic and Forensic as well as Environmental and Industrial toxicology. **Industrial toxicology** is the study of the adverse effects that substances used or manufactured in the industrial environment have in the health and safety of humans. Toxic substances are common in our environment. They exist as solids, gases or liquids depending on pressure or temperature variations. Brief exposures to common household toxic substances typically do not cause injury or incapacitation, however, substances encountered in the industrial environment may be potentially harmful. Industrial toxicology studies the susceptibility of workers exposed to industrial strength substances, from the raw material and its derivatives to the finished product. Industrial toxicologists, by default, investigate the nature and effect of substances used or produced in industry. Retrospective studies are conducted with the purpose of identifying substances to which workers have been exposed. They are essential in the recognition of hazardous substances.

Many substances are inherently harmful while others do not cause harm or adversely impact the working environment except for the conditions of their use. Generally, hazardous substances do not present a hazard if properly managed and secured. A hazard constitutes the establishment of contact between the substance and the individual, especially if it presents a threat to health and safety. The Comprehensive Environmental Response Compensation and Liability Act (CERCLA) defines a hazardous substance as

any chemical regulated by the Clean Air and Water Act, the Toxic Substances Control Act, or the Resource Conservation and Recovery Act. Hazardous materials are defined by the U. S. Department of Transportation as “a substance or material, including a hazardous substance, which has been determined by the Secretary of Transportation to be capable of posing an unreasonable risk to health, safety and property when transported in commerce”. Hazardous wastes are solid wastes, which are “any discarded material (i.e. garbage, sludge, refuse or other discarded material). A more comprehensive review of hazardous substances can be found in the General Industry Standards for Toxic and Hazardous Substances Title 29 CFR, Part 1910, Subpart Z.

Mechanisms of Action:

Toxins evoke a series of chemical processes after the initial event through specific action sites or through action at receptor sites throughout the body. The resultant effect is usually related to the concentration of the toxin. However, one must understand that the final biological result may not correlate to the specific property of the toxin and that different toxins can produce similar reactions. One example would be strychnine that acts on the central nervous system but resultant effects are skeletal muscle contractions. Toxins can also affect the enzymatic system producing both reversible and irreversible reactions. Enzymes are catalysts that perform essential biochemical cellular functions. Enzymes are complex protein molecules with specific sites of action. Interference with these sites affects the function of the enzyme and interferes with the intended biological action. Nerve agents developed for chemical warfare are examples of these types of actions. Organophosphates form an irreversible bond at the site of action of acetyl cholinesterase, the principal enzyme in the breakdown of the neurotransmitter Acetylcholine. Other types of enzyme inhibitors include heavy metals such as lead, arsenic and mercury. Some toxins induce disease or injury, including lethal effects, by the development of by-products. For example, methanol is enzymatically degraded to formaldehyde, which has a predilection for the optic nerve thus inducing blindness. Carbon monoxide poisoning results from the tighter and greater affinity that carbon monoxide has for the binding site on the hemoglobin molecule. Other agents lead to illness by enhancing natural processes and affecting the body's ability for regeneration. Agents such as p-aminosalicylic acid, nitrites, quinine and primaquine among others, produce methemoglobin as a result of hemoglobin oxidation. In conditions such as Beta thalassemia, with a diminished capacity for hemoglobin regeneration, and neonates that have a limited ability to regenerate hemoglobin, a build-up of methemoglobin diminishes the effective transport of oxygen.

Some toxins accumulate in the cells and depress cellular activity causing a narcotic or anesthetic effect. General anesthetics such as ether and halothane, as well as glues, organic solvents, gasoline and other halogenated compounds tend to produce an anesthetic reaction. In the clinical setting these substances have a fairly wide safety range, however, this is not the case with workplace organic solvents, which carry a substantial risk of death. Naturally occurring substances like atropine, norepinephrine, nicotine and curare affect cellular function by their actions on neurotransmission. These agents affect the neurotransmitters acetylcholine or norepinephrine by mimicking or

