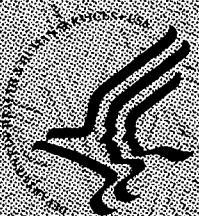


PB94 - 206620



NIOSH

Reproductive Hazards *in the Workplace* Bibliography



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health

CDC
CENTERS FOR DISEASE CONTROL
AND PREVENTION

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REPRODUCTIVE HAZARDS IN THE WORKPLACE

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4676 Columbia Parkway
Cincinnati, Ohio 45226

April 1994

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INTRODUCTION

The purpose of this publication is to provide a summary of activities of the National Institute for Occupational Safety and Health (NIOSH) related to reproductive hazards in the workplace. This publication is divided into two parts. Part I includes a brief description of the NIOSH reproductive hazards program and full- or partial-text copies of eight references on reproductive hazards.

Part II contains a comprehensive listing of NIOSH documents on reproductive hazards, as well as a brief listing of selected non-NIOSH references. Each document citation includes the title and year of publication, the number of pages, and where applicable, identifying number(s) and ordering information (see below). Citations are arranged in ten sections by type of report. A brief description of each report type precedes the listing of documents in that section.

All documents listed in Part II may be obtained in one or more of the following ways:

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PART I

SELECTED NIOSH AND NON-NIOSH DOCUMENTS ON REPRODUCTIVE HAZARDS

A. NIOSH ACTIVITIES ON REPRODUCTIVE HAZARDS

Occupational reproductive hazards have been of significant concern to the National Institute for Occupational Safety and Health (NIOSH) since its formation in the early 1970s. A 1973 NIOSH-sponsored conference included a presentation which highlighted occupational hazards to the pregnant worker (Behavioral Toxicology - Early Detection of Occupational Hazards, NIOSH Publication No. 74-126, pp. 470-477, 1973). Shortly thereafter, a report on occupational health problems of pregnant women was published (Hunt, 1975, Occupational Health Problems of Pregnant Women). This report, prepared for the Office of the Secretary, Department of Health, Education, and Welfare (HEW), described the current research at NIOSH and other government agencies and recommended future research into occupational reproductive hazards. In 1976, the Society for Occupational and Environmental Health, with support from NIOSH, convened a national conference focusing on reproductive hazards to women in the workplace (Bingham, 1977, Proceedings: Conference on Women and the Workplace). The American College of Obstetricians and Gynecologists, under contract to NIOSH, formulated a set of "Guidelines on Pregnancy and Work" (NIOSH Publication No. 78-118, 1977), and provided NIOSH with a comprehensive bibliography on the effects of the work environment on the mother and her conceptus (Comprehensive Bibliography on Pregnancy and Work, NIOSH Publication No. 78-132, 1978). In 1978, NIOSH, along with the Society for Occupational and Environmental Health, convened a workshop addressing methodologies for assessing reproductive hazards in the workplace (Proceedings of a Workshop on Methodology for Assessing Reproductive Hazards in the Workplace, April 19-22, 1978, NIOSH Publication No. 81-100, 1978). In the 1980s, NIOSH developed its top ten priorities for research, including a "National Strategy for the Prevention of Disorders of Reproduction" (NIOSH Publication No. 89-133, 1988).

Concern for occupational reproductive hazards came in the aftermath of the thalidomide tragedy of the early 1960s, in which some 10,000 infants were born with congenital malformations as a result of their mothers taking thalidomide, an anti-nausea medication, during pregnancy. Subsequently, the Food and Drug Administration (FDA) implemented requirements for premarket testing of new drugs for their ability to produce birth defects. Similarly, the initial concern for occupational reproductive hazards focused on the ability of industrial chemicals and physical agents to produce birth defects. Consequently, NIOSH established several research programs in the latter part of the 1970s with a goal of detecting occupational developmental toxicants. These research programs included laboratory studies involving experimental animals, as well as field studies involving workers in a variety of occupations.

The initial concern about birth defects and occupational exposures soon expanded to include all phases of reproductive health. In 1977, dibromochloropropane (DBCP) was found to produce infertility in male pesticide workers (Whorton et al., 1977, Infertility in Male Pesticide Workers). This event extended concern for reproductive hazards to the male, as evidenced by a NIOSH report (National Strategy for the Prevention of Disorders of Reproduction, NIOSH Publication No. 89-133, 1988), as well as an Office of Technology and Assessment report on reproductive

hazards in the workplace (United States Congress, Office of Technology Assessment, 1985, Reproductive Health Hazards in the Workplace). Subsequently, concern extended from pregnant women to all women of reproductive capacity, including those whose ability to become pregnant might be affected by occupational exposures. In 1988, NIOSH held a "Symposium on the Assessment of Reproductive Hazards in the Workplace" (Scialli, ed., Reproductive Toxicology 2(3/4), 1988). This symposium summarized the research direction in male reproductive toxicology over the ten years from the discovery of the spermatotoxicity of DBCP. The need to investigate the reproductive toxicology of female fecundity (fertility) was also highlighted as an area for intensified research.

NIOSH has also been a vital part of the National Toxicology Program (NTP) Developmental and Reproductive Toxicology (DART) research program. This program has selected potential hazards for study in the NTP testing program as well as conducted joint projects studying the reproductive effects observed in animal models compared to those seen in human exposures. As a result of this research, scientists from the National Institute of Environmental Health Sciences (NIEHS) and NIOSH, as part of NTP, conducted consensus meetings to establish standardized methods for evaluating rat sperm in toxicology studies and human semen in field studies. Also in collaboration with the NTP, NIOSH researchers are evaluating a method to detect and prioritize developmental toxicants for more extensive testing in animals.

All adverse reproductive outcomes are of concern to NIOSH, such as reduced fertility, menstrual disorders, altered libido, mutagenic effects in eggs or sperm, miscarriages, birth defects, low birth weight, learning disabilities and other behavioral disorders in children, and transplacental carcinogenesis. Exposure to toxicants of infants and children, whether through maternal breast milk or more directly (e.g., from parents' contaminated work clothing), is also of concern.

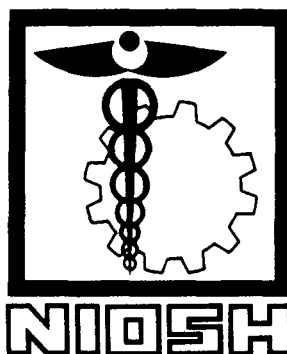
With increasing evidence that reproductive hazard information will be used in the risk assessment process (U.S. General Accounting Office, 1991), NIOSH has ongoing field and laboratory research programs in several areas of reproductive health. Since the discovery of the reproductive toxicity of DBCP, NIOSH has conducted evaluations in over a dozen worksites for the possible effects of occupational exposures on the male reproductive system. Several studies of pregnancy outcomes also have been conducted, and studies focusing on female reproductive health, such as menstrual function and ovulation, have been initiated. Much more information on potential reproductive hazards is needed, and NIOSH will continue to evaluate potential exposures.

CENTERS FOR DISEASE CONTROL

MMWR

MORBIDITY AND MORTALITY WEEKLY REPORT

B. Prevention of Leading Work-Related Diseases and Injuries



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control
National Institute for Occupational Safety and Health

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Leading Work-Related Diseases and Injuries — United States

The National Institute for Occupational Safety and Health (NIOSH) has recently developed a suggested list of the 10 leading work-related diseases and injuries (Table 1). Three criteria were used to develop the list: the disease's or injury's frequency of occurrence, its severity in the individual case, and its amenability to prevention. The list is suggested with three purposes: 1) to encourage deliberation and debate among professionals about the major problems in this field of public health, 2) to assist in setting national priorities for efforts to prevent health problems related to work, and 3) to convey to a diverse audience the concerns of the leadership of NIOSH and the focus of the Institute's activities. The list is intended to be dynamic; it will be reviewed periodically for necessary updating as knowledge increases and as conditions change and are brought under better control.

Table 1. The 10 leading work-related diseases and injuries — United States, 1982*

1 Occupational lung diseases asbestosis, byssinosis, silicosis, coal workers' pneumoconiosis, lung cancer, occupational asthma	6 Disorders of reproduction. infertility, spontaneous abortion, teratogenesis
2 Musculoskeletal injuries disorders of the back, trunk, upper extremity, neck, lower extremity, traumatically induced Raynaud's phenomenon	7 Neurotoxic disorders. peripheral neuropathy, toxic encephalitis, psychoses, extreme personality changes (exposure-related)
3 Occupational cancers (other than lung). leukemia, mesothelioma, cancers of the bladder, nose, and liver	8 Noise-induced loss of hearing
4 Severe occupational traumatic injuries: amputations, fractures, eye loss, lacerations, and traumatic deaths	9 Dermatologic conditions: dermatoses, burns (scaldings), chemical burns, contusions (abrasions)
5 Cardiovascular diseases. hypertension, coronary artery disease, acute myocardial infarction	10 Psychologic disorders. neuroses, personality disorders, alcoholism, drug dependency

*The conditions listed under each category are to be viewed as *selected examples*, not comprehensive definitions of the category.

The following articles contain detailed discussions of the 10 leading work-related diseases and injuries.

DISORDERS OF REPRODUCTION

Since antiquity, certain chemical and physical agents have been recognized as having detrimental effects on human reproduction. For example, the effect of industrial lead poisoning in inducing abortions was noted by the Romans and again in the first decade of this century (6). Evidence from more recent laboratory studies and clinical investigations indicates that a wide range of microbiologic, physical, and chemical agents, such as *Brucella*, rubella, ionizing and nonionizing radiation, heat and vibration, tobacco, alcohol, and certain drugs, can adversely affect reproductive outcomes. At least 50 chemicals—including heavy metals, such as lead and cadmium, glycol ethers, organohalide pesticides, organic solvents, and chemical intermediates, such as styrene and vinyl chloride—in widespread use in industry have been shown to produce impairment of reproductive functions in animals (7).

Until recently, the potential hazards to human reproduction posed by occupational exposures received little attention. However, adverse effects after thalidomide exposure in the 1960s and the occurrence in 1970 of methylmercury poisoning among residents of Minamata, Japan, dramatically demonstrated the teratogenic potential of chemical exposures. Those events and the increasing entry of women into the workforce focused greater attention on the potential hazards to female reproductive function of occupational exposures. In the late 1970s, the demonstration of sterility among male workers exposed to dibromochloropropane was described; this drew attention to the concomitant potential for hazards to male reproductive function (8).

Occupational exposures can produce a wide range of adverse effects on reproduction. The effects of parental exposure before conception to agents toxic to reproductive functions may be evident as reduced fertility, unsuccessful fertilization or implantation, or an abnormal fetus. Maternal exposure after conception may result in death of the fetus or structural and functional abnormalities in the newborn. Other possible adverse outcomes include spontaneous abortions (both early and late), major and minor birth defects, perinatal death, low birth weight, altered sex ratio, developmental or behavioral disabilities, and transplacental exposure to carcinogen (9-11).

Estimates of the prevalence of adverse reproductive outcomes indicate that these events occur with considerable frequency in the U.S. population. For example, an estimated 560,000 infant deaths, spontaneous abortions, and stillbirths occur each year. The March of Dimes estimates that 200,000 live infants with some type of birth defect—benign or disabling—are born in the United States each year (9).

The causes of most of these adverse outcomes are unknown. For example, 6%-30% of the infertile couples have no recognized anatomic or physiologic abnormalities to account for the infertility (10); neither the etiology of sperm abnormalities nor the cause of sister-chromatid exchange in spontaneous abortions has been established (11,12). The causes for as many as 65%-70% of the birth defects are not known (13).

Maternal Exposures. Studies of occupational reproductive hazards to date have consisted mainly of epidemiologic surveys of pregnancy outcomes following maternal exposures. Such studies have shown increased rates of spontaneous abortions among laboratory and chemical workers (14,15) and among workers exposed to lead (16), ethylene oxide (17), and anesthetic gases (18,19). Studies of adverse outcomes of pregnancy, however, are subject to several methodologic limitations. For example, the detection of rare outcomes, such as birth defects, requires the study of several thousand pregnancies, and retrospective studies are subject to problems of recall and misclassification, both of reproductive events and of exposures (20,21). The timing, duration, and frequency of exposure before and during pregnancy may critically

affect reproductive outcomes (22). For example, exposure to ionizing radiation during the first trimester may result in microcephaly and mental retardation, and exposure during the third trimester may produce low birth weight and neonatal death (11). Other studies have been limited by the selection of inadequate comparison groups or the failure to examine the influence of other factors, such as alcohol and tobacco consumption or maternal age, that affect reproductive outcomes.

Paternal Exposures. Since azoospermia (absence of living spermatozoa in the semen) and oligospermia (subnormal concentration of spermatozoa) were reported in 1977 among workers exposed to dibromochloropropane (8), at least 14 studies have examined the quality of semen in workers exposed to lead, carbon disulfide, anesthetic gases, ionizing radiation, toluenediamine, dinitrotoluene, carbaryl, and several other pesticides (10). Adverse effects on the quality of semen were reported in workers exposed to lead or ionizing radiation. In other studies (e.g., of exposures to ethylene dibromide) results were inconclusive because of problems in design of the study or inadequate numbers of participants (10). CDC recently used data collected by the Metropolitan Atlanta Congenital Defects Program to examine the risk of serious structural birth defects among the children of male Vietnam veterans; no statistically excessive risks were noted (23). In general, relatively few studies have been conducted of reproductive outcomes associated with paternal exposures (9).

Extent of potential exposures. Estimates have been made of the number of workers potentially exposed to selected agents known or suspected to be toxic to reproductive function (Table 1). NIOSH estimates that approximately 200,000 workers are potentially exposed to various glycol ethers (24), several of which exhibit marked testicular toxicity in animals (25).

TABLE 1. Estimated numbers of workers potentially exposed to selected substances known or suspected to cause adverse reproductive outcomes

Agent*	Estimated no. workers
Dibromochloropropane	11,362
Cadmium	157,383
Chloroprene	343,596
Ethylene glycol	2,060,470
Ethylene oxide	139,000
Formaldehyde	1,658,151
Lead (inorganic)	1,401,831
Radiofrequency/microwave radiation	9,000,000
Waste anesthetic gases	50,000

*Examples of agents have been selected on the basis of positive animal and/or human data; inclusion or exclusion of agents does not constitute an evaluation of their potential reproductive toxicity in humans.

An estimated 9 million workers are exposed to radiofrequency/microwave radiation (26), which has been shown to cause embryonic death and impaired fertility in animals but which has yet to be studied adequately in humans. NIOSH has estimated that approximately 50,000 personnel in hospital operating rooms are potentially exposed to waste anesthetic gases, and 139,000 hospital and other industrial workers may be exposed to ethylene oxide (24); both agents have been linked to an increased risk of spontaneous abortions in humans.

Reported by Industrywide Studies Br, Surveillance Br, Div of Surveillance, Hazard Evaluations, and Field Studies, National Institute for Occupational Safety and Health, CDC.

Editorial Note: The extent to which occupational exposures in American workers produce adverse reproductive outcomes is largely unknown. However, the information presented here

September 6, 1985

suggests that the problem is both widespread and serious. Epidemiologic and toxicologic research into the reproductive effects of occupational exposures is in its infancy. There is a continuing effort to elucidate the etiology of adverse reproductive outcomes, such as fetal chromosomal abnormalities or abnormal spermatogenesis and to develop improved animal models for screening agents for possible mutagenic and toxic effects related to human reproduction. Registries for the surveillance of outcomes of reproduction, such as CDC's Birth Defects Monitoring Program (9), and improved methodologies developed to evaluate such parameters as quality of semen (12) and outcomes of pregnancy (20), will permit further identification of specific occupational hazards to reproduction. When such hazards are identified and controlled in the workplace, the prevention of reproductive disorders in the population as a whole will be substantially improved.

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C. Proposed National Strategy for the Prevention of Disorders of Reproduction

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control
National Institute for Occupational Safety and Health
1988

DHHS (NIOSH) Publication No. 89-133

Introduction

This document, *A Proposed National Strategy for the Prevention of Disorders of Reproduction*, summarizes what actions need to be taken to prevent occupational disorders of reproduction. It was developed in 1985 at a conference sponsored by the National Institute for Occupational Safety and Health (NIOSH) and The Association of Schools of Public Health (ASPH), which brought together over 50 expert panelists and 450 other occupational safety and health professionals.

In addition to the strategy for disorders of reproduction, NIOSH and ASPH have published strategies for the other nine leading occupational diseases and injuries: occupational lung diseases, musculoskeletal injuries, occupational cancers, severe occupational traumatic injuries, occupational cardiovascular diseases, neurotoxic disorders, noise-induced hearing loss, dermatological conditions and psychological disorders.

The proposed strategies were originally published in a two volume set, *Proposed National Strategies for the Prevention of Leading Work-Related Diseases and Injuries, Part 1 and Part 2*. These proposed strategies are not to be considered as final statements of policy of NIOSH, The Association of Schools of Public Health, or of any agency or individual who was involved. Hopefully, they will be used in the quest to prevent disease and injury in the workplace.

To learn of the availability of the complete texts of Part 1 and Part 2, or to obtain additional copies of this or other Strategies, contact NIOSH Publications, 4676 Columbia Parkway, Cincinnati, Ohio 45226. Telephone (513) 533-8287.

BANK

A Proposed National Strategy For the Prevention of Disorders of Reproduction

I. Introduction

Disorders of reproduction and hazards to reproductive health have become prominent public health issues. In the 1960s, the use of thalidomide sensitized the public to chemically induced birth defects. Early in the 1970s, young women whose mothers had taken diethylstilbestrol during pregnancy were found to have vaginal adenosis and clear-cell adenocarcinoma. Later in that decade, it was discovered that men occupationally exposed to dibromochloropropane (DBCP) were subject to varying degrees of testicular toxicity, potentially culminating in infertility. In addition, widely publicized episodes of environmental contamination such as that at Love Canal have engendered a general sense of apprehension and concern for adverse health effects, including disorders of reproduction. These events have heightened sensitivities to potential occupational, therapeutic, or environmental hazards to reproduction, even when epidemiologic and surveillance studies have not proven that disorders of reproduction were produced in the exposed populations. (It is unclear whether the studies were negative because little or no risk existed, or because the studies had insufficient statistical power to detect small increases in risk).

This perception of risk has led to a corresponding perception that action is needed to protect people from hazards and to prevent disorders of reproduction. Programs to prevent infectious diseases have been highly successful, the most notable example being the worldwide eradication of smallpox. Some occupational disorders (e.g., silicosis, asbestosis, noise-induced hearing loss) can be successfully controlled through aggressive prevention programs and may even be eradicated eventually. Prevention of occupational disorders of reproduction, however, is much more problematic. As will be illustrated later, efforts to prevent occupational disorders of reproduction face major gaps in knowledge. Because disorders of reproduction arising from nonoccupational factors cannot always be distinguished from those caused by occupational factors, a differential diagnosis may be difficult. The incidence and geographic distribution of health problems related to reproductive systems are very poorly described, and disorders of reproduction cannot be controlled or eliminated by controlling or eliminating any single etiologic agent. When occupational etiologic factors do become known, it will rarely be possible to totally eliminate them from the workplace. Because both the processes of reproduction and the factors contributing to disorders of

reproduction are complex, simple solutions should not be expected. Rather than seeking to eradicate all disorders of reproduction, health practitioners should set pragmatic goals for protection, such as constant vigilance to ensure recognition and control of specific agents.

Because uncertainties surround disorders of human reproduction, particularly the specific influence of occupational conditions, this proposed prevention strategy focuses considerable attention on research needs. Selected disorders of reproduction can be successfully prevented now on a relatively limited scale (e.g., testicular toxicity caused by occupational exposure to DBCP). Primary prevention of most disorders of reproduction, however, will require successful research programs to improve our understanding of reproductive and developmental biology and to identify etiologic agents and populations at risk before intervention programs can be implemented.

II. Definitions and Estimated Scope of the Problem

The many observable dysfunctions classified as disorders of reproduction include infertility, impotence, menstrual disorders, spontaneous abortion, low birth weight, birth defects, congenital mental retardation, and various genetic diseases. Although disorders of reproduction are more common in humans than is generally realized, the causes of these disorders are largely unknown. Depending on the stage of life at which an agent (chemical, physical, or biologic) acts, it might be classified as 1) a "reproductive toxicant," i.e., an agent that affects post-pubertal reproductive or sexual function; or 2) a "developmental toxicant," i.e., an agent that affects growth, development, or acquisition of normal organ function between conception and puberty. By these definitions, teratogenesis is one expression of developmental toxicity, and genotoxic agents (mutagens) may exhibit both reproductive and developmental toxicity.

The NIOSH *Registry of Toxic Effects of Chemical Substances* currently contains entries for over 79,000 chemicals. Almost 20% of these (over 15,000) cite data on reproductive effects, but the quality and accuracy of these citations has not been evaluated. Over 2,800 chemicals have been evaluated for teratogenicity in animals, and about 38% exhibited some teratogenic potential (1).

Despite these disturbingly large numbers, only 30-40 chemical, physical, and biologic agents are generally recognized as human teratogens (2, 3). This discrepancy in the number of teratogens known for animals and humans could reflect difficulties in identifying causal associations in humans, differences in specificity of response, or human resistance to some animal teratogens. Clearly, humans are subject to developmental toxicity, but establishing causal associations in humans can be quite difficult for a variety of reasons, and this undoubtedly accounts for some failures to confirm the effects observed in animals. Specificity may be a significant factor; an agent may interfere with developmental processes in many or all species but not necessarily with the same end result in each. A broader spectrum of response can be monitored more accurately in animal experiments than in humans, and a difference in specificity could be mistaken for failure to respond. Similarly, present analytic methods have failed to demonstrate the induction of germ-line mutations in humans by any chemical or physical agent (e.g., ionizing radiation) (4). Possibly overshadowing all these factors is the relatively limited research thus far directed to identify hazards to human reproductive health.

The prevalence of infertility — clinically defined as the failure to conceive after unprotected intercourse for one year — is very difficult to estimate, but it is believed to afflict 10%-15% of American couples (5). Reliable estimates of the prevalence of

such disorders as impotence, reduced libido, or altered menstrual cycles are not available. Live births may result from as few as 25%-33% of conceptions (i.e., many or most conceptions are lost early in development and are, therefore, unrecognized) (6, 7). Of the recognized pregnancies, 10%-25% are spontaneously aborted by the 28th week of gestation (5, 8). Chromosomal abnormalities are observed in about 50% of early spontaneous abortions (9). When pregnancies reach full term, approximately 2%-4% end in stillbirth, and about 2%-4% of the liveborn children have congenital malformations detectable at birth (1,5,6). When physical and functional disorders detected within the first year of life are included, an estimated 6% of liveborn children are affected, but a figure of 15% has also been suggested (10). Low birth weight affects approximately 13% of liveborn children (11), placing them at increased risk of neonatal death. About 20%-25% of congenital malformations are believed to be due to inherited genetic traits and chromosomal abnormalities, and another 10% are attributed to such environmental factors as drugs, chemicals, and maternal infections or other conditions (e.g., metabolic disorders, nutritional deficiency). The etiology for the remaining 65%-70% of human malformations is unknown (1,7,12,13).

An estimated 560,000 infant deaths, stillbirths, and recognized spontaneous abortions occur in the United States annually (1), and birth defects, whether benign or disabling, affect 200,000 or more liveborn infants each year (1, 6). In 1984, congenital malformations were the fifth leading cause of years of potential life lost before the age of 65 (684,000 years), prematurity was sixth (470,000 years), and sudden-infant-death syndrome was seventh (314,000 years) (14). At the state government level, leading health expenses for chronic diseases have been attributed to mental retardation and developmental disabilities (15). In fiscal year 1984, such costs were over \$60 million in state funds (exclusive of federal grants, local funds, fees, reimbursements, etc.) compared with \$35 million for renal disease, the second largest category. Single-gene disorders are estimated to be responsible for about 190 years of life lost and 150 years of impaired life per 1,000 live births (16), while chromosomal disorders may be responsible for about 89 years of life lost and 90 years of impaired life per 1,000 live births.

III. Biologic Basis for Disorders of Reproduction

Despite the large number of biologic processes that may be affected, we can detect effects on reproduction only in specific observable outcomes, some of which are listed in Table 1. Spontaneous abortion, for example, may result from genetic disorders (either preexisting in one or both parents or newly arising in the affected fetus) or from maternal exposure to chemical, physical, or biologic agents that impair maternal functions or affect the fetus directly. Birth defects, too, may be due to preexisting or induced genetic conditions or to specific environmental factors. Although the underlying mechanisms for some specific disorders are known, (e.g., trisomy 21 in Down's syndrome) more generally no classes of observable disorders of reproduction have single underlying biologic bases, so it is difficult or impossible to identify specific causes in individual cases. Furthermore, disorders of reproduction represent an interaction between individual genetic makeup; environmental conditions; and the intensity, duration, and timing of exposure to those conditions. Thus, not all individuals who experience similar exposures to chemical, physical, or biologic agents will respond in the same way, further complicating the determination of etiologies.

"Reproductive toxicants" are defined as chemical, physical, or biologic agents that adversely affect the sexual or reproductive performance of sexually mature persons, whether male or female. These toxicants impair reproduction by interfering with or

altering normal physiologic processes, regulatory mechanisms, organ function, or the genetic integrity of sperm or egg cells in an exposed person. Thus, an extremely broad range of potential targets and biologic mechanisms may be involved.

Table 1. Observable disorders of reproduction following exposure to various types of reproductive hazards

Potential Outcome	Reproductive Toxicants				Developmental Toxicants Female
	Non-mutagenic Male	Non-mutagenic Female	Mutagenic Male	Mutagenic Female	
Infertility	X	X	X	X	X
Spontaneous abortion normal karyotype abnormal karyotype	X	X	X X	X X	X
Prematurity					X
Birth defect			X	X	X
Delayed development					X
Low birth weight					X
Postmaturity					X
Semen abnormality	X		X		X*
Sexual dysfunction	X	X			X*
Dysfunction of other organ systems					X*
Childhood cancer			X	X	X*

* Abnormalities in children or adults resulting from in utero exposure

For example, the human reproductive system is subject to complex hormonal controls. Chemicals may mimic hormone activity, block hormone receptors, or inhibit or stimulate hormone production or degradation. In males, establishing and maintaining an erection involves complex interactions between the nervous and vascular systems; and chemical, physical, or biologic agents that affect either system might cause impotence. Similarly, libido — or sex drive — may be influenced by the psychological state as well as by a variety of drugs, chemicals, or physical conditions. Spermatogenesis is extremely sensitive to heat, and elevated testicular temperature can impair or arrest sperm production. Antisperm antibodies can be produced by both males and females and may cause infertility. Successful conception requires active transport of sperm, oocyte, and zygote in the female reproductive tract.

The germ-cell populations of males and females differ fundamentally, and this may result in special sensitivity to a particular toxicant in either sex. In general, however, neither sex can be said to be the more vulnerable. Unspecialized “stem cells” are present in males from the fetal period but are quiescent until puberty, when they begin to multiply actively. Some stem cells undergo specialization to produce a continuous supply of sperm, but the stem-cell population is maintained by those cells

that continue to divide without specialization. Although sperm production may be interrupted, recovery may be possible as long as stem cells are not eliminated. A constant high rate of cellular activity, however, may make the testis particularly sensitive to disruption.

