

# **REPRODUCTIVE AND DEVELOPMENTAL HAZARDS: A GUIDE FOR OCCUPATIONAL HEALTH PROFESSIONALS**

## PURPOSE

This Manual provides guidance to Navy occupational health (OH) professionals in the evaluation and management of reproductive and developmental (ReproDev) hazards in the workplace.

## ACKNOWLEDGEMENTS

This Manual is a major revision and update to the first edition (NEHC-TM92-2). Major contributors to this edition include: John Muller, MD, MPH; John Bishop, CIH; CAPT Lawrence Betts, MC, USN, from the Navy Environmental Health Center; and LT Cynthia Kukoski, MSC, USN, from Naval Medical Center, Portsmouth. Significant reviews and changes were contributed by CAPT Robert Brawley, MC, USN, from the Navy Environmental Health Center, CAPT Gregory R. Moore, MC, USN, from Naval Hospital, Camp Lejeune, North Carolina, and Melissa McDiarmid, MD, University of Maryland.

In support of the goal to make the Navy Environmental Health Center a leader in web-enabled technology for Population Health Support, established by CAPT David M. Sack, MC, USN, our Commanding Officer, please use the imbedded hyperlinks to further your knowledge and clarify questions in Disease and Injury Prevention and Health Promotion.

## DISCLAIMER

This Manual does not establish policy. It is to be used to assist in decision-making and execution of an overall program to control hazards in the workplace. Where a conflict in this manual exists between a regulatory or statutory reference or a requirement, the default is to the basic reference or requirement. Assistance in interpretation or clarification of statements or concepts contained in this Manual can be obtained from the Occupational and Environmental Medicine Directorate, Navy Environmental Health Center. The authors do not take any responsibility for any references or links, or for the maintenance of web sites and web documents other than those under the auspices of the Navy Environmental Health Center.

## USING THE MANUAL

The Manual contains numerous references and hyperlinks to sources other than those maintained by the Navy. Hyperlinks are marked by colored text, and PubMed numbers are hyperlinked to abstracts (in the format [PMID 0000000](#)). Internet hyperlinks are supplied to expand the utility and versatility of this document. References (many of which are hyperlinked to PubMed abstracts) are supplied to enable health professionals in the field to access more detailed information, or to document the basis for statements that may not be commonly known or that represent recent scientific knowledge. Other recognized sources providing ReproDev guidance not cited in this manual should be considered using professional judgment.

## COMMENTS

Comments are always appreciated and will assist in continual improvement of this manual. They may be sent to the OEM Directorate, Navy Environmental Health Center, 2510 Walmer Ave., Norfolk, VA 23513, or e-mail [repro@nehc.med.navy.mil](mailto:repro@nehc.med.navy.mil).

# (I) CONTENTS

(I) CONTENTS .....	3
(II) ABBREVIATIONS AND ACRONYMS USED IN THIS MANUAL .....	5
(III) INTRODUCTION .....	6
Table 1 - Definitions.....	7
(IV) EVALUATION AND MANAGEMENT OF WORKPLACE REPRODUCTIVE AND DEVELOPMENTAL HAZARDS .....	8
A) INTRODUCTION .....	8
B) INDUSTRIAL HYGIENE.....	9
C) OCCUPATIONAL AND ENVIRONMENTAL MEDICINE .....	9
D) WORKER INQUIRIES .....	10
Figure 1 – Evaluation of a Reproductive and Developmental Hazard.....	11
Figure 2 – HCP Consultation.....	12
E) COMMAND ISSUES.....	13
F) INVESTIGATION OF UNDESIRABLE OUTCOMES .....	13
(V) REPRODUCTIVE AND DEVELOPMENTAL HAZARDS IN OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION STANDARDS.....	15
A) INTRODUCTION .....	15
B) ETHYLENE OXIDE .....	15
C) LEAD.....	15
D) 1,2-DIBROMO-3-CHLOROPROPANE.....	17
E) CADMIUM.....	17
F) GLYCOL ETHERS (ETHOXYETHANOL OR “CELLOSOLVE”, METHOXYETHANOL OR “METHYLCELLOSOLVE”).....	17
(VI) EVALUATING AND MANAGING THE PREGNANT EMPLOYEE .....	19
A) INTRODUCTION .....	19
B) OCCUPATIONAL HISTORY .....	19
Table 2 - Contaminants That Have Caused Health Effects Among Workers' Families.....	19
C) PHYSIOLOGIC AND ANATOMIC CHANGES OF PREGNANCY .....	20
D) MODIFICATION OF THE WORK ENVIRONMENT.....	22
E) RECOVERY FROM DELIVERY .....	23
F) BREASTFEEDING.....	23
1) Overview .....	23
2) Occupational Exposures and Breastfeeding .....	23
(VII) THE BIOLOGY OF REPRODUCTIVE AND DEVELOPMENTAL HAZARDS .....	25
A) INTRODUCTION .....	25
B) NORMAL REPRODUCTIVE AND DEVELOPMENTAL BIOLOGY .....	25
1) Hormonal Control.....	25
2) Male .....	25
3) Female.....	25
4) Embryogenesis and Fetal Development.....	26
Figure 3 - Critical Periods of Development.....	27
C) REPRODUCTIVE DYSFUNCTION .....	28
Table 3 - Lifetable of Reproductive and Developmental Success .....	28
D) REPRODUCTIVE AND DEVELOPMENTAL HAZARDS.....	28
1) Reproductive Hazards.....	28
2) Genetic Toxicology.....	29
Table 4 – Genetic Hazards .....	30
3) Developmental Hazards.....	30
Table 5 – Selected Developmental Toxicants and Their Period of Toxic Activity.....	31
4) Drugs in Pregnancy and Lactation .....	31

E) EFFECT OF WORKPLACE EXPOSURES ON REPRODUCTIVE AND DEVELOPMENTAL DYSFUNCTION .....	32
1) <i>Libido and Potency</i> .....	32
2) <i>Pituitary</i> .....	32
3) <i>Ovary</i> .....	32
4) <i>Sperm</i> .....	32
Table 6 – Effects of Selected Occupational Exposures On Sperm Parameters .....	32
5) <i>Mutations</i> .....	33
6) <i>Pregnancy</i> .....	33
7) <i>Breast Milk</i> .....	33
Table 7 – Types of Reproductive and Developmental Risk Factors .....	34
<b>(VIII) OCCUPATIONAL CHEMICAL REPRODUCTIVE AND DEVELOPMENTAL HAZARDS LIST 35</b>	
A) INTRODUCTION .....	35
Table 8 – Chemical Reproductive and Developmental Hazards List, December 20, 2000 .....	36
<b>(IX) DRUG REPRODUCTIVE AND DEVELOPMENTAL HAZARDS..... 48</b>	
A) INTRODUCTION .....	48
B) HEALTH CARE WORKERS AND HAZARDOUS OCCUPATIONAL EXPOSURES .....	48
C) ANTINEOPLASTIC AGENTS .....	48
D) DRUG PREGNANCY RISK CATEGORIES.....	49
Table 9 - ReproDev Pregnancy Risk Category Key .....	49
E) DRUG REPRODUCTIVE AND DEVELOPMENTAL HAZARDS LIST.....	50
Table 10 – Drug and Pharmaceutical Reproductive and Developmental Toxicants List.....	50
<b>(X) OCCUPATIONAL BIOLOGICAL REPRODUCTIVE AND DEVELOPMENTAL HAZARDS..... 82</b>	
A) INTRODUCTION .....	82
Table 11 –Occupational Biological Reproductive and Developmental Hazards List .....	82
<b>(XI) OCCUPATIONAL PHYSICAL REPRODUCTIVE AND DEVELOPMENTAL HAZARDS ..... 87</b>	
Table 12 - Occupational Physical Reproductive and Developmental Hazards List.....	87
A) PHYSICAL EXERTION – GENERAL .....	87
Table 13 – American Medical Association Guidelines for Continuation of Various Levels of Work During Pregnancy .....	89
B) LIFTING.....	90
C) SHIFT WORK AND EXTENDED HOURS OF DUTY .....	90
Table 14 - Occupational Physical Factors Associated with Low Birth Weight or Preterm Deliveries .....	91
D) HEAT STRESS (ENVIRONMENTAL CONDITIONS) AND HEAT STRAIN (PHYSIOLOGIC RESPONSE) .....	91
1) <i>Effects on Fertility</i> .....	91
2) <i>Effects on Pregnancy</i> .....	91
3) <i>Effects on Development</i> .....	92
E) SOUND AND VIBRATION .....	93
1) <i>Fetal Sound Exposure</i> .....	93
2) <i>Fetal Sound Response</i> .....	93
3) <i>Sound Exposure Effects</i> .....	93
4) <i>Vibration Effects</i> .....	94
5) <i>Maternal Noise and Vibration Exposure Guidelines</i> .....	94
F) IONIZING RADIATION.....	95
<b>(XII) OCCUPATIONAL EXPOSURES OF REPRODUCTIVE AND DEVELOPMENTAL CONCERN - SUPERVISOR'S AND WORKER'S STATEMENTS..... 96</b>	
<b>(XIII) FEDERAL AND NAVY REGULATIONS RELATED TO PREGNANCY ..... 99</b>	
A) GENERAL PRINCIPLES .....	99
B) REGULATIONS CONCERNING PREGNANT FEDERAL CIVIL SERVICE PERSONNEL .....	99
C) REGULATIONS CONCERNING PREGNANT SERVICEWOMEN.....	99
D) REGULATIONS CONCERNING THE DEFINITION OF HEALTH CARE PRACTITIONERS.....	100
<b>(XIV) REFERENCES ..... 101</b>	

## (II) ABBREVIATIONS AND ACRONYMS USED IN THIS MANUAL

ACGIH	American Conference of Governmental Industrial Hygienists
BUMED	Navy Bureau of Medicine and Surgery
CFR	Code of Federal Regulations
DBCP	1,2-dibromo-3-chloropropane
DON	Department of the Navy
ETO	ethylene oxide
FSH	follicle-stimulating hormone
HCP	health care practitioner
HCW	health care worker
Hg	mercury
HIV	human immunodeficiency virus
HMIS	Hazardous Materials Information System
HQMC	Headquarters Marine Corps
IH	industrial hygiene
IUGR	intrauterine growth retardation
LH	luteinizing hormone
L/min	liters per minute
LMP	last menstrual period
MSDS	Material Safety Data Sheet
MTF	Medical Treatment Facility
NAVENVIRHLTHCEN	Navy Environmental Health Center
NAVENVPVNTMEDU	Navy Environmental and Preventive Medicine Unit
NAVHOSP	Naval Hospital
NAVMEDCLINIC	Naval Medical Clinic
NAVOSH	Navy Occupational Safety and Health
NIOSH	National Institute for Occupational Safety and Health
OEM	Occupational and Environmental Medicine
OH	Occupational Health
OSH	Occupational Safety and Health
OSHA	Occupational Safety and Health Administration
Pb	lead
PCBs	polychlorinated biphenyls
PEL(s)	Permissible Exposure Limit(s)
PHEL	Physiological Heat Exposure Limits
ppb	parts of substance per billion parts
ReproDev	reproductive and developmental
RDA	Recommended Dietary Allowance
REL	Recommended Exposure Limits
TCDD	2,3,7,8-tetrachlorodibenzo-para-dioxin
TLV	Threshold Limit Value
TV	tidal volume
TWA	time-weighted average
WBGT	Wet-Bulb Globe Temperature

### (III) INTRODUCTION

This Manual provides general guidance to Navy medical department personnel in the recognition, assessment, and control of workplace ReproDev hazards to both male and female uniformed and civil service personnel (hereafter collectively referred as “workers”). Strategies for managing potentially-exposed workers are presented, and potential command concerns about ReproDev issues are addressed. This Manual promotes a consistent, scientific and evidence-based approach to the assessment and disposition of workplace ReproDev issues throughout the Navy.