inhibitory actions at the receptor sites. Cholinergic receptors that use acetylcholine for their action have either muscarinic or nicotinic receptors; adrenergic transmission is mediated by either epinephrine or norepinephrine action. Atropine and nicotine are cholinergic receptor inhibitors and act at the neuromuscular junction to induce relaxation of the skeletal muscle. Other examples of this action include the effects of Botulinus toxin, shellfish poisoning, tetrodotoxin and puffer fish poisoning. Yet others have different forms of action. Some will affect the DNA duplication process and inhibit cell division while others prevent RNA transcription. More commonly known products exert their effects by altering protein synthesis and affecting amino acid chain reconstruction: i.e., tetracycline and chloramphenicol interfere with ribosomal action; streptomycin and gentamycin interfere with mRNA translation.

Immunologic Reactions:

Repeated exposure to toxins or other substances alert the body's immune system to develop a defensive response. This sensitization process can be initiated passively, as through the use of vaccinations, or actively through direct contact with an agent or substance in the environment. The passive immunologic response is commonly a controlled process. An active response, on the other hand, can lead to a hypersensitivity response manifested by a simple allergic reaction or advance to an anaphylactic response. Most initial contacts may manifest with disturbing or annoying symptoms such as a skin rash. Repeated exposures or an increase in the intensity of the substance can lead suddenly to an anaphylactic response.

Direct contact with chemical irritants can lead to a chemical tissue reaction. Typically they affect the skin, eyes, mucous membranes and upper respiratory tissues. In the military setting or in bioterrorist activities the use of mustard gases or blistering agents can lead to a severe blistering dermatitis; phosgene and chlorine can lead to pulmonary edema; and nitrous oxide fumes can irritate the mucous membranes. Another irritant many of us have also experience is the lacrimal irritation produced by tear gases, such as acrolein and bromacetone.

Defense Mechanisms:

Barrier membranes protect our bodies, in order for us to maintain a constant homeostatic environment. However, these seemingly impenetrable barriers are imbedded with proteins with the specific function of allowing the transport of nutrients into our bodies as well as the elimination of wastes. Exposure to a substance does not necessarily mean absorption. In order for a substance to be absorbed it must first make physical contact and cross the membrane barrier. Depending on the hydro (water) or lipo (lipid) properties of the substance, toxic agents can penetrate these barriers and produce unwanted effects. Substances can cross these barriers by several methods: diffusion across a concentration gradient; facilitated diffusion through the use of carrier proteins; active transport; and phagocytosis. The action of these substances can also be dependent on the route of absorption or penetration. The four most important routes of entry are discussed below: skin; ocular; pulmonary; and gastrointestinal.

INTEGUMENT

The skin is the second most common risk source for absorption of toxic chemicals. It consists of an external keratinized epithelial layer and a deeper dermal layer designed to resist the penetration of foreign substances as well as insulating the body from excessive water loss. The skin is a large waterproof organ inhibiting the absorption of hydrophilic substances. However, a break in this layer through cuts, abrasions, burns or punctures can increase the risk of absorption and allow the systemic penetration of toxic substances. Toxins can also be introduced through insect or animal bites and high-pressure systems. The use of products such as moisturizers, creams and lotions as well as perspiration, sweat and oily materials can increase the risk of absorption. Products such as benzene, carbon tetrachloride, insecticides and nerve gases are examples of products that can be absorbed through the skin and lead to serious injury or death.

OCULAR

The eye is a major sensory organ responsible for creating and providing visual images to the retina and delivering these images through the optic nerve to the ocular center. The eye resides in a bony socket covered with moist epithelial tissue which secretes a lubricant to facilitate its movement but which also promote absorption. The eyes are not only susceptible to traumatic injury caused by flying objects, but they can also be adversely affected by a host of other environmental physical agents. For example, arc welding, flash burns, radiation and even lasers, now commonly applied in the industrial setting, can induce ocular and retinal damage. In the environmental setting a potential yet inadvertent injurious agent is ultraviolet light, which can lead to an acute exposure (corneal burn) or long-term damage from chronic exposure (cataracts). The proper use of personal protective devices is paramount in the industrial setting.