By contrast, germ cells in the ovary reach their maximum numbers prenatally and are arrested by the first meiotic division in late prenatal or early postnatal life. The lifetime supply of oocytes is therefore present at birth as primary follicles in the ovary. Beginning at puberty, oocytes are steadily lost to ovulation and spontaneous degeneration, or atresia. The reproductive life of a woman can therefore be limited by the initial supply of primary follicles, by the rate of atresia, and by the onset of menopause.

Mutagens can alter the genetic code, or DNA, carried in the nucleus of every cell. Genetic damage may be produced in any dividing cell of an organism, and if that damage occurs in somatic cells, cancer is a possible consequence. Theoretically, a mutation-induced non-neoplastic alteration in organ or tissue function might also contribute to other disorders, including reproductive disorders. If the genetic code in a germ cell is damaged, genetic disease or birth defects could occur in a child who inherits that damage. Genetic damage (if recognized) might appear as a reduction in fertility or an increase in spontaneous abortion for an individual who produced damaged germ cells (ova or sperm). It is essentially impossible at present to detect the induction of mutations in the human germ line.

Germ-line mutations can be expressed only if the sperm or eggs bearing them are involved in conception. In theory, such mutations could be harmless, but they can also be so devastating that the embryo carrying them cannot survive beyond early gestation. A continuum of possibilities exists between these two extremes. The genetic material may be defective in only a single gene, or the defect may involve chromosomal changes resulting in a net deficiency or surplus (duplication) of chromosomal material. Even if no chromosomal deficiency or excess exists, a simple rearrangement of genes on the chromosome could produce genetic disease if the change in sequence causes an inappropriate expression of otherwise normal genes. Chromosomal duplications or deficiencies tend to be incompatible with life and are seen in a high percentage of spontaneous abortions (5). Chromosomal defects in liveborn children are often associated with serious malformations, mental retardation, and reduced life expectancy. Trisomy 21 (associated with Downs syndrome) is a well-known example. Single-gene mutations may be dominant (expressed if only a single copy is present), semidominant (expressed in varying degrees if one or two copies are present), or recessive (expressed only when two copies are present). Thus, induced recessive mutations would not affect the children who inherited them, but could be responsible for future appearances of genetic disease if the defective gene were passed to successive generations and spread through the population.

“Developmental toxicants” are defined as chemical, physical, or biologic agents that adversely affect the growth or development of an embryo, fetus, or immature (prepubertal) individual. These include transplacental carcinogenesis, lactation effects, and altered postnatal interactions between mother and child that could influence the child’s development. A teratogen is a chemical, physical, or biologic agent that causes abnormal morphogenesis and results in a structural malformation or birth defect. Typical expressions of developmental toxicity are intrauterine death, teratogenesis, delayed growth or development, and impaired functional integrity. Intrauterine death is expressed as spontaneous abortion or stillbirth, but very early losses could appear as a failure to conceive. Retarded fetal growth would generally be seen as low birth weight, which is associated with reduced postnatal survival. Impaired functional status of organ systems — such as the heart, lung, or brain — may be expressed early or late after birth.

Although specific mechanisms of developmental toxicity are poorly understood, known or potential mechanisms include gene or chromosomal mutations, interference with gene expression, lack of required substrate or precursor molecules, altered patterns of programmed cell death, enzyme inhibition, altered membrane properties, and mitotic inhibition. Teratogens typically produce abnormal morphogenesis over a relatively narrow range of doses and may be effective only during very specific embryonic stages. Because of their plasticity and repair capacity, embryos exposed to a teratogen very early in development may exhibit an all-or-none response: either death or no apparent effect. Because organ systems independently undergo first a rising then a falling period of susceptibility, a teratogen may produce profoundly different spectra of malformations at various stages of development. The period of peak sensitivity for structural malformations in humans occurs in the first 60-70 days of gestation.

Developmental toxicity cannot be properly evaluated without considering the relationship between developmental and maternal toxicity. A fundamental principle states that any agent can be developmentally toxic if given to a sensitive species in a large enough dose, possibly maternally toxic, and at the appropriate time during pregnancy. Considering the expressions of developmental toxicity alone, in isolation from toxicity to the maternal animal, is inadequate. High-risk agents are developmentally toxic at doses well below those required to produce maternal toxicity (i.e., developmental toxicants of primary concern are agents selectively, or preferentially, toxic to the embryo or fetus). For example, thalidomide produced malformations in humans at a dose perhaps 1% of that required for maternal toxicity (1). Similar considerations should be applied in evaluating risks posed by reproductive toxicants. Because of this requirement for perspective, the overall complexity of the biologic systems involved, and the interactions between systems, investigations in intact mammals are indispensable to a study of reproductive and developmental toxicology.

IV. Occupational Hazards to Reproductive Health

Although a very large number of chemical, physical, and biologic agents are documented as reproductive or developmental toxicants in laboratory animals (1,17), few are known to produce similar effects in humans (2). Therapeutic drugs constitute most of the chemical agents for which effects are established in humans (1,12); biologic agents are mainly infectious organisms (2,13). In certain cases, fetal disorders are recognized at doses that are toxic for the mother (e.g., fetal alcohol syndrome). Under current conditions of occupational exposure, only a very small number of agents have been established as reproductive or developmental toxicants in humans. This absence of proven disorders stemming from current occupational exposure might suggest that such effects are rare, but it could also reflect limited research in this area or the difficulties inherent in detecting disorders and ascribing causes in human populations.

Proving a causal association between workplace conditions and reproductive health is extremely difficult. This subject has recently been reviewed (5,6,8,18,19) and will not be discussed in detail here. Although the different types of observable reproductive outcomes are limited, each class of outcomes can result from a variety of different agents, acting through several biologic mechanisms. The reverse is also true: a single toxicant can produce a variety of adverse outcomes, depending on the specific conditions of exposure. In most studies of potential occupational disease, evaluation is confounded by occupational exposure to mixed agents, by nonoccupational factors (e.g., age, personal habits, hobbies), and by the need to evaluate any association relative to a background incidence of the outcomes studied. Recall bias in a retrospective study might follow reproductive dysfunction. Affected persons may

either be motivated to remember and report possible contributing factors or may neglect to report important confounding factors.

In addition to these biologic and data-collection factors, statistical considerations also influence our ability to evaluate whether a health hazard exists. These include the background incidence of the outcome studied, the minimal increase that must be detected, and the level of statistical certainty desired in the research. All these influence the number of observations that must be made. Table 2 illustrates the group sizes required for studies of various endpoints. The study populations must be large enough and the durations long enough to observe sufficient numbers of pregnancies or live births. For example, an estimated 52 pregnancies and 44 births occur per year per 1000 working women (20). Thus, two populations (exposed and comparison groups) of 3096 women each would be required to observe 161 pregnancies per group (Table 2) in a year, or 3659 women each to observe 161 births per group. Studies of this kind are often inconclusive or difficult to interpret because either the conditions of exposure are poorly defined or the populations studied are too small. Thus, many negative studies cannot be used as strong evidence that no hazard to reproduction exists, and, conversely, clusters of events occurring in small populations cannot stand alone as strong evidence that a hazard to reproduction does exist. The clusters do, however, raise concerns that are difficult to dispel.

Table 2. Sample size required
to detect a doubling of background incidence*

Size of Each Group Studied	
Infertility	161 Couples
Spontaneous abortion	161 Pregnancies
Stillbirth	161 Pregnancies
Low birth weight	293 Live Births
Major birth defects	316 Live Births
Infant deaths	928 Live Births
Severe mental retardation	4493 Live Births
Chromosome abnormalities	8951 Live Births

* Alpha = 0.05, two-tailed; Beta = 0.20
Adapted from (6)

A growing number of reports are appearing that evaluate semen quality (i.e., characteristics of various components of semen) in occupational groups. Studies of semen quality may be more practical measures of reproductive health than are studies of pregnancy outcome because smaller group sizes are required (Table 3), and every exposed male is a potential subject. However, the absence of standardized techniques and accepted normal values, extreme inter- and intra-personal variation for some indices, problems in obtaining unbiased participation by control and exposed populations, and the failure to evaluate reproductive disorders for females may cause difficulties with this approach. These studies do not permit definitive conclusions about the reproductive status of a given man or group of men (i.e., they do not reveal

who is fertile or infertile, or predict the ability to father a healthy child) because no cutoff point for seminal characteristics distinguishes "normal" from "abnormal." Studies of semen quality do, however, offer the opportunity to detect shifts in testicular function on a population basis. If reduced semen quality is related to occupational conditions, an adverse effect on testicular function is suggested. Properly conducted studies of semen quality should help identify workplaces where some types of hazards to reproduction exist, preferably before irreversible testicular damage or other profound disorders of reproduction occur. Recent advances in evaluating female gonadal function and detecting early pregnancy loss may soon make similar studies of women feasible.

Table 3. Sample size required for human semen studies*

Sperm characteristics (percent of sperm)	Difference between groups studied	Samples per group
Motile	10%	35
Normal head shape	20%	16
Viable		
By dye exclusion	10%	26
By hypo-osmotic stress	10%	20

* Alpha = 0.05, two-tailed, Beta = 0.20

Power calculations based on data from NIOSH field studies

Several reviews on occupational hazards to reproductive health are available (6,18,21-24). Some differ as to whether specific agents are "suspected" or "proven" responsible for disorders of reproduction in occupationally exposed groups. All undisputed episodes of occupational disorders of reproduction in the recent past have involved male workers. The best known of these involved exposure to DBCP, which resulted in low sperm counts (oligospermia) or the complete absence of sperm (azoospermia) in the ejaculate and infertility. Some men gradually recovered testicular function after exposure ceased. Reduced sperm counts, impaired sperm motility, abnormal sperm morphology, and systemic effects (including toxic neuropathy) also occurred in men occupationally exposed to chlordecone (Kepone). Male workers exposed during the manufacture of synthetic hormones experienced alteration in secondary sex characteristics (swelling and tenderness of the breasts) and female workers similarly exposed experienced intermenstrual bleeding and menorrhagia.

Despite routine exposure to probable or known reproductive toxicants, no other instances of suspected occupational disorders of reproduction have been proven conclusively. Occupational exposure to inhalational anesthetic agents has been associated with adverse outcomes of pregnancy in both female operating-room personnel and the wives of exposed men. Exposure to sterilizing agents — primarily ethylene oxide — has been associated with increased risk of spontaneous abortion. Historically, lead has been known as a hazard to the reproductive systems of both sexes, but conflicting data have been reported for modern workplaces. Other metals (arsenic, cadmium, and mercury), also known as reproductive toxicants, have been inadequately studied for the effects of current occupational exposure. Physical agents — such as ionizing and microwave radiation, heat, and vibration — are recognized as hazards to reproduction in both animals and heavily exposed humans, but occupa-

tionally exposed populations have not been properly evaluated. Disorders of reproduction have also been associated with several industrial processes or broad classes of chemicals (e.g., rubber manufacture, laboratory work, exposure to organic solvents) but no specific agent has been identified. One or more agents associated with these occupations or workplaces could be toxic to reproductive systems under certain conditions, but the evidence has not been developed to either clear or indict the conditions in these suspected occupations or workplaces.

In several instances where disorders of reproduction were suspected in a workplace, no etiologic agent was immediately apparent. These have been reported primarily as “clusters” of spontaneous abortions, stillbirths, or birth defects, first noted usually by the workers themselves in relatively small populations. Causative agents have been suggested for some clusters (e.g., video display terminals) but supporting evidence was lacking that the putative agent could be a reproductive toxicant under a defined condition of exposure. Some clusters have received wide publicity and have generated profound concern, but researchers were unable to suggest an objective cause for the disorders, and the clusters were usually explained as only a statistical anomaly. A recent review cited the video display controversy as an example of why these situations are so difficult to resolve satisfactorily (25).

In the absence of exposure to toxicants or severe physical or emotional stress, employment outside the home does not in itself appear to be a factor in disorders of reproduction for women (26-28). Nevertheless, women are most often the focus of questions about occupational hazards to reproduction. This may reflect a tendency to view only birth defects or other adverse pregnancy outcomes as disorders of reproduction. In addition, as women move into previously all-male jobs, their reproductive health may be a matter of concern while men, who have traditionally been in the workplace, are assumed to be unaffected even though little information is available to substantiate this.

Another reason for the different approach for males and females is the possibility that women may, knowingly or not, bring a third party — the embryo/fetus — into the workplace. The human embryo is most sensitive to developmental toxicity in the first weeks of pregnancy, when the woman may not yet recognize her pregnancy. Thus, in addition to dealing with the health of reproductive systems, the employer may face the added uncertainty of future liability if a child is born with disabilities. This is uncharted legal territory (some aspects of current legal issues have been reviewed elsewhere [29]) and may explain why some employers simply opt to exclude women with childbearing potential. Legal precedent is being established almost daily, sometimes based on inadequate judicial understanding of the underlying biologic principles. Multiple and potentially conflicting interests are possible, e.g., the “right to birth with sound mind and body,” the woman’s right to self-determination and equal employment opportunity, suits for “wrongful life,” and society’s interest in minimizing the social and economic costs of disorders of reproduction, especially developmental disabilities. These “rights” and self-interests may come into conflict, often in unexpected and paradoxical ways. The lack of consistent treatment of these legal matters across jurisdictions only adds to the unsettled atmosphere.

The weight of scientific evidence demonstrates that thresholds exist for nonmutagenic reproductive and developmental effects so that exclusionary policies based on sex are inappropriate and unnecessary in principle. Thus it is possible, in principle, to provide a safe and healthful workplace for all employees regardless of sex or pregnancy status.

V. Research Needs

In recent years, current knowledge of occupational and environmental hazards to reproduction has been reviewed, and recommendations for research have been published by many groups (5,6,8,18,30-32). Each reviewer approached the issue from a slightly different perspective, but all concluded that serious gaps in knowledge exist, and most made broadly similar recommendations for research. As the most recent review pointed out: "A major conclusion of every symposium on the reproductive toxicity of suspected hazards over the past several years has been the absolute necessity for increased knowledge through additional experimental study" (6). If efforts to promote health and prevent disorders of reproduction using a knowledge of occupational (and environmental) etiologies are to succeed, research programs such as those suggested here will be needed to redress current information gaps.

A. Laboratory Research

1. Many agents have been evaluated in in vitro and in vivo genotoxicity assays, including cytogenetic assays in human somatic cells. A subset of these agents has also been studied in various reproductive toxicity assays. The existing data must now be reviewed and analyzed extensively to:
 - a. Evaluate the ability of established genotoxicity assays — including both in vitro and in vivo test systems for somatic mutations — to predict the mutagenicity of chemicals in mammalian germinal tissue. Although these assays are well established in many industrial, academic, and government laboratories, their value for predicting the potential for genetic damage in the mammalian germ line has not been adequately determined. These assays have contributed significantly in the search for genotoxic and potentially carcinogenic chemicals in the occupational environment. They should now be investigated as surrogates for whole-animal testing to detect reproductive toxicants that may cause germ-cell mutations leading to genetic disorders, infertility, or embryonic death.
 - b. Establish the relationship between signs of genotoxic events in human somatic cells (e.g., chromosomal aberrations or sister chromatid exchanges in peripheral lymphocytes) and the reproductive health of affected individuals or populations. Sensitive methods exist for detecting somatic mutations in humans. Although these tests sometimes suffice to show that members of a population have been exposed to a mutagen, it is not known whether somatic mutations correlate with germ-cell mutations or whether they are associated with adverse health consequences. If somatic mutations could serve as an index for germinal mutations, then current tests for genotoxic events in somatic cells could be used to monitor human populations for potential reproductive toxicity.

This evaluation of existing scientific data may be carried out by a panel of experts identical to or closely interacting with the panel proposed in V. Research Needs, B. Surveillance and Epidemiology, Section 1.

2. Numerous currently available methodologies can be applied directly to address specific concerns in the testing for reproductive toxicity. Coordinated efforts are needed to:
 - a. Conduct routine testing of chemical and physical agents present in the occupational environment for teratogenic or genotoxic potential and for

other adverse effects on reproductive systems. Protection of healthy human reproductive capacity demands the identification of chemical and physical hazards to reproduction as a prelude to risk assessment and risk management. This imposes a continuing need for testing using whole-animal models, which are the only definitive test for hazards to reproductive health other than evidence based on human exposures. Alternative in vitro and improved in vivo techniques should be developed, validated, and employed whenever appropriate. For the foreseeable future, however, tests using whole-animal models will be indispensable for identifying hazards and for risk assessment.

- b. Improve understanding of the xenobiotic metabolism and the disposition of chemicals in standard laboratory animal species. This includes both hepatic and extrahepatic metabolism (especially gonadal metabolism), fetal metabolism, placental transfer and metabolism, and the relationship of administered dose to target dose. Much interspecies variability in general toxic response is related to differences in the metabolism, tissue distribution, and excretion of chemical agents. Therefore, to accurately interpret and extrapolate across species, the data on reproductive and developmental toxicology will require a more complete knowledge of the similarities and differences in xenobiotic metabolism and chemical disposition between humans and laboratory animal species. Understanding these relationships will permit selection of optimal animal bioassay systems that model human response to potential reproductive and developmental toxicants.
- c. Investigate the influence of genetic variability on the response to reproductive and developmental toxicants. About 20% of the congenital malformations in humans are attributed to inherited genetic traits or chromosomal abnormalities. Defects may not be expressed in genetically susceptible individuals during development unless triggered by environmental factors, and the toxicity of some agents may vary considerably in individuals with different genetic constitution. By investigating the role of the genome in enhancing or reducing the adverse effects of toxins, both in humans and in laboratory animals, general principles can be derived for use in making risk assessments and determining adequate exposure limits for single agents.
- d. Perform studies to determine whether heritable genetic damage or dominant lethal mutations can be induced in early stages of postconception development. As high as 50% of early spontaneous abortions in humans may be related to cytogenetic abnormalities. These abnormalities may be present in the parents, may arise spontaneously after conception, or may be induced by genotoxic agents at an early stage of embryogenesis. Nonlethal genetic damage in the undifferentiated embryonic cells could also lead to genetic disease or genetic load in the human population. No information is available on this subject. If genetic disease or dominant lethal mutations can be induced in the early stages of embryogenesis, systems should be developed for their detection and used for risk assessment.
- e. Determine whether fetal abnormalities can result from exposure of the male parent alone and, if so, by what mechanism. Several studies have reported an increased incidence of birth defects in laboratory animals when chemically exposed males were mated with unexposed females. Likewise, a few clinical and epidemiologic studies have reported an increased risk of birth

defects in infants whose fathers were exposed to chemical or physical agents in the workplace. If male-mediated fetal abnormalities actually occur, then exposure to known or potential teratogens in the workplace will become a concern for both male and female workers, not female workers alone.

- f. Determine whether exposure of both male and female laboratory animals to known developmental toxicants causes greater toxicity in the offspring than exposure of either parent alone. Such information is needed to assess the risk of adverse effects on the offspring when both parents have been exposed to developmental toxicants.
3. Although the usefulness of current methods for identifying reproductive toxins that have specific characteristics (e.g., mutagenicity) is well recognized, new methodologies should be developed to address the unique complexities of reproductive processes. Innovative methods and clarification of mechanisms are important to:
 - a. Determine the mechanism of action for known germ-cell toxicants, including the reason different stages of spermatogenesis have differential sensitivity to toxicants. Understanding the mechanisms of action of a broad spectrum of germ-cell toxicants would help to identify potential gonadal toxicants and evaluate human risk.
 - b. Establish the mechanism of action for known teratogenic agents, including those that affect the embryo directly and those that act indirectly by disturbing normal maternal physiology or placental functions. Research on carcinogenesis benefited from the discovery of a common mechanism for induction of many tumors, i.e. somatic mutations. By contrast, although several potential mechanisms exist for teratogenesis, the fundamental mechanism of action has been identified for only a few teratogens. A more detailed understanding of the mechanisms of action for a broad spectrum of teratogens would help to identify potential teratogens and evaluate human risk.
 - c. Develop tests to monitor important aspects of reproductive function in both humans and animals. The function of both male and female reproductive systems is very complicated and consists of several discrete processes. Tests that could monitor these processes in common laboratory animals or especially in humans have either not been developed or are of questionable validity. To properly monitor and determine causes of reproductive toxicity, valid and useful tests must first be developed for normal reproductive function in both humans and laboratory animals. For example, tests are urgently needed for early pregnancy and for germ-cell depletion in women to determine the true background incidence of adverse reproductive outcomes in the human population and to monitor the increased incidence of such outcomes following exposure to occupational or environmental toxins.
 - d. Develop techniques to detect the presence of chromosomal aberrations, including aneuploidy, in human sperm and ultimately to detect more subtle genetic changes. Suitable animal models must be developed before these techniques can be applied to human sperm. It is currently impossible to detect whether occupational or environmental exposure to mutagenic agents produces mutations in the human germ plasm. Current efforts to detect mutagenic events by monitoring human populations have two major

disadvantages: 1) they can detect only major effects; and 2) they rely on detecting disease and disability in the descendants of exposed persons. The ability to detect chromosomal or other DNA changes in human sperm would permit both a more sensitive monitoring of human populations and a detection of mutagenic exposures in the exposed population rather than in their descendants.

- e. Increase basic research in developmental biology. The details of ontogeny (i.e., development from a single cell to an adult organism) remains one of the most difficult and least understood questions in biology. Powerful new methods in molecular biology and "genetic engineering" are only now being applied in developmental biology. Strong support is needed for fundamental research to stimulate increased application of these new tools. A better understanding of developmental biology will permit better interpretation and evaluation of developmental toxicity.
 - f. Expand studies of transplacental carcinogenesis. Little information is available on human transplacental carcinogenesis, but agents are known (e.g., ionizing radiation, diphenylhydantoin, and diethylstilbestrol) that show this activity. Chemicals found in the workplace may be transplacental carcinogens that contribute to the overall cancer incidence or to childhood cancer. Improved animal models and surveillance of human populations are required to evaluate transplacental carcinogenesis. Structure/activity relationships should be investigated to develop possible predictive models.
 - g. Expand research to develop and validate in vitro test systems for reproductive and developmental toxicants. Research has already demonstrated the value of in vitro systems for investigating mechanisms of toxicity and identifying active or inactive metabolites of suspected toxicants. However, the usefulness of these tests as surrogates for whole animal-assays remains to be established. Whole-animal tests are too expensive and too time-consuming to test all new chemicals that enter commerce each year in addition to the backlog of important chemicals that have never been tested for reproductive or developmental toxicity. Rapid, inexpensive in vitro or in vivo tests that have good predictability would be extremely valuable for identifying hazards and setting priorities for further testing of chemical and physical agents.
 - h. Expand the development, validation, and application of tests for the developmental toxicity that is expressed as impaired functional integrity of organs or systems such as the liver, kidneys, immune system, and central nervous system. Neurobehavioral tests in rodents have shown that the central nervous system is a sensitive target for developmental toxicants. Changes in behavior and the learning ability of offspring may be produced at exposure levels below those required to produce morphological abnormalities. Functional deficits have also been demonstrated for other organs and systems, but the development and validation of these tests has been limited compared with such efforts on tests for central nervous system function. Toxicants that act on immature organs, either pre- or postnatally, may be responsible for significant human morbidity and mortality.
4. An important consideration in any routine toxicity evaluation is the fact that worker exposure may not be confined to a single agent. Interactive effects may result from exposure to complex mixtures in the workplace or confound-

ing exposure to environmental agents outside the workplace. Research is needed to:

- a. Investigate the interactions between common physical and chemical agents, both naturally occurring and man-made, in the workplace. Many workers are exposed simultaneously to multiple chemical and/or physical agents. These agents may act synergistically to produce adverse reproductive or developmental effects at levels that are nontoxic when the agents are administered separately. For example, mild hyperthermia (1° C elevation of body temperature) has been shown to increase the toxicity of common chemicals in rats by factors of 2 to 200. By determining the degree to which the reproductive or developmental toxicity of an agent is modified by the presence of other agents, general principles may be derived that can be used in making risk assessments and in determining appropriate exposure limits for single agents.
- b. Develop suitable assay systems to detect reproductive and developmental toxicants in the occupational environment. Workers in many occupational settings are exposed to complex mixtures of substances that may be toxic individually and that may produce synergistic interactions in mixtures. Thus, assay systems are needed that can be applied *in situ* in the occupational environment. These systems could be biologic monitors that reveal exposure to genotoxic or other toxic conditions in the workers themselves (e.g., via semen or serum analyses), or they could be surrogate *in vitro* or *in vivo* test systems. The results of *in situ* studies using biologic monitoring may provide important information about potential reproductive hazards in the occupational setting and may also be useful for developing strategies to control exposures.
- c. Determine in laboratory animals how factors unrelated to the presence of chemical and physical agents in the workplace affect reproduction and development. The influence of alcohol, smoking, drugs (both pharmaceutical and illegal), diet, hormonal imbalances, and other common factors on reproductive health should be investigated. Stress, whether occupational or personal in origin, is often a serious problem and may have a significant impact on otherwise healthy reproduction. The effects of changes in the immune system on reproduction and development should also be studied. This knowledge is needed to properly assess the causes of adverse reproductive effects in workers and to help design surveillance programs and epidemiologic studies properly to account for such confounding factors.

B. Surveillance and Epidemiology

The 1980 document from the Department of Health and Human Services, "Promoting Health, Preventing Disease: Objectives for the Nation," highlighted the need for a more intense and systematic effort by the public health community to identify impediments to reproductive health, to communicate them to the public, and to develop and implement programs for reducing these impediments or eradicating the conditions. These goals were echoed in the 1986 report, "Improving Assessment of the Effects of Environmental Contamination on Human Reproduction," developed by The Working Group on Human Reproductive Outcomes, sponsored by Child Trends, Inc., and financed by grants from the National Science Foundation and the Environmental Protection Agency. Following a review of this document, Directors of the CDC's Center for Environmental

Health, Center for Health Promotion and Education, NIOSH, and Agency for Toxic Substances and Disease Registry, called for joint actions to promote healthy reproduction.

Various epidemiologic research approaches were included as important elements in these efforts. These research approaches provide data to identify in humans disorders of reproduction that may be related to occupation. Surveillance activities identify high-risk populations by monitoring the magnitude and distribution of disease in various populations. In-depth etiologic studies can then identify specific etiologic agents and provide quantitative exposure-response information within high-risk populations. The epidemiologic data obtained from these research approaches can be used to stimulate control of occupationally induced disorders of reproduction through education and by implementing regulatory standards and control technology. Thus, it is important to both reevaluate and reemphasize those epidemiologic activities that will develop the knowledge needed to direct preventive efforts.

Surveillance of hazards to reproduction has been limited in this country, due in part to the lack of available data. For this reason, many requirements for a meaningful evolution of surveillance and epidemiologic research pertain to establishing and linking data bases.

Etiologic research on hazards to reproduction has been a subject of major interest for the past ten years, but few etiologic studies of reproduction have examined the potential impact of occupational conditions on reproduction. Such research has been the subject of several workshops and is now a major program area in many agencies and research groups working in the field of environmental health. Etiologic studies are needed to improve understanding of toxic effects of specific agents on human reproduction.

The following research programs and special efforts are recommended to facilitate epidemiologic studies of potential occupational hazards to reproduction and the health of human infants.