A *hazard* is a source of danger that has the ability to cause injury or harm. Hazards may be chemical, physical, biological, psychological, and ergonomic agents and conditions. The hazard associated with a toxic substance is a function of its toxicity and the potential for exposure to the substance. *Toxicity* refers to effects caused by chemicals (in any form—solid, liquid, gas, dust, vapor, fume, etc.). The probability of exposure to the substance resulting in an untoward effect is described as the *risk*. A *reproductive hazard* is a hazard that alters male or female fecundity or that affects couple-specific factors (factors related to the ability of two specific individuals to produce offspring), and results in an alteration in fertility at a dose below that which causes harm to the individual. A *developmental hazard* is a hazard that alters the structure or function of a developing embryo or fetus, apparent either before or after birth. Reproductive hazards are of concern when exposed workers have the potential to initiate conception. Developmental hazards are of significance to workers actively trying to conceive, pregnant workers, breastfeeding workers, and workers who have young children at home. A *birth defect* or *congenital malformation* is a structural, functional, or biochemical abnormality that is either genetically determined or induced during gestation, and is not produced by birth trauma. [Table 1](#) contains more definitions related to reproduction and development.

Although the occupational environment for a given worker may not be of scientific or medical significance in terms of ReproDev risks, people may consider the workplace the single greatest threat to their ability to parent normal offspring. Workers’ concerns must be promptly recognized and adequately addressed, regardless of the level of actual ReproDev risk. An effective ReproDev hazard control program must include worker participation, management support, and scientific and medical knowledge. Emphasis should be placed on worker/supervisor education and compliance, including appropriate work practices and healthy lifestyles. Thorough, cooperative workplace evaluations for ReproDev hazards by safety, industrial hygiene (IH), and other occupational health (OH) professionals are necessary. Identified hazards should be controlled to the greatest degree possible. Elimination is preferred when practical; however, steps to minimize exposure may also be effective. Appropriate medical surveillance and counseling regarding risks to health, including ReproDev health, must be provided for workers potentially exposed to existing hazards.

**Table 1 - Definitions**

<b>Chromosome</b> <sup>†</sup>	A structure in the nucleus of a cell containing a linear thread of DNA that transmits genetic information and is associated with RNA and histones.
<b>Deformity, birth</b> <sup>†</sup>	Distortion of a part or general disfigurement of the body.
<b>DNA</b> <sup>†</sup>	A carrier of genetic information for all organisms except the RNA viruses.
<b>Embryo</b> <sup>†</sup>	In animals, those derivatives of the fertilized ovum that eventually become the offspring during their period of most rapid development, i.e., after the long axis appears and until all major structures are represented. In humans, the developing organism is an embryo from about two weeks after fertilization to the end of the seventh or eighth week.
<b>Embryotoxicity</b> <sup>†</sup>	Adverse effects on the embryo as a result of a substance that enters the maternal system and crosses the placental barrier. The effects, expressed as embryonic death or abnormal development of one or more body systems, can also be deleterious to maternal health.
<b>Fecundity*</b>	The capability of the male, female, or couple to produce offspring.
<b>Fertility*</b>	The actual production of offspring.
<b>Fetotoxicity</b> <sup>†</sup>	Adverse effects on the fetus as a result of a substance that enters the maternal system and crosses the placental barrier. The effects usually are deleterious to maternal health and are expressed as fetal death, fetal growth retardation, or retardation of osseous development.
<b>Fetus</b> <sup>†</sup>	The unborn offspring in the post-embryonic period after major structures have been outlined. In humans, this occurs from seven or eight weeks after fertilization and continues until birth.
<b>Gene</b> <sup>†</sup>	The biologic unit of heredity, self-reproducing and located at a definite position on a particular chromosome.
<b>Infertility*</b>	A couple's failure to achieve a clinically recognized pregnancy and usually is defined as 1 year of unsuccessful attempts.
<b>Mutagen</b> <sup>†</sup>	A chemical or physical agent that induces genetic change in form, quality, or some other characteristic.
<b>Subfertility</b>	A reduction in the expected birth rate due to factors other than choice.* This includes a delay in time to conception.
<b>Teratogen</b> <sup>†</sup>	An agent or factor that causes the production of physical defects in the developing embryo.
<p>Definitions marked <sup>†</sup> are from the American Medical Association Council on Scientific Affairs Report: Effects of Toxic Chemicals on the Reproductive System. JAMA 253:3431-3437, copyright 1985, American Medical Association. Reprinted with permission.</p> <p>* Definitions from Mattison, DR, Cullen, MR. Disorders of reproduction and development. In Rosenstock R, Cullen MR. Textbook of Clinical Occupational and Environmental Medicine. W B Saunders; 1994:448. Reprinted with permission.</p>	

## **(IV) EVALUATION AND MANAGEMENT OF WORKPLACE REPRODUCTIVE AND DEVELOPMENTAL HAZARDS**

### **A) INTRODUCTION**

Questions and inquiries concerning possible ReproDev hazards in the workplace may arise in a variety of settings. Healthcare providers should strive to provide thorough, timely responses in a sensitive manner to address workers' concerns.

The identification and evaluation of potential ReproDev hazards is an ongoing process. Workers with concerns about potential ReproDev hazards from specific stressors may request evaluation from their local medical treatment facility (MTF), Occupational and Safety Health (OSH) office, or IH office. This request should include information such as the occupational situation in which the material/stressor is encountered, a current Material Safety Data Sheet (MSDS) for each substance of concern, and, if applicable, the scientific or medical information upon which the concern is based.

When assessing the possible physiologic effects of potential ReproDev hazards, occupational health (OH) professionals should consider the nature of the hazard (chemical, biological, physical, or ergonomic), the dose (concentration/level and duration), the potential route of exposure, the frequency and duration of the exposure, and the timing of exposure within the reproductive or developmental process. To assist in this assessment, Chapter [\(VII\)](#) contains a brief review of reproductive biology and the critical periods of embryonic development.

Qualified OH personnel, such as nurses and physicians, should utilize exposure assessment information from the current IH survey of a worksite or task when evaluating health risk to a worker, or group of workers, from potential ReproDev hazards. Further collaboration with the industrial hygienist may be necessary to fully understand the nature and intensity of worker exposure to ReproDev hazards. In addition, supervisory and OSH personnel may be contacted regarding specific workplace conditions or requirements that may pose special safety risks to the worker (particularly the pregnant worker), such as climbing ladders, working at heights, heat stress conditions, lifting, pushing, pulling, or respirator use. The healthcare provider or professional should first consult local medical resources (Obstetrician/Gynecologist or Occupational and Environmental Medicine (OEM) physician). If these medical specialists are not available locally, the OEM Directorate at the Navy Environmental Health Center (NAVENVIRHLHCEN) can provide a response that addresses the OEM considerations.

Chapters [\(VIII\)](#) and [\(IX\)](#) and [\(X\)](#) contain lists of recognized chemical, biological, physical, and ergonomic ReproDev hazards. The lists are limited to **known** ReproDev hazards. Objective criteria are used for adding or removing agents from the lists. The chemicals and medications lists in Chapters [\(VIII\)](#) to [\(IX\)](#) were adopted from other similar lists, such as the [State of California's Reproductive and Developmental Toxicity List](#).<sup>1</sup> Although the potential for significant exposure to workers by some of the agents is considered remote, all known current chemical and pharmacological agents with ReproDev toxicity are included. The lists will assist in preventing procurement of these materials into the Navy supply system and to identify those already in the system for their control or elimination.

## B) INDUSTRIAL HYGIENE

Based on all available information and using Chapters [\(VIII\)](#), [\(IX\)](#), and [\(X\)](#), the industrial hygienist, in consultation with the OEM staff, determines the existence of known ReproDev hazards in the workplace and identifies the tasks that require further evaluation. If the OEM department does not have the services of an industrial hygienist, IH support may be requested from the cognizant Naval Medical Center (NAVMEDCEN)/Naval Hospital (NAVHOSP)/Naval Medical Clinic (NAVMEDCLINIC), Navy Environmental and Preventive Medicine Unit (NAVENVPVNTMEDU), or NAVENVIRHLTHCEN.

The current IH survey of the worksite, the hazardous materials inventory, and the authorized use list are used to develop a list of ReproDev hazards at a supported command. If a comprehensive IH survey has not been performed, or if the previous survey needs to be updated, additional measurements and evaluation will be required to update the worksite evaluation to specifically address ReproDev hazards. The workplace exposures identified must be discussed with workers and documented in their medical records.

In instances where the duration of use is too short to adequately characterize the potential exposure, professional judgment must be applied to estimate the hazard. In these instances, the industrial hygienist performing this critical function must be qualified and competent by virtue of specialized training, education, and experience (see the [Navy Industrial Hygiene Field Operations Manual](#)).<sup>2</sup> Consideration should be given to the frequency of the potential exposure as well as to a “worst case” exposure scenario.