PULMONARY

The respiratory system carries the greatest risk of exposure by industrial hazardous substances. Absorption is very high once inhalation has occurred. Gases, fumes, vapors, aerosolized liquids and dust particles are rapidly absorbed and/or deposited on lung tissue. The absorption and resultant action of toxic substances depends on the level of penetration reached by these agents within the pulmonary tree and the defensive mechanisms found at that level. The upper portion of the respiratory system, including the nose and upper pharynx, is susceptible to absorption, while filtering many coarse particles from the air. This is the case with the snorting of cocaine. Irritants in this area produce sneezing, which clears many of the larger particles (>5 microns). The mid portion of the respiratory tree, including the trachea and bronchial tubes, are lined with cilia. These hair-like structures along with mucous membrane secretions trap smaller irritant particles (2-5 microns) and induce a cough that moves them upward to where they are swallowed or expectorated. The lower portion of the respiratory tree, the alveoli, is exposed to some of the smallest irritants (<2 microns). Particles deposited in this region are phagocytized in an attempt at removal. Occasionally the end result is the development

of scar tissue and fibrosis leading to progressive loss of pulmonary function. This is typical of the reaction to by-products of the burning of coal.

Chemical agents that irritate the respiratory system may induce a significant inflammatory response leading to constriction of the airways and decreased respiratory volume, commonly manifested as reactive airway disease (asthma). If the reaction is severe pulmonary edema can ensue. Among many well-known agents, chlorine, phosgene, bromine, ammonia gases and hydrogen chloride can induce these types of reaction.

GASTROINTESTINAL

The GI system is the least likely route of exposure in an industrial setting. However, inadvertent ingestion of toxins can result through contaminated food or drink and from contact of contaminated hands and fingers with the oral mucosa (lips, tongue, mouth). Once ingested substances are rapidly absorbed, though the degree of absorption may be dependent on the amount of food ingested, types of food products and the pH of the digestive tract. Absorption is also affected by the rate of transit - the slower the movement the greater the absorption. The physical health of the worker, age, nutritional status, concomitant disease processes and medications can also affect the level of absorption. Likewise the use of motility agents, regurgitants and purgatives can enhance elimination and decrease absorption.

Metabolism:

Once absorbed substances undergo chemical transformation as a result of enzymatic action. Although natural products are metabolized anywhere in the body, foreign substances are metabolized mainly in the liver but can also be metabolized in the lung, brain, kidney, skin and intestines. These enzymatic reactions can occur through four different mechanisms: oxidation, reduction, hydrolysis and synthetic conjugation. The cytochrome P450 mechanism is the most important group of oxidative enzymes. Through the use of monooxygenases, oxygen atoms are introduced into the substance, thus, altering its chemical composition. Conjugation reactions join two substances together with the resultant substrate having different characteristics making it more easily extractable.

Excretion:

The kidneys are the primary elimination sites of toxic substances, although the liver, lungs, sweat, tears, and biliary system can also eliminate toxins from the body. It should be noted that the rate of renal excretion is dependent on the pH of the urine. Chemicals are excreted by the kidney through passive glomerular filtration and passive or active tubular secretion.

The liver is another important excretory organ. The liver filters blood from the GI tract before it reaches the systemic circulation. As a result, the liver can remove toxins before

they are distributed throughout the body. Many agents cleared by the liver enter the biliary system and are available for excretion. Products such as lead, arsenic and manganese are among the compounds excreted into the bile.

The lungs eliminate products usually in the gaseous phase. Alveolar diffusion may be another mechanism for the lungs to eliminate blood toxins.

Toxins can also be eliminated through breast milk, sweat, saliva, skin, hair and nails. Elimination of toxins through these sites can often provide clues to the nature of the toxin and degree of absorption.

Reproductive Hazards:

Chemical exposures can be associated with infertility. Proximity to toxic sites, drinking contaminated water or contact with contaminated clothing brought into the home from the worksite are among the most common sources of exposures. A case study from the ATSDR monograph series (“Reproductive and Developmental Hazards”) is presented here. This case study and the discussion of the case clearly illustrate the reproductive dangers of chemical toxins in our environment.