1. An extensive literature review and analysis of existing data, similar to that suggested previously in V. Research Needs, A. Laboratory Research, Section 1, should be carried out to:
 - a. Develop a taxonomy for classifying agents that are toxic to human reproductive processes, which includes both the mechanism of action and the level of existing evidence. Such a taxonomy could possibly be developed by several strategies, two of which are: 1) a workshop designed to derive a consensus from the different scientific perspectives involved in research on reproductive problems, or 2) a panel of experts that could interact at a symposium with the various perspectives expressed by the community of scientists who are researching hazards to reproduction. The taxonomy must be based on available epidemiologic and toxicologic data to avoid the need to document in humans a significant number of adverse effects on reproduction before preventive action could be taken.
 - b. Survey world literature (both epidemiologic and toxicologic) to identify occupations, chemicals, biologic agents, physical agents, or combinations of exposure conditions that have been associated with disorders of reproduction in humans or experimental animal models. Substances can be identified from this information for which data are: 1) sufficient to clas-

sify the substances as reproductive toxicants for humans; 2) limited but indicative of a potential hazard to human reproduction; 3) inadequate to classify the substances as reproductive toxicants for humans; or 4) sufficient to state that based on available information an agent is not a potential hazard to reproduction and additional research is not necessary.

- c. Monitor and evaluate existing data sets to target various occupations or industry groups that may be at excess risk of identifiable adverse pregnancy outcomes (e.g., low-birth-weight infants).
- d. Develop, validate, and make generally available improved questionnaires or modular sections for eliciting reproductive histories. Using these instruments, data on demographics and on potentially hazardous exposures or other risk factors could be collected in a standardized format and the collection of appropriate data in a consistent and accurate fashion could be enhanced. This would make it possible to corroborate the existence of a hazard by comparing the results of many studies and monitoring responses to these standard questions over time. A consensus workshop involving researchers who are studying effects on female and male reproduction might be an effective method of facilitating an improved questionnaire instrument.

2. Programs should be established to:

- a. Expand the spectrum of endpoints that can be monitored as indices of human reproductive health. As knowledge about the complicated processes involved in human reproduction increases, those processes can be characterized with increasing detail. It is not always possible, however, to interpret the implications of these details when trying to evaluate human reproductive health (e.g., the ultimate importance of shifts in sperm-head shape). A concerted effort is needed to define essential functional characteristics of the human reproductive system, to determine which can be evaluated reliably, and to establish their value as indices of healthy reproductive systems. Studies are needed to establish what should be considered normal (i.e., to adequately characterize individual as well as population distributions). Endpoints to be considered should include but not be limited to: chromosomal abnormalities (structural as well as numerical), functional defects and developmental disabilities, pregnancy loss, structural malformations, semen characteristics (e.g., sperm count and motility), menstrual cycles, and psychological factors (e.g., libido).
- b. Collect baseline data for large segments of the population on birth weight, infertility, semen quality, spontaneous abortions, congenital malformations, and other potential endpoints that might be used for epidemiologic studies. These data should be collected for persons in occupational and domestic settings where there is no evidence of exposure to agents acting on the reproductive system. These data could not only provide comparison groups for epidemiologic studies but could also provide a basis for determining which personal characteristics and behaviors are related to adverse effects on reproductive systems.
- c. Develop programs to monitor exposure to known or suspected hazards to reproduction. This would help determine surveillance characteristics of exposure and reproductive health in exposed populations. Such programs should be based not only on an index of records profiling potential

occupations and exposures of interest, but also on field sampling of the hazards to measure the extent and characterize the nature of exposure in working environments.

3. Existing data sources should be adapted to provide reliable information on maternal and paternal occupation and industry. This would permit discernment of associations between occupations or industries and increased risk of specific outcomes (e.g., low birth weight, congenital malformations). Efforts should be increased to:
 - a. Promote national and regional data systems that incorporate occupation and industry for both parents and the specific endpoints of reproductive function. These systems would provide population-based data for monitoring the progress in resolving recognized disorders. They would also provide early warnings of changing patterns in disorders of reproduction, thereby accelerating the identification of emerging hazards and the implementation of interventions to reduce their impact. The ability to assess relationships between workplace exposures and specific adverse effects on reproductive systems would also be enhanced.
 - b. Record on all birth and fetal death records data on parental occupation and the industry of employment. NIOSH has supported the inclusion of information about parental employment on the U.S. Recommended Standard Fetal Death Certificate and the U.S. Recommended Standard Live Birth Certificate. Beginning in 1989, information about parental employment will be included on the Recommended Standard Fetal Death Certificate but will not yet be included on the Recommended Standard Live Birth Certificate. The public health community should support all efforts to have such information included on birth certificates as a state option. Information on the mother's employment should span the period from conception to termination of pregnancy.
 - c. Evaluate existing national surveys to include or expand information collected on occupation and industry of employment, possible hazardous exposures found in the workplace, and reproductive history. The cooperation of many agencies is required (e.g. collection by the Census Bureau of usual information on occupation and industry would provide the capability for generating national estimates). NCHS conducts several national surveys that provide important information for studies of human reproduction and with minor modifications at least one of these could provide additional information. Three surveys warrant specific mention: the National Survey of Family Growth, the National System of Infant and Maternal Health Survey, and the National Health and Nutrition Examination Survey. The latter is a large-scale effort that could, if modified to include specific information on parental occupations during critical periods, serve as an excellent source for surveillance research on occupational hazards to reproduction.
 - d. Develop standard techniques for assigning exposure to parental employment data. Exposure and job classification data from the National Occupational Hazard Survey (NOHS) and National Occupational Exposure Survey (NOES) should be assessed to determine whether it can be accurately linked to the SIC data usually collected on parental employment. If such linkage is inadequate, efforts should be made to remedy

the inadequacies. If the linkage capability is adequate, then standard techniques that enable this linkage should be published and made available to the research community.

- e. Encourage hospitals, insurance companies, employers, and other health providers to include parental occupation and industry of employment, reproductive history, and reproductive outcome (where applicable) as data elements they routinely collect.
4. The productivity of surveillance and epidemiology programs can be greatly enhanced by concerted efforts to:
 - a. Standardize industry and occupation codes to insure comparability, permit aggregation, and improve the quality of the data. Definitions, classifications of specific outcomes of reproduction, and other data important to the surveillance of reproduction should also be standardized. NIOSH and other agencies are promoting use of the U.S. Census system as the standard for coding employment data because it is supported by a framework that includes procedural manuals, training programs, and quality control procedures. Continued support is required to expand these program activities.
 - b. Train data providers and coders (e.g. hospital personnel) to insure that the data collected are specific, complete, and accurate. Computer software programs, particularly those for use on desktop computers, should be developed and made generally available not only to improve the quality of data but also to increase cost-effectiveness.
 - c. Expand the linkage of data resources over a wide geographic area to increase the extent and variety of information and the number of records available. Validated questionnaires for reproductive history — developed and field tested as discussed above — will facilitate this. Collecting appropriate and accurate data in a consistent fashion is essential for conducting certain types of studies on adverse pregnancy outcomes and for comparing results of multiple studies to corroborate the existence of hazards.
 - d. Develop and validate tools and approaches for surveillance of reproductive health in employed populations. For example, computer software programs could be developed to assist states in quality control of the occupational and industry information recorded on vital registration system records (e.g., death certificates) and parental information recorded on birth and fetal death records.
 5. Risk assessment may require specialized statistical techniques and mathematical modeling to:
 - a. Develop and apply statistical techniques that will allow the proper and effective analysis of epidemiologic reproductive data. Several analytical problems must be addressed to make the best use of these data. First, occupational study groups are often of limited size so that these studies frequently require the analysis of several pregnancies for each worker. This requires an improved technique to analyze non-independent events. Second, several reproductive endpoints that may be related to the sus-

pect exposure could be analyzed in a simultaneous evaluation to determine the potential for competing risks. Methods for such an analysis have not been developed.

- b. Develop mathematical models that are biologically plausible for risk assessment of hazards to reproduction. Decision-making for regulation often requires the use of very limited data. The maximum use must be made of all available data, and modeling is central to the decision-making process. The effectiveness of regulatory decisions is strongly dependent on how well the underlying biologic process is modeled during risk assessment.

C. Control Strategies

Occupational hazards to healthy reproduction should be controlled whenever possible by the application of sound engineering control technology. Emphasis should be placed on programs to:

1. Assess controls under working conditions, especially in terms of effectiveness related to expense and ease of implementation. Most Americans work for firms that employ fewer than 100 persons, and many small companies may not have the financial resources to make large capital outlays for control improvements. Providing ready access to information detailing existing control measures that are efficient, cost-effective, and easy to implement would be a rapid and inexpensive way to give large and small employers practical ways to reduce marginally high exposures to safe levels.
2. Develop and make generally available inexpensive control technologies that are practicable for use by small employers. Some control systems may be too expensive or complicated for use except by the largest industries. Development and dissemination of new and innovative engineering control techniques appropriate for use by small businesses can potentially affect a large proportion of the workforce.
3. Investigate the feasibility of possible substitute materials for the known reproductive hazards. These studies should address not only the costs but also the change of product quality, the nature of required process modifications, and the health hazard posed by the substitute material.
4. Develop new and innovative approaches for engineering control of workplace contaminants and processes. Some hazards to reproduction can be controlled by current engineering-control techniques, but the standard engineering-control methods can be significantly improved for other processes or chemicals. In addition, new industries or industrial processes often require new or specially modified engineering controls tailored to unique conditions. Engineering research programs are needed to apply the latest engineering concepts to these needs.
5. Develop control strategies for the classes of substances and processes most often associated with reproductive disorders. This development should include mathematical models and other methods to predict contaminant concentrations as a function of physical layout, process parameters for the no-control situation, and various control alternatives. This approach may lead to innovative and more effective controls for known hazards and will provide initial recommendations for control of newly identified substances and processes.

6. Support research programs to evaluate the ergonomic needs of pregnant workers. In general, pregnant women can continue accustomed activities throughout pregnancy. However, some job redesign or equipment modification may be needed late in pregnancy for lifting, stretching, standing, bending, climbing, etc. If product substitution is not feasible and the exposure cannot be adequately curtailed by engineering controls (or pending the installation of engineering controls), it may be necessary to provide personal protective equipment for the workers. In most instances, it is not known how (or if) a pregnant worker is more adversely affected by the added physical stresses associated with personal protective devices than is her nonpregnant coworker. For example, women in late pregnancy may have a reduced tolerance for the added heat burden imposed by some protective clothing or for the increased respiratory resistance imposed by some respirators (both factors may also be applicable to other workers).

VI. Action Plan for the Prevention of Occupational Disorders of Reproduction

Initially, prevention requires the recognition of individual toxicants, potentially hazardous work conditions, and environmental contaminations that can have adverse biologic effects on human reproduction or development. Workers (and the general population) can then be protected from these hazardous agents or conditions through development and application of appropriate engineering controls, product substitution, industrial hygiene practices, waste disposal, and regulatory action.

Education can increase the sensitivity to and awareness of reproductive health. This can be extremely important not only for the training and continuing education of professionals but also for the general public and specific occupational groups. Worker awareness has been responsible for the recognition and eventual correction of many unsafe or unhealthy conditions. Educational programs can contribute not only to disease prevention through avoidance of adverse influences, but to health promotion through active encouragement of positive influences such as proper nutrition and prenatal care. Even if all hazards are not completely identified, education can indirectly reduce human disorders of reproduction through a generally heightened awareness of the requirements for good health.

The causes of human disorders of reproduction are currently unknown in the majority of cases. The causes that are known fall predominantly into three broad categories: preexisting and spontaneously arising genetic factors; personal choice factors such as teenage pregnancy, drug and alcohol abuse, smoking, and sexual practices contributing to high rates of venereal diseases; and societal factors influencing health care and nutrition. The disorders of reproduction that can be attributed to specific occupational hazards can be eliminated, or at least reduced, as the hazards are identified, as workers are protected from them, and as education succeeds in promoting healthy working environments and behaviors. Although disorders of reproduction will remain a significant issue in public and occupational health planning for the foreseeable future, a coordinated national program that addresses personal choice and socioeconomic factors as well as occupational and environmental factors can achieve significant gains immediately.

The following strategic efforts are proposed to improve the recognition of occupational hazards to reproduction, to reduce those hazards, and to promote a healthy reproductive potential for American workers.

A. Public Policy

Consistency of national efforts to protect against hazards to healthy reproduction requires either regulatory action or some type of national consensus on policy. This includes a need to:

1. Recommend regulatory action for substances that have been adequately documented as hazards to human reproduction. To reduce and eliminate occupational disorders of reproduction, public health agencies, business, and labor must support regulatory standards that provide enforceable limits to occupational exposure.
2. Encourage the use of a unique personal identifier to index health records. This identifier could be assigned at birth (or even before, during prenatal medical examinations) or at the point of entry for immigrants or aliens. It would facilitate both surveillance and etiologic research on all health hazards, including hazards to reproduction. It has been demonstrated in several countries throughout the world that such an identifier can be used for research purposes and still insure individual privacy. In the United States, the social security number is a possible existing identifier that could be used. (Assignment of a SSN may soon be required at birth or shortly after for tax purposes.) This type of system is subject to several problems, (such as duplicate assignments of numbers), and appropriate safeguards must also be developed for the confidentiality of medical records. But such an identifier might be a special aid to research on the outcomes of reproduction because it would eliminate the problem of linking the reproductive histories of women through name changes. The goal of establishing a national system of personal identifiers for health research should have high priority not only for studying disorders of reproduction but also for other areas of health research.
3. Establish a national clearinghouse to collect and collate information on hazards to reproductive health, to gather data on the extent and patterns of occupational or environmental exposure to those hazards, to identify appropriate engineering controls or less hazardous substitutes for those hazards, and to facilitate the dissemination of all this information to employers, workers, and regulatory and research agencies. This clearinghouse would also serve as a focal point to stimulate and coordinate collaborative research addressing reproductive health, and should be designed to provide technical support and standard procedures for surveillance activities by defining a minimum data set and methods to conduct such efforts. The planning, establishment, and operation of this activity should include collaboration by all parties interested in promoting reproductive health, including federal, state, and local agencies; public foundations; universities; private research organizations; unions; employers; and trade associations. Collaboration also would help the state agencies and other organizations establish efforts that are parallel and complimentary to those developed by federal agencies. This clearinghouse could assist in promoting national and regional data systems that incorporate the occupation and industry of employment for both parents and the specific endpoints of reproductive function, as was discussed in the first subpoint of Section V.,B.,8.
4. Provide adequate public funding of basic and applied research, including studies with laboratory animals, epidemiologic and surveillance surveys, and studies in allied disciplines, such as statistics, computer science, and engineering. Although the further development and application of in vitro techniques

is advocated here, makers of public policy must recognize the indispensable role of in vivo mammalian models and fund that research adequately. Whole animal studies remain the only definitive test for hazards to reproductive health other than studies in human subjects.

5. Stimulate more widespread interest at the local and state level for detecting, reporting, and preventing disorders of reproduction by encouraging the placement of personnel who are experienced and knowledgeable about hazards to healthy reproduction. Individuals with pertinent training and experience would be a key source of information and data for surveillance systems and could act as a conduit for disseminating the latest research results and techniques in control strategies to the "grassroots" level.
6. Support inclusion of minimum requirements for premarket testing of reproductive and developmental toxicity in federal legislation that deals with toxic substances.

B. Laboratory Research

Leadership, coordination, and funding should be provided to:

1. Organize consensus workshops to develop guidelines for routine testing of potential reproductive and developmental toxicants as well as guidelines for evaluating and interpreting study data on reproductive and developmental toxicology.
2. Organize periodic consensus workshops to establish priorities for research needs in reproductive and developmental toxicology and to provide recommendations to funding agencies and organizations.
3. Establish a committee to evaluate the existing literature on reproductive and developmental toxicology, publish a periodic assessment of the reproductive and developmental toxicity of chemical and physical agents, and recommend priorities for testing such agents. This committee could be organized under the auspices of the recommended national clearinghouse.

C. Surveillance and Epidemiology

Leadership, coordination, and funding should be provided to:

1. Conduct detailed epidemiologic investigations of those substances for which a comprehensive literature search found "limited but indicative" or "inadequate" data to classify them as reproductive toxicants for humans. Criteria used to set priorities for studies of these substances should include known or suspected toxic effects in animal studies, evidence for adverse effects in humans, and the occurrence and extent of human exposure to the agent.
2. Conduct in-depth epidemiologic surveys of agents recommended for regulation as reproductive hazards to monitor and ensure resolution of the adverse health effect.

D. Control Strategies

Application of effective control strategies requires action to:

1. Identify appropriate control measures for all known reproductive hazards. These may be control measures already in use or technology that could be adapted from other industrial processes or exposures.
2. Disseminate to affected employers and workers information already available about which substances are reproductive hazards and how to control exposure to them. There would be significant value in just documenting which controls are being used, which have been abandoned, and what lessons were learned. Not only should the information be available upon request from a single, easily accessible, well-publicized source, but a program should also be developed to actively communicate essential information to the people who need it.
3. Target efforts toward those industries or processes in which workers are subject to adverse effects on reproduction to:
 - a. Identify less hazardous alternative chemical, physical, or biologic agents or processes so that the hazard can be eliminated from those workplaces.
 - b. Install effective engineering controls if the hazardous chemical, physical, or biologic agents or processes cannot be eliminated from the workplace.
 - c. Develop training programs and educational materials tailored to the hazards identified and monitor their implementation and effectiveness. Existing regulations, such as worker right-to-know or labeling laws, and resources such as material safety data sheets can provide a ready framework for implementing these programs, which should target both employers and employees.
4. Determine some characteristics of the known reproductive hazards and the processes in which they are used that would suggest a general classification scheme on which to base further research on control. Pertinent characteristics would include physical and chemical properties and the nature of the workers' involvement with the substance or process.
5. Develop a general compilation of available methods of engineering control technology, organized by physicochemical characteristics and industrial usage patterns. Employers could consult this reference to ensure that appropriate controls are in place when a chemical or process in their workplace is identified as potentially hazardous to reproduction. Engineering techniques properly selected on the basis of physicochemical properties of the hazard, conditions of use, the exposure limit that must be observed, etc., can effectively control exposure and thereby reduce the risk of disorders of reproduction. Once a specific agent or process is identified as adversely affecting reproduction, health professionals should disseminate knowledge about it by the most effective methods available, and appropriate state and federal regulatory agencies must ensure that the affected industries or other users of the hazardous agent implement controls.

6. Stimulate more active and aggressive development of control systems by major employers. Industry should take the lead in developing control systems tailored to meeting the specific needs of each workplace rather than relying on outside authorities to develop improvements in engineering controls. Employers with a detailed knowledge of the workplace, production requirements, etc., are best suited to adapt and install engineering controls with the greatest potential for optimal cost-effectiveness and efficiency.

E. Public Information and Education Programs

The public needs improved educational resources about those occupational and life-style factors that influence reproductive health or may constitute hazards to reproduction. Such information should be integrated into the educational curriculum from grade school through college and incorporated into worker notification programs. Too often the public is subjected to nonspecific or ill-founded alarms without access to the necessary information for an educated evaluation of the facts. The public's heightened awareness and concern about environmental and toxic chemical exposures and the potential adverse effects of these exposures demand the attention and action of the professional occupational health community. There is an obligation to provide accurate information to the general public. Public education should be directed toward decreasing unwarranted fears, increasing awareness of known occupational hazards to reproduction, and heightening awareness of how life-style and personal choices may affect an individual's health. With accurate information about both occupational and nonoccupational reproductive hazards, individual workers will be better equipped to influence particular industries to control occupational hazards and to make informed choices with respect to personal risk or life-style factors.

The plan targets five areas to accomplish this goal: 1) employers and employees (e.g., trade associations and labor unions); 2) the news media; 3) educational institutions; 4) public health/medical care systems; and 5) evaluation of educational programs.

1. **Employers and Employees** (corporate management, trade associations, labor unions): Programs are needed that would provide information to all interested employers and employees on hazards to reproductive health. Training materials should be specific for particular exposures found in a given workplace, but information should also familiarize employees with significant personal risk or life-style factors. Educational programs should include the information necessary to put both occupational and nonoccupational risks into perspective so that the relative importance of each can be judged. A clearinghouse to amass and disseminate information on reproductive hazards would greatly enhance this effort, particularly if it included a 24-hour hot line. Videotapes can be an effective training method, and some videotapes on the subject already exist (e.g., "Reproductive Hazards," produced by the International Brotherhood of Painters and Allied Trades). A thorough search to identify existing tapes should be a first step. Successful and popular NIOSH publications on the topic should be updated and reprinted. Examples are the Comprehensive Bibliography on Pregnancy and Work, NIOSH 78-132; and Guidelines on Pregnancy and Work, NIOSH 78-118.
2. **The News Media:** Balanced and scientifically accurate articles should be written for the popular press explaining what is known and what is not known about reproductive hazards. These articles should highlight known occupational hazards and emphasize not only life-style factors that contribute to

disorders of reproduction (smoking, drug and alcohol abuse, etc.) but also those that contribute to reproductive health in general (adequate nutrition, pre- and postnatal care, etc.). Network or public television should be encouraged to produce documentaries (e.g., a NOVA segment) that address the issues of occupational hazards to reproduction. Videotape copies of these documentaries could be used for education programs in educational institutions or the workplace and by employers, employees, or public interest groups.

3. Educational Institutions: Better information on the maintenance of reproductive health and the avoidance of recognized hazards to reproduction should be presented in primary and secondary schools. Young people need to be educated about the hazards to reproductive health because they experience tremendous pressures to experiment with sex, drugs, alcohol, and tobacco. Adolescents must also cope with their own sexuality and their ability to reproduce. They are a prime audience for information about controllable hazards. Current on-the-job educational programs would be more effective if workers had previously been alerted as adolescents to occupational hazards, including (but not limited to) hazards to reproduction. Professional education associations should be identified to help develop appropriate educational materials, and the Department of Education should be solicited to encourage school systems to incorporate these educational materials into their curricula.
4. Public Health/Medical Care Systems: Increased public awareness of occupational hazards to reproduction should be stimulated by preparing information resources (e.g., pamphlets and NIOSH Current Intelligence Bulletins) that discuss these issues. Existing public agencies (e.g., local and state health departments) and organizations such as the March of Dimes, Healthy Mother/Healthy Baby should be encouraged to participate in the development and distribution of these materials. Distribution would be through local and state public health departments and through private clinics and physicians. These materials should use general, nontechnical terms to discuss occupational and nonoccupational hazards. The objective is to make individuals aware that hazards to reproductive health exist and to stimulate a self-examination of personal choice in life-style factors, workplace exposures, and work practices. This awareness should lead to discussions between individuals and health care providers on how occupation and life-style may affect health.
5. Evaluation: The effectiveness of educational programs should be monitored to include baseline data on workplace exposures and life-style practices both before and after educational programs are established. In this way, ineffective programs can be identified and improved, while beneficial programs can be modeled in other settings.

F. Professional Information and Education Programs

The education of health professionals should be enhanced to place greater emphasis on the effects occupational exposures can have on reproductive health. This should involve programs to:

1. Establish contacts with schools of engineering and business to encourage development of lectures and courses on occupational health and disease prevention. Control of hazards to safety and health in the workplace is most efficiently and productively implemented during the design phase of an industrial process. If controls are employed from the outset, the exposure of workers will always be minimal. Thus, it is imperative that the engineering and business

communities be educated and sensitized to the need for including occupational safety and health considerations (e.g., engineering controls) as an integral part of business planning and engineering design. Concepts of occupational safety and health should be incorporated into all undergraduate engineering and business curricula.

2. Establish contacts with schools of medicine, nursing, and public health to encourage development of lectures and courses on occupational reproductive hazards for the undergraduate and graduate education of health professionals. Increased awareness is needed by medical and other health professionals of the potential effect of occupation on a patient's health. Concepts of occupational safety and health should be integrated into the curricula at these schools, and the fundamental importance of obtaining an accurate, up-to-date, occupational history should be emphasized at all levels of training for medical and other health professionals. Persons who specialize in occupational medicine or nursing or in genetic counseling need specific training and continuing education on potential occupationally induced disorders of reproduction. The occupational health community should work with schools of medicine, nursing, and public health and with professional societies to develop appropriate educational materials. Articles or letters to the editor should be written for medical journals to solicit support from the medical community for education about occupational disorders of reproduction and the need to heighten the awareness of physicians.
3. Encourage occupational health professionals to work with public and private health organizations to provide educational materials, information, and speakers for meetings. Occupational health professionals have an obligation to serve as resources for both the public and their professional colleagues. For example, groups such as the Reproductive and Developmental Toxicology Specialty Section of the Society of Toxicology could identify a group of expert members to present seminars at meetings of other professional societies (e.g., the National Family Planning and Reproductive Health Association, the American Management Association) or other public meetings. Such a group also could help prepare and distribute educational literature or audiovisual materials.

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Contributors

to the Proposed National Strategy for the Prevention of Disorders of Reproduction

NIOSH WORKING GROUP MEMBERS

Bryan D. Hardin, Ph.D., Chair

Jean G. French, Dr.P.H.

Sharon L. Kercher

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AFL-CIO

D. Developmental and reproductive hazards : an overview of adverse outcomes from industrial and environmental exposures

B.K.Nelson

National Institute for Occupational Safety and Health, Cincinnati

Abstract. This paper reviews some general principles regarding reproductive and developmental toxicity hazard research, and discusses representative disorders which may be produced by chemical and physical hazards in the workplace or more generally in the environment. These disorders include genetic defects, sterility or reduced fertility, menstrual disorders, decreased libido, spontaneous abortions, stillbirths and infant mortalities, malformations, growth retardation, disease states, and functional deficits. The ever increasing number of women entering the workforce and seeking wider job opportunities, together with the increasing number of hazardous agents which can be encountered in our environment, raise concern about the conditions which pose developmental and reproductive risk. Health professionals must be alert to a wide variety of adverse outcomes potentially induced by reproductive and developmental toxicological hazards.

Key Words. Reproductive toxicology. Teratology. Mutations. Fertility. Transplacental carcinogenesis. Reproductive hazards. Environmental contaminants. Spontaneous abortions. Birth defects.

In many countries throughout the world, women are entering the workforce in numbers equal to those of men. This influx of women into work situations traditionally reserved for men has heightened concern about potential reproductive and developmental toxicants in the workplace. Since many workplace contaminants are spread into the general environment, these concerns extend to potential chemical and physical agents which may affect reproduction. A number of important medicolegal questions have been addressed, particularly focusing on different company policies on placing women in jobs for which a risk of exposure to potential teratogens may make the company liable for congenital malformations in their children (e.g., Brent, 1977; Fantel & Fantel, 1981). Should women of childbearing capacity be barred from jobs in which they may be exposed to potential teratogens? Are men just as susceptible as women to reproductive hazards? Although answers to such questions are beyond the scope of this paper, they provide the impetus for research either needed or being undertaken. Several companies

have developed policies regarding such hazards (e.g., Perrin, 1978), and programs directed to evaluating reproductive hazards for both reproductive and developmental toxicants have been established in several American federal agencies (e.g., Hunt, 1974; Bingham, 1977; NIOSH, 1977a, 1978).