## C) OCCUPATIONAL AND ENVIRONMENTAL MEDICINE

The OEM Department plays a coordinating role in the evaluation and management of ReproDev hazards and the medical management of exposed workers. In this role, the OEM Department:

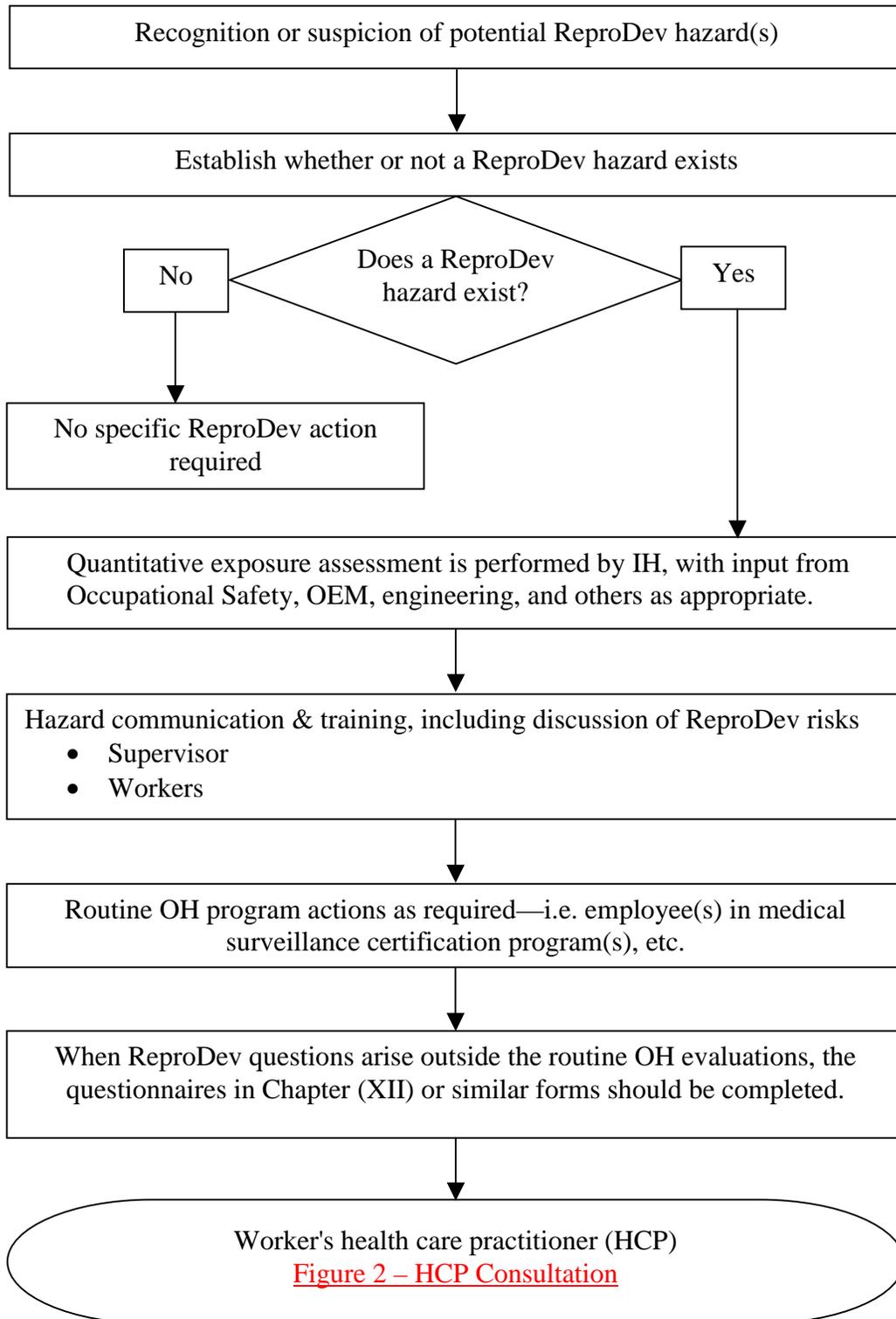
1. Reviews the list of safety and health hazards in the worksites of the supported command (maintained by command’s OSH office and compiled by the IH Departments).
2. When necessary, requests additional IH evaluations (exposure measurement and characterization), and actual worksite visits to directly evaluate ReproDev stressors and work practices and control ReproDev hazards.
3. Compiles or reviews data on occupational illnesses and injuries at the worksite to identify conditions and outcomes that may have potential adverse effects on reproduction or development. If applicable, review and analyze pregnancy outcomes, looking for trends potentially related to the work environment.
4. Assists in the assessment of the hazards in the workplace. Using the ReproDev hazards lists—Chapter [\(VIII\)](#) to Chapter [\(XI\)](#)—determine the level of ReproDev risk for a given task or workplace. If sufficient OEM support is not available locally, consultation may be obtained from the OEM department (located at many larger Navy Medical Clinics and most Naval Hospitals) or NAVENVIRHLTHCEN.

#### D) WORKER INQUIRIES

Workers, individually or through a collective group such as a union or rate/specialty association, may raise questions about the ReproDev risk of an agent or condition. Frequently, review of the agent or condition in light of the available literature or information, and discussion with the inquiring party (or parties) by an OH professional, is sufficient to satisfactorily answer these questions. Occasionally, a worker with concerns about issues of reproduction or development may request job modification or even removal from exposure to a specific hazard. These instances require a review of the worker's actual exposure—to determine if there is a potential ReproDev hazard and, if there is, to what extent that exposure occurs (amount, concentration level, frequency, and duration). If additional information is necessary, a worksite visit may be required. Chapter [\(XI\)](#) is a summary of physical agents and conditions (hazards) that should be considered when reviewing potential ReproDev hazards in the workplace. Chapter [\(XII\)](#) contains a two-page questionnaire that may be used for any worker with ReproDev concerns. This questionnaire includes the worker's self-assessment of his/her occupational/non-occupational exposures to physical, chemical, biological, and environmental agents. These questionnaires and the pertinent MSDSs should be reviewed by the OEM physician and/or the worker's personal physician. If needed, the OEM physician may call upon IH to assist in quantifying workplace exposures. Once the OEM practitioner makes a medical management decision, it must be discussed with the worker and his or her personal physician. [Figure 1](#) and [Figure 2](#) are flow charts that can be used by the OH staff in managing a worker's request for job modification or reassignment.

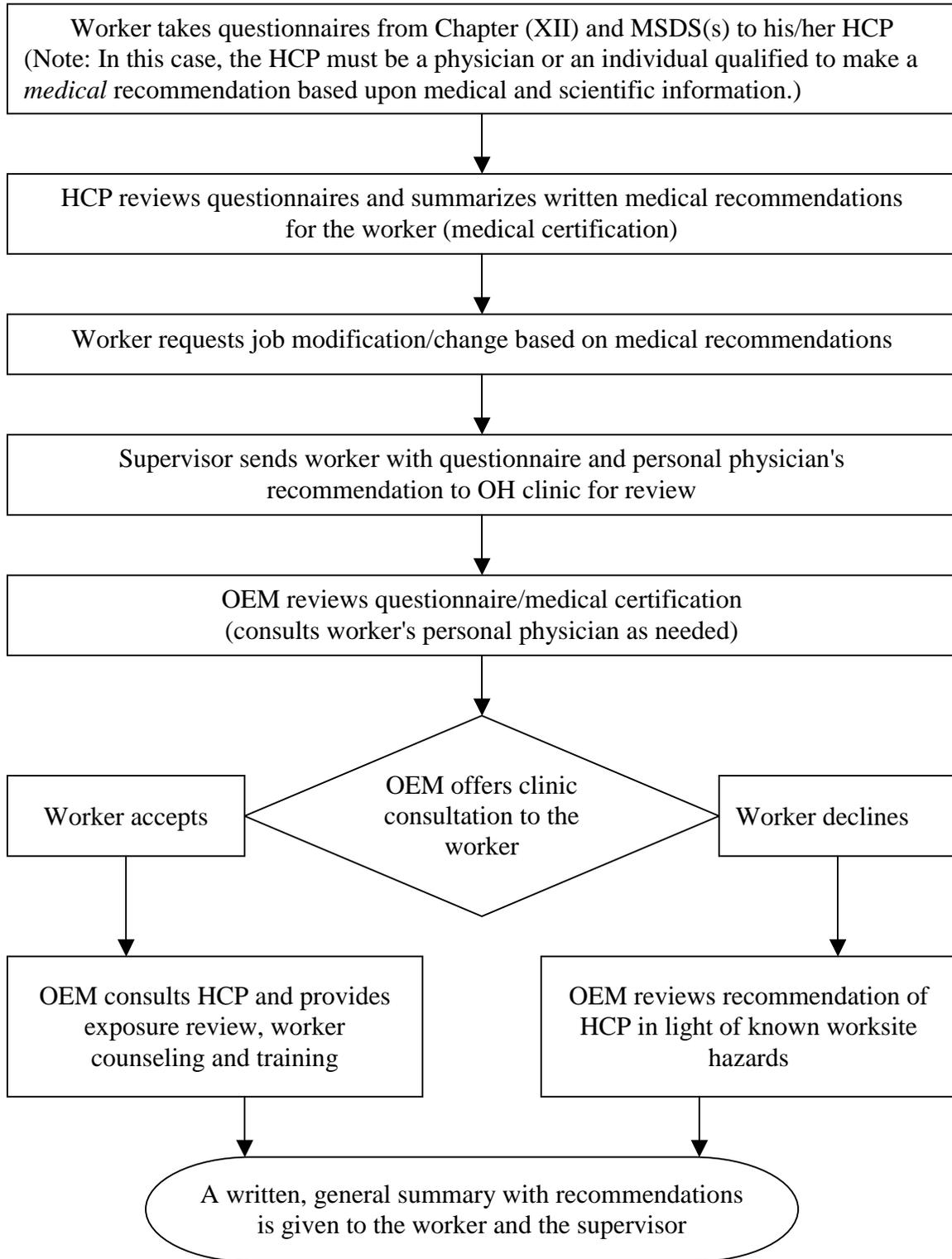
If a pregnant active duty member or civil service employee asks for a change of duties or assignment, she should provide the OEM physician a medical certification from her personal physician, stating that work limitations are necessary. This document must state specifically what duties she can perform, and under what conditions these duties can be performed. This written certification is in turn reviewed by the OEM physician. It is recommended that both physicians discuss the individual's specific requirements. The employing activity should make every reasonable effort to accommodate these requests<sup>[jm1]</sup>.

**Figure 1 – Evaluation of a Reproductive and Developmental Hazard**



**Figure 2 – HCP Consultation**

**Figure 2 – HCP Consultation**



## E) COMMAND ISSUES

Requests for information concerning ReproDev hazards associated with specific exposures or jobs may be directed to the local OEM Department. The command's IH survey may have already addressed the ReproDev issues associated with the process where the material is used. The supporting OSH office may also be contacted for assistance as necessary.

## F) INVESTIGATION OF UNDESIRABLE OUTCOMES

The occurrence of an undesirable event (such as spontaneous abortion or birth defect), or cluster of undesirable events, may lead to the request for an evaluation of the workplace to investigate a possible connection with workplace exposure. The association of an untoward outcome and occupational exposure does not prove that the exposure and the outcome are causally related. Establishing causality requires further scientific investigation. “Clustering” of events in time and place may occur in natural or disease conditions and may be due to chance alone [[PMID 1820268](#)].<sup>3</sup> The OEM Department has the primary responsibility of determining whether or not the event or cluster may have occurred by chance or from exposure to ReproDev hazards in the workplace. The physician or other OEM practitioner should work closely with the industrial hygienist, OSH manager, and other command personnel as appropriate from the very beginning of an investigation.

The collection of complete information at the outset of an investigation is critical. The information may reveal that individual events are dissimilar and not related—or are not attributable to workplace exposures. The type of birth defect (congenital malformation) may not be uniform, spontaneous abortions may have been caused by individual medical conditions, or the job requirements and exposures of the employees concerned may not be the same. Satisfactory (complete) investigations of such clusters may require evaluation of reproductive or developmental outcomes observed at other commands. Documenting and evaluating all undesired ReproDev outcomes of workers are good practices and enable epidemiological evaluation and identifying trends. Combining individual outcomes (collective data) allows identification of a rare event.

