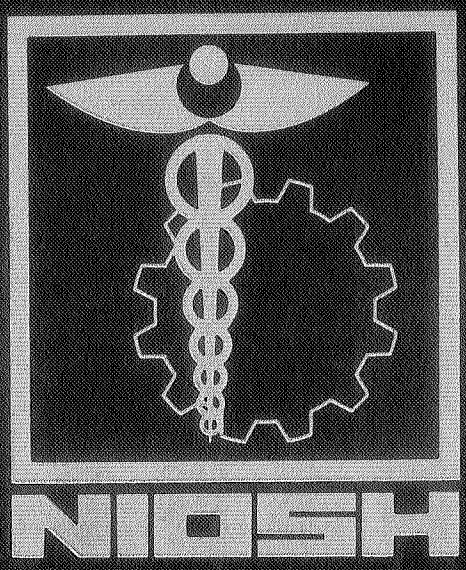

Proposed National Strategies for the Prevention of Leading Work-Related Diseases and Injuries

• 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

Proposed National Strategy for the Prevention of Disorders of Reproduction

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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.

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

	Reproductive Toxicants				Developmental Toxicants
	Non-mutagenic		Mutagenic		
Potential Outcome	Male	Female	Male	Female	Female
Infertility	X	X	X	X	X
Spontaneous abortion					
normal karyotype	X	X	X	X	X
abnormal karyotype			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 nonneoplastic 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-stye 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.

VII. References

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