This paper is directed, not to the occupational or public health physician who may have received specialized training in this area, but toward other technical staff such as industrial hygienists and nurses who are responsible for the day to day safety and health of those exposed to industrial and environmental agents. The paper is not intended to provide an in-depth review of occupational reproductive hazards since several reviews are available (e.g., Nishimura, 1973; Wilson, 1977; Strobino et al., 1978; Hemminki, 1980; Messite & Bond, 1980). Rather, it is intended to sensitize public health specialists to the broad range of different outcomes which might be affected by reproductive and developmental hazards (Miller, 1983).

Background

One of the first studies to demonstrate that exogenous chemicals could produce birth defects incriminated a naturally occurring toxicant. A series of studies initiated before the thalidomide episode in Europe (Stern, 1981) showed that birth defects in sheep--previously assumed to be of genetic origin--were caused by the consumption of a range plant (*Veratrum californicum*) by pregnant ewes (Binns et al., 1963). In subsequent years, still other naturally-occurring compounds were found to be teratogenic to animals (Keeler, 1975).

Despite this research on environmentally-induced congenital defects, attention to occupational and environmental teratogens has been slow in coming. Illustrative of the problem is the fact that developmental or reproductive effects were noted in the bases for recommended American Con-

of evidence substantiating such effects. Most chemicals have not had adequate testing to determine if there is a hazard of reproductive and developmental toxicity. A case in point is the class of industrial solvents referred to as glycol ethers. Although one report in the literature had documented reproductive effects of 2-ethoxyethanol administered by gavage, it was not until several studies with the solvent administered by inhalation reported adverse effects that regulatory action was initiated. Research in our laboratory found that behavioral deficits occurred in offspring of animals inhaling 100 ppm 2-ethoxyethanol (which was at that time one half of the legal standard in the United States) for typical workday exposure hours during the gestation period of rats. No offspring survived three times this concentration (Nelson et al., 1981). Perhaps of even greater concern was an interaction of 2-ethoxyethanol with a commonly abused drug,

Table 1. Agents for which Reproductive Effects Serve as Important Factors in the Basis for ACGIH Recommended Standards

<i>Chemical</i>	<i>Effect in animals</i>
n-Butyl Glycidyl ether	mutagenic
Captan	reduced fertility
Carbaryl	(?) ¹ teratogenic
Chloroform	embryotoxic (not teratogenic)
Cyclohexylamine	(?) embryotoxic (not teratogenic)
Dieldrin	embryotoxic
Dimethylaniline	testes degeneration
Ethylene chlorohydrin	(?) mutagenic; not (?) teratogenic
Ethylene dibromide	mutagenic; reduced fertility
Ethylidene norbornene	testicular atrophy
Heptachlor	embryotoxic
Isophorone diisocyanate	"testes variation"
Nickel carbonyl	teratogenic
Oxygen difluoride	irritant of internal genitalia
Phenyl phosphine	irreversible testicular degeneration
<i>Physical</i>	
Ionizing radiation	teratogenic, mutagenic

¹ Question marks reflect that the effect is not conclusive

ference of Governmental Industrial Hygienists (ACGIH) standards in only 15 of the 575 chemicals for which ACGIH had developed standards in 1980 (see Table 1). This lack of notations for reproductive and developmental effects stems, not from a lack of concern for these effects, but from the lack

of ethanol, given in the home cage drinking water following each day's exposures, again in the offspring (Nelson et al., 1982a,b, 1984; see also a review by Hills & Venable, 1982, on the interaction of ethanol and industrial chemicals). Numerous other glycol ethers have also been shown to be

developmental toxicants, and several glycol ethers have also been shown to be reproductive toxicants (see Hardin & Lyon, 1984, and the proceedings of the NIOSH Symposium on Toxic Effects of Glycol Ethers in the same reference). Unfortunately, however, developmental and reproductive toxicity assessments have been made for relatively few of the industrial and environmental compounds in widespread use today.

Not more than two decades ago, papers on occupational reproductive and developmental hazards were uncommon, and focused almost exclusively on working pregnant women (e.g., Diddle, 1970; Yager, 1973). Toward the end of the 1970s, however, numerous papers were published covering a variety of concerns and issues in both reproductive and developmental toxicology (e.g., Stillman, 1978; Ward, 1978; Warshaw, 1978; Haas & Schottenfeld, 1979; Krause, 1979; McCullough, 1979; Messite, 1979; Nemec, 1979; O'Connell, 1979; Stellman, 1979; Warshaw, 1979). The present paper will review some general principles of developmental toxicology and provide an overview of different reproductive outcomes that must be kept in mind when assessing the possible adverse reproductive effects of industrial and environmental agents.

1. Principles of Developmental Toxicology

As a preface to discussing different types of effects which may be observed following exposure to reproductive and developmental toxicants, some general principles will be reviewed briefly. Though generated from experimental teratology (Wilson, 1977), these principles have wider applicability and are useful in considering the broader range of outcomes discussed in this paper.

A. Subject Selection

Susceptibility to reproductive and developmental toxicity depends upon the genetic characteristics of the subjects involved and how the genetic makeup interacts with environmental factors and the toxicant. Different individuals, strains, and species often react to a particular hazard in very different ways. For example, primates are remarkably susceptible, and rodents are unusually

resistant, to the teratogenic effects of thalidomide (see Warkany, 1971).

B. Nature of the Hazard

Access of adverse environmental influences to sensitive tissues depends on the physicochemical properties of the particular hazard. Highly lipid soluble compounds which are unionized at physiological pH and of low molecular weight would generally cross biological membranes relatively freely to exert biological effects (Mirkin, 1973; Nau, 1986). Though in many cases, the mechanism of action of a reproductive/developmental hazard is unknown, different toxicants can produce similar effects by interfering with different steps of the same biochemical process (Grabowski, 1970).

C. Critical Periods

Susceptibility to toxicity often varies with the developmental stage at the time of action of a toxic agent. During pregnancy, the period of organogenesis is generally most susceptible to adverse effects. However, alterations can be induced throughout development. For example, the nervous system is susceptible to damage throughout prenatal life and into childhood (Nelson, 1978). Complicating the issue of critical periods in the observation that acute exposure may produce effects very different from those of chronic exposure, likely due to enzyme induction or altered pharmacokinetic patterns (e.g., King et al., 1965).

D. Dose/effect Relationships

Manifestations of developmental and reproductive toxicity generally increase in degree as dosage increases, from the no-detectable-effect level to the totally lethal level. In teratology, for example, functional deficits, growth retardation, and malformations occur at dosage levels lower than those which cause intrauterine death-although there is often overlap in these dose/effect curves (e.g., Wilson, 1977; Nelson, 1981).

II. Examples of Adverse Effects of Reproductive/Developmental Toxicants

Having briefly reviewed some general principles relative to reproductive and developmental toxicology, let us proceed to discuss a number of

major effects of reproductive toxicants along with typical examples of occupational and environmental hazards which have been reported to produce such effects. The list is not an exhaustive one, but it does provide public health workers with an overview of different outcomes which may be affected by exposure of parents. The order in which the types of effects are discussed is not intended to signify importance. Rather, these effects are introduced by the time during which they would be expected to occur, beginning prior to fertilization, continuing through pregnancy, and finally those manifesting themselves throughout the lifespan of the offspring (Fig.1). The reproductive cycle may be affected by toxicants at any of these stages, and may include some outcomes not typically included in a medical definition of reproduction. With regard to the postnatal period, numerous drugs and environmental chemicals can be passed to infants through breast milk (e.g., Nomura, 1973; Schoental et al., 1974; Forrest, 1976; Berlin, 1980; Poland & Cohen, 1980; Wolff, 1983). Differences in cultural norms and practices obviously dictate the importance of toxicants passed through maternal milk. In approximately one half of the societies analyzed by one reviewer, women return to work within two weeks after delivering a baby (Jimenez & Newton, 1979). Children may also be exposed to toxic agents carried home on the clothes of their parents,

although public awareness of this problem is likely reducing the frequency of this exposure.

A. Effects Prior to Conception

1. *Genetic defects* are alterations in germ cells that can be passed from one generation to the next. Though somatic cell mutations can be deleterious to the organism in which the genetic defect occurs, it is primarily those that occur in germ cells which are of concern in reproductive and developmental toxicology assessments. For example, radiation and numerous chemicals are known to be mutagenic (Fishbein et al., 1970). Some 20% of human malformations are known to be due to transmissible genetic defects (Wilson, 1973). Since the etiology of about 60% of human malformations is unknown, it may be that a portion of this percentage can be attributed to spontaneous or environmentally induced genetic alterations.

2. *Sterility or reduced fertility* have become of concern primarily since the report of infertility among men who formulated the pesticide 1, 2-dibromo-3-chloropropane (DBCP; Whorton et al., 1977). Concern over the reproductive effects of DBCP broadened with the reports that applicators of this pesticide also showed decreased fertility (Glass et al., 1979; Sandifer et al., 1979). Carbaryl exposure has also been shown to alter sperm head morphology in exposed workers (Wyrobek et al.,

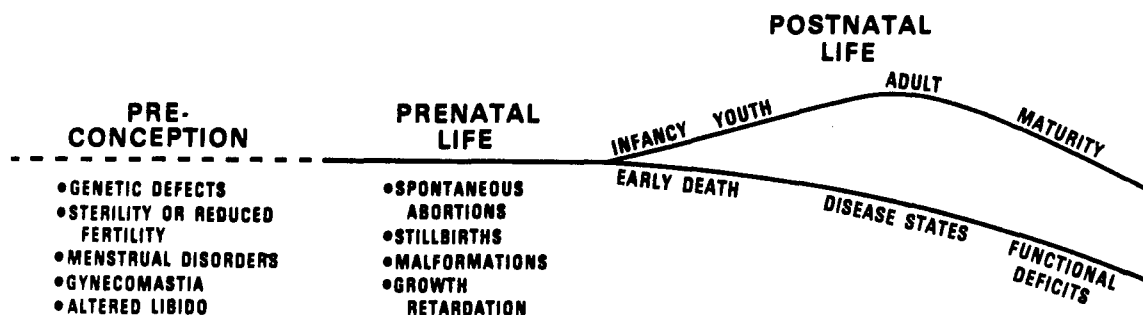


Fig. 1. Outcomes reflecting potential effects of human exposure to reproductive and developmental toxicants

1981). A review of the environmental agents known to adversely affect male reproduction included some 50 drugs and environmental chemicals affecting male experimental animals. About one half that number of agents were reported to produce reproductive toxicity in humans, including heavy metals, pesticides, solvents, food additives and contaminants, alkylating agents, antibiotics, and synthetic steroids (Manson & Simons, 1979; Joffe & Soyka, 1981).

3. *Menstrual disorders* have not been examined very closely, perhaps because of the range and subjectivity of possible effects. A few studies, however, have detected gynecological disturbances in exposed individuals. For example one study found differences from controls in "single phase menstrual cycles, hypoestrogenism, hyperestrogenism, and more painful and copious menstruations" among women engaged in the production of enamel insulated wire (Syrovadko & Malysheva, 1977). Such effects deserve greater consideration in reproductive and developmental toxicology investigations.

4. *Gynecomastia and impotence or decreased libido* are somewhat subjective but important considerations in males, and the latter possibly in females as well. These effects have been reported following occupational exposure to synthetic estrogens (Harrington et al., 1978a,b), DBCP (Whorton et al., 1979), and DMAPN (Pestronk et al., 1980).

B. Prenatal Effects

1. Increases in *spontaneous abortions* have been reported following both maternal and paternal exposure to workplace contaminants such as waste anesthetic gases (NIOSH, 1977b). An increase in spontaneous abortions was also observed among female textile workers in Iran, and the investigators hypothesized that the increases may be due to industrialization in general (Kavoussi, 1977). Early spontaneous abortions may be difficult to detect since the conceptus may be passed with the menstrual bleeding and thus not be observed. However, early aborted embryos may represent one of the common manifestations of reproductive and

developmental hazards in the workplace and environment. Both the frequency of spontaneous abortions and the prevalence of malformations in the conceptuses have been recommended as early warnings of environmental teratogens (Kline et al., 1977).

2. The rate of *stillbirths* and/or *neonatal mortality* can be affected by environmental agents. For example, Kavoussi (1977) reported increased infant mortality at birth among female textile workers, although other factors could explain the differences in that study. Death of the conceptus is the most common adverse reproductive effect observed in experimental teratology studies (Wilson, 1973). Consequently, it is not improbable that increased prenatal and/or postnatal mortalities may be important manifestations of deviant development in humans as well, since the majority of defective conceptuses are lost through mortality (Warkany, 1981).

C. Postnatal Effects

1. *Birth defects* are malformations present at birth, regardless of the cause. Historically, birth defects have been thought of in terms of structural malformations, but that definition is expanding (Schardein, 1985). In this category, the emphasis remains on malformations, and on those that are induced by teratogenic agents, as opposed to those that are inherited, as were discussed previously. Sporadically, reports appear in the literature which hypothesize environmentally-induced increases in birth defects (e.g., Holmberg, 1977; Jones & Tauscher, 1978). Since two third of human birth defects have no known cause, observations on small numbers of cases can be misleading. That is, sporadic malformations will occur by chance, and observations of defects in a small exposure population may cause undue alarm even though they occurred only by chance. While it is likely that environmental factors play a key role in many malformations, especially in view of possible interaction effects (Fraser, 1977), it should be emphasized that "environmental factors" is a very broad category, which includes many non-chemical factors. For example, alcohol is a known human teratogen,

cigarette smoking is reported to affect human reproduction adversely, and caffeine is a reported teratogen in experimental animals (although not confirmed to produce malformations in humans). These and other pharmacologic agents which are in widespread use, as well as numerous environmental conditions such as contaminants in waste dumps or water supplies, infectious agents, temperature extremes, etc., may interact not only with one another but also with industrial chemicals to alter human reproductive function adversely.

2. *Growth retardation* may be apparent at birth, or may not be obvious for a long period of time (Redmond, 1979). Frequently, a growth-retarded child has accompanying health problems, such as an underlying disease or functional deficit (e.g., Castells et al., 1974). Low birth weight babies have been associated with smoking during pregnancy (U.S. Dept. HEW, 1979). Thus, children who have reduced birth weights and/or failure to thrive postnatally should be examined carefully for health disorders.

3. Of a variety of *disease states* that could potentially occur during life as a result of increased sensitivity developed during prenatal life, cancer induced by transplacental carcinogens is the best documented. Since Herbst et al. (1971) reported adenocarcinomas of the vagina following in utero exposure to the synthetic hormone diethylstilbestrol (DES), research in transplacental carcinogenesis has gained momentum (Rice, 1973; Tomatis et al., 1973; Miller, 1977). In addition to the carcinogenic effects of DES, other transplacental effects have been reported in human females (Goldstein, 1978; Schmidt et al., 1980; Veridiano et al., 1981) as well as males (Henderson et al., 1976; Hills & Bongiovanni, 1978), although cancer has not been reported in males. Transplacental alterations have also been noted in female (Boylan, 1978) and male (McClachlan et al., 1975) experimental animals. Other chemicals have been implicated as possible human transplacental carcinogens (e.g., Wagoner et al., 1977; Infante et al., 1978; Peters et al., 1981). Animal research has verified the transplacental carcinogenicity of a

number of chemicals, primarily after administration late in gestation, including vinyl chloride (Maltini & Lefimine, 1975), urethane (Nomura, 1974), and a number of other compounds (Dimant & Beniashvili, 1978; Napalkov, 1979)-- although similar effects from these chemicals have not been documented in humans.

4. *Functional deficits* may be apparent at birth, but most functionally deficient animals appear normal at birth, and the defects may not be detected for years. In one clinical report, for example, a phenotypically female sexagenarian with chronic infertility, who had apparently never sought medical attention for that condition, was examined for other medical complications, and was found to have inguinal testes (Khodr, 1979). Between these two extremes of age lies a lifespan during which functional deficits may become apparent. There is a growing body of experimental evidence that certain transplacental toxicants may induce a variety of functional deficits in offspring of animals exposed during gestation (Riley & Vorhees, 1986). Human functional deficits due to teratogenic factors have not been frequently reported, with the notable exceptions of fetal alcohol syndrome (Jones & Smith, 1973) and congenital methylmercury poisoning (Spyker, 1974). Nevertheless, a number of drugs and industrial chemicals have been shown to produce behavioral deficits in humans after prenatal exposure (see Gal & Sharpless, 1984; Adams, 1986; Vorhees & Mollnow, 1987; Kimmel, 1988; Nelson, in press). In experimental animals, a variety of functional deficits have been reported following prenatal exposure to a number of agents, including cardiac abnormalities (Olsen, 1977; Grabowski & Payne, 1980; Toraason & Breitenstein, 1988), endocrine imbalances (Cranmer et al., 1978), dental asymmetry (Siegel et al., 1977), hepatic dysfunction (O'Callaghan & Holtzman, 1976; Burke & Fenton, 1978; Robbins et al., 1978), gastrointestinal defects (Schroder et al., 1977), immune system disturbances (Luster et al., 1978), reduced fertility (Heronkohl, 1979), respiratory malfunction (Armenti & Johnson, 1979; Matthews et al., 1981), and a host

of behavioral abnormalities such as hyperactivity, learning deficits, and neuromotor disturbances (Butcher, 1976; Zenick, 1977; Nelson, 1978; Riley & Vorhees, 1986). In addition to these long-lasting effects, transitory effects may be observed following perinatal exposures (Habib & McCarthy, 1977; Rementeria, 1977), and long-term consequences of such effects are unknown. It should also be noted that "postnatal effects" have been reported in offspring following exposure of the male experimental animal to a variety of agents (Friedler & Wheeling, 1979; Adams et al., 1984; Auroux & Dulioust, 1985; Robaire et al., 1985). Furthermore, studies report that some functional effects following maternal exposures carry over into the second and third generations (Walz et al., 1983).

III. Research Problems

The longer the time lag between exposure to a hazardous agent and the manifestation of its adverse effect(s), the less likely it is that a causal connection will be made between the agent and the effect, particularly if the effect occurs naturally in the population. Consequently, the last categories of effects discussed (viz., those being manifest in postnatal life) likely pose the most problems from a research standpoint. Especially with these effects, but not exclusively with them, extraneous variables may intervene between the exposure and the observed effect, and alleviate or exacerbate the adverse effect. These intervening variables decrease the power of epidemiological studies to detect reproductive hazards, but such studies must nevertheless be utilized in the overall strategy to reduce exposure to potential hazards (Klingberg & Papier, 1979).

As with other forms of toxicity screening, detection of reproductive and developmental hazards through animal research is clearly preferable to allowing these hazardous agents to be manifest in humans. However, extrapolating results from studies in animals to man has definite limitations (Brent, 1974; Warkany, 1974; Nau, 1986). Notwithstanding these limitations, it is prudent to consider a positive response in experimental animals as presumptive, at least on a qualitative

basis, of risk to humans (Sullivan, 1974; Infante & Legator, 1980).

Conclusion

This paper has reviewed different factors to consider in evaluating occupational and environmentally-induced reproductive and developmental toxicity. It has reviewed a number of different types of outcomes which might be affected by industrial chemicals. It provides public health technicians and specialists with an overview of reproductive effects which may be encountered in human populations exposed to industrial chemicals. Clearly, the potential adverse outcomes are far broader than may be suspected by people outside the field, and this calls for considerable vigilance on the part of public health specialists who may be the first to confront reproductive and developmental toxicity endpoints in humans.

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B.K. Nelson
National Institute for Occupational Safety and
Health
Division of Biomedical and Behavioral Science
4676 Columbia Parkway
Cincinnati, OH 45226, U.S.A.

E. Evidence for Behavioral Teratogenicity in Humans

B. K. Nelson

Division of Biomedical and Behavioral Science, NIOSH C-24, 4676 Columbia Parkway, Cincinnati, OH 45226, USA

Key words: behavioral teratology; teratology; developmental toxicology; developmental neurotoxicology; behavioral disorders; mental retardation; hyperactivity; reproductive toxicology; children; pregnancy.

Central to both the scientific development of behavioral teratology and the attention paid to this field as an important area of study is establishing that prenatal exposure of pregnant females to exogenous agents leads to neurobehavioral disorders in their offspring. This tenet may not be questioned by the majority of toxicologists, but others may not be convinced. This paper serves as a brief review of the accumulated evidence that prenatal exposure to a number of drugs and environmental/industrial agents produces behavioral disorders in human infants.

A central issue in behavioral teratology or developmental neurotoxicology is the establishment of prenatal causes of developmental behavioral disorders. Only in recent years has sufficient evidence accumulated to document a linkage between prenatal exposure and adverse postnatal outcome for a series of drugs and industrial chemicals in both humans and animals. This linkage is crucial to the scientific development of the field of behavioral teratology, and also has implications for the extent of research support that this field will obtain. These linkages, however, do not appear to be well recognized, and this lack of recognition may contribute to the lack of widespread support of research in the field of developmental neurotoxicology. This paper summarizes the published evidence of neurobehavioral disorders in humans induced by prenatal exposure to exogenous agents to encourage further the development of the field of developmental neurotoxicology.

Huge societal costs result from the array of childhood disorders and dysfunctions identified in the United States, and many of these disorders persist into adulthood. Some 15–20% of American children have some form of ongoing physical health problem, many of which may be of prenatal origin.¹ Mental retardation (defined as an IQ score of <70) afflicts some 6 million people in America (about 3% of the population), and over 100 000 newborn children are added to this population each year.² Developmental disabilities (e.g. asthma, diabetes, epilepsy, speech or hearing impairment) affect some 3.9 million Americans under the age of 22, and it is estimated that 25% of the total US population has some form of psychological disorder.^{3,4} Learning disabilities plague ca. 4% of the school children in the United States.⁵

The degree to which prenatal factors contribute to the childhood disorders and dysfunctions noted above has not been established. However, the incidence of some correlated problems has been established. It is generally accepted that the incidence of birth defects is 2–3% of liveborn babies.⁶ In 1985, birth defects were the leading cause of infant mortality in the United

States and the fifth leading cause of shortened life span.^{7,8} Birth defects contribute significantly to chronic disease morbidity and related medical costs; ca. 30% of all admissions to pediatric hospitals are associated with birth defects, and expenditures for medical care have been estimated at \$1.4 billion per year;⁹ these figures may not include costs of otherwise normal babies born prematurely or with low birth weight. In addition to these figures for birth defects, another 7–8% of babies have malformations or mental deficiencies that are identified only after birth but before one year of age. In fact, this figure would be higher if other behavioral dysfunctions, for which prenatal factors may play a contributory role, were added to the total. These dysfunctions include seizure disorders, autism, childhood schizophrenia, early onset emotional disturbances and attention deficit disorders.

Despite the fact that birth defects and functional disorders affect a significant portion of the human population, the causes of these problems are not well established. The period between exposure to a causative agent and detection of the resulting functional pathology interposes numerous confounding factors, which may mask the etiological agent. Despite the difficulties inherent in detecting behavioral teratogens in humans, several such agents have been identified, frequently because the behavioral effects accompany other congenital malformations (at least at high exposure levels). Human infants who show evidence of growth retardation have a 33–50% chance of having a learning disability and some 26–61% of infants with mental retardation have associated congenital anomalies.¹⁰ For example, mental retardation resulting from prenatal ethanol abuse has been associated with the abnormal appearance of the children (often, microcephaly). As noted below, evidence from animal research and/or isolated reports in human infants suggest other agents as possible human behavioral teratogens.

Vorhees and Mollnow¹¹ have reviewed the evidence that various drugs and environmental agents are human behavioral teratogens (see also Refs 12 and 13). Based

on published animal and clinical evidence of behavioral teratogenicity (excluding non-specific causes, such as birth trauma accompanied by hypoxia), agents were categorized as established, probable or suspected behavioral teratogens; these agents are presented in Table 1. The 'established' category is based on evidence for both animals and humans published in the peer-reviewed research literature. The category of 'probable' behavioral teratogens identifies those agents for which the published evidence of behavioral teratogenesis in animals is strong but cannot yet be considered conclusive because of the scarcity of human data. The third category, 'suspected' behavioral teratogens, includes those agents for which evidence is only suggestive of behavioral teratogenicity, usually from published work involving a limited number of animal experiments.

The accumulated evidence described above (from animal research, as well as human observations) clearly establishes the existence of human behavioral teratogens. What is less clear is the extent to which these and other, as yet undiscovered, behavioral teratogens contribute to the overall incidence of behavioral disorders among humans. The discovery of a broad range of pharmacological agents that produce such disorders resulted directly from the extensive testing requirements imposed on drugs. These tests have provided much evidence regarding behavioral teratogens.¹⁴⁻¹⁸ A similar, aggressive program of testing for environmental and industrial agents would likely reveal a number of behavioral teratogens for these agents as well.

The focus on therapeutic agents for investigation resulted directly from the thalidomide tragedy of the early 1960s. Some 10 500 malformed infants were born, primarily in Europe, as a result of maternal ingestion of the sedative-hypnotic and anti-nausea medication,

thalidomide, during pregnancy (see Ref. 19). Although this drug was never approved for use in the United States, the Food and Drug Administration (FDA) reacted strongly to this event by establishing guidelines that required teratology evaluations of new drugs with experimental animals. Most industrialized countries subsequently developed similar requirements for new drugs. Had thalidomide also induced behavioral dysfunction, perhaps detection of functional disorders would have been included in the guidelines. Clearly, research interest was concentrated on drugs, both in standard teratology and in the fledgling field of behavioral teratology.²⁰⁻²⁴ US regulatory agencies now appear likely to follow the lead of several other developed countries in requiring behavioral teratology evaluations for some classes of drugs and industrial chemicals.^{13,25-35}

The thalidomide tragedy was the major stimulus for research in teratology, whereas ethanol was the primary stimulus for research in behavioral teratology. Since Jones and Smith published their paper describing the fetal alcohol syndrome,³⁶ an extensive literature has accumulated on the behavioral teratogenic effects of ethanol, both in humans and experimental animals.³⁷⁻³⁹ The most noted feature of this syndrome is behavioral and intellectual dysfunction characterized by hyperactivity, delayed motor development and mental retardation in human infants.⁴⁰ Some researchers have argued that ethanol represents the most preventable cause of mental retardation in humans.⁴¹

While public and research interest in the 1960s and early 1970s focused on the teratogenicity of drugs, the focus in the late 1970s and the 1980s expanded to include the teratogenicity of environmental and industrial chemicals. With increasing numbers of women entering the workforce,^{42,43} and with more

Table 1. Human behavioral teratogens.

Established	Probable	Suspected
Ethanol	Cigarette smoking ^b	Anxiolytics (e.g. diazepam)
Ionizing radiation	Nicotine	Antidepressants (e.g. imipramine)
Organic mercury	Narcotics	Anesthetics (e.g. halothane)
Inorganic lead	Several hormones (e.g. progestin)	Aspirin
Several anticonvulsants ^a	PCBs ^b	Marijuana
Vitamin A ^a		Neuroleptics (e.g. chlorpromazine)
		Thalidomide
		Other ^c

^a Vorhees and Mollnow¹¹ included anticonvulsants and vitamin A in the 'probable' category, but subsequent research provides evidence that these drugs now meet the criteria for the 'established' category (see Refs 69, 70, 71). The anticonvulsants include hydantoin, trimethadione and valproate.

^b As evidence accumulates that cigarette smoking⁷² and PCB exposure⁷³ during pregnancy affects children's performance, cigarette smoking and PCBs should perhaps be shifted to the 'established' category as well.