The extent of the evaluation by the staff of each MTF will depend on the situation and resources locally available. A complete investigation may require assistance obtained in accordance with local procedures, which may be from the OEM Department at the supporting MTF. These activities can arrange supplemental assistance from NAVENVIRHLTHCEN if needed.

The investigation process includes the following steps:

1. Schedule an individual appointment with the OEM physician for each involved worker. In some cases, it is prudent to also allow the worker's spouse to be present. Adequate time must be allowed for the worker to fully explain his/her concerns or complaints. After a thorough and complete history is obtained, a medical examination may be indicated by the situation. A consult with another specialist may be required. There must be documentation in the medical record, and the worker must be assured that the medical information will remain confidential.

2. Obtain signed release of medical records/information forms that authorize the attending physician to release a copy of each involved worker's appropriate medical information.
3. Review the diagnosis and the medical records of the cases in question. Determine if the worker (or workers) has/have a past history of a similar event. Consider factors that may affect the event in question, such as illness, drug use (prescribed, over-the-counter, or illicit), and activities outside of the work environment. Coordination with the worker's HCP may facilitate identification of cases due to causes other than occupational exposure. The worker's privacy must be protected at all times during the conduct of the investigation.
4. Review the list of ReproDev hazards in that task/worksite. Consult IH for past and present records of sampling. Additional sampling may be needed to complete a satisfactory evaluation. Visit the worksite to identify stressors and work practices or conditions that may be associated with an adverse effect on reproduction or development.
5. Determine the timing and duration of exposure, and ascertain if the onset of exposure is consistent with the occurrence of the event (this is discussed in detail in Chapter [\(VII\)](#)).
6. If more than one worker is involved, determine if the affected workers have a common exposure and if a particular task, shift, or location is over-represented.
7. Review this manual and other medical literature to determine if the stressors to which the worker(s) is/are exposed have been found to produce adverse reproductive or developmental effects—and under what specific conditions.
8. When the OH Department cannot confidently rule out a cluster, it may request supplemental assistance from NAVENVIRHLTHCEN.
9. Complaints of infertility should be recorded (and handled as confidential) to alert both the OH and the OSH Departments. When evaluated collectively, such complaints may reveal an increased incidence of infertility in the worksite over the expected rate for the general population. If a medical cause cannot be identified after taking a complete personal, occupational, and environmental history, then a workplace assessment for possible stressors should be considered. Individual worker infertility problems will require a specialist in this field.

## **(V) REPRODUCTIVE AND DEVELOPMENTAL HAZARDS IN OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION STANDARDS**

### **A) INTRODUCTION**

The potential for hazardous substance exposure to cause adverse reproductive or developmental effects is becoming an increasingly important issue, particularly in the American workforce. In the past, ReproDev effects have not been a significant toxicity of concern in setting standards for a substance. However, several comprehensive Occupational Safety and Health Administration (OSHA) standards have been written with greater consideration of the potential effects of hazardous substance exposure on the reproductive health of exposed individuals. OSHA standards that include consideration of ReproDev effects of chemicals are ethylene oxide (ETO) ([29 CFR 1915.1047](#)),<sup>4</sup> lead (Pb) ([29 CFR 1910.1025](#)<sup>5,6,7</sup> and [29 CFR 1926.62](#)<sup>8</sup>), and 1,2-dibromo-3-chloropropane (DBCP)([29 CFR 1910.1044](#)<sup>9,10,11,12</sup> and [29 CFR 1926.1144](#)),<sup>13</sup> and cadmium (Cd) ([29 CFR 1910.1027](#)). Reproductive toxicity of glycol ethers is currently being considered as another such standard with this emphasis and a discussion of this class of compounds is included here. Moreover, reproductive health outcomes are now routinely given greater consideration in writing new standards. OSHA standards now require a reproductive history in medical surveillance programs for substances known to cause reproductive toxicity.

The comprehensive health standards mentioned above specifically discuss ReproDev health effects requiring medical intervention. Medical intervention is triggered by an "action level" for ETO and Pb. An *action level* is the exposure concentration at which an employer must begin compliance activities specified in the OSHA standard. The action level is defined normally as an exposure of one-half of the Permissible Exposure Limit (PEL) of a particular chemical. For DBCP, there is no defined action level. The medical interventions ordinarily required for substances causing potential ReproDev health harm include targeted ReproDev history-taking, worker education, and specialty medical referral for infertility evaluations in some circumstances. These standards are discussed below.

### **B) ETHYLENE OXIDE**

ETO is a highly reactive epoxide that has a variety of uses and consequently is a major industrial chemical produced in the United States. ETO is primarily found in chemical factories, where it is produced and used in the manufacture of ethylene glycol for automotive antifreeze, polyester fibers and films, and detergents. ETO is also used for gas sterilization of equipment and supplies in hospitals and health care facilities, and as a fumigant in the manufacture of food and medical products and in libraries and museums. The major use of ETO in the Navy and Marine Corps is gas sterilization of medical devices, equipment, and supplies. ETO is also used for sterilization of non-medical items within Naval activities. Exposure to ETO has been linked to an increased risk of cancer and to ReproDev effects, including decreased male fertility, fetotoxicity, and spontaneous abortions.

### **C) LEAD**

Since the 19th Century, it has been well known that exposure to Pb can have serious effects on reproductive function in both males and females, and on development. Workers with the

greatest exposure include smelters, metal workers (including welders), painters, typesetters, glass artists, firing range personnel, and those involved in the manufacture of batteries, paint, ink, ceramics, pottery, ammunition, textiles, and leaded gasoline. Additionally, workers in the construction sector involved in demolition, bridge painting and repair, and other such tasks are also at risk. The concentration of Pb has been greatly lowered in many types of commercial and residential paints; however, industrial paints used to protect bridges and other structures, as well as marine (Navy) applications, still contain significant concentrations. With respect to Naval forces, Pb exposure may occur from paint removal operations (use of deck-crawlers, needle guns, grinders, sanders); “hot operations” (welding or cutting of metal products that have been painted with Pb-containing paints); and indoor weapons firing and range operations.

In males, the reproductive effects of Pb exposure include decreased libido (sex drive), impotence (inability to have or maintain an erection), malformed sperm, decreased number of healthy sperm, decreased total sperm count, decreased sperm motility, and sterility. Of note, decreased sperm count [[PMID 3579367](#)]<sup>14</sup> and sperm motility [[PMID 9987558](#)]<sup>15</sup> and production of malformed sperm [[PMID 1442789](#)]<sup>16</sup> have been found at elevated blood Pb levels (40 µg/dl<sup>i</sup> has been noted in a review article)[[PMID 9764095](#)].<sup>17</sup>

Higher incidence of infertility, premature births, spontaneous abortions, pre-eclampsia, hypertension in pregnancy, and premature rupture of membranes have been reported in women exposed to high Pb levels [[PMID 8247405](#)].<sup>18</sup> Pb is known to cross the placental barrier, with resulting levels in the umbilical cord blood at birth comparable to concentrations in the mother's blood [[PMID 10025415](#)].<sup>19</sup> Fetal blood Pb levels have been noted to increase with maternal occupational exposure [[PMID 7448135](#)].<sup>20</sup>

Fetal and infant/child neurological damage may occur at blood Pb levels less than 20 µg/dl [[CDC](#)],<sup>21</sup> and may be manifested by childhood learning difficulties [[PMID 7679348](#)].<sup>22</sup> Infants of mothers with Pb poisoning have been found to have low birth weight, slow growth, increased risk of death during the first year, and nervous system disorders.

Considering the demonstrable ReproDev risks associated with untoward exposure to Pb, including the risk of genetic damage in both the ovum and sperm, the Pb standard promulgated in 1978 established a 30 µg/100g maximum permissible blood level in both males and females who wish to bear children.<sup>23</sup> However, given scientific advances on the ReproDev effects of Pb, clinicians may reasonably counsel patients to achieve even lower blood levels prior to conceiving. Good work practices and current IH control technologies, including the availability of effective respiratory protection, makes achievement of lower blood Pb levels (< 20 µg/dl) easily attainable. Elevated blood Pb levels during pregnancy have been attributed to mobilized skeletal Pb stores [[PMID 9242366](#)].<sup>24</sup> It has been recommended that blood Pb levels be below 20 µg/dl preceding conception and during pregnancy, and that a woman with a blood Pb above 20 µg/dl and desiring to become pregnant be advised to avoid uncontrolled Pb exposure for 1 to 2 years before attempting pregnancy.<sup>25</sup>

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<sup>i</sup> Laboratory values of measurements in blood are usually reported in units per deciliter. However, some references and OSHA standards are given in units per 100 grams of blood.

Clinicians treating or counseling male and female workers with significant exposure to Pb should take a careful and complete ReproDev history including history of infertility, impotence, loss of libido, abnormal menstruation, miscarriages, stillbirths, or children with birth defects. A ReproDev history should also be considered in formulating work plans, including establishing alternative duty assignment, when a woman is trying to conceive or is pregnant. Comprehensive guidance for the administrative and healthcare management of pregnant servicewomen is provided elsewhere.<sup>26</sup>

#### D) 1,2-DIBROMO-3-CHLOROPROPANE

1,2-Dibromo-3-chloropropane (DBCP) is a nematocide (pesticide used to control worms) that was widely used in agriculture in the U.S. and abroad from the mid-1950s until 1977. The discovery of adverse reproductive effects in humans led to the United States imposing a partial ban in 1977 and a total ban in 1987.

DBCP has been shown unequivocally to produce testicular toxicity and sterility in exposed male workers in a dose-response relationship [[PMID 556420](#)].<sup>27</sup>

OSHA requires that employers ensure that no employee is exposed to an airborne concentration of DBCP in excess of 1 part per billion (ppb) of air as an 8 hour time-weighted average (TWA). Also, as DBCP has been shown to cause reproductive dysfunction, OSHA requires that physical examination be part of a DBCP medical surveillance program. Testicle size, semen analysis, and serum determination of levels of reproductive hormones including follicle-stimulating hormone (FSH), luteinizing hormone (LH), and (in females only) estrogen, are to be included.