NOTE: You may obtain additional CME credits directly from ATSDR by taking and submitting the answers to the case study’s posttest. You will find the post-test following the suggested reading list.

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 pregnancy. 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.

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

§ Not applicable because no adverse outcomes were observed.

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.

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

- ❑ **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.**

(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

Organ	Embryonic period (weeks 3 to 8 postconception)					Fetal period (weeks 8 to 38 [full term])				
	3	4	5	6	7	8	12	16	20-36	38
CNS	xxxxxx	xxxxxx	xxxxxx	xxxxxx	xxxxxx	-----	-----	-----	-----	-----
Heart	xxxxxx	xxxxxx	xxxxxx	xxxxxx	xxxxxx	-----	-----	-----	-----	-----
Limbs	-----	-----	xxxxxx	xxxxxx	xxxxxx	-----	-----	-----	-----	-----
Ear	-----	-----	xxxxxx	xxxxxx	xxxxxx	xxxxxx	xxxxxx	xxxxxx	xxxxxx	xxxxxx
Eyes	-----	-----	xxxxxx	xxxxxx	xxxxxx	xxxxxx	xxxxxx	xxxxxx	xxxxxx	xxxxxx
Teeth	-----	-----	-----	-----	-----	xxxxxx	xxxxxx	xxxxxx	xxxxxx	xxxxxx
Palate	-----	-----	-----	-----	-----	-----	xxxxxx	xxxxxx	xxxxxx	xxxxxx
External genitalia	-----	-----	-----	-----	-----	xxxxxx	xxxxxx	xxxxxx	xxxxxx	xxxxxx

* period of high sensitivity = xxxxxx; period of less sensitivity = -----

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
<i>o,p</i> -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 than 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 counselor 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 ($\mu\text{g/L}$).
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 $\mu\text{g/deciliter}$ (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

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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.

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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 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 Clinicians*, by M. Paul and S. Kurtz, University of Massachusetts, 1990.

Arizona

Arizona Poison and Drug Information Service. Arizona Health Sciences Center, Tucson, AZ. Serves Arizona only: (602) 626-6016 or (800) 362-0101 (for Arizona other than Maricopa County)

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: (800) 325-5391

Colorado

Teratogen Information and Education Service, Denver, CO: (303) 372-1825

Florida

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

Illinois

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

Massachusetts

Teratogen Information Service, Boston, MA. Serves primarily Massachusetts but will accept calls from practitioners nationwide: (617) 466-8474 or (800) 322-5014

Nebraska

Nebraska Teratogen Project, University of Nebraska Medical Center, Omaha, NB. Serves primarily Nebraska but will accept calls from practitioners in surrounding states: (402) 559-5071

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) 328-2229 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

Washington 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, amnio-centesis, 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

POSTTEST: REPRODUCTIVE and DEVELOPMENTAL HAZARDS

Circle all correct answers and transfer your answers to page 35.

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 oocyte 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 34 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
2. a b c d
3. a b c d
4. a b c d
5. a b c d
6. a b c d
7. a b c d
8. a b c d

Evaluation Questionnaire

Please complete the following evaluation by circling the appropriate number.

	STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
1. As a result of completing this monograph, I will be able to:					
Describe the factors contributing to reproductive and developmental hazards.	1	2	3	4	5
Identify adverse reproductive and developmental outcomes that may be caused by environmental or occupational exposures.	1	2	3	4	5
Identify evaluation and treatment protocols for adverse reproductive and developmental outcomes.	1	2	3	4	5
List sources of information on reproductive and developmental hazards.	1	2	3	4	5
2. I am more likely to ask questions about possible environmental exposures as a result of reading this issue.	1	2	3	4	5
3. I will recommend this issue to my colleagues.	1	2	3	4	5
4. I will keep this issue as a reference.	1	2	3	4	5
5. How much time (in minutes) was required to read this monograph and complete the posttest?	40	60	80	100	120

Comments: _____