^c Includes some maternal infections, other heavy metals (e.g. cadmium and organotin), some industrial solvents and insecticides.

births being delayed until women are in their thirties (i.e. until after a number of years of work exposure), the risk of birth defects in offspring following exposure to industrial chemicals has become a major concern of working women.⁴⁴⁻⁵¹

Concern about exposure of pregnant women to environmental and industrial agents, and the resulting behavioral effects on their offspring, was heightened following several outbreaks of congenital methylmercury poisoning.⁵²⁻⁵⁴ The most widely publicized outbreak resulted from the release of effluent from an acetaldehyde plant into Minamata Bay, Japan.⁵⁵ Methylmercury entered the human food supply through fish in Minamata Bay (i.e. the fish were consumed by local villagers). In 1955, some 1600 adult cases of neurological disease were found in the Minamata area of Kyushu, Japan, with symptoms similar to those of cerebral palsy.⁵⁶ Several years later, investigators concluded that methylmercury also was responsible for the development of microcephaly, mental retardation and cerebral palsy in 26 infants as a result of *in utero* exposure to methylmercury.⁵⁶

A similar, but less dramatic, event occurred later when pregnant Swedish women mistakenly consumed seed grain treated with mercury. The congenital poisoning resulting from this consumption caused several cases of cerebral palsy with mental deficiency in the children of these women.⁵⁵⁻⁵⁷ An independent incident in Iraq added evidence to the hypothesis that the Swedish cases could have resulted from mercury exposure. In Iraq, seed grain treated with methylmercury was diverted to make bread, which then was consumed by a large number of Iraqis.^{56,58} Thousands of Iraqis were hospitalized and ca. 460 died in hospitals as a result of this exposure. A small number of pregnant women were among those who survived the initial exposure. At least six of the 15 infants born to these exposed women showed gross impairment of motor and mental development, including cerebral palsy, microcephaly, deafness and blindness.⁵⁹

Lead is another industrial chemical with widespread application. The behavioral teratogenic effects of lead have been demonstrated only recently, whereas the neurotoxic and adverse reproductive effects of this metal have been recognized since antiquity.⁶⁰⁻⁶² These effects have been reviewed recently in the human clinical and experimental animal literature,^{62,63} so an extensive coverage of this literature is not attempted here. However, subclinical exposure of children to lead has been shown to be associated with deficits in intelligence, auditory perception, attention and classroom performance.⁶¹ A recent review⁶² stated that blood lead levels of 10–15 $\mu\text{g dl}^{-1}$ in children are known to result in neurobehavioral performance decrements. Centers for Disease Control (CDC) guidelines for lead screening in children were reduced from 30 $\mu\text{g dl}^{-1}$ in 1978 to 25 $\mu\text{g dl}^{-1}$ in 1984,⁶¹ and these levels are likely to be reduced further in light of finding positive effects at still lower levels. Owing to lead's persistence in the body, chronic low-level lead exposure of women can result in adverse effects in their progeny born years later.⁶⁴

In summary, numerous drugs and environmental and industrial agents have been documented to produce behavioral teratogenicity in humans.⁶⁵ The etiology of the vast majority of human developmental disorders, however, is unknown. If additional etiological agents are to be discovered, data must be obtained from a variety of sources, including surveillance programs,^{7,66,67} epidemiological studies, animal research and clinical perspicacity. Clues as to certain chemicals with a high probability of producing developmental disorders can be drawn from structure–activity relationships and from the pattern of toxicological effects observed with adult animals.⁶⁸ Finally, the existence of childhood disorders and dysfunctions, accompanied by the lack of knowledge concerning the etiology of such disorders, highlights the need for additional research in developmental neurotoxicology.

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F. OCCUPATIONAL AND ENVIRONMENTAL FACTORS AND MALE INFERTILITY

Steven M. Schrader, PhD

The origin of toxicology can be traced to early man as he learned which plants were poisonous and which were safe to eat. The empiric observations of the relationship between toxic chemicals (toxics) and reproduction are not well documented. Early observations were based primarily on adverse pregnancies. In the Old Testament (Judges 13:7), the woman who was to bear Samson was warned "Behold, thou shalt conceive and bear a son: and drink no wine or strong drink." This citation indicates that there was some knowledge of the adverse effect of alcohol consumption on pregnancy. In 1736, in a report on the "gin epidemic" that was submitted to the English parliament, this relationship was again noted:

The contagion has spread even to the female sex. Unhappy mothers habituate themselves to these distilled liquors, whose children are born weak and sickly. . . .²⁸

Incredibly, fetal alcohol syndrome was not recognized until the mid-1970s.²⁴ In the 15th century, Catharine Deshayes (also known as La Voisine) was noted as a paid poisoner with skills including abortions and love potions.⁸ However, not until this century have the effects of toxics on pregnancies become an important area of study. This area of research was spurred by the major tragedies resulting from the therapeutic use of thalidomide³² and the environmental exposure to mercury in Minamata Bay, Japan.²⁶ These experiences illustrated that human fetuses were at risk owing to chemical exposures.

There is less information on male reproductive toxicology than on developmental toxicology. In 1775, the English physician Percival Pott reported a high incidence of scrotal cancer in chimney sweeps. This observation led to safety regulations in the form of bathing requirements for these workers.⁵⁰ This repre-

From the Division of Biomedical and Behavioral Science, National Institute for Occupational Safety and Health, Centers for Disease Control, Cincinnati, Ohio

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sents one of the earliest occupational safety interventions involving the male reproductive system. Although male reproductive toxicology had been an area of interest during the intervening 200 years, it was not until the findings by Whorton in 1977, who studied the effects of dibromochloropropane (DBCP) on male workers, that this area of human toxicology was firmly established.⁵⁷ As early as 1961, animal toxicologists reported that DBCP reduced testicular weights in rodents.⁵³ However, their report went essentially unnoticed until workers became infertile and in some cases sterile owing to occupational exposure to this pesticide.

In the 15 years since the DBCP discovery, several other human male reproductive toxicants have been identified. These include lead, other pesticides, and organic solvents. There have been several attempts to develop a list of male reproductive toxicants. The assimilation of such a list is complicated by the quality of reported studies, whether to include animal studies, and whether to include pharmaceuticals. To make a determination of the quality of a study requires an intense evaluation by qualified individuals.

Excluding a potential toxicant from this list owing to a qualitatively poor study may suggest that a chemical has a "clean bill of health." Results from animal studies often complicate matters. These include the extrapolation of species differences, dose, and often the route of exposure. Pharmaceuticals that are designed and produced specifically for their effects on the reproductive system (e.g., androgens, estrogens) are frequently not included on lists of reproductive toxicants. However, there are potential occupational exposures in the manufacturing and dispensing of such drugs.

Some lists of male reproductive toxicants have been created. The Genetox list⁵⁹ evaluated human studies with acceptable statistical designs (as determined by a committee). This list contained 52 chemicals (including drugs) that had clearly established adverse effects on male reproduction. Another source for such a list is the Registry of Toxic Effects of Chemical Substances (RTECS).⁴⁰ Using a computer search program of RTECS called CCINFO,⁵ a list of 1191 chemicals that have effects on the male reproductive system can be generated. However, RTECS includes all substances (including drugs) that have tested positive in either human or animal studies. No attempt was made to determine the quality of the referenced study. New laws similar to California Proposition 65,⁴ which requires the governor of the state to formulate a list of toxic agents,⁴³ will require that lists of reproductive toxicants be established.³⁶

IDENTIFICATION OF TOXICANTS

Each year several hundred new compounds are added to the 70,000 compounds and 4 million mixtures already in commercial use.⁵⁵ The identification of those that are reproductive toxicants is derived from several sources. Manufacturers of chemicals have a responsibility to test "new" chemicals under the Toxic Substances Control Act of 1976. The results of these tests are submitted to the United States Environmental Protection Agency. "Old" chemicals or chemicals for which more information may be needed are tested by manufacturers under Toxic Substances Control Act Section 4, the National Toxicology Program, or the Interagency Testing Committee. Anyone may nominate a chemical for testing by the National Toxicology Program or the Interagency Testing Committee by submitting a letter stating the name of the compound, the tests desired, and the rationale for testing the compound. Additional information on production, use,

exposure, and so forth is useful if it is available. Nominations to the National Toxicology Program should be addressed to Chemical Nominations, National Toxicology Program, Room 2B-55 Building 31, National Institutes of Health, Bethesda, Maryland 20892.²¹ The address of the Interagency Testing Committee is TS-792, 401 M Street, S.W., Washington, DC 20460. The National Institute for Occupational Safety and Health (NIOSH) studies the effects of potential toxicants on the American worker. Employers, employees, or their representatives who suspect toxic effects from a chemical exposure or health hazard in the workplace can request a NIOSH Health Hazard Evaluation to assess the problem by calling 1-800-35-NIOSH. NIOSH also conducts research projects employing potential toxicants identified from information derived from the literature, the National Toxicology Program, and the Environmental Protection Agency. The Food and Drug Administration requires all new drugs that are to be used by women or men of reproductive age to undergo extensive preclinical testing to assess the drug's effects on reproductive processes.³⁸ These federal programs, as well as extensive research by academia and private industry, have and will continue to identify reproductive toxicants.

REPRODUCTIVE PROFILE IN HUMAN TOXICOLOGY STUDIES

It is necessary to establish a male reproductive profile for the assessment of reproductive potential for both individuals and populations. The assessment profile described here is being used by NIOSH to assess populations exposed to potential reproductive toxicants. The same profile could be used in both individual and population studies, but there are some basic differences in methodology. A summary of assessments and specific methodologies follows. Differences between assessing the individual versus the population will be noted. If individual data (versus population comparisons) are to be used, care should be taken to compare the results with the normal range of results of the laboratory conducting the analyses and not previously published values. If a population-based study is being conducted, a concurrent comparable cohort must be used, and the analyses should be blind to exposure status.

Semen analyses provide a useful profile of the function of the male reproductive system. Exact instructions should be provided to each man to ensure that the semen sample is collected by masturbation after a set time of abstinence (usually 2 days). The semen sample should be delivered to the laboratory within 1 hour from the time of ejaculation. The men should be instructed to maintain the semen at room temperature to avoid any temperature shock to the sperm cells. NIOSH has produced a videotape with basic instructions that is shown to all participants in NIOSH semen studies.⁶ At the time of collecting the semen sample, each subject should record the duration of abstinence, time of semen collection, and any information regarding spillage. A label attached to the collection jar facilitates the recording of this information.

Semen analyses can be conducted in two phases. The initial evaluation of the sample should be conducted when the sample arrives at the laboratory or field site. This evaluation consists of recording the temperature, turbidity, color, liquefaction time, volume, osmolality, and pH of the semen. Sperm counts, viability estimates, video recordings for motility assessments, preparation of slides, and preservation of seminal plasma should also be conducted at this time. Morphologic and morphometric analyses of sperm on slides and motility and

velocity analyses of the sperm recorded on videotapes may be conducted at a later time. The motility analyses may be performed manually or using a computer-assisted sperm analysis system (CASA). If CASA is used, several sperm motility variables can be measured (Table 1). These variables provide information on the progression of sperm cells (curvilinear velocity, straight-line velocity, and linearity) and the sperm motility pattern (lateral head amplitude and beat-cross frequency).

Sperm viability may be determined by two methods—eosin Y stain exclusion¹¹ and hypo-osmotic swelling (HOS assay).²⁰ These techniques test for the structural and functional integrity of the cell membrane, respectively.⁴⁵ Sperm concentration and motility characteristics should be measured in a chamber at least 10 μm deep in order for the sperm to move freely in all dimensions.

Measurements of sperm motility and velocity should be conducted using a microscope stage warmed to 37°C. An attempt to record 200 motile sperm per sample is desirable if one is interested in the distribution of velocity measurements,⁴⁴ but 50 motile sperm will suffice if means are to be compared.⁴⁹ If the videotapes are being used to calculate the percent motility, one should avoid "hunting" for motile sperm. All fields examined or searched should be included in the calculations. Therefore, recording a certain number of arbitrary fields is advised. Some researchers have found it useful to record a given number of fields to determine sperm concentration and percent motility, and then additional fields for velocity estimates. If a CASA system is being used for motility and velocity estimates, the number of sperm per field needs to be reduced to minimize cell collisions. Using a chamber that is 10 to 20 μm deep, the sperm concentration should be less than 40 million/mL.⁵⁶ Diluents (including seminal plasma), however, alter sperm velocity up to a dilution of about 1:1.⁷ The current recommendation is to dilute *all* samples one part semen in one part isoosmotic buffer.⁴⁴ If this dilution does not reduce the sperm concentration below 40 million/mL, then an additional dilution in the same buffer should be performed on those concentrated samples.

Sperm morphology should be estimated on air-dried, stained semen smears. During the past 30 years, several schemes have been presented for the assessment of normal and abnormal sperm morphologies. Variation in sperm size and shape is not distinct, but rather a continuum. This provides a challenge within and especially among laboratories to establish a repeatable system for morphologic classification.^{17-19, 34} With recent advances in computerized image analyses, several methods of sperm morphometry have been introduced.^{10, 22, 25, 31, 42, 47, 54} These morphometric analysis systems provide objective assessments of individual sperm head size and shape. Comparisons of measurements between different analysis systems should be avoided. Sperm morphometry is now routinely used as part of the assessment of reproductive hazards to the male worker.⁴⁶

**Table 1. SPERM MOTILITY MEASUREMENTS USING
COMPUTER-ASSISTED SPERM ANALYSIS**

Percent motile
Curvilinear velocity
Straight-line velocity
Linearity
Lateral head amplitude
Beat-cross frequency

IMPACT OF TOXIC EXPOSURE

Toxicants can affect the male reproductive system at one of several sites or at multiple sites. These sites and the assays associated with their respective functions are discussed individually. This does not imply, however, that there exists an absolute one-to-one relationship between a particular measurement and the associated site of action. These sites include the neuroendocrine system, the testes, accessory sex glands, and sexual function.

Neuroendocrine System

The endocrine system, in concert with the nervous system, coordinates function of the various components of the reproductive axis. This system draws upon external (e.g., sexual cues, temperature) and internal (e.g., checks and balances between endocrine tissue function, metabolic status) inputs. The reproductive endocrine status of the man is best established by measuring the hormones in the circulation or in the urine. The hormones of interest are luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, and prolactin.

Urinary testosterone levels may be assessed by measuring the parent compound, a metabolite, or hydrolysis of testosterone metabolites to measure testosterone. When measuring steroid hormone metabolites in urine, consideration must be given to the possibility that the exposure being studied may alter the metabolism of excreted metabolites. This is especially pertinent because most steroid metabolism occurs in the liver, which is a target of many toxicants. Lead, for example, was shown to reduce the amount of sulphated steroids that were excreted into the urine.¹

Follicle-stimulating hormone, LH, testosterone, and prolactin can all be evaluated in a population-based study by assessing the hormone levels in a single blood sample from each man. If possible, samples should be collected about the same time of day to avoid circadian variations. In the study of an individual, three blood samples should be collected 20 minutes apart or urinary assessment of testosterone metabolites and gonadotropins (FSH, LH) should be conducted.

Testes

Sperm count, sperm morphology, and sperm head morphometry all provide indices of the integrity of spermatogenesis and spermiogenesis. Thus, the number of sperm in the ejaculate is directly correlated with the number of germ cells per gram of testis,⁶¹ whereas abnormal morphology is probably a result of abnormal spermiogenesis. Azoospermia is probably the most severe observation because it is often an indication that type A spermatogonia have been lost and recovery is unlikely. New methods that assess DNA stability and DNA adducts promise to provide information about spermatogenesis at the genetic level.

Some toxicants have been shown to exhibit an effect at the testis site, including spermatogenesis and spermiogenesis. Exposure to DBCP reduced sperm concentration in ejaculates to 46 million cells/mL in exposed workers compared to a median of 79 million cells/mL in unexposed men.⁵⁸ Upon removing the workers from the exposure, men with reduced sperm counts experienced a partial recovery, whereas those who had been azoospermic remained sterile.

Testicular biopsy revealed that the target of the DBCP was the spermatogonia. This substantiates that the severity of the effect is most pronounced when stem cells are the target of toxicants. There were no indications that DBCP exposure of men was associated with adverse pregnancy outcome.³⁷ Another example of a toxicant that targeted the testis is ethylene dibromide. Workers exposed to ethylene dibromide had more sperm with tapered heads and fewer sperm per ejaculate than did controls.³⁹

Genetic damage is difficult to detect in human sperm because most methods require induced replication, which cannot occur in haploid cells. Genetically damaged sperm may alter fertilization and lead to developmental anomalies or spontaneous abortions. Epidemiologic studies of large populations have demonstrated increased frequency of spontaneous abortions in women whose husbands were working as motor vehicle mechanics³³ or had exposure to lead.²⁹ Such studies indicate a need for methods to detect genetic damage in human sperm. A growing research emphasis on germ cell genetics is beginning to unfold.

Accessory Sex Glands

Seminal plasma is not essential for fertilization. This is demonstrated by the fact that artificial insemination with sperm collected from the epididymis results in conception. On the other hand, seminal plasma contributes importantly to the normal coitus-fertilization scenario. Seminal plasma serves as a vehicle for sperm transport, a buffer from the hostile acidic vaginal environment, and an initial energy source for the sperm. Cervical mucus prevents passage of seminal plasma into the uterus. Some constituents of seminal plasma, however, are carried into the uterus to the site of fertilization by adhering to the sperm membrane.

The viability and motility of spermatozoa in seminal plasma are typically a reflection of seminal plasma quality. Alterations in sperm viability, as measured by stain exclusion or by hypo-osmotic swelling, or alterations in sperm motility parameters would suggest an effect on the accessory sex glands producing seminal plasma.

Biochemical analysis of seminal plasma provides insights into the function of the accessory sex glands. Chemicals that are secreted primarily by each of the glands of this system are typically selected to serve as a marker for each respective gland. For example, the epididymis is represented by glycerylphosphorylcholine, the seminal vesicles by fructose, and the prostate gland by zinc. Note that this type of analysis provides only gross information on glandular function and little or no information on the other secretory constituents. Measuring semen pH and osmolality provides additional general information on the nature of seminal plasma.

Seminal plasma may be analyzed for the presence of a toxicant or its metabolite. Heavy metals have been detected in seminal plasma using atomic absorption spectrophotometry,⁵¹ whereas halogenated hydrocarbons have been measured in seminal fluid by gas chromatography after extraction⁵¹ or protein-limiting filtration.⁶⁰

A toxicant or its metabolite may act directly on accessory sex glands to alter the quality or quantity of their secretions. Alternatively, the toxicant may enter the seminal plasma³⁰ and thereby affect the sperm, be carried to the site of fertilization on the sperm membrane and affect the ova or conceptus, or be absorbed into the body of the female partner after intercourse.

There are few reports of toxicant effects on the accessory sex glands in humans. Ethylene dibromide is one example of a toxicant that exerts post-testicular effects. Short-term exposure to the toxicant reduced sperm velocity and semen volume.⁴⁸ Chronic exposure decreased sperm motility and viability, decreased seminal fructose levels, and increased semen pH.³⁹ An ethylene dibromide metabolite was present within the semen of some exposed workers.⁶⁰ Other potential toxicants that have been detected in semen include lead, cadmium, hexachlorobenzene, hexachlorocyclohexane, dieldrin, and polychlorinated biphenyls.⁵¹

Sexual Function

Human sexual function refers to the integrated activities of the testes and secondary sex glands, the endocrine control systems, and the central nervous system-based behavioral and psychologic components of reproduction (libido). Erection, ejaculation, and orgasm are three distinct, independent, physiologic, and psychodynamic events that normally occur concurrently in men. If details on function or mechanisms are desired, several reviews and in-depth reports are available.^{9, 27, 52}

Assessment of anomalies of sexual function induced by occupational exposure is difficult. The researcher usually must rely on the testimony and memory of the worker regarding his sexual function. This testimony may often be confounded by the bias of the individual to guard his ego or masculine image or to attribute a preexisting libido problem to exposures at work.

Burris et al³ recently reported application of a monitor for assessing erection at home. If these results are substantiated, this may provide a convenient, nonclinical means by which to evaluate erectile function of exposed workers.

The assessment of ejaculate volume may provide information on the integrity of the emission phase of ejaculation. This is, of course, complicated by effects on the secretory capacity of the accessory sex glands. Thus, a semen sample of reduced volume but with a normal ratio of constituents (marker endogenous biochemicals) supports a diagnosis of an emission-phase defect.

PROMISING NEW METHODS

Several methods are being evaluated for the assessment of the effects of toxicants on the male reproductive system. The sperm penetration assay, also known as the zona-free hamster egg penetration assay, provides information on sperm function. To perform this assay, human sperm are capacitated and then incubated with hamster eggs with the zona pellucida removed. The frequency of sperm penetration is then calculated. This procedure has become quite routine in several laboratories. With the development of an overnight capacitation system, samples can be sent to an analysis laboratory by overnight delivery.⁴¹ Incubating the sperm/egg complex until the formation of the male pronucleus may be useful in sperm chromosome karyotyping.³⁵

The DNA stability assay may provide information regarding genetic damage to sperm. In this assay, the sperm DNA is stressed thermally or chemically and then stained with acridine orange. Double-stranded DNA is stained green, whereas single-stranded DNA is stained red (note that very little, if any, RNA is present in mature sperm).¹⁴ This analysis is performed with a flow cytometer.

Animals exposed to known mutagens demonstrate increased amounts of single-stranded DNA,^{12, 13, 15} indicating an increase in genetic damage. The fertility rate of bulls is positively correlated with the percentage of double-stranded DNA.² A recent report indicates that the DNA stability assay is highly repeatable between ejaculates from the same man.¹⁶ This procedure has been developed in only a few laboratories at this time; however, the sperm can be frozen on dry ice and shipped to the analysis laboratory without affecting the results.¹⁶

Methods to evaluate DNA adducts and DNA probes are on the horizon and may be useful in the future. DNA adducts, the complex formed between a toxicant or its metabolites and the sperm nucleotides, may be carried in the sperm chromatin to the site of fertilization. New methods for labeling nucleotides may permit the detection of these adducts in ejaculated sperm. DNA probes are monoclonal antibodies to distinct modifications of the DNA molecule.²⁰ These antibodies serve as specific probes that may allow for the detection of subtle changes in the DNA code.

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Address reprint requests to

Steven M. Schrader, PhD
National Institute for Occupational Safety and Health
4676 Columbia Parkway
Cincinnati, OH 45226

G. PRIORITY HEALTH CONDITIONS

An Integrated Strategy To Evaluate the Relationship Between
Illness and Exposure to Hazardous Substances

Edited by
Jeffrey A. Lybarger, M.D., M.S.
Robert F. Spengler, Sc.D.
Christopher T. DeRosa, Ph.D.

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Chapter 2. Birth Defects and Reproductive Disorders

Heraline E. Hicks, Ph.D.
Gina Terracciano, D.O., M.P.H.
Brent Hamar, D.D.S, M.P.H.

A growing body of scientific evidence has implicated environmental and occupational chemical exposures in the etiology of human adverse reproductive outcomes. These chemical exposures can affect human reproductive function in many ways. The male and female reproductive systems are major organ systems which are known to be sensitive to a large variety of physical and chemical agents, including drugs, radiation, pesticides, and industrial chemicals. The wide range of adverse reproductive outcomes includes reduced fertility, spontaneous abortion, low birth weight, birth defects, and developmental disabilities.

The relationship between hazardous substance exposure and reproductive disorders is complex because exposure of either or both parents may influence the reproductive outcome in their children. For instance, parental exposure(s) might have occurred some time in the past, immediately prior to conception, or during gestation (the period of development from fertilization to birth). Parental exposure to environmental agents can also adversely affect the developing fetus. Among pregnancies of less than 20 weeks duration, 15 percent are affected by spontaneous abortions (1). An estimated 3 percent of newborn infants have some kind of major developmental defect detected at the time of birth. Additionally, approximately 7 percent of newborns are born prematurely (before the 37th week) and 7 percent of infants born at full term have low birth weights (2,500 grams or less). During early childhood, other birth defects can become apparent and the frequency of major and minor malformations increases to about 16 percent of live births (2).

Relatively little is known about the thousands of chemicals used in our society which might cause birth defects. Presently, only 7 to 11 percent of birth defects can be associated with a known agent (such as radiation, drugs, chemicals, infection, or maternal metabolic imbalance). No cause can be identified for 55 to 70 percent of birth defects observed in children today (3).

This chapter focuses mainly on the principal ways in which exposure to environmental toxicants have been shown to affect reproductive functions and human development. The discussion will include the anatomy and physiology of the male and female reproductive systems, pathophysiology, biomarkers, environmental toxicants, data needs, and future research areas.

Anatomy and Physiology

Reproductive Systems

The organs of the male and female reproductive systems are adapted to produce and unite gametes, or sex cells, which contain specific genes. The functions of the male reproductive system are to produce the male gametes, spermatozoa (sperm), and to transfer them to the female through the process of coitus (sexual intercourse), or copulation. The female not only produces her own gametes, called ova, and receives the sperm from the male, but her reproductive organs are specialized to provide a site for fertilization, implantation of the blastocyst, pregnancy, and delivery of a baby.

In males, the primary sex organs are called gonads, specifically the testes. Gonads produce sperm, and produce and secrete the male sex hormones. Spermatogenesis occurs within the seminiferous tubules of the testes, produced from interstitial cells (Leydig cells). The sperm passes into the epididymis, where it matures for 2 to 4 weeks and is stored in the vas deferens before entering the urethra just prior to ejaculation. A normal male usually produces several million sperm per day; sperm are continually produced throughout a male's reproductive life.

Hormonal regulation in males involves the hypothalamus, which secretes a releasing hormone that stimulates the anterior pituitary to produce gonadotrophic hormone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH). FSH promotes spermatogenesis and LH promotes the production of testosterone (the male sex hormone) in Leydig cells. Testosterone stimulates growth of the male genitals during puberty and is necessary for maturation of sperm and development of the secondary sex characteristics (4).

The female reproductive system consists of ovaries and the secondary sex organs, including the vagina, uterine (fallopian) tubes, uterus, and mammary glands. The ovary produces the ova and the female sex hormones

estrogen and progesterone. The uterine tubes transport the ovum to the uterus after ovulation, and are the normal site of fertilization with sperm. The uterus is where implantation and development of the embryo occurs. Mammary glands are also considered secondary sex organs because, after delivery, breast milk provides nourishment to the baby.

Hormonal regulation in females is quite complex, involving several glands and the hormones they secrete. The hypothalamus secretes gonadotropic-releasing hormone (Gn-RH), the anterior pituitary secretes FSH and LH, and the ovaries secrete estrogen and progesterone from the onset of puberty until menopause. Estrogens are responsible for the development of female sexual characteristics, including breast development, growth of pubic hair, and widening of the pelvis. Progesterone acts on the lining of the uterus and prepares it for implantation of the fertilized egg. The gonadotrophic and sex hormones are not present in constant amounts in the female; instead, they are secreted at different rates during a monthly ovarian cycle which lasts an average of 28 days. Gn-RH released from the hypothalamus stimulates the anterior pituitary to secrete FSH and LH at different times. FSH, which peaks at day 10 of the cycle, stimulates follicular maturation. At day 14 of the cycle, ovulation occurs due to increased levels of LH and estrogen. FSH stimulates secretion of estrogen which, in turn, inhibits FSH/Gn-RH. At the end of the ovarian cycle, LH promotes the development of the corpus luteum, which secretes progesterone. Increased levels of progesterone inhibit LH secretion. When the level of progesterone falls, new synthesis of FSH/Gn-RH occurs and the cycle begins again (5).