#### E) CADMIUM

Cadmium is a metal with toxic qualities that is encountered in industry, especially in metalworking (including welding), as well as elsewhere (such as in cigarettes). Among other adverse health effects, cadmium is associated with decreased birth weight (with inhalation exposure, ATSDR),<sup>28</sup> placental toxicity (Miller),<sup>29</sup> preterm delivery ([PMID 8094678](#)),<sup>30</sup> and possibly with prostate cancer ([29 CFR 1910.1027 App D](#)).<sup>31</sup> OSHA requires that employers provide a pre-placement detailed medical and work history, to include a reproductive history ([29 CFR 1910.1027 App D](#))<sup>32</sup> with an emphasis on reproductive dysfunction ([29 CFR 1910.1027](#)).<sup>33</sup>

#### F) GLYCOL ETHERS (ETHOXYETHANOL OR “CELLOSOLVE”, METHOXYETHANOL OR “METHYLCELLOSOLVE”)

Two members of the large family of “glycol ethers”, ethylene glycol monomethyl ether and ethylene glycol monoethyl ether and their acetates, have been associated with male reproductive effects. The glycol ethers (including the ones specifically addressed above) are widely used as solvents in the manufacture of lacquers, varnishes, resins, printing inks, textile dyes, and as an anti-icing additive in jet fuel. They are also used in consumer products such as latex paints and cleaners. Naval exposures may result from the use of these substances. It is important to recognize that the other chemical members of the “glycol ether” family have not been demonstrated to cause reproductive or developmental effects. ReproDev effects are the primary health concerns associated with exposure to glycol ethers because of exhibited abnormalities in the blood and male reproductive system of exposed workers. The major reproductive effect observed among exposed male workers is a reduced sperm count.

The final glycol ether rule is pending, but it has been proposed that a reproductive history will be required in the applicable medical surveillance program. Other specific tests have not been proposed. The current PELs for different glycol ethers vary widely depending on the specific chemical, and new PELs are being proposed.

## **(VI) EVALUATING AND MANAGING THE PREGNANT EMPLOYEE**

### **A) INTRODUCTION**

Exposure to ReproDev hazards can affect workers, or their children, in a variety of ways. Important concerns are the potential for mutagenesis, abnormal development of the fetus, and interference with the physiology of pregnancy leading to spontaneous abortion, premature delivery, or fetal injury. Unfortunately, the guidance for occupational exposures provided by consensus standards, such as Threshold Limit Values (TLVs), rarely provide adequate guidance when dealing with the pregnant worker. The same limitation is found with the statutory PELs, as these standards are based upon exposure to the average non-pregnant worker. (In other words, just because TLVs or PELs say nothing about ReproDev hazards, it does not imply there is no hazard or that any substance with a given TLV or PEL is “OK” in regards to ReproDev issues.) Therefore, evaluating and caring for the pregnant worker often requires an individualized approach ([AMA, 1999](#)).<sup>34</sup> Industrial hygienists, OEM physicians, and obstetrical practitioners need to be involved in a combined effort.

### **B) OCCUPATIONAL HISTORY**

The first step in evaluating the pregnant worker is to take a detailed personal, social, occupational, and environmental history. The occupational history should consider past and current jobs, including job title and a description of actual tasks performed, duration of employment, and occupational exposures (chemical, physical, biological, radiological, and psychological stressors). A spousal history, if available, should be taken as well, preferably directly from the spouse. This may be important, as workers may unknowingly take home toxicants from the workplace (in the form of dust, dirt, or stains on their skin, clothes, shoes, etc.), or may work with toxicants in the home (in the so-called “cottage industry”). Such exposure mechanisms have been known to affect other family members, including children [[PMID 8352287](#)].<sup>35</sup> A NIOSH study of contamination of workers' homes with hazardous chemicals and substances (including infectious agents) transported from the workplace noted that the problem is worldwide and has “resulted in a wide range of health effects and death among workers' families exposed to toxic substances and infectious agents” ([NIOSH](#)).<sup>36</sup> Contaminants of ReproDev concern identified in the study include the following ([NIOSH](#)).<sup>37</sup>

**Table 2 - Contaminants That Have Caused Health Effects Among Workers' Families**

Lead	Pesticides
Mercury	Chlorinated hydrocarbons
Arsenic	Estrogenic substances
Cadmium	Infectious agents

Taken from: NIOSH. Protect your family--reduce contamination at home a summary of a study conducted by the National Institute for Occupational Safety and Health. U.S. Department of Health And Human Services Public Health Service Centers For Disease Control And Prevention, National Institute for Occupational Safety and Health. Cincinnati, Ohio. DHHS (NIOSH) Publication No. 97-125.

Chapter [\(XII\)](#) contains forms which should be completed as part of this evaluation. IH data must be incorporated into the evaluation. Existing exposure data relative to ReproDev concerns should be used when available. In the absence of data, IH needs to be involved in assessing the workspaces and processes, and in characterizing exposures.

As part of the OH history, the worker may be asked if she, or any co-worker(s), has had signs or symptoms that may raise the index of suspicion for occupational illness, such as chronic cough or skin irritation. It is important to ascertain the temporal relationship of these signs and symptoms to work exposures. Prior work experience, especially if the worker is relatively new to the job, should be addressed. Special attention needs to be paid to agents which accumulate in the body and have prolonged half-lives, such as Pb and polychlorinated biphenyls (PCBs).

Community and home exposures can be significant, and should be part of the evaluation, including:

- Personal habits, such as diet and the use of tobacco, alcohol, and nutritional supplements
- Proximity to a toxic waste site or incinerator
- Pesticide application (indoor and outdoor)
- Air pollution
- Prolonged intense sound exposure
- Known water contamination
- Use of household products (cleaning solvents, paints)
- Hobbies and crafts (such as ceramics, photography, stained glass, or furniture refinishing) and home renovations
- Exposure to hazardous substances from household members (environmental tobacco smoke, or Pb or other toxic dust brought home on work clothes)

Prior to making a “work prescription” it is necessary to know something about the workplace environment and worker attitudes (e.g. interpersonal relationships), job flexibility, the possibility of temporary assignment, the worker's preference, and the availability of amenities (toilets and rest facilities, and, after childbirth, breastfeeding/pumping areas).

### C) PHYSIOLOGIC AND ANATOMIC CHANGES OF PREGNANCY

There are many normal maternal changes that occur during the course of a pregnancy. Occupational and environmental exposure during pregnancy may cause effects to either the mother or the developing child. The attending HCP must differentiate normally occurring events from those caused by an occupational or environmental exposure. The exposure must be of sufficient dose (concentration and duration), and occur at the hazard-specific critical time period during pregnancy, to cause an adverse developmental effect

**PLACENTA:** The “fetal-placental unit” is unique to pregnancy. This functional unit provides a partial barrier to some chemicals and limits their transfer from the maternal blood to the fetal blood. Chemicals with a small molecular size (molecular weight <500 Daltons) cross the placenta rapidly by simple or facilitated transport. Small, uncharged, unbound, lipid soluble molecules will cross the placenta most readily [[PMID 7758253](#)].<sup>38</sup>

**CARDIOVASCULAR SYSTEM:** The maternal cardiovascular system undergoes significant changes during pregnancy. Blood volume increases 30-40% beginning in the first trimester and peaks at 32 weeks (well into the third trimester). Cardiac output parallels volume change, increasing 1-1.5 liters/minute (L/min), greatly influenced by body position. Cardiac volume

increases about 10%. The resting heart rate increases 10-15 beats per minute. The change in cardiac output is greater with twins or other multi-fetal gestations than with the usual single pregnancy. With multiple gestations, there is also an increased force of cardiac contraction (positive inotropic effect) that possibly indicates a decreased cardiovascular reserve.<sup>39</sup> The enlarging uterus presses on the inferior vena cava causing venous pressure to rise in the lower extremities, contributing to the development of hemorrhoids and varicose veins.

**PULMONARY SYSTEM:** The pulmonary system similarly undergoes marked changes during pregnancy. Diaphragmatic excursion is increased during pregnancy, and tidal volume (TV) increases almost 40%. The diaphragm is elevated about 4 cm, which is not offset by the 6 cm increase in thoracic circumference. Residual volume falls 20%, with a net minute ventilation increase from 7 to 10 L/min.<sup>40</sup> Due to this increased ventilatory volume, the pregnant worker breathes in more air and is exposed to a larger dose of airborne contaminants than are either non-pregnant females or males of comparable size. Although pregnancy increases the oxygen demand, it is less than the increased TV and increased hemoglobin in the circulation provide. Thus, the arterio-venous oxygen difference is decreased in pregnancy. Since respiratory rate does not change significantly, there is a relative "hyperventilation", with the decreased arterial pCO<sub>2</sub> (32 mm Hg) and respiratory alkalosis partially compensated for by a decrease in plasma bicarbonate.<sup>41</sup> These changes make the pregnant female (and fetus) more sensitive to the toxic effects of carbon monoxide. Capillary dilation occurs throughout the respiratory tract, leading to increased sensitivity to dusts and airborne irritants. The anatomic and physiologic changes of pregnancy (especially later in pregnancy) may make it increasingly difficult to use some types of respirators.

**EYE:** Changes in the eye noted during pregnancy include decreased intra-ocular pressure, decreased corneal sensitivity (later in pregnancy), slightly increased corneal thickness, and transient loss of accommodation (also noted during lactation). Brown-red opacities on the posterior surface of the cornea ("Krukenberg spindles") may be increased. Visual fields are probably not affected by the increased pituitary size associated with pregnancy.<sup>42</sup>

**SKIN:** The skin of pregnant females may undergo changes including hirsutism, hyperpigmentation (of nipples, areola, nevi, linea alba, and freckles, and the "mask of pregnancy," called melasma or chloasma—irregular brown facial pigment changes), striae gravidarum, palmar erythema, arterial spiders, and increased sweating. Increased pigmentation may alter the response of the skin to sun exposure. To avoid increased (and usually uneven) tanning, avoidance of unnecessary sun exposure or the use of pregnancy-safe sun block preparations may be advised. Several skin conditions (dermatoses) are unique (or nearly unique) to pregnancy. Pruritic urticarial papules and plaques of pregnancy ("PUPP") is a common cause of itching during pregnancy.<sup>43</sup> The lesions begin on the abdomen and move to the extremities and usually spare the face. Resolution of pruritus is complete and spontaneous following delivery. Papular dermatitis and prurigo gestationis are pruritic conditions generally appearing late in the second or during the third trimester of pregnancy. Herpes gestationis (pemphigoid gestationis) is a serious, rare (1 in 50,000 pregnancies) blistering, pruritic condition usually seen in late pregnancy (but may be seen from early pregnancy to one week postpartum). It is not herpes virus-induced (despite the name), and recurs in subsequent pregnancies. Impetigo herpeticiformis is a rare condition of late pregnancy, and may persist for months after delivery. Erythematous patches surrounded by sterile pustules are seen, usually in

conjunction with systemic symptoms and mild pruritus. In order to appropriately treat and avoid exposure to the causal agent(s), the etiology of dermatologic conditions must be evaluated. A dermatologist should be consulted to evaluate skin conditions or complaints in pregnant workers in order to ensure proper treatment and disposition.

**MUSCULOSKELETAL SYSTEM:** Pregnancy places marked stress on the musculoskeletal system. There are significant weight changes and the center of gravity changes almost daily as the uterus rises and the breasts become heavier. With accentuated curvature of the spine (lordosis of the lumbar spine and kyphosis of the upper back), low backache is a common problem. The redistribution of weight and the center of gravity increases the risk of falls, and may necessitate removal of pregnant women from jobs where balance is crucial. Pregnant workers should wear low-heeled shoes with non-slip soles. The ability to lift objects can be significantly compromised since the horizontal distance of a load from the axial skeleton becomes progressively greater. Of particular operational concern is the potential difficulty that pregnant women may experience in emergency or escape situations.