Damage to germ cells may arise from adverse effects on the male and female reproductive system. A female is born with about one million eggs, and no new ones are formed after birth. Abnormalities in the eggs can occur as the eggs are being formed, but the errors associated with DNA replication will not occur in the adult female. Mutations affecting sperm appear to be more likely to result from adult exposures to hazardous substances or agents than mutations affecting ova.

Human Development

There are three developmental phases leading from a fertilized egg to a live birth.

- Ovum** This period extends from the time of fertilization of the ovum in the fallopian tubes to the time of implantation, usually 8 to 10 days.
- Embryo** During the period from day 14 through days 55 to 60, the embryo begins to assume a human appearance. Beginning with the central nervous system (CNS) and the heart, all organ systems undergo development during this phase.
- Fetus** The fetal period is usually defined as the third through ninth months of pregnancy. This period is largely a time of maturation and growth of structures that have already been formed.

Pathophysiology

Developmental Deformations

Deformations are common problems affecting approximately 2 percent of newborn infants. Most deformations are caused by generalized compression of the growing fetus by abnormal biomechanical forces, leading eventually to a variety of structural abnormalities. The most common example of fetal compression is known as uterine constraint. Between the 35th and 38th weeks of gestation, rapid increase in the size of the fetus outpaces the growth of the uterus, and the relative amount of amniotic fluid (which acts as a cushion) also decreases. This deficiency of amniotic fluid may result in distortion of the fetal form. Although a normal fetus is subjected to uterine constraint, several factors may increase the likelihood of excessive compression of the fetus. These factors include maternal conditions such as first pregnancy, small uterus, malformed (bicornuate) uterus, and leiomyomas. Factors relating to the fetus, such as multiple fetuses, oligohydramnios, and abnormal fetal presentation, may also be involved (6).

Inherited Abnormalities

Abnormalities can be either inherited or acquired. Inherited abnormalities are a result of the action of the genes transmitted through the egg or sperm. Anomalies of this type tend to recur generation after generation in a more or less definite pattern, following the laws of heredity. New characteristics may make their appearance as a result of mutations (spontaneous changes

in genes) or changes in chromosome numbers. Such changes have been produced experimentally in animals and plants by exposing the germ cells to X rays or radioactive substances.

Malformations that are known to be genetic can be divided into two groups: those associated with chromosomal aberrations and those arising in single-gene mutations. Virtually all of the chromosomal syndromes are characterized by congenital anomalies. Chromosomal abnormalities are present in approximately 4 to 5 percent of live-born infants with congenital malformations. Only one chromosomal abnormality—trisomy 21 (Down's syndrome)—reaches the birth frequency of 1 in 1,000 total births. Other examples of chromosomal abnormalities are Klinefelter's syndrome and Turner's syndrome. Transmissible chromosomal abnormalities like the translocation form of Down's syndrome can be passed from one generation to the next, thus constituting a familial pattern of structural abnormalities (7).

Single-gene mutations which underlie major malformations follow Mendelian patterns of inheritance. On the whole, these anomalies are uncommon and do not have a birth frequency as high as 1 in 1,000 births. Among these rare entities are limb malformations: polydactyly (supernumerary digits), syndactyly (webbed digits), and brachydactyly (short digits). In addition, there are a number of malformation syndromes in which multiple anomalies occur, resulting in various disorders such as Marfan's syndrome, osteogenesis imperfecta, photophobia, color blindness, and hemophilia (8).

Acquired Abnormalities

Acquired abnormalities are due to some environmental factor or influence which acts on the developing embryo or fetus. The developing embryo undergoes a process of rapid development and change in a relatively short period of time. Depending on the stage of development, toxic injury can have different results. In the process of fetal development, each organ or tissue passes through a critical period, at which time the growth rate is accelerated and differentiation processes are brought into play. During this sensitive period, exposure to harmful substances can alter normal formation of organs and tissues and render the developing embryo or fetus unable to survive. The result is resorption, spontaneous abortion, or stillbirth. These kinds of substances are known as being embryotoxic—incompatible with

survival of the conceptus (the developing infant, which includes all stages of development). Chemical substances can also be teratogenic in that they may cause irreversible structural or functional anomalies observed in newborns or later in life (9).

If a chemical injury occurs before implantation of the embryo, lethality rather than teratogenicity appears to be the most probable outcome. After implantation has been accomplished, organogenesis (the development and growth of organ systems) starts to take place. Teratogenic changes are the most likely outcome of adverse chemical exposures at this time. The type of defect seen in the newborn or infant will depend on the stage of organogenesis the embryo is in when the chemical injury occurs. Most human teratogens have been shown to alter several organ systems. Critical times of development for different tissues and organs range from one day to the entire period of organogenesis (7).

Chemical exposure during fetal development is more likely to be toxicologic in nature rather than teratogenic. Chemical insult during this period of development can lead to a broad range of effects, including growth retardation, stillbirth, premature birth, low birth weight, and toxic syndromes or withdrawal symptoms in the neonate (infant during the first 4 weeks after birth). The perinatal period of life (period shortly before and after birth) is a time when there is an increased susceptibility to carcinogenesis. Factors responsible for this susceptibility include the incomplete development of the immune system and the high rate of cell replication that is occurring at the time. In addition, the xenobiotic transforming enzymes (enzymes that metabolize foreign chemical substances) of the infant are functioning at reduced capacities. Normal enzyme activity levels are not reached until a year or more after birth (10).

In general, most abnormalities have their origin during the embryonic period (second through eighth week). Some of the environmental factors which may modify embryonic development are radiation, chemical substances, and disease and disease-producing organisms.

Radiation

Tissues in which cells are multiplying rapidly are particularly susceptible to the effects of radioactive substances. Such tissues include the spermatogenic cells of the testes and the hemopoietic cells of the bone

marrow (8). In a developing embryo or fetus, sublethal doses of X rays, radium, and atomic radiations have been shown to be mutagenic. Radiation, in addition to being mutagenic and carcinogenic, is teratogenic. Exposure to heavy doses of radiation during the period of organogenesis leads to malformations such as microcephaly (abnormal smallness of the head), blindness, skull defects, and spina bifida. Children born to women who received x-ray treatment during pregnancy are more likely to have birth defects, developmental anomalies, or cancer (11).

Chemical Substances

Nutrients and chemical substances in the mother's blood can cross the placenta to the fetus. These include vitamins and other nutrients, alcohol, illicit drugs, and medications, as well as potentially poisonous industrial and agricultural chemicals. A lack of essential nutrients can be responsible for damage to the developing embryo or fetus. The presence of environmental toxicants can result in too much or too little of an essential substance entering the mother's blood or can interfere with the proper use (metabolism) of nutrients by the developing embryo or fetus. Moreover, toxicants can mimic or block the effects of nutrients after the embryo or fetus has absorbed proper amounts. Additionally, toxicants also have the potential of directly injuring tissues, leading to damage in the most affected organ systems. The list of chemicals and drugs definitely known to cause malformations includes thalidomide, folate antagonists, androgenic hormones, alcohol, anticonvulsants, warfarin (oral anticoagulant), and 13-cis-retinoic acid (used in the treatment of acne) (7).

Disease and Disease-Producing Organisms

Viruses and bacteria to which the mother might have been exposed during pregnancy can induce malformations in the fetus and infant. Many viruses have been implicated, including the agents responsible for rubella (German measles), cytomegalic inclusion disease, herpes simplex, varicella-zoster infection, influenza, mumps, enterovirus infections, and human immunodeficiency virus. With all viruses, the gestational age at which the infection occurs in the mother is critically important. For example, the at-risk period for rubella infection extends from shortly before conception to the 16th week of gestation, the hazard being greater in the first 8 weeks than in the second 8 weeks. The incidence of malformations is reduced significantly if rubella infection occurs in the second or third month of gestation. The

syphilis bacterium may cross the placenta and also infect the embryo, resulting in a newborn with blindness and/or numerous anatomical malformations. The number of stillbirths among syphilitic mothers is much higher than among nonsyphilitic mothers (7).

Reproductive Disorders

In the male reproductive system, a substance can act on one or more stages of spermiogenesis, resulting in the failure of sperm to reach maturity. For example, the various processes (stages) of spermiogenesis occur in the presence of specific hormones. Substances can act on interstitial (Leydig) cells, producing alterations in the secretion of these hormones. Additionally, substances can cause adverse effects to accessory organs of reproduction, inhibiting formation of their products. Sterility can result from physical agents, such as temperature and radiation. In the testes, the different cell populations in various stages of spermatogenesis are sensitive to radiation. The male reproductive system is also vulnerable to sexually transmitted infections. Specific infections—including syphilis, gonorrhea, and genital herpes—can affect various organs such as the urethra, prostate, seminal vesicles, and epididymis. Inflammation can lead to abscesses in the epididymis, resulting in extensive damage of the organ. Diseases such as mumps and tuberculosis can lead to sterility in males (7).

Disruption of female reproductive functions can result from hormonal disturbances that lead to reduced fertility. For example, women can be troubled by symptoms arising from the normal activity of the reproductive organs, including menstrual disorders (such as an anovulatory cycle or inadequate luteal phase) and problems associated with childbirth. In females, sterility can also result from exposure to radiation, principally because of the destruction of the ovarian follicles. Cessation of menses and menopausal changes can be temporary or permanent depending on the radiation dosage (7).

Spontaneous Abortions

At least 600,000 spontaneous abortions occur each year before the 20th week of pregnancy (12). Studies have indicated that this number represents 20 to 25 percent of all conceptions (13). Spontaneous abortions are most likely to occur early in the pregnancy, especially within the first

12 weeks. After the 20th week, fetal loss due to spontaneous abortion is uncommon. Changes in the normal chromosomal number of 46 (23 pairs) and structural chromosomal abnormalities have been detected in approximately 60 percent of recognized spontaneous abortions (14,15). Structural malformation is another major cause of fetal death (13). Uterine infections involving the inflammation of placental tissue also account for spontaneously aborted fetuses that appear normal. The role that exposures to hazardous chemicals in the environment have in spontaneous abortions is not well understood, and represents another area where more knowledge and research are needed.

Adverse health problems associated with altered reproductive systems and abnormal embryo or fetal development are often not recognized until final reproductive outcomes (such as spontaneous abortions or birth defects) occur. Various biological aspects of the male and female reproductive process, as well as embryonic and fetal development, are internal in nature. Thus, abnormal function or development is often not apparent. Laboratory biological tests (biomarkers) have the potential of detecting adverse reproductive function and development earlier on, and can help prevent or mitigate adverse health outcomes.

Biomarkers

There is a great deal yet to be learned about the frequency of birth defects and reproductive disorders caused by exposures to toxic chemicals, and the mechanisms by which toxicants can cause effects. From an environmental health science perspective, biomarkers can be used to help identify: (1) reproductive and developmental susceptibility to the toxic effects of environmental pollutants; (2) exposure to toxicants; and (3) reproductive and developmental effects resulting from exposure(s) to chemicals in the environment (16). Biomarkers are tools that, hopefully, will serve to increase the knowledge base on reproductive disorders and help to identify their specific causes. Studies using biomarkers might identify preventive measures that could be instituted to stop or mitigate birth defects and reproductive disorders attributed to toxic chemical exposures.

Biomarker tests are available which can analyze body fluids for chemical substances that might be responsible for birth defects and adverse effects on the male and/or female reproductive systems. These tests,

indicating chemical exposures, are able to directly measure the specific chemical substances or their metabolites (chemical compounds produced as a result of chemical reactions inside the human body). Blood, urine, hair, feces, and semen are examples of human biological specimens that are relatively easy to obtain for these types of tests. Follicular fluid, obtained from women by use of an invasive laparoscopic procedure, has also been used in these types of tests (17,18).

At present, few of these reproductive and developmental biomarkers have been used in environmental health research. Biomarkers are being used routinely in clinical medicine to help diagnose reproductive diseases in adults, as well as certain problems in the developing fetus. Fetuses at risk of neural tube defects can be detected by using a clinical biomarker test for alpha-fetoprotein (AFP), a substance produced in the yolk sac and fetal liver. AFP is found normally in both the amniotic fluid and the maternal serum. An increase in the concentration of AFP signifies a greater probability of a developing fetus with a neural tube defect (19,20). AFP levels also help in identifying Down syndrome offspring (21,22). Another biomarker test useful in diagnosing developmental fetal problems is the assay measuring the lead concentration in pregnant women's serum. Elevated lead concentrations have also been associated with neurologic changes in the developing fetus (23-25).

A host of other clinical biomarker tests are in use today to help diagnose both pregnancy problems and problems associated with the conceptus. Special diagnostic tests can be used to aid in the diagnosis of women who are unable to become pregnant. Routine tests for female infertility include the postcoital test, tubal patency test, thyroid function test, and culdoscopy (26). For disorders of the menstrual cycle or for monitoring ovulation, measurements of serum estrogen and progesterone concentrations can be used. Serum- β -human chorionic gonadotropin (β -hCG) is another clinical biomarker of effect used in diagnosing spontaneous abortions. Following a spontaneous abortion, the level of β -hCG becomes nondetectable within 9 to 35 days. Other biomarkers associated with pregnancy include sonography and Doppler monitoring. Ultrasound technology allows the monitoring of fetal growth, location, size, and movement throughout the pregnancy. With Doppler monitoring, uterine blood flow velocity, umbilical blood flow velocity, and fetal cardiac function can be monitored.

Fetal blood and tissue specimens can now be obtained and tested for the presence of xenobiotic substances (chemicals foreign to the human biologic system). Amniocentesis can be used to detect fetal diseases of teratologic, genetic, endocrine, maturational, and infectious origins. With this technique, amniotic fluid is obtained by aspiration after a needle is inserted through the mother's abdominal wall and uterus. The combined use of ultrasound, amniocentesis, and AFP analysis can detect more than 700 fetal disorders prenatally (27). Chorionic villus sampling is another invasive technique in which cells taken from the placenta can be analyzed to determine the genetic makeup of the developing fetus (28). Additionally, other various biomarkers of effect and susceptibility can be used to help account for any adverse fetal effects which might have resulted due to exposures to hazardous chemicals. These techniques aid in diagnosing conditions before birth occurs (29).

Two major classes of concerns are associated with the male reproductive system and its response to toxic insult: pathophysiologic changes that might be associated with a change in fertility status and inheritable genetic damage that might lead to defects in offspring. Pathophysiologic changes include a reduction in sperm concentration, a decrease in sperm motility, and an increase in sperm with abnormal forms. Biomarkers used in assessing the pathophysiologic reproductive status of males include potency, fertility, serum concentration of gonadal steroids and pituitary hormones, and semen characteristics. Biomarkers used in characterizing semen include sperm count, volume, sperm motility, sperm morphology, and prostatic secretions analysis. Specialized sex chromatin biomarker tests can be used to help reveal chromosomal damage, sentinel phenotypes (such as achondroplasia) seen in offspring, and structural changes in macromolecules (such as proteins and nucleic acids), which can drastically alter normal function. Invasive testicular biopsies can also be used to help diagnose problems associated with the male reproductive system (26).

The use of biomarkers in detecting adverse reproductive and developmental defects is progressing, and many biomarkers are now in the developmental stage. Biomarkers developed for reproductive and birth defects research will take on an increasingly important role in future health studies of individuals living near hazardous waste sites. These tests will play an instrumental part in determining whether specific populations have actually been exposed to or affected by hazardous substances.

Environmental Toxicants

An estimated 50,000 to 60,000 chemicals are in common use throughout society today. Hundreds of new chemicals (and drugs) are introduced each year (30). From scientific research, a growing list of chemicals known to be animal teratogens is being compiled. *Thomas Sheppard's Catalog of Teratogenic Agents* lists over 900 agents responsible for congenital anomalies in laboratory animals, with only 30 of these known to cause physical or structural malformations in humans (31). Moreover, the list of environmental chemicals known to have adverse health effects on male or female reproductive systems is limited. Future research should identify other chemical agents that have a strong potential for adversely affecting human reproductive systems and developing embryos and fetuses.

Few studies have focused on adverse health effects attributed to hazardous chemical substances in the environment to which the public may be exposed. These studies have serious limitations because few have measured human exposure or controlled for important confounding factors, and many exposures have involved mixtures of chemicals. Many of the case reports have focused on human exposures to high doses. In addition, experimental animal studies involved only high doses, which makes it difficult to interpret what the low-dose effects might be.

Following is a review of available scientific literature on adverse reproductive and developmental human health effects that have been associated with metals and nontherapeutic chemical substances (Table 2-1). It should be noted that not all hazardous chemicals/substances are included in this review. A selection of chemicals is presented in which epidemiologic studies, occupational exposure data, or animal data indicate an association between exposure and adverse human reproductive or developmental effects.

Metals

Arsenic and Cadmium

Occupational exposures to arsenic and cadmium have been associated with adverse reproductive outcomes. Several epidemiologic studies indicate inorganic arsenic can cause developmental effects in humans. Studies of smelter workers in Sweden (32-36) provided limited evidence of decreased

Table 2-1. Environmental toxicants and adverse reproductive outcomes.

Exposure	Associated Outcome
Aldrin	Spontaneous abortion, premature labor
Arsenic	Spontaneous abortion, decreased birth weight, congenital defects, developmental defects
Benzene	Spontaneous abortion, low birth weight, menstrual disorders, ovarian atrophy
Cadmium	Low birth weight
Carbon disulfide	Menstrual disorders, spontaneous abortion, adverse effects on sperm
Chlorinated compounds (TCE, PCE, Chloroform)	Eye, ear, and oral cleft anomalies, CNS disorders, perinatal deaths, childhood leukemia
1,2-dibromo-3-chloropropane	Adverse effects on sperm, sterility
Dichloroethylene	Congenital heart disease
Dieldrin	Premature labor, spontaneous abortion
Hexachlorocyclohexane	Hormonal imbalances, premature labor, spontaneous abortion
Lead	Stillbirth, preterm delivery, low birth weight, spontaneous abortion, neurobehavioral deficits, mental retardation, adverse effects on sperm and testes
Mercury	Menstrual disturbances, spontaneous abortion, blindness, deafness, mental retardation, delayed development, brain damage
Polycyclic aromatic hydrocarbons	Decreased fertility
Polychlorinated biphenyls	Preterm delivery, low birth weight, reduced head circumference, growth deficiencies, neurobehavioral effects
Trichloroethylene	Congenital heart disease

birth weight and congenital defects in children and increased abortion rates in women working in the smelter plants or living nearby. Women who were occupationally exposed to high levels of cadmium by inhalation while pregnant had children with lower birth weights than children of women who were not exposed (37). In contrast to this reported outcome, a nonsignificant decrease in birth weight was found in the children of women with some occupational exposure to cadmium in France (38).

Lead

Lead is probably one of the most studied chemical substances known to adversely affect both reproduction and development in humans. A large body of scientific literature clearly indicates that high levels of lead can cause adverse effects on human reproductive functions, particularly miscarriages and stillbirths when women are exposed during pregnancy. The mechanisms responsible for these effects are unknown, but several factors could contribute to these outcomes, from the indirect effects lead can have on maternal nutrition or hormonal status before and during pregnancy to the more direct effects involving the fertility status of males. Several studies on adverse reproductive and developmental effects in humans after exposure to lead are briefly discussed.

A cross-sectional study of 236 mothers and their infants in Glasgow, Scotland, reported reductions in gestational age with increasing fetal cord blood or maternal blood lead levels (39). A study of 831 pregnant women in a lead smelter town of Port Pirie, South Australia, found significantly higher blood lead levels during pregnancy and at delivery (11.2 micrograms per deciliter ($\mu\text{g/dL}$)) than in women who lived in adjacent towns or rural areas (7.5 $\mu\text{g/dL}$) (40). The relative risk of preterm delivery (before 37 weeks of pregnancy) increased more than fourfold at blood lead levels of $>14 \mu\text{g/dL}$ in comparison with blood lead levels of $8 \mu\text{g/dL}$. The incidence of low birth weight (less than 2,500 grams at 37 weeks of pregnancy) and miscarriages were greater in Port Pirie than in the surrounding areas.

Prenatal exposure to lead has been shown to interfere with the mental development of children. Neurobehavioral testing of 592 children at 24 months of age from the Port Pirie study identified reduced scores on the Bayley Mental Development Index test that were significantly associated with high postnatal blood lead levels (41-43). A followup of these children at 4 years of age still indicated neurobehavioral deficits (44). Another study

of 185 inner city children born in Cincinnati, Ohio, also demonstrated a correlation between prenatal or fetal cord blood lead levels and performance on the Bayley Mental Development Index test (45,46). A case-control study of retarded children involving drinking water contaminated with lead showed mental retardation significantly associated with increased lead content in drinking water and in blood (47). A number of studies have associated intelligence quotient (IQ) deficiencies to children with blood lead levels as low as 25 µg/dL (48,49).

The large body of knowledge regarding the known association of lead exposure with a high likelihood of spontaneous abortion has led to the exclusion of women from high-exposure occupations (50). Additionally, because of the susceptibility of infants and young children to adverse health effects from exposure to lead (either maternally or directly), the Centers for Disease Control and Prevention has recently lowered the blood lead levels of concern from 25 to 10 µg/dL (51).

Lead-induced effects on male reproductive functions have been reported in humans. Research has indicated that adverse effects on testes or sperm may result from chronic lead exposures of men at blood lead levels of 40 to 50 µg/dL (52,53). Other studies of male lead workers with higher blood lead levels (66 µg/dL) indicate that lead acts directly on the testes to cause a reduced sperm count and peritubular testicular fibrosis, and also produces reduced testosterone synthesis (54-56).

Mercury

Studies in women chronically exposed to metallic mercury vapor showed increased frequencies of menstrual disturbances and spontaneous abortions (57). In another study involving 349 women exposed to metallic mercury vapors and 215 nonexposed women, the rates of pregnancy and labor complications were higher among women exposed to mercury and depended on "the length of employment and concentration of mercury vapors" (58).

The developing fetus is especially sensitive to methylmercury (organic mercury) exposure. In 1955, a mercury poisoning outbreak occurred in Minamata, Japan, where individuals had consumed fish contaminated with methylmercury (59). Infants born to mothers who had consumed organic mercury had varying degrees of severe brain damage, mental retardation,

delayed development, CNS damage, blindness, and deafness (59-61). Other poisoning outbreaks occurred in Iraq in 1956 and 1960 from ingestion of contaminated bread prepared from wheat and other cereals treated with a methylmercury fungicide (62). Fourteen of thirty-one pregnant women died from ingesting the contaminated bread. Infants born with blood mercury concentrations of 250 µg/dL suffered severe brain damage. A similar outbreak occurred in Iraq from 1971 to 1972, and neurological damage was reported in infants exposed prenatally (63). Follow-up studies of the children who were exposed to a wide range of methylmercury levels indicated that milder effects (such as delayed development, subtle neurologic abnormalities, and psychomotor retardation) can occur at low-level exposures (64,65).

Industrial Chemicals

Carbon Disulfide

Among women occupationally exposed to carbon disulfide, an increased incidence of spontaneous abortion was reported at levels of exposure as low as 2 parts per million (ppm) (66,67). However, other epidemiologic studies have not corroborated these reports. Another study reported that, although women exposed to 0.5 to 4.7 ppm had significantly more menstrual disorders than nonexposed women, there were no increases in the rates of spontaneous abortion, stillbirth, premature delivery, or congenital malformation (68). In a community study of spontaneous abortion, occupation, and air pollution, investigators found no relationship between carbon disulfide concentrations and miscarriage rates (69). Abnormal sperm, decreased sperm motility, deficient numbers of sperm, and decreased libido have been reported in males occupationally exposed to carbon disulfide (70).

Benzene

Occupational research suggests that women occupationally exposed to benzene might have more spontaneous abortions, menstrual disturbances, and ovarian atrophy (71,72). Study limitations, however, prevent definite conclusions from being drawn. Benzene is known to cross the human placenta and be present in the cord blood in amounts equal to those in maternal blood (73). Conflicting results have been reported by studies conducted in Love Canal, New York, where over 200 chemicals, including

benzene, were found at the dump site. One study suggested a possible increased incidence in low birth weight infants born to exposed women (74). Another study at Love Canal found an increased prevalence of shorter stature children associated with proximity to the dump site (75). However, a previous study found no clear association or increase in the occurrence of spontaneous abortion, birth defects, or low infant birth weight in women living next to the contaminated canal site (76). A Pennsylvania study involving a hazardous waste site contaminated with benzene and other chemicals found no significant increase in birth defects associated with proximity to the site (77). Limitations of studies conducted at these sites where multiple exposures are involved include problems in identifying exposed populations, limited followup, a lack of data on exposure levels, inadequate sample size, and simultaneous exposures to more than one chemical.

Polycyclic Aromatic Hydrocarbons

Polycyclic aromatic hydrocarbons (PAHs) are common chemical compounds found in vehicle exhausts, asphalt roads, coal tar, smoke from fires, and tobacco smoke. PAHs can also be attached to dust and other types of particles in the air; exposure typically involves a mixture of PAHs. Research has shown that enzymes present in the human body can react with a number of PAHs and produce chemical compounds that are capable of inducing tumor formation. Most studies looking at possible reproductive and developmental effects caused by PAHs have been with animals. These studies do suggest, however, that there is an increased probability of adverse reproductive effects occurring as a result of exposure to PAHs (such as benzo[a]pyrene) (78). Human epidemiologic studies have shown a decrease in the ability to conceive children in women who were exposed prenatally to cigarette smoke containing PAHs (that is, their mothers smoked while pregnant) (79,80).

Polychlorinated Biphenyls

Results from studies in the United States on women who consumed contaminated fish with polychlorinated biphenyls (PCBs) suggest that exposure to PCBs causes developmental effects in newborns and infants. The newborn infants of mothers who, at least 6 years prior to and during their pregnancy, consumed fish with high PCB content showed statistically significant decreases in birth weights, decreased gestational age, and

reduced head circumference compared with a control group (81,82). These effects were attributed by the authors to intrauterine exposure to PCBs by way of the mothers' diet of contaminated fish. In a follow-up study of the children at 7 months of age, neurobehavioral effects were observed in depressed responsiveness and poor performance on visual recognition memory tests (83). At 4 years of age these children continued to show deficiencies in weight gain, poorer performance in recognition memory tests, and weaker reflexes in comparison with children not maternally exposed to PCBs (84).

In another study, neurodevelopmental effects were observed in children of mothers who were exposed to PCBs (85). Children from these mothers exhibited neurological deficiencies similar to those observed in other studies, such as hyporeflexia. This study suggested that long-term exposure to low levels of PCBs in the environment can cause adverse human health effects, especially in susceptible populations such as fetuses, nursing infants, and young children.

There have been several studies of accidental exposure to PCBs involving human populations in Taiwan and Japan (86). A mass poisoning occurred in Taiwan in 1979 and in Japan in 1968 from cooking oil contaminated by thermally degraded polychlorinated biphenyls. In 1985, 117 children born to women who ingested contaminated rice oil and 108 unexposed children were examined and evaluated in Taiwan; children born to mothers who consumed contaminated rice oil were shorter and weighed less than children not exposed *in utero*. In follow-up studies of these exposed children, growth deficiencies were evident; they were observed to have autonomic disturbances; exhibited sluggish, clumsy, and jerky movements; and had an average IQ in the low 70s. Japanese infants also exposed maternally to PCBs exhibited similar developmental and neurobehavioral effects (87,88).

Halogenated Hydrocarbons

1,2-dibromo-3-chloropropane

The toxicity of 1,2-dibromo-3-chloropropane (DBCP) to the human male reproductive system has been reported in groups of occupationally exposed workers in several studies (89-98). Changes in sperm counts ranging from oligospermia (deficiency in the number of spermatozoa in the

semen) to azoospermia (absence of spermatozoa in the semen) were found among exposed workers. Two studies have suggested that DBCP-induced sterility can be permanent (90,99). An epidemiologic investigation in Fresno County, California, evaluated reproductive and developmental outcomes in a population exposed to DBCP in their drinking water. The study failed to show a correlation between low birth weights, birth defects, or changes in birth rates associated with DBCP-contaminated drinking water (the range of concentrations of DBCP was 0.004 to 5.7543 parts per billion (ppb)) (100,101).

Chlorinated Compounds

Epidemiologic studies of women occupationally exposed to tetrachloroethylene in the dry-cleaning industry suggest that they might have an increased risk of adverse reproductive effects, primarily menstrual disorders and spontaneous abortions (102). Other chlorinated compounds have been implicated as possibly causing adverse health effects. An association, but no cause and effect relationship, was found between elevated levels of trichloroethylene and dichloroethylene in drinking water in Tucson, Arizona, and congenital heart disease in children whose parents were exposed to this contaminated water (103). Another study in Woburn, Massachusetts, suggested that residents exposed to drinking water contaminated with chemicals (including 267 ppb trichloroethylene, tetrachloroethylene, and chloroform) resulted in childhood leukemia; perinatal deaths; a combination of eye and ear anomalies; and a combination of CNS disorders, chromosomal disorders, and oral cleft anomalies (104). However, several scientists have questioned the biological relevance of the unusual grouping of these anomalies for purposes of statistical analysis (105,106). An excess number of spontaneous abortions were identified in women exposed to drinking water contaminated with trichloroethane in Santa Clara County, California (107). The study suggested an association, but no direct cause and effect relationship was established.

Pesticides/Insecticides

Aldrin and Dieldrin

The available scientific literature on pesticides and insecticides suggests that pregnant women, fetuses, nursing infants, and very young children might be at greater risk of adverse health effects from pesticide and

insecticide exposures than the general population. Aldrin and dieldrin are the common names of two structurally similar insecticides. Aldrin readily changes into dieldrin once it enters either the environment or the human body. There are two studies of aldrin/dieldrin levels in women and in their fetuses following premature labor or spontaneous abortion. In one study, women who had premature labor or spontaneous abortion had significantly higher levels of aldrin/dieldrin than women with normal deliveries (108). The second study revealed detectable levels of dieldrin in the placenta, amniotic fluid, and fetal blood (109). These results suggest that dieldrin can pass through the human placenta and accumulate in the developing fetus. Additional evidence indicates that embryos, fetuses, and newborns up to 3 months of age might be at increased risk of adverse effects following pesticide and/or insecticide exposure due to incomplete development of their enzyme detoxification systems (110).

Hexachlorocyclohexane

Hexachlorocyclohexane (HCH), formerly known as benzene hexachloride, is a synthetic chemical that exists in eight forms (isomers). Gamma-HCH (lindane) has commonly been used as an insecticide on fruit, vegetable, and other crops. Alterations in reproductive hormones and increased blood levels of gamma-HCH and total HCH isomers have been detected in women who experienced spontaneous abortion and premature delivery. Similarly, changes in male hormone levels have been reported in men occupationally exposed to gamma-HCH and total HCH isomers, as well as to other organochlorine pesticides (108,111,112). One group of investigators has suggested that the reproductive effects in women resulted from exposure to organochlorine pesticides (including gamma-HCH), which produce hormonal imbalances that are incompatible with pregnancy (108,113). The biological significance of altered hormonal levels in humans is difficult to assess, although the data do suggest that HCH might potentially affect reproductive capability.

Data Needs

General Deficiencies in Previous Studies

Relatively few studies have addressed the area of adverse reproductive outcomes as a result of environmental contamination. Many environmental epidemiology studies have been limited by inadequate sample size, uncertain

documentation and quantification of exposure levels, lack of an appropriate control group, and concomitant exposures to other potentially hazardous chemicals. The studies looking at reproductive effects have exhibited similar methodological limitations. One of the problems relates to the low prevalence of birth defects and other reproductive outcomes in the general population. Interpretation of studies which focus on low-prevalence disease can be difficult due to the low statistical power associated with small sample sizes (114).

Evidence pertaining to the health risk from hazardous waste sites has largely been obtained from ecologic or descriptive studies. These ecologic studies are often unable to control for important confounding variables. Caution should be used when estimating exposure from geographic location or proximity to a hazardous waste site (115).

There are very few studies which help define the toxicologic effects of environmental contaminants. The mechanism of action of toxicants, the interaction between a toxic agent and an individual, and the interaction between multiple potentially hazardous chemicals are areas of continuing uncertainty. The relationship between the exposure scenario and the probability of occurrence of health effects (dose-response) needs to be defined for many chemicals.

Previous studies have been valuable for hypothesis generation. There is a need to conduct studies which collect and use more individual exposure information; this will enhance the assessments of exposure and reproductive outcomes. Effort needs to be given to the development of additional studies, including case-control, cohort, and ecologic study designs. Examples of research projects are given within five broad areas of applied research to address adverse reproductive outcomes.

Outcomes of Interest

The following health outcomes should be evaluated through the use of varied study designs: early and late spontaneous abortion, fetal death, congenital malformations, functional deficits, prematurity, growth retardation, and infertility (male and female). Each of these health outcomes should be considered for susceptible populations and minority populations.

Assessments of Health Outcomes

Evaluations of the occurrences of adverse health outcomes might be accomplished by using symptom and disease prevalence questionnaires for community-based studies. The utility of monitoring sentinel health events in large populations to estimate background rates for adverse reproductive outcomes needs to be explored (12). Disease counts are continuing in different states through the use of birth defect and adverse reproductive outcome registries. The registry entries could be linked to ZIP codes to help define exposure locations, such as hazardous waste sites and contaminated groundwater plumes. Surveillance studies can use existing vital records and school records for case ascertainment of the outcomes of interest.

Analytic Epidemiology Studies

Additional studies to identify risk factors for adverse reproductive outcomes need to be initiated. Potential reproductive outcomes to be evaluated have been suggested by the results of several cross-sectional, ecologic, case report, and animal toxicity studies. Consideration should be given to the development of case-control and cohort (incidence) protocols to study the following adverse outcomes: facial clefts, major cardiac defects, male infertility, neural tube defects, low birth weight, and limb reduction deformities. Cross-sectional multisite studies or metaanalyses could resolve some of the problems associated with small sample sizes at individual sites.

Biomedical Measures of Exposure and Outcome

Approximately one-fourth of all pregnancies are spontaneously aborted. In order to determine if there is an increased risk of spontaneous abortion secondary to environmental contamination, it will be necessary to develop tests to detect early fetal loss, even at the preimplantation stage. Currently, reliable clinical indicators of reduced fertility do not exist (116). The lack of readily usable, reliable, and validated biomarkers is complicated further by the complex mechanisms and interactions of the male and female reproductive systems.

Alpha-fetoprotein level (maternal serum and amniotic fluid) is a marker for neural tube defects that has been used for individual diagnosis, and has the potential to be used as the first stage of a screening process. A potential

marker for genetic effect is hypoxanthine phosphoribosyl transferase. Other potential markers which require further development are cytogenetic studies, and somatic, DNA, and sperm adducts (12).

Assessments for Improving Diagnosis and Treatment

A limited number of validation studies of biomarkers of exposure, effect, and susceptibility for use in environmental epidemiology have been performed (115). The paucity of validated markers for reproductive outcomes could result in inaccurate determinations of the relationship between reproductive performance and toxicant exposure (117). Studies of the reproductive systems involve male-, female-, and fetus-specific factors; therefore, there is a need for sensitive measures that explain the wide variation in characteristics and expression (115).

Animal Toxicity Studies

Further studies in animals that focus on identifying the threshold for developmental effects following oral and inhalation exposure would be valuable in judging the risk of developmental effects occurring in humans exposed to various toxicants near hazardous waste sites.

Research is needed to aid in determining the types and/or levels of exposure that might present significant risks of adverse health effects in humans exposed to specific substances. Several types of studies are recommended to provide substance-specific data needs. Studies are needed to provide dose-response data for acute-, intermediate-, subchronic-, and chronic-duration oral and inhalation exposures. These studies should include extended reproductive organ histopathology and evaluation of neurobehavioral and neuropathological end points. Studies of two-species developmental toxicity via inhalation are recommended. Comparative toxicokinetic studies for characterization of absorption, distribution, and excretion need to be developed. Additionally, multigeneration reproductive toxicity studies should be conducted (118).

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H. Workplace Hazards to...

...Reproductive Health



A Resource for Workers



State of Washington

Department of
Labor and Industries

This booklet was prepared by Catherine Karr, MS. Mary Miller, ARNP, Eileen Kirkpatrick, MS, Nicole Villacres and James Hawk, JD assisted this effort. It was reviewed and edited by the staff of the Department of Labor and Industries. It is largely adapted from "If I'm Pregnant, Can the Chemicals I Work With Harm My Baby?" produced by the Hazard Evaluation System and Information Service (HESIS), California Department of Health Services, 2151 Berkeley Way, Annex 11, Berkeley, CA 94704. Funding for printing was provided by the WISHA Right-To-Know Program.

Illustrations by Jane Norling.

November 1991.

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This publication may be obtained from:

Department of Labor and Industries
Attn: Consultation Section
P.O. Box 44640
Olympia, WA 98504-4640
Telephone No: 206-956-5638



Safety & Health Assessment & Research Program
Department of Labor & Industries
1011 Plum St., Building 5, M/S: HC 170
Olympia, WA 98504
(206) 753-2226

“I am/we are planning to become pregnant. Is my job safe for my fertility and child?”

If you are pregnant, or planning a pregnancy, you may worry that exposure to chemicals or certain activities at work will harm your fetus (unborn baby) or affect your fertility. Concern about workplace chemicals is understandable, especially since doctors encourage women not to expose the baby to other chemicals such as those found in medications, tobacco smoke and alcohol. Most men and women probably don't need to worry. But if you use chemicals at work, you should get more information about them.

This fact sheet will help you sort out what to do when you are concerned about workplace hazards to fertility and pregnancy and tells you what information you need to gather.

“Do I need to be worried?”

If you use chemicals often at work or home, you should find out what they are and if your exposure to them might harm you, your fetus, or your fertility. This fact sheet provides tips on how to do this.

Many men and women will find out that they don't need to worry. In some cases, they are not working with chemicals that can harm a fetus or affect fertility. For example, working with strong acids, strong caustics or other strongly irritating chemicals is not likely to harm your fetus or your fertility. In other cases, exposures are too brief or too small to create a hazard. For example, occasional exposures to small amounts of substances such as paint fumes or roofing tar fumes are also not likely to harm your fetus or fertility.

“What harmful effects can chemicals have on my ability to have healthy children?”

Some chemicals can cause lowered sex drive,

infertility, miscarriage, slower growth of the fetus or birth defects. In addition, a very few of the chemicals that can cause cancer may reach the fetus and later cause cancer in the child or young adult. Finally, some chemicals can find their way into breast milk and a child can be exposed during breastfeeding. When we refer to effects on fertility or pregnancy in this factsheet, we mean to include all of these types of effects.

There is much more known about how chemicals affect the fetus than how they may affect other aspects of reproduction. This is why this fact sheet has more information about a woman's pregnancy and less about fertility in men or women.

During the first three months of pregnancy the organs and limbs are being formed. This is the period when the fetus is most sensitive to chemicals which cause birth defects.

During the last six months of pregnancy, exposures to harmful chemicals can slow down the growth of the fetus or affect brain development, but are less likely to cause physical birth defects. If growth is slowed down, the fetus may weigh less than normal at birth. Low birth-weight babies are more likely to get sick during their first year of life. Effects on brain development may appear as slow learning ability, hyperactivity, coordination problems or, in severe cases, mental retardation. Because a woman may not know that she is pregnant during the first three months, it is important for her to find out about workplace hazards before she gets pregnant.

Men also should find out about the chemicals they use at work before starting a family. Men produce sperm throughout their adult life and some chemicals (or physical agents such as radiation) may interfere with this and affect fertility.

See “For More Information” on pages 8 - 9 and “Things You Need to Find Out” on pages 5 - 7 for help in finding out about workplace hazards to fertility or having a healthy child.

“What about non-chemical hazards?”

Chemical exposure is the best recognized and most important category of workplace hazards to child-bearing. However, biological agents and physical factors may also affect pregnancy or fertility. Viruses such as hepatitis B and rubella (German measles) are examples of potentially hazardous biological agents. Some of the physical factors that may influence reproduction are ionizing radiation, extreme heat or cold, and heavy physical effort such as repeated heavy lifting.

“What makes a chemical hazardous to my baby or my fertility?”

Whether the fetus or your fertility is affected depends on several things. The most important are:

- What chemicals you use.

Some chemicals can harm the fetus or your fertility, but many cannot.

- How much, how often and how long you are exposed.

In general, the less you are exposed, the less chance that you or your fetus will be affected.

- Whether the chemical gets into your body and reaches the fetus.

To harm the fetus, a chemical must get into your body, be absorbed into your blood and reach the fetus.

“How do chemicals enter the body to affect me and/or reach the baby?”

Chemicals can enter your body through the air you breathe, through contact with your skin or through your digestive system if you accidentally swallow them. They may reach the organs that control a man or woman's reproductive system. The fetus is exposed if the chemical passes from the mother's blood, through the placenta, to the fetus. Your baby may be exposed if the chemicals

you work with get into breast milk or if you bring home contaminated dust on your skin, workclothes or shoes.

Some chemicals are strong irritants which react with the first tissue they contact -- usually your eyes, nose, throat or skin. Very little of these chemicals enters the bloodstream. Therefore, they are unlikely to affect other parts of your body, including the fetus.

Other chemicals, however, can be absorbed into the blood stream. Some of them can be harmful to a man or woman's reproductive system or the fetus. A few concentrate in breast milk. Because there are so many considerations involved, it is not possible to list here all the chemicals that can be harmful to fertility or pregnancy. A few examples are listed below.

A Few of the Chemicals Which May Affect The Fetus or Your Fertility:

anesthetic gases
benzene
cancer chemotherapy (anti-cancer drugs)
carbon disulfide
carbon monoxide
ethanol (alcohol)
ethylene oxide
glycol ethers
lead
mercury
toluene

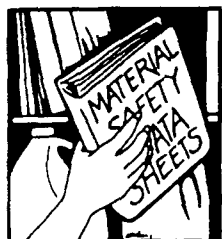
Some Common Chemicals Which are Unlikely to Harm The Fetus or Your Fertility:

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

“How do I figure out if the chemicals that I work with will harm my baby or my fertility?”

Your employer is responsible for finding out about workplace hazards to fertility and pregnancy, telling you about the hazards and protecting you from these hazards as much as possible. Sometimes, you may not get all the information you need from your employer, or you may not be able to understand it. You may even feel uncomfortable asking your boss for this information. In these situations, you'll need to get help from a doctor, nurse practitioner, genetics counselor, union representative, member of the workplace health and safety committee, Department of Labor and Industries representative or other health professional. However, before anyone can help you, you need to:

Find out what chemicals you work with. Ask your supervisor for the Material Safety Data Sheets



(MSDS) for the products you use. The MSDS is a form that lists the hazardous ingredients in a product. It must include information on hazards to child-bearing. Unfortunately, the information provided is rarely adequate. Your employer is

required by law to give you a copy of the MSDS if you ask for it. Your employer also must give this information to your doctor if it is requested. By law you have the right to know what chemicals you work with and what their hazards are. Your employer has the legal responsibility to give you this information and to train you to use the chemicals safely (Right-To-Know or Hazard Communications regulations are found in the Washington General Occupational Health Standards WAC 296-62-054 through -05427).

Find out how much, for how long, and how often you are exposed to these chemicals. Ask your supervisor if the air levels of chemicals in your work area have been measured. If monitoring has been done, you have a legal right to see the results

(WAC 296-62-052). In most cases, monitoring will not have been performed. In these situations, your exposure can be roughly estimated by answering the questions on the worksheet, “Things You Need to Find Out,” on pages 5 - 7.

After you have completed the worksheet, share this information with your doctor or other health professional, such as a nurse practitioner or genetics counselor. If your health care provider needs help determining if there is a problem, suggest that he or she consult with a board-certified occupational medicine physician or other occupational health specialist.

Even when you know what chemicals you work with and how much you are exposed to, it may not be possible to answer the questions, “Is my job safe for my fertility?” or “Will the chemicals I work with harm my fetus?” We simply don’t know whether many chemicals can affect fertility or pregnancy. *The best way to protect yourself and your fetus is to keep your exposure to all chemicals as low as possible.*

“What can be done to reduce my exposure?”

Exposure to hazardous chemicals can be reduced in several ways:

- **Replace a hazardous product with a safer one.**

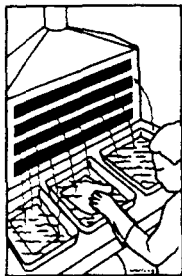
This is the best way to reduce hazardous chemical exposure. However, a safer substitute is not always available, or your employer may believe that substitution is not feasible. Also, check to make sure the substitute is truly safer. If you have a union in your workplace, contact your representative for assistance.

- **Use safe work practices.**

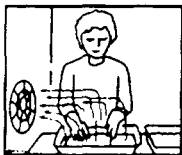
Store chemicals in sealed containers when not in use. Do not eat, drink or smoke in work areas. Avoid skin contact with chemicals. If chemicals are spilled on you, change out of contaminated clothing and wash yourself with soap and water.

- **Improve workplace ventilation.**

Exhaust ventilation removes contaminated or stale air and brings in clean air. The best type of



exhaust ventilation is at the source of exposure, which takes away contaminated air *before* it reaches the air you breathe. If source controls are not in place, it is especially important to have good room ventilation systems which bring in fresh outside air to dilute the chemicals in the workroom air. Most workers do not have much control over the ventilation in their workplaces. However, if you think the ventilation system in your work area is not getting adequate maintenance or is not effective in reducing your exposure, talk to your supervisor. Find out if it is always turned on when you are using chemicals or if it can be "turned up." If you do not have any kind of ventilation in your work area, you may want to talk to your supervisor about acquiring ventilation. In the meantime, opening windows and doors may help.



- **Ask about the use of personal protective equipment.**

You may be able to wear personal protective equipment such as gloves or a respirator to reduce your exposure. An industrial hygienist or other knowledgeable person should be consulted when choosing protective equipment. Required respirator use by any worker must be evaluated by a qualified person, usually the person in charge of the respirator program. Most women can probably use a respirator without harm except under certain complications of pregnancy such as high blood pressure.



"Can I keep working if I can't be sure it is safe for my baby?"

Whether to work during pregnancy is a personal decision. Some women may be able to transfer to

a different job with less or no chemical exposure. Others may be able to continue working but take steps to reduce their exposure to harmful chemicals. Some women choose to stop working but only after serious consideration of the consequences, such as a reduction in family income.

"Do I have any rights as a pregnant worker?"

Yes. There are laws protecting pregnant workers from discrimination. An employer cannot refuse to hire, assign or promote a woman because she is or may become pregnant. The laws also provide for limited disability and unemployment benefits. In addition, if you leave your job, you can keep your health insurance through the company's health plan for 18 months ("COBRA" rights). You will have to pay the premiums, but it can be less expensive than getting insurance on your own, and you'll be guaranteed continued coverage for your pregnancy. These laws will not solve all the problems that you may face, but they may help. Some employers offer benefits in addition to those required by law. Find out if your employer or union contract provides other benefits. Any benefits or special accommodations, such as temporary transfers, available to other temporarily disabled employees must be available to employees disabled due to pregnancy. For information on your legal rights, or help with a specific problem, see "For More Information" on page 14.

"Is there anything else I should know?"

Yes. It is important to remember that working with chemicals is only one of many things that can affect your fertility or fetus. In the general population, 15 percent of couples are infertile, as many as 40 percent of all pregnancies may end in miscarriage and about 3 percent of newborns have a serious birth defect. For women, two factors that have a big effect on the fetus are nutrition (what you eat) and seeing your health care provider regularly during your pregnancy. Take care of yourself. Eat well and start seeing your doctor early in your pregnancy.

Things You Need to Find Out

This questionnaire is for men and women who use chemicals frequently at work or may be exposed to other hazardous conditions.

Instructions for Workers: Collect the information you need to complete these questions. Share the information with your doctor or other health professional, such as a nurse or genetics counselor. He or she can help you determine if the chemicals you work with can harm you, your fertility or your fetus. If your health care provider needs help in determining if there is a problem, suggest that he or she consult with a board-certified occupational medicine physician or other occupational health specialist. See page 8 for others who can help.

1. What is your current job title? (If you are not currently working, when were you last employed and what was your job title?) _____

2. Describe the tasks or activities you perform at work. _____

3. What does your company manufacture, or what kind of services does it provide? _____

4. Write the names of any chemicals you work with in the column at the left. If you use more than one, list them in order of how frequently you use them. Put the one you use most frequently in the top space.

In the column on the right, describe how you use each chemical. Write when and for how long you use them. For example, "twice a day for ten minutes each time." Also, write how much of each chemical or product you use each time you work with it. For example, "1-2 gallons."

Brand names aren't very helpful. Sometimes a product label has ingredient information, but often the information on labels is incomplete and unreliable. The best way to find out what chemicals are in the product(s) being used is to get a copy of the *Material Safety Data Sheet (MSDS)* for that product from the employer. An MSDS lists the hazardous ingredients in a product. *Employers are required by law (WAC 296-62-054 through -05427) to provide workers with a copy of the MSDS, upon request. Employers must also provide this information to a treating doctor on request.*

<u>Chemical Name</u>	<u>How and When I use them, how much I use</u>
Most Freq Used _____	_____
_____	_____
Less Freq Used _____	_____
_____	_____

5. In your work area, how many other people also use these chemicals? _____

6. Besides the chemicals that you work with, what other chemicals do people in your area use? _____

7. List any of these chemicals that you or other workers in your area use that are heated. Also, write the temperature to which they are heated.

<u>Chemicals that are heated</u>	<u>Temperature</u>
_____	_____
_____	_____
_____	_____

8. Can you smell or taste any chemical fumes or vapors where you work?

If yes, list them by chemical name.

9. Do you feel sick when you work with any of the chemicals? If yes, list which chemicals in the column on the left. In the column on the right, describe how you feel when you work with each chemical.

Chemicals

Symptoms

10. If working with any chemicals makes you sick, do you feel better at other times? Yes _____ No _____ If yes, please explain when you feel better. _____

11. If you are pregnant, did you have these symptoms before becoming pregnant? Yes _____ No _____

12. List any of the chemicals that you work with that get on your skin. _____

13. Do you do any of the following in the work area?

EAT Yes _____ No _____

DRINK Yes _____ No _____

SMOKE Yes _____ No _____

APPLY MAKEUP Yes _____ No _____

The following questions are about protective measures used in your workplace.

14. Mark the type of VENTILATION used in your work area.

_____ hood with power exhaust

_____ general ventilation (wall fans, roof fans, ceiling vents)

_____ natural ventilation (open windows and doors)

15. Do you think the ventilation is effective in reducing your exposure? Yes _____ No _____

16. Is the ventilation always turned on when you are using chemicals? Yes _____ No _____

17. Does the ventilation usually work well? Yes _____ No _____

18. Describe the types of PROTECTIVE CLOTHING you wear on the job.

Type of Gloves _____

Type of Apron/Coat _____

Type of Eyewear _____

Ear Protection _____ Yes _____ No

19. Do chemicals leak through your gloves or clothing? Yes _____ No _____ If yes, explain. _____

20. Mark the kind of RESPIRATORY PROTECTION you use on the job.

_____ paper dust mask

_____ paper mask with filter

_____ half-face mask with cartridges

_____ full-face mask with cartridges

_____ air-supplied respirator

If you wear a cartridge respirator:

21. What kind of cartridge? _____

22. When do you wear a respirator? _____

23. For what chemicals do you wear a respirator? _____

24. Have you been fit-tested and trained to use your respirator? Yes___ No___

25. Have you received instructions about changing your cartridges and other maintenance? Yes___ No___

26. Are there any unusual situations at work, such as equipment breakdowns or spills, that may expose you to any other chemicals or to larger amounts of those you use routinely? Yes___ No___ If yes, explain. _____

27. What types of instructions and warnings has your employer given you about the use of chemicals? _____

28. Have the air levels of chemicals in your work area been measured? Yes___ No___

If monitoring has been done, you have a legal right to see the results relevant to your work area (WAC 296-62-052). If you are a member of a union, the union can help you enforce this right.

If you know the results, write them here. _____

29. Do you do any other work outside your regular job, or have any hobbies, that involve exposure to chemicals?

Yes___ No___ If yes, describe them. _____

30. If you are involved in any of the following physical activities on the job, please describe them and write how many hours per day you perform each below.

Description	Hours/day
Lifting _____	
Climbing _____	
Bending _____	
Twisting _____	
Sitting _____	
Standing _____	

31. If you are exposed to any of the following on your job, describe them by writing when, how often and how much you are exposed to each:

Noise _____

Temperature Extremes _____

Radiation _____

Infectious Agents _____

Psychological Stress _____

For More Information

Workplace Health and Safety

In addition to this fact sheet, the Washington State Department of Labor and Industries (L&I) has also published a more technical booklet titled, "Workplace Hazards to Reproductive Health: A Resource for Health Care Providers, Health and Safety Personnel, and Employers." Copies of both are available from any of the L&I regional offices listed below.

Olympia: (206) 753-6503 or 1-800-547-8367

Everett: (206) 356-2950

Spokane: (509) 456-2978

Seattle: (206) 281-5470

Yakima: (509) 575-2653

Tacoma: (206) 593-2866

Regulations and Whether To File a Complaint

L&I's safety and health division ("WISHA") is responsible for workplace health and safety in Washington. It establishes Permissible Exposure Limits (PELs) for the amounts of certain chemicals in workroom air. You have a



right to a safe and healthy workplace. If you feel you are being overexposed to a chemical, it is usually best to first talk to your employer. If you are unsatisfied

with your employer's response or are concerned about being discriminated against for bringing up a safety or health issue, contact WISHA for information. By law, employees have a right to file a confidential complaint and the right not to be discriminated against for exercising their rights to a safe workplace under the Washington Industrial Safety and Health Act. You may first wish to discuss the merits of a complaint with an inspector. The WISHA regional offices are listed above.