Ergonomic factors require special attention. As pregnancy progresses, modification of the intensity, frequency, or pattern of physical tasks often is necessary. Work that requires long periods of standing during the third trimester contributes to decreased utero-placental blood flow and preterm births and reduced birth weight [[PMID 8899916](#)][[PMID 2306429](#)][[PMID 2293743](#)].<sup>44,45,46</sup> Excessive sitting (including during prolonged trips) or standing (promoting venous stasis, thought related to the increased incidence of deep vein thrombosis in pregnancy) may cause blood clots in legs and exacerbate hemorrhoids, as well as back and leg pain (see [Table 13](#) for guidelines). Pregnant women are at increased risk for carpal tunnel syndrome, therefore attention should be directed toward prevention. Active prevention and protection efforts to reduce the chances of physical trauma should be made. With increased body size and weight, and a changing center of gravity, the pregnant worker may be slow to react to quickly changing or dangerous situations. Even minor blows to the abdomen can cause placental abruption with potential fetal and maternal death. The protuberant maternal abdomen may also be a hazard in certain situations where inadvertently bumping equipment or personnel may be dangerous.

#### D) MODIFICATION OF THE WORK ENVIRONMENT

Specific guidelines for management of pregnant servicewomen are described elsewhere.<sup>47</sup> The basic principles involved in providing a workplace free from ReproDev hazards are the same as those used in the practice of OH in general:

1. Product substitution (replace a hazardous condition or substance with a less hazardous one). Unfortunately, this cannot always be done soon enough to assist with an individual pregnancy as the pregnancy is often not identified sufficiently early. A program to utilize less hazardous products and correct hazardous conditions can help the command move toward a more healthful workplace;
2. Engineering controls (improving exhaust, enclosing processes, powered lift assistance);
3. Administrative controls (rotation or reassignment); and, as a last choice,
4. Personal protective equipment (use of aprons, gloves, or respirators).

The industrial hygienist can be very helpful in recommending measures that can most effectively minimize exposures.

#### E) RECOVERY FROM DELIVERY

After delivery, a variety of important physiological, psychological, and physical adaptations of the postpartum period take place. Recovery from blood loss and resumption of non-pregnant physiology, as well as wound healing, is accomplished. Mothers who do not breastfeed will experience several weeks of breast tenderness. Breastfeeding mothers will experience several weeks of nipple soreness and cracking. For the most part, however, these conditions should be well under control when the worker returns to the job.

#### F) BREASTFEEDING

##### 1) Overview

Depending on personal desires, breastfeeding may go on for one year or more. Breastfeeding provides significant benefits to both mother and infant. Babies who are fed breast milk have fewer illnesses and there may be a better "bond" established between the mother and baby. Breastfeeding is certainly more cost effective than formula feeding and can be a major benefit in helping the mother lose weight gained during pregnancy. Unfortunately, the rate of breastfeeding in the United States is sub-optimal, and work conditions are generally not supportive of breastfeeding. A recent review found a strong and consistent association of breastfeeding with maternal age and level of education, and a consistent negative association between maternal smoking habits and breastfeeding duration. Also found was evidence to suggest that fathers play an important role in the breastfeeding decision and that intended duration is a strong predictor of actual duration [[PMID 10197366](#)].<sup>48</sup> The likelihood of returning to work for breastfeeding mothers is approximately half that of non-breastfeeding mothers one to three months after delivery, and one-third that of non-breastfeeding mothers nine to 12 months after delivery [[PMID 8829985](#)].<sup>49</sup>

An [American Academy of Pediatrics policy statement](#) notes many advantages of breastfeeding, including "reduced employee absenteeism for care attributable to child illness." The same statement calls for "employers to provide appropriate facilities and adequate time in the workplace for breast-pumping."<sup>50</sup> This is relatively simple to do. To allow successful breastfeeding, an employer must provide flexible time (a "nursing break") for feeding or pumping, a clean room with running water, and a refrigerator for pumped milk. This minimal level of support will often make the difference between whether or not a mother continues breastfeeding. In general, breastfeeding should be encouraged under most circumstances despite the presence of trace amounts of environmental toxins [[PMID 7702761](#)].<sup>51</sup>

##### 2) Occupational Exposures and Breastfeeding

There are some occupational medicine concerns related to working mothers who breastfeed. A variety of chemicals, both toxic and non-toxic, can be excreted in breast milk. Most substances in the maternal circulation cross into breast milk to a certain extent. Human milk is high in fat and therefore fat-soluble substances can exist in higher concentrations in milk than in plasma. Examples of toxic substances that can be found in breast milk include Pb, mercury (Hg), pesticides, radioisotopes, and PCBs. Workplace exposures must be evaluated with respect to potential and actual conditions and levels of exposure. A specific area requiring attention is

exposure to surgical (medical, dental, or veterinary) anesthesia. When anesthetic gases are used, both fetal and breast-fed infant exposures to substances with potential ReproDev toxicity are possible. Halothane is fat soluble (as are other anesthetic gases), and it has been found in breast milk at a concentration of 2 ppm [[PMID 986147](#)].<sup>52</sup> Hospital operating rooms usually use a “scavenging” system to remove anesthetic gases. However, post-anesthesia care units (recovery rooms) often have no scavenging system, and post-operative surgical patients may give off anesthetic gases. Health care workers (HCWs) in such situations should not breast feed unless there are adequate, functioning scavenging systems in place (McDiarmid).<sup>53</sup>

Breastfeeding women should not handle antineoplastics or work in areas where they are handled (McDiarmid).<sup>54</sup> These agents may contaminate surfaces in pharmacy drug preparation areas and drug administration areas [[PMID 10428450](#)]<sup>55</sup> and even occasionally penetrate gloves [[PMID 10595805](#)].<sup>56</sup> The assessment of any of these types of exposures should be performed by a qualified IH in consult with appropriate medical staff (OEM, OB/GYN, Pharm D).

## **(VII) THE BIOLOGY OF REPRODUCTIVE AND DEVELOPMENTAL HAZARDS**

### **A) INTRODUCTION**

Reproduction requires the proper and timely functioning of multiple body systems, both prior to and throughout the reproductive process.

### **B) NORMAL REPRODUCTIVE AND DEVELOPMENTAL BIOLOGY**

#### **1) Hormonal Control**

The hypothalamus, located at the base of the brain, initiates many of the processes leading to sexual development and reproductive capacity. Gonadotropin releasing hormone is secreted by the hypothalamus and triggers the pituitary to secrete LH and FSH. The function of the testes and ovaries are directly dependent on the action of LH and FSH.

#### **2) Male**

Under the influence of LH and FSH, testes produce sperm and synthesize testosterone. Testosterone and related compounds are responsible for the growth and development of sexual organs and secondary sexual characteristics (deep voice, male body hair distribution, and male muscle development).

In adult males, sperm are continuously produced from cells known as spermatogonia. The process, called spermatogenesis, takes an average of 74 days. If the spermatogonia are damaged, the ensuing decrease in sperm production may prevent reproduction. Depending on the injury, damage to spermatogonia may be reversible or irreversible. Sperm are released from the body in seminal fluid by ejaculation, which is under sympathetic control involving the first and second lumbar spinal cord nerve fibers.

#### **3) Female**

In the female, LH and FSH regulate the development and release of oocytes (eggs) from the ovaries. The number of oocytes is established in early childhood and declines in adulthood.<sup>57</sup> By puberty, approximately 400,000 oocytes exist, whereas after age 36 there are less than one-tenth that number.<sup>58</sup> If oocytes are damaged, no mechanism exists for their replacement. In the adult female, the cyclical release of LH and FSH establishes the menstrual cycle. The LH and FSH promote the development of estrogen-producing ovarian follicles (the group of cells surrounding an oocyte).

Estrogens are instrumental in the preparation of the uterus for the implantation of the fertilized ovum. Estrogens are also responsible for the development and maintenance of secondary sex characteristics (breast development, body fat pattern) and the changes in cervical mucus associated with the menstrual cycle.

During each menstrual cycle, usually one ovarian follicle matures and releases an ovum. This process is termed ovulation. Union of the ovum and sperm usually occurs in the fallopian tube. After the release of the ovum, the cells of the ovarian follicle produce both progesterone and estrogen to prepare the uterus to receive the fertilized ovum. If the fertilized ovum is not

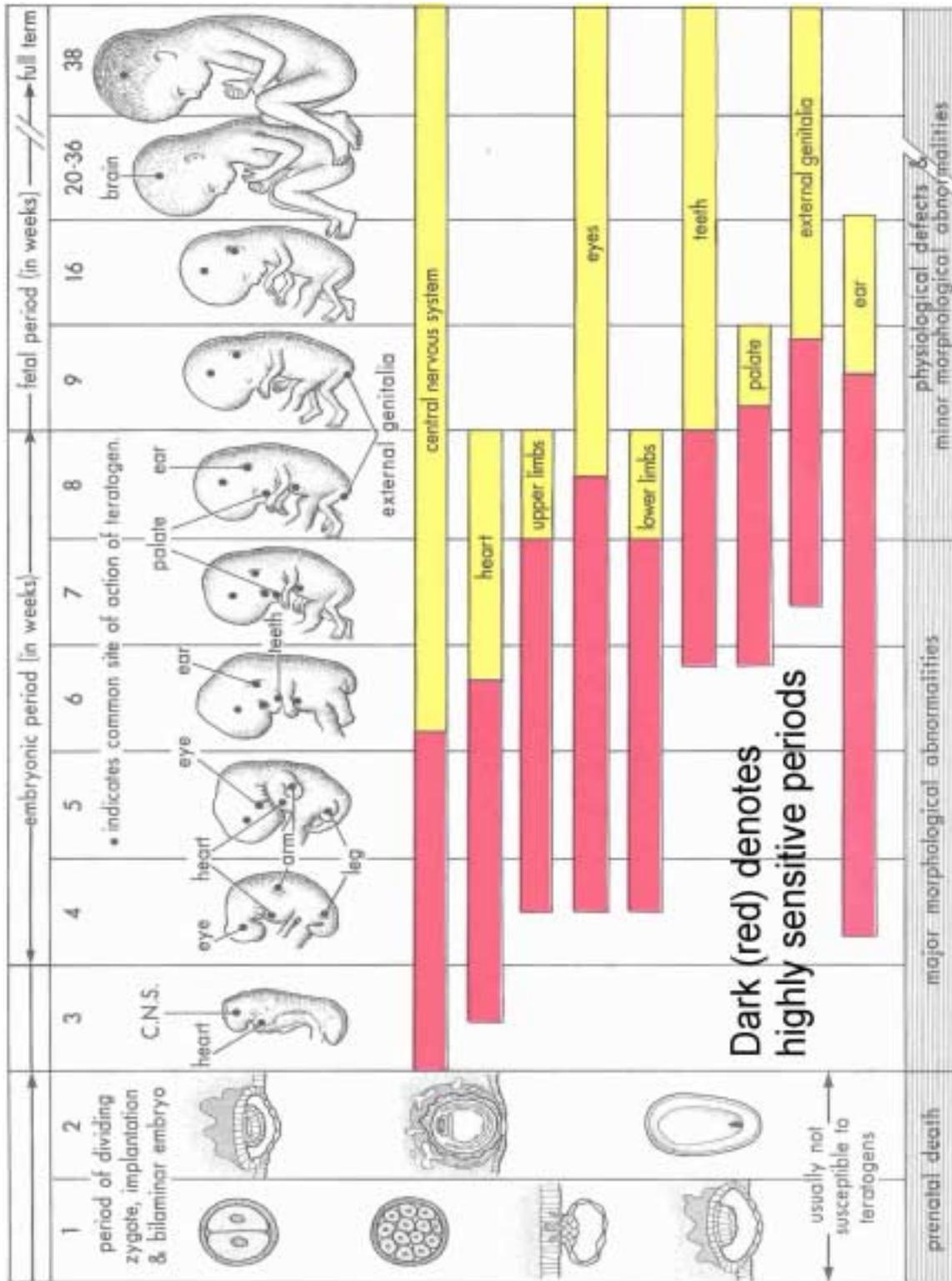
implanted in the uterus, the ovarian secretion of hormones is decreased, the lining of the uterus is discharged, and menstruation occurs.