When your Health Care Provider Needs Assistance

- A board-certified occupational medicine physician or other occupational health specialist. There are several occupational medicine physicians in Washington State. Also, the University of Washington Occupational Medicine Program is the Pacific Northwest training site for occupational medicine professionals. The program provides consultation to other health care providers.

University of Washington
Occupational Medicine Program
325 9th Avenue, ZA-66
Seattle, WA 98104
(206) 223-3005

Finding Out About Hazards to Reproduction from Specific Chemicals

Drugs and Infectious Agents:

- Your health care provider
- County Health Department

Local health departments can inform you where to go for prenatal care. Look for the number of the health department nearest you under the "County Offices" heading in the "Government Offices" section found in the front part of your phone book.

Exposure to chemicals at work or home when immediate information is needed:

- Washington State Poison Center Network
 - Seattle: 1-800-732-6985
 - Spokane: 1-800-572-5842
 - Tacoma: 1-800-542-6319
 - Yakima: 1-800-572-9176

Workplace Exposures:

- Your health care provider
- Your company doctor or other health personnel
- Material Safety Data Sheets

General Information on Health Effects of Toxic Agents:

Washington State Department of Health
Office of Toxic Substances
Mail stop: LD-11
Olympia, WA 98504-0095
(206) 586-5401

Safe Handling Procedures for Chemicals and Ways of Reducing your Exposure

- Material Safety Data Sheets
 - Your company health and safety officer or industrial hygienist or your supervisor
 - Your union
 - Department of Labor and Industries Voluntary Services Program (employer requested services)
- Voluntary Services is an employer assistance program of L&I's Division of Industrial Safety and Health. It provides free, no hassle, confidential, and penalty-free assistance to employers in the evaluation and control of workplace health and safety hazards. Employers should see "State Offices" listings under the "Government Offices" section of the phone book.

Your Legal Rights

For questions regarding maternity leave regulations, concerns regarding discrimination during pregnancy or your legal rights if you are considering pregnancy but are worried about possible harmful workplace exposures, you may contact the local office of the Federal Equal Employment Opportunity Commission, or the Washington State Human Rights Commission.

Human Rights Commission
Evergreen Plaza Building, Suite 402
711 S. Capital Way, MS FJ-41
Olympia, WA 98504

Western Washington: 1-800-233-3247

Eastern Washington: 1-800-662-2755

Equal Employment

Opportunity Commission

2815 2nd Ave, Suite 500

Seattle, WA 98121

(206) 553-0968

For specific legal questions, you may need to contact an attorney. The telephone yellow pages list local area lawyers. Also, the Washington State Bar Association provides referrals 1-800-522-0787.

Unemployment Insurance Benefits:

- Employment Security Department
- See "State Offices" listings under the "Government offices" section at the front of your phone book.

Disability Benefits (when injured or disabled on the job):

- Department of Labor and Industries - Division of Industrial Insurance.
- See "State Offices" listings under the "Government Offices" section at the front of your phone book.

Additional Information on Workplace Issues

- Your Union

Whether or not you are a member of a union, the Washington State Labor Council will answer questions about the presence of workplace reproductive exposures, your employer's responsibilities regarding such exposures or how your questions can be addressed through labor/management interaction.

Washington State Labor Council,
AFL-CIO
906 S. Columbia St. #330
Olympia, WA 98501
(206) 943-0608

[. Workplace Hazards to...

...Reproductive Health



A Resource for Health Care Providers,
Health and Safety Personnel
and Employers



State of Washington

Department of
Labor and Industries

This booklet was prepared by Catherine Karr, MS. Mary Miller, ARNP, Eileen Kirkpatrick, MS, Nicole Villacres and James Hawk, JD assisted this effort. It was reviewed and edited by the staff of the Department of Labor and Industries. It is largely adapted from "Workplace Chemical Hazards to Reproductive Health: A Resource for Worker Health and Safety Training and Patient Education" and "Reproductive Hazards Training and Information Manual" produced by the Hazard Evaluation System and Information Service (HESIS), California Department of Health Services, 2151 Berkeley Way, Annex 11, Berkeley, CA 94704. Funding for printing was provided by the WISHA Right-to-Know Program.

Illustrations by Jane Norling.

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Safety and Health Assessment and Research Program
Department of Labor and Industries
1011 Plum St., Building 5, M/S: HC 170
Olympia, WA 98504
(206) 753-2226

Introduction



Many men and women wonder if chemical substances at work, at home, or in their communities affect their ability to have healthy children. They are concerned that exposure to toxic agents or other hazards might cause reproductive health problems such as infertility, miscarriage, birth defects, mental deficiencies, or cancer in their children. This concern is understandable, since the ability to bear healthy children is often one of the most cherished aspects of life.

Responsibility for responding to worker concern about exposure to reproductive hazards belongs to health care providers, workplace health and safety personnel and employers. While each plays a specific role and offers unique expertise, worker protection relies on: 1) communication and cooperation among these groups, and 2) mutual understanding of each other's responsibilities.

This booklet contains sections of background information designed to provide a common framework for the variety of readers interested in recognizing, evaluating and reducing workplace reproductive hazards. In addition, it includes specific sections intended to address issues of most concern for health care providers, people responsible for workplace health and safety, and employers. Readers with stronger scientific backgrounds may choose to skip past some of the initial sections that discuss basic physiology and toxicology of reproduction.

Overall, this booklet is intended as an aid to understanding how occupational factors can affect reproductive health and how harm can be prevented. The Washington State Department of Labor and Industries also has published a less technical fact sheet on this topic for workers. Both this booklet and the fact sheet are available from any of the service locations listed on page 41.

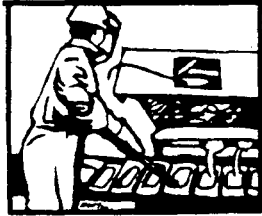
The Impact of Workplace Exposures On Reproductive Function

Reproductive disorders and adverse pregnancy outcomes occur frequently in the general population. In most cases, the causes are not known, although poor nutrition, alcohol, other prescription or illicit drugs, smoking, lack of prenatal care, age and heredity all can have profound effects on reproduction.

The extent to which workplace exposures contribute to reproductive impairment is not clear. Most workplace exposures to chemicals, physical conditions and biological agents have not been adequately tested for their ability to affect reproduction. For this reason, it is not usually possible to conclude with certainty whether or not a particular substance or activity can cause harm. However, even when reproductive or developmental toxicity information is incomplete, it may be possible to reasonably evaluate potential risk based on what we do know. If workplace exposure is controlled to protect workers from all other health effects, workers may be protected from harmful reproductive effects as well. However, for some agents, a reproductive effect may be the most sensitive toxic effect and may occur at levels close to or below the PEL (Permissible Exposure Limit) or the odor threshold.



INTRODUCTION



While we are uncertain about how much workplace exposures contribute to reproductive health problems, we do know that they are a preventable cause of reproductive dysfunction. The use of work practices that reduce or prevent exposure to hazardous agents or job activities does not have to wait until we know the exact magnitude of the risk associated with these exposures.

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PART II

REPRODUCTIVE HAZARDS BIBLIOGRAPHY

A. NIOSH PUBLICATIONS/REPORTS

1. NUMBERED PUBLICATIONS *are formal publications issued by NIOSH that document the results of research conducted by or for NIOSH. Included in this category are Criteria Documents, Current Intelligence Bulletins, Alerts, Health and Safety Guides, technical reports of scientific investigations, compilations of data, worker-related booklets, symposium and conference proceedings, and administrative and management reports.*

Alert - Request for Assistance in Preventing Lead Poisoning in Construction Workers, 1991.

NIOSH PUB NO: 91-116a. 25 pp.
Available from NIOSH No Charge
NTIS NO: PB92-205194 \$17.50

Assessment of Deep Body Temperatures of Women in Hot Jobs, 1977.

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Current Intelligence Bulletin 22 - Ethylene Thiourea, 1978.
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Abstracts of Selected Research: Reproductive Hazards in the Workplace, July 1980.

CONTRACT NO: 210-79-0075. 176 pp.

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An Industrywide Industrial Hygiene Study of Ethylene Dibromide, December 1977.

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An Investigation of Electric and Magnetic Fields and Operator Exposure Produced by VDTs, Final Report, September 1990.

PURCHASE ORDER NO: 90-37729. 290 pp.

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Case Comparison Study of Parental Employment and Fetal Outcome, February 1982.

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NTIS NO: PB83-111179 \$19.50

Chronic Inhalation Toxicity of 1,2-Dibromoethane in Rats, With and Without Dietary Disulfiram, November 1980.

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Cytogenetic Evaluation of Spermatogonial Cells in the Rat Following Long-Term Inhalation Exposures to Nitrous Oxide Plus Halothane, Final Report, November 17, 1976.

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CONTRACT NO: 210-76-0154. 376 pp.

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Screening of Priority Chemicals for Potential Reproductive Hazard, January 1983.

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Screening of Priority Chemicals for Potential Reproductive Hazard, Final Report, Hazelton Study, December 6, 1983.

CONTRACT NO: 200-82-2542. 152 pp.

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Screening of Priority Chemicals for Reproductive Hazards, I, Final Report, *January 4, 1983*.
CONTRACT NO: 210-81-6010. 108 pp.
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Screening of Priority Chemicals for Reproductive Hazards, II, Final Report, *January 9, 1984*.
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CONTRACT NO: 210-78-0026. 180 pp.
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CONTRACT NO: 210-78-0026. 191 pp.
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CONTRACT NO: 210-78-0026. 189 pp.
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Bis(2-Methoxyethyl) Ether, Report # 34, *July 7, 1981*.
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CONTRACT NO: 210-78-0026. 179 pp.
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CONTRACT NO: 210-78-0026. 203 pp.
NTIS NO: PB83-126607 \$38.50

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2,5-Hexanedione Alters Microtubule Assembly:
I. Testicular Atrophy, Not Nervous System Toxicity,
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Boekelheide K [1987]. *Toxicology and Applied
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GRANT NO: R01OH01972.

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6. HEALTH HAZARD EVALUATIONS *are studies of a workplace, such as a particular department in a factory, industrial plant, office building, or other worksite. The study is conducted by NIOSH in response to concerns expressed by employees, employee representatives, or employers, to find out whether there is a health hazard to employees caused by exposure to hazardous materials (chemical or biological contaminants) or working conditions (e.g., noise, heat, musculoskeletal stresses). The reports resulting from these studies are generally referred to as Hazard Evaluation and Technical Assistance (HETA) reports. Please note that each report discusses the conditions only at the specific worksite evaluated. NIOSH has conducted several hundred HHEs related to reproductive hazards. Listed below are some of the more significant studies.*

BASF Wyandotte Corp., Rensselaer, NY, *January 1985.*
HETA NO: 80-008-1546. 31 pp.
NTIS NO: PB86-105343 \$17.50

Budd Company, North Baltimore and Carey, OH, *June 1988.*
HETA NO: 84-459-1905. 92 pp.
NTIS NO: PB89-120588 \$19.50

J. Butler, D.D.S., Wellston, OH, *November 1984.*
HETA NO: 84-090-1533. 26 pp.
NTIS NO: PB85-208254 \$17.50

Chemical Fabrics Corp., North Bennington, VT, *April 1984.*
HETA NO: 81-129-1455. 34 pp.
NTIS NO: PB85-185189 \$17.50

Davis & Geck, Inc., Danbury, CT, *September 1984.*
HETA NO: 84-014-1507. 17 pp.
NTIS NO: PB85-224020 \$17.50

Department of Energy, Martin Marietta Energy Systems, Inc, Health Evaluation of Y-12 Workers Formerly Exposed to Mercury, *May 1989.*
HETA NO: 83-422-L1965. 232 pp.
NTIS NO: PB90-119918 \$38.50

Edwin Cooper Co., Sauget, IL, *December 1982.*
HETA NO: 80-228-1241. 26 pp.
NTIS NO: PB84-172568 \$17.50

Electric Boat Division, General Dynamics Corporation, Groton, CT, *January 1989.*
HETA NO: 84-474-1946. 115 pp.
NTIS NO: PB89-188098 \$27.00

Emanuel Hospital, Portland, OR, *July 1983.*
HETA NO: 82-256-1342. 14pp.
NTIS NO: PB85-102945 \$17.50

Fairmont General Hospital, Fairmont, WV, *October 1990.*
HETA NO: 90-218-2079. 14 pp.
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Federal-Mogul Metal Removal Tooling Division, Chicago, IL, *May 1981.*
HETA NO: 80-058-874. 12 pp.
NTIS NO: PB82-215351 \$17.50

General Telephone Co. of Michigan, Alma, MI, *July 1985.*
HETA NO: 84-297-1609. 16 pp.
NTIS NO: PB86-143609 \$17.50

Houston Chemical Co., Beaumont, TX, *April 1978.*
HHE NO: 77-119-481. 23 pp.
NTIS NO: PB-291672 \$17.50

Immunology Branch Laboratory, Centers for Disease Control, Atlanta, GA, *November 1982.*
HETA NO: 82-089-1213. 28 pp.
NTIS NO: PB84-172535 \$17.50

Indiana Army Ammunition Plant, Charlestown, IN, *April 1982.*
HETA NO: 81-277-1089. 11 pp.
NTIS NO: PB83-198697 \$17.50

K & M Company, Torrance, CA, *July 1986.*
HETA NO: 85-153-1714. 37 pp.
NTIS NO: PB87-117065 \$17.50

Lear Siegler, Inc., San Diego, CA, *December 1981.*
HETA NO: 81-270-1012. 13 pp.
NTIS NO: PB82-185166 \$17.50

Lederle Laboratories, Pearl River, NY, *July 1990.*
HETA NO: 87-412-L2054. 8 pp.
NTIS NO: PB91-132894 \$12.50

Long Island Railroad, New York, NY, *September 1982*.
HETA NO: 80-039-1179. 12 pp.
NTIS NO: PB84-148923 \$17.50

Louisiana-Pacific Corporation, Missoula, MT, *June 1988*.
HETA NO: 87-309-1906. 14 pp.
NTIS NO: PB89-130132 \$17.50

Manhattan Eye, Ear and Throat Hospital,
New York, NY, *October 1982*.
HETA NO: 82-016-1206. 26 pp.
NTIS NO: PB84-173004 \$17.50

Manufacturing Chemists, Inc., Indianapolis, IN,
March 1985.
HETA NO: 82-257-1571. 47 pp.
NTIS NO: PB86-117561 \$17.50

Maui Land and Pineapple Inc., Kahuli, HI, *January 1990*.
HETA NO: 81-162-1935. 34 pp.
NTIS NO: PB91-108779 \$17.50

Medical College of Pennsylvania, Philadelphia, PA,
February 1984.
HETA NO: 83-217-1425. 14 pp.
NTIS NO: PB85-179240 \$17.50

National Broadcasting Co., New York City, NY,
December 1981.
HETA NO: 81-417-1008. 13 pp.
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National Cover of Atlanta, Inc., Lawrenceville, GA,
June 1988.
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NTIS NO: PB89-120620 \$17.50

Occidental Chemical Co., Lathrop, CA, *March 1978*.
HHE NO: 77-103-474. 20 pp.
NTIS NO: PB82-197443 \$17.50

Olin (formerly Allied) Chemical Co., Moundsville, WV,
August 1982.
HETA NO: 81-295-1155. 32 pp.
NTIS NO: PB84-150465 \$17.50

Pacific Gas and Electric/Western Canal Co., Nelson, CA,
December 1981.
HHE NO: 80-163-1026. 21 pp.
NTIS NO: PB82-182726 \$17.50

Pan American Tannery, Gloversville, NY, *January 1990*.
HETA NO: 89-125-2021. 48 pp.
NTIS NO: PB91-108217 \$17.50

Planned Parenthood of South Central Indiana,
Bloomington, IN, *January 1988*.
HETA NO: 83-258-1859. 19 pp.
NTIS NO: PB88-221585 \$17.50

Precision Castparts Corporation, Portland, OR,
May 1986.
HETA NO: 84-415-1688. 33 pp.
NTIS NO: PB87-108320 \$17.50

Red Wing Shoe Co., Red Wing, MN, *November 1982*.
HETA NO: 81-455-1229. 31 pp.
NTIS NO: PB84-172592 \$17.50

Rockcastle Manufacturing, Mount Vernon, KY,
March 1990.
HETA NO: 87-349-2022. 33 pp.
NTIS NO: PB91-107946 \$17.50

Seamless Hospital Products Company, Fayette, AL,
June 1984.
HETA NO: 83-159-1473. 21 pp.
NTIS NO: PB85-184174 \$17.50

Social Security Administration, New Brunswick, NJ,
December 1983.
HETA NO: 83-136-1398. 10 pp.
NTIS NO: PB85-181246 \$12.50

Southern Bell, Atlanta, GA, *August 1984*.
HETA NO: 83-329-1498. 21 pp.
NTIS NO: PB85-208379 \$17.50

University of Massachusetts, Amherst, MA, *August 1979*.
HHE NO: 79-000-003. 37 pp.
NTIS NO: PB80-148125 \$17.50

USA Today/Gannett Co., Inc., Rosslyn, VA, *April 1990*.
HETA NO: 89-069-2036. 38 pp.
NTIS NO: PB91-120501 \$17.50

Westview Press, Boulder, CO, *August 1984*.
HETA NO: 83-425-1500. 14 pp.
NTIS NO: PB85-220846 \$17.50

7. CONTROL TECHNOLOGY REPORTS *represent the results of field study surveys that evaluate health hazard control systems. The field studies begin with walk-through surveys which provide preliminary evaluations of control systems to identify those worthy of in-depth study. In-depth surveys are performed to provide a detailed evaluation of selected control systems.*

In-Depth Survey Report: Control of Anesthetic Gases in Dental Operatories at University of California at San Francisco, Oral Surgical Dental Clinic, San Francisco, CA, July 25-28, 1988.

CT NO: CT/166.12B. 127 pp.

NTIS NO: PB91-152033 \$27.00

Walk-Through Survey Report: Control of Methylene Chloride in Furniture Stripping at Remington House Antiques, Remington, OH, January 1991.

CT NO: CT/170.15. 19 pp.

NTIS NO: PB91-173575 \$17.50

8. INDUSTRYWIDE STUDY REPORTS represent the results of industrial hygiene field studies that assess whether specific occupational exposures or particular workers are associated with adverse health effects. The majority of these reports document information obtained during brief 1- to 2-day walk-through surveys at plant sites to evaluate their suitability for industrywide studies. In-depth survey reports present detailed exposure information collected during a 1-week survey at a plant site.

An Extent-of-Exposure Assessment in Industries Using Ethylene Glycol Ethers, Summary Report, *April 1989*.
IWS NO: IW/134.20.19. 47 pp.
NTIS NO: PB89-215651 \$17.50

Industrial Hygiene Survey Report of BASF Corporation, Coatings and Coolants Division, Anaheim, CA, *May 23-25, 1988*.
IWS NO: IW/134.20.18. 22 pp.
NTIS NO: PB89-186654 \$17.50

Industrial Hygiene Survey Report of Cain Chemical, Inc., Petrochemical Division, Pasadena, TX, *June 1-2, 1988*.
IWS NO: IW/134.20.11. 25 pp.
NTIS NO: PB89-164685 \$17.50

Industrial Hygiene Survey Report of Defense Fuel Support Point, Cincinnati, OH, *June 28-30, 1988*.
IWS NO: IW/134.20.14. 21 pp.
NTIS NO: PB89-186621 \$17.50

Industrial Hygiene Survey Report of Delta Air Lines, Inc., Technical Operations Center, Hartsfield Atlanta International Airport, Atlanta, GA, *June 13-14, 1988*.
IWS NO: IW/134.20.12. 21 pp.
NTIS NO: PB89-186605 \$17.50

Industrial Hygiene Survey Report of Ford Motor Company, Kansas City Assembly Plant, Kansas City, MO, *August 2-3, 1988*.
IWS NO: IW/134.20.16. 19 pp.
NTIS NO: PB89-186639 \$17.50

Industrial Hygiene Survey Report of Texon U.S.A., Russell Plant, Westfield, MA, *August 30-31, 1988*.
IWS NO: IW/134.20.13. 19 pp.
NTIS NO: PB89-186613 \$17.50

Industrial Hygiene Survey Report of TRW Electronics Products, Inc., Colorado Springs, CO, *September 13-14, 1988*.
IWS NO: IW/134.20.17. 20 pp.
NTIS NO: PB89-186647 \$17.50

Industrial Hygiene Survey Report, Precision Castparts Corp., Portland, OR, *April 1984 and June 1984*.
IWS NO: IW/134.14. 18 pp.
NTIS NO: PB87-108395 \$17.50

Industrial Hygiene Survey Report, Worker Exposures to Organotins, Red Panther Chemical Co., Clarksdale, MS, *June 25, 1985*.
IWS NO: IW/136.12. 27 pp.
NTIS NO: PB86-117504 \$17.50

Industrial Hygiene Walk-Through Survey Report, Amoco Chemicals Corp., Chocolate Bayou Plant, Chocolate Bayou, TX, *June 21, 1984*.
IWS NO: IW/147.16. 15 pp.
NTIS NO: PB85-207835 \$17.50

Industrial Hygiene Walk-Through Survey Report, ARCO Chemical Co., Lyondell Chemical Complex, Channelview, TX, *April 18, 1985*.
IWS NO: IW/147.12. 16 pp.
NTIS NO: PB85-239754 \$17.50

Industrial Hygiene Walk-Through Survey Report, El Paso Products Co., Corpus Christi Butadiene Plant, Corpus Christi, TX, *July 12, 1984*.
IWS NO: IW/147.19. 14 pp.
NTIS NO: PB85-207769 \$17.50

Industrial Hygiene Walk-Through Survey Report, Exxon Chemical Americas, Baton Rouge Chemical Plant, Baton Rouge, LA, *March 21, 1985*.
IWS NO: IW/147.18. 16 pp.
NTIS NO: PB85-234375 \$17.50

Industrial Hygiene Walk-Through Survey Report, Shell Chemical Co., Deer Park Manufacturing Complex, Deer Park, TX, *May 9-10, 1984*.
IWS NO: IW/147.10. 16 pp.
NTIS NO: PB85-207827 \$17.50

Industrial Hygiene Walk-Through Survey Report,
Texaco Chemical Co., Neches Butane Products Plant,
Port Neches, TX, *April 18, 1985.*

IWS NO: IW/147.14. 13 pp.

NTIS NO: PB85-241271 \$17.50

Industrial Hygiene Walk-Through Survey Report, Texas
Petrochemicals Corp. (formerly Petro-Tex-Chemical-
Corp.), Houston, TX, *May 3, 1984.*

IWS NO: IW/147.13. 15 pp.

NTIS NO: PB85-207801 \$17.50

Industrial Hygiene Walk-Through Survey Report, Union
Carbide Corp., Taft Plant, Taft, LA, *June 13, 1984.*

IWS NO: IW/147.17. 16 pp.

NTIS NO: PB85-207819 \$17.50

Occupational Exposure to Inhalation Anesthetics in
Veterinary Operating Room, *October 1979.*

IWS NO: IW/039.07. 51 pp.

NTIS NO: PB82-231358 \$19.50

Walk-Through Survey Report, Avtex Fibers, Inc.,
Front Royal, VA, *July 14-15, 1977.*

IWS NO: IW/075.15. 4 pp.

NTIS NO: PB88-252978 \$ 9.00

Walk-Through Survey Report, Randolph Air Force Base,
Aircraft Refueling Operation, San Antonio, TX,
November 6, 1984.

IWS NO: IW/134.10. 12 pp.

NTIS NO: PB85-222891 \$17.50

Walk-Through Survey Report, Western Electric Co.,
Atlanta Service Center, Atlanta, GA, *March 27, 1984.*

IWS NO: IW/134.12. 9 pp.

NTIS NO: PB85-103810 \$12.50

9. MISCELLANEOUS NIOSH REPORTS *include documents that do not fit into one of the proceeding sections.*

A Retrospective Study of Inferred Fertility of Married Men Occupationally Exposed to Ethylene Dibromide (EDB), *November 1977*. 22 pp.
NTIS NO: PB90-142506 \$17.50

A Review of the Evidence in Support of a Short Term Exposure Limit for Occupational Exposure to Ethylene Oxide. [No Date.] 30 pp.
NTIS NO: PB90-130212 \$17.50

Developmental Toxicity of Diethylene Glycol Monomethyl Ether (diEGME), *May 14, 1985*. 22 pp.
NTIS NO: PB91-235325 \$17.50

Health Effects of Occupational Exposure to Carbon Disulfide, *July 2, 1984*. 201 pp.
NTIS NO: PB85-110229 \$38.50

Investigation of Spontaneous Abortion Among Video Display Terminal Users, Final Report, *March 1991*. 23 pp.
NTIS NO: PB91-189209 \$17.50

Male Fertility Effects of Glycol Ethers--A Quantitative Analysis, *December 1988*. 120 pp.
NTIS NO: PB89-164149 \$27.00

NIOSH - The Changing Nature of Work and Workforce, Proceedings of the Third Joint U.S.-Finnish Science Symposium, *October 22-24, 1986*. 125 pp.
NTIS NO: PB87-189304 \$27.00

NIOSH Publications on Video Display Terminals (Revised), *June 1991*. 92 pp.
Available from NIOSH No Charge
NTIS NO: PB92-109230 \$19.50

NIOSH Report on Occupational Safety and Health for FY-1988 Under Public Law 91-596, *1991*. 41 pp.
NTIS NO: PB91-185280 \$17.50

Occupational Health Problems of Pregnant Women. A Report and Recommendations for the Office of the Secretary DHEW, *April 1975*. 164 pp.
NTIS NO: PB-254032 \$27.00

Paternal Exposure to Carbon Disulfide and Spouse's Pregnancy Experience, *July 1983*. 45 pp.
NTIS NO: PB85-220754 \$17.50

Report on Women Pharmaceutical Workers and Adverse Reproductive Outcomes, *June 1983*. 27 pp.
NTIS NO: PB84-148956 \$17.50

Reproductive Effects of Glycol Ethers in Females--A Quantitative Analysis, CTPID 89-7, *July 1989*. 105 pp.
NTIS NO: PB90-129222 \$27.00

Reproductive Outcomes in Wives of Lead Exposed Workers, *December 1984*. 47 pp.
NTIS NO: PB85-220879 \$17.50

Scientific Workshop on the Health Effects of Electromagnetic Radiation on Workers, Bibliography, *January 30-31, 1991*. 280 pp.
(Also see Proceedings on page 135.)
NTIS NO: PB91-173351 \$38.50

Semen Study of Papaya Workers Exposed to Ethylene Dibromide. [No Date.] 54 pp.
NTIS NO: PB86-221447 \$19.50

Serum Testosterone and Static Magnetic Field Exposure. [No Date.] 8 pp.
NTIS NO: PB86-105384 \$12.50

The Occupational Health Implications of Video Display Terminals: A Bibliography, *1981-1985*. 18 pp.
NTIS NO: PB91-184549 \$17.50

Use of Biological Markers and Pharmacokinetics in Human Health Risk Assessment, *1989*. 37 pp.
NTIS NO: PB89-215644 \$17.50

B. SELECTED NON-NIOSH REFERENCES

This section includes references on reproductive hazards selected from non-NIOSH sources.

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- Chapin R, Heindel J, eds. [1993]. Methods in toxicology: male reproductive toxicology, Vol. 3A. 389 pp. Academic Press, New York, NY.
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