#### 4) Embryogenesis and Fetal Development

*Fertilization* (the successful union of sperm and ovum) generally occurs two minutes to several hours after ovulation.<sup>59</sup> The fertilized ovum begins cell division and is known as a *blastocyst*. After three to four days, the blastocyst reaches the uterus and is implanted. During the following two weeks, the extra-embryonic membranes (which become the amniotic sac and placenta) differentiate, and the three main cell lines of the embryo develop (endoderm, mesoderm, and ectoderm).

The *embryonic period* or phase begins the third week after conception and ends with completion of major organogenesis (end of week eight). This is a critical period of development for each organ and a period in which there is the greatest sensitivity to teratogens—but many women are unaware of their pregnancy during the majority of this period! The *fetal period* starts at eight weeks (day 56) and continues to delivery. Exposures during this period may result in growth retardation or functional defects. During this period, the developing fetus may have increased sensitivity to carcinogens. During periods of rapid growth or differentiation, organs are more susceptible to damage by infections, toxicants, trauma, or compromise in blood flow. Critical periods of development are depicted in **Figure 3 - Critical Periods of Development**.

**Figure 3 - Critical Periods of Development**



Adapted from Moore, K. The developing human, 3<sup>rd</sup> edition. Page 152. Copyright 1982 W. B. Saunders Company. Used with permission.

**C) REPRODUCTIVE DYSFUNCTION**

During the normal reproductive process, there are many opportunities for the process to fail and not result in a normal pregnancy. In young, fertile women, fertilization after exposure to spermatozoa occurs only 88 percent of the time.<sup>60</sup>

Up to 50 percent of embryos fail to survive the first two weeks following fertilization. Thus, by the time a pregnancy is recognizable, for each occasion the sperm reaches the ovum, the “normal” estimated probability of a resulting live birth is about 30 percent (see [Table 3](#)).

**Table 3 - Lifetable of Reproductive and Developmental Success**

Reproductive or developmental event	Outcome
Couples attempting pregnancy	1000
Conception (occurs at mid-cycle 14 days before menses)	600-1000
Preimplantation loss (30% to 50% loss between conception and implantation)	(300-500)*
Chemical pregnancy (+ hCG—from 7 days before missed menses until 7 weeks)	300-700
Unrecognized pregnancy loss (15% to 60% up to 7 weeks)	(45-420)*
Clinical pregnancy (clinically recognized)	200-300
Clinically recognized spontaneous abortion (15% to 25%)	(30-75)*
Continuing pregnancy (beyond 28 weeks)	170-300
Stillbirth (beyond 28 weeks, <3%)	(10-15)*
Premature, postmature, growth retardation (about 10%)	(20-30)*
Term births	110-300
Developmental abnormality (3 to 5% identified at birth) (5-15% identified over first year of life)	(3-12)* (6-36)*
*The numbers in parentheses represent reproductive or developmental loss or failure. Taken from Rosenstock R, Cullen MR. Textbook of Clinical Occupational and Environmental Medicine. W B Saunders; 1994:448. Used with permission.	

**D) REPRODUCTIVE AND DEVELOPMENTAL HAZARDS**

**1) Reproductive Hazards**

**(i) Stressors**

If a discussion of hazards was limited only to the untoward or harmful effects of chemicals (toxicity), the phrase "developmental and reproductive toxicology" or "DART" would be used to describe that specific category of hazard. However, the term "hazard" includes other exposure conditions that do not occur from chemicals. Exposures can occur to other categories of agents that are commonly referred to in OH jargon as "stressors". In addition to chemical agents, stressors include physical, biological, psychological, and ergonomic factors. Physical agents include ionizing radiation, heat, intense sound, and vibration. Viruses, bacteria, and fungi are examples of biological agents. Psychological factors give rise to the mental and emotional effects of working and living in general—“stress”. Ergonomic factors and physical activity are stressors that affect the musculoskeletal and nervous systems as a consequence of human interaction with mechanical systems.

## (ii) Timing

As with all health hazards, determinants of ReproDev risks include factors such as route of exposure and dose (including the total amount, concentration, and duration of exposure, and whether exposures are single, multiple, extremely high, etc.). In addition, timing of exposure—exactly when in the ReproDev process the exposure occurs—is critical. For example, in humans, thalidomide caused ear abnormalities and duplication of thumbs when administered 34 to 38 days after the last menstrual period (LMP), but leg phocomelia (short, missing, or otherwise abnormal limbs) 42 to 47 days after the LMP.<sup>61</sup> Pb exposure causes decreased fecundity before pregnancy,<sup>62</sup> but developmental delays during later pregnancy and in early childhood.

If a person is exposed to a ReproDev hazard, there may or may not be a risk to that person's child or children. Specifically, inclusion in one or more of the lists in this manual does not mean exposures to that factor pose a ReproDev risk. For example, exposure to sound is unavoidable, and generally is not a threat to pregnancy. However, some exposures to sound during pregnancy may pose a risk, not a certainty, of impaired hearing in the child—but only exposure to high sound levels, and only after ear development has begun.

In addition to directly decreasing libido and fecundity, reproductive effects can occur at many points in reproduction:

- death of stem cells
- gametogenesis—arrested development, aberrant development, reduced number
- decreased semen production
- interference with fertilization—oocyte penetration, flagella movement
- interference with ovum transit through the oviduct
- interference with implantation—shedding of the zona pellucida
- interference with cleavage and development of the ovum
- embryogenesis

Agents that affect development can impact fetal growth, birth, and/or lactation.

Developmental effects occur after the establishment of the embryo and continue through the remainder of pregnancy and through childhood.

## 2) Genetic Toxicology

A reproductive or developmental agent may cause damage through action at a specific site on a chromosome or it may affect the entire chromosome. Gene mutations and chromosomal aberrations in a somatic (general body) cell can affect that particular cell and the future daughter cells (cells produced as a result of cell division). This may result in a change in function or structure of that cell line (for example, resulting in carcinogenesis). Alterations in the DNA of germ cells (spermatozoa or oocytes) become incorporated into the genetic makeup of every cell in the new organism and are passed on to offspring. These changes can result in damage or death. From the biological point of view, it should be noted that many, but not all, mutations are harmful or deleterious to a cell, tissue, organ, or organism.

**Table 4 – Genetic Hazards**

benzene
chemotherapy agents (for example, adriamycin, cyclophosphamide, cisplatin)
coal tars
cyclophosphamide
ethylene oxide
ionizing radiation
nickel compounds
styrene
vinyl chloride

3) Developmental Hazards

In the context of biological reproduction, *embryonic* and *fetal* (prenatal) *development* refers to the period commencing with fertilization and ending at term delivery (40 weeks).

Developmental hazards cause deleterious effects during one or more critical time periods of prenatal development, but as discussed above, developmental hazards may affect the child after birth.

Deficiency of an essential factor may also adversely affect development. Folic acid is a vitamin found to be critical in early pregnancy. Deficiency of folic acid around the time of conception has been associated with neural tube defects (spina bifida, anencephaly, and encephalocele). Thus, folic acid supplementation has been recommended for all women with child-bearing potential.

Developmental hazards that have been identified include chemical, biological, and physical agents, as well as psychological conditions as listed below.

**Table 5 – Selected Developmental Toxicants and Their Period of Toxic Activity**

Fertilization	Pre-implantation		Development
	Body and/or brain weight deficit, or embryo lethality	Exposure leading to fetal malformations	
Ethylene oxide (e.g., HCWs using gas sterilization) Ethylnitrosourea (e.g., researchers working with this laboratory reagent) Triethylene melamine (trisaziridinyltriazine)	DDT (e.g., personnel exposed outside of continental US, such as in malaria control) Nicotine Methyl mercury (contaminated seafood from Minimata Bay, Japan)	Methylnitrosourea (neural tubular defects, cleft palate) Cyproterone acetate Medroxyprogesterone (e.g., all the above drugs may be exposure hazards to HCWs distributing or administering them)	Metals Cadmium (e.g., welders, painters) Arsenic (e.g., pesticide and wood preservative applicators, metal workers) Hg (operators of instruments containing Hg; chemical, dental, and nursing technicians) Pb (metal workers, painters and paint removers, battery workers) Recreational drugs (including cigarette smoke) Drugs of abuse (ethanol, cocaine)

4) Drugs in Pregnancy and Lactation

The use of prescription and non-prescription drugs during pregnancy and lactation presents a challenge to health care professionals. While the physician and pharmacist are the parties primarily responsible for prescribing and dispensing medications, personnel may be occupationally exposed in the manufacturing, distributing, or dispensing of pharmaceuticals, “recreationally” exposed through smoking, alcohol use, and use of illicit drugs, and “environmentally exposed” through the use of “over-the-counter” (non-prescription) medications and dietary supplements (including vitamins and natural products). Exposure to these agents must also be considered in the overall assessment and evaluation of potential ReproDev hazards.

**E) EFFECT OF WORKPLACE EXPOSURES ON REPRODUCTIVE AND DEVELOPMENTAL DYSFUNCTION**

1) Libido and Potency

Agents that alter hormone secretion or that affect the central or peripheral nervous system may affect libido and/or potency. This may or may not be largely dependent on the effect on the hypothalamus, which is the main central nervous system influence on the pituitary gland. In the male, Pb and Hg have been implicated as affecting libido and potency.

2) Pituitary

Agents that mimic, antagonize, or bind estrogen or testosterone may interfere with LH and FSH secretion by the pituitary. Direct damage to the pituitary (such as by radiation, tumor, infarct, or trauma, whether occupational or non-occupational) may also affect hormone secretion.

3) Ovary

Interference in release of LH or FSH by the pituitary, as well as factors that impede the ovary from recognizing the pituitary hormones, may prevent ovulation. Ovarian dysfunction may also result in defective ova being released or in an unsuitable secretion of estrogen and progesterone.

4) Sperm

Decreased motility, decreased number, or altered morphology of sperm may prevent fertilization. The following have been noted.<sup>63</sup>

**Table 6 – Effects of Selected Occupational Exposures On Sperm Parameters**

<b>Lowered number of sperm</b>	<b>Altered sperm transfer</b>	<b>Abnormal sperm shape</b>
Bromine vapor	Bromine vapor	Bromine vapor
DBCP	2,4-Dichlorophenoxy acetic acid (2,4-D)	Carbaryl (Sevin™)
Dinitrotoluene	Ethylene dibromide	2,4-Dichlorophenoxy acetic acid (2,4-D)
Ethylene dibromide	Heat	Ethylene dibromide
Ethylene glycol monoethyl ether	Kepone	Pb
Heat	Pb	Perchloroethylene
Military radar	Perchloroethylene	Plastic production (styrene and acetone)
Pb	Radiation	Radiation
Radiation	Welding	Welding
Toluenediamine		

Adapted from [NIOSH. The Effects of Workplace Hazards on Male Reproductive Health. 549-180/40015, Publ. No. 96-132. Washington, DC: U.S. Government Printing Office: 1996.](#)

Direct measurement of a substance in semen or sperm, rather than its measurement in blood, may be of theoretical—but currently not practical—value in evaluating reproductive toxicity. Elevated levels of aluminum in spermatozoa of industrial employees were associated with decreased sperm motility [[PMID 9512240](#)].<sup>64</sup> Semen Pb was not found to be a valuable adjunct

to blood Pb monitoring [[PMID 9787850](#)].<sup>65</sup> An animal (rabbit) study found no consistent significant decrease in fertilization by sperm exposed to cadmium (Cd<sup>2+</sup>) or lead (Pb<sup>2+</sup>) at levels much higher than semen concentrations reported in exposed workers [[PMID 10613392](#)].<sup>66</sup> Measurement of the concentration of zinc and copper in seminal plasma was felt to have “little value in the routine investigation of infertility” [[PMID 6628713](#)].<sup>67</sup>

#### 5) Mutations

A mutation is a change in a gene due to chromosomal (DNA) damage. Chromosomal damage may occur in the ova or sperm prior to or during fertilization. If a mutation only occurs in the ova or sperm, the mutation may not be evident in either of the parents but result in a birth defect in the offspring. Spermatozoa are constantly produced, so if the agent producing chromosomal damage in sperm is removed, production of normal sperm may resume. Chromosomal damage to ova is permanent and can affect the survival of the embryo. Although attributing birth defects to parental exposures months or years before conception may be theoretically plausible, whether the literature actually supports such a hypothesis is questionable.<sup>68</sup>

#### 6) Pregnancy

Fetal exposures to hazardous agents may cause spontaneous abortion, fetal death, growth retardation, malformation, organ malfunction, preterm delivery, low birth weight, developmental delay or disability, or cancer. Agents that interfere with embryonic or fetal development are known as *teratogens*. Functional and biochemical effects can occur that are not grossly apparent but result in a significant negative impact on the embryo or fetus. *Structural teratogens* cause visible, physical defects of the embryo and fetus.

#### 7) Breast Milk

Breastfeeding is widely regarded as the preferred method of infant feeding. Inert material, such as silicone, or environmental toxicants, such as organophosphate pesticides, chlorinated hydrocarbons, solvents, and heavy metals, have been identified in human milk [[PMID 7702761](#)].<sup>69</sup> Breast milk concentrations of various substances may be at levels 1/100 to 100 times maternal plasma levels. Some substances (especially those that are fat-soluble) are concentrated in breast milk. Breast milk concentration of a chemical increases with fat solubility, low molecular weight, high pH (basic rather than acidic molecules), and low polarity (neutral molecules).<sup>70</sup> The nursing infant can receive a significantly greater dose (mg/kg body weight) of a fat-soluble substance than the working mother originally received.

**Table 7 – Types of Reproductive and Developmental Risk Factors**

<b>Sociocultural</b>	<b>Individual</b>	<b>Pregnancy-specific</b>
Health of population	Age	Time since last pregnancy
Economic status of population	Reproductive history	Number of prior pregnancies
Food availability and quality	Fertility	Pregnancy-induced hypertension
Ethnic group	Anatomic abnormalities of reproductive organs	Gestational diabetes
Customs and traditions	Endometriosis	Bleeding
Transportation	Obstetric history (if applicable)	Infections
Medical care availability	Nutrition and body weight	Placental disorders
General medical care	Exercise routines	Injuries
Prenatal care	Chronic medical problems	Amniotic fluid volume problems
Hospital care	Hypertension	Rh or other blood group immunization
Neonatal intensive care	Diabetes	Intrauterine growth retardation (IUGR)
Health insurance	Autoimmune disorders	Premature rupture of membranes
Education	Asthma	Idiopathic preterm labor
Spouse or partner	Other	
Domestic violence	Sexually transmitted diseases	
Social support	Use of pharmaceuticals	
Workplace culture	Tobacco, alcohol, caffeine	
	Use of illegal drugs	
	Genetic profile	
	Social demands and support	
	Income	
	Health insurance status	
	Work tasks	
	Toxic exposures	
	Spouse or partner	
	Age	
	Reproductive history	
	Medical problems	
	Habits	
	Genetic profile	
	Occupational exposures	
	Fetus (e.g., genetic disorder)	

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## **(VIII) OCCUPATIONAL CHEMICAL REPRODUCTIVE AND DEVELOPMENTAL HAZARDS LIST**

### **A) INTRODUCTION**

This list contains chemical substances **known** to cause ReproDev toxicity in humans, or **known** to cause ReproDev toxicity in animals by mechanisms of action directly applicable to humans. It generally does not include agents considered "possible" hazards. Sources used to compile this list include those published by state and federal agencies and the recognized scientific literature. The list contains chemical ReproDev hazards to which Navy personnel may be exposed.

Statutory or recommended occupational exposure levels are not included in this list. Current exposure standards are generally based on human health effects other than those related to the reproductive system. Workers are usually exposed to many hazardous substances and conditions. Repetitive, "low-level" exposures to a combination of ReproDev hazards may have a greater effect on an individual than a single, "high-level" exposure to a single hazard. Additionally, the timing of the exposure before, during, or after pregnancy can have a dramatic effect on the outcome (see previous sections).

When using this list, **it is recommended that each worker be evaluated on a case-by-case basis**. Chemicals generally administered to people (i.e., pharmaceuticals, drugs of abuse, etc.) are listed separately in Chapter **(IX)**. While exposure to most of these chemical hazards may be assumed to occur at worksites, it should be noted that potential for exposure of Navy personnel to pharmaceuticals may occur when pharmaceuticals are handled (in manufacture, distribution, dispensing, or inadvertent or intentional non-prescribed ingestion).

Frequent reference is made to JL Schardein's "Chemically induced birth defects 2nd ed., rev. and expanded," Marcel Dekker, Inc., New York, 1993, to which the reader is directed for further information.

The list is meant to be inclusive, but cannot be exhaustive, as information on the ReproDev toxicity of many chemicals is unknown at this point. For some listed substances, while the toxicity to humans is unknown, the mechanism of toxicity to animal species, or the consistency of toxicity among several animal species, is such that human toxicity must be suspected. Without human data, controversy will always exist as to the degree of certainty with which one may hold that a particular substance is hazardous to humans. The position of this manual is one of hesitancy to include a suspected substance without substantial supporting data. Thus, some substances included in other listings (for example, California Proposition 65) are not included here. Not including a substance on this list does not represent an endorsement of the safety of the substance nor does it represent a criticism of any other list.

**Table 8 – Chemical Reproductive and Developmental Hazards List, December 20, 2000**

Agent	CAS Number	Date Added	Notes
$\alpha$ -Naphthyl-N-methylcarbamate	63-25-2		(See Carbaryl)
Acetaldehyde	75-07-0		Category X [Briggs] (primary metabolite of ethanol) [PMID 9105505] <sup>71</sup> [PMID 1789375] <sup>72</sup>
Alcohol			(See Ethanol)
Arsenic	7440-38-2		Pregnancy: Occupational exposure to inhaled inorganic arsenic associated with increased incidence of congenital malformations and decreased birth weight [ATSDR]; <sup>73</sup> Ingested inorganic arsenic has been reported in association with premature delivery and subsequent neonatal death [ATSDR]. <sup>74</sup> Placental toxicity Appears in cord blood in almost same levels as maternal blood [PMID 9742656] <sup>75</sup> Breastfeeding: Low concentrations in breast milk [PMID 9742656] <sup>76</sup>
Aspartame	22839-47-0	07/05/00	Category B [Briggs 4th] <sup>77</sup> Category C in women with phenylketonuria [Briggs 4th] <sup>78</sup> Breastfeeding: With caution if mother or infant has phenylketonuria [AAP] <sup>79</sup>
Benzene	71-43-2	03/10/00	Pregnancy: Spontaneous abortion, premature births, neonatal complications [Schardein] <sup>80</sup>
Benzimidazoles	---		(See Carbendazim)
Bischloroethyl nitrosourea	154-93-8	09/30/94	Category D [USPDI] <sup>81</sup> Breastfeeding: Contraindicated [Briggs 1997] <sup>82</sup>
1,3-Butadiene	106-99-0	07/25/00	No human data. Animal data (inhalation exposure)[ATSDR]. <sup>83</sup> Male: Increased incidence of sperm-head abnormalities and testicular atrophy (mice) Female: Increased incidence of ovarian atrophy (mice)
Butiphos	---	06/27/00	Pregnancy: Malformations, stillbirths, and difficult deliveries from occupational contact (one report) [Schardein] <sup>84</sup>

Agent	CAS Number	Date Added	Notes
Cadmium	7440-43-9	2-11-00	<p>Males (inhalation exposure): No consistent effect [ATSDR];<sup>85</sup> OSHA notes an increased risk of prostate cancer (<a href="#">29 CFR 1910.1027 App D</a>).<sup>86</sup></p> <p>Pregnancy: Decreased birth weight (with inhalation exposure) [ATSDR],<sup>87</sup> placental toxicity [Miller],<sup>88</sup> associated with preterm [<a href="#">PMID 8094678</a>].<sup>89</sup></p> <p>Breastfeeding: No reported effect [<a href="#">AAP</a>].<sup>90</sup></p>
Carbarsone	121-59-5	03/06/00	Category D (contains 29% Arsenic) [Briggs 4th]. <sup>91</sup>
Carbaryl	63-25-2	06/07/00	<p>Males: Abnormal sperm shape [<a href="#">PMID 6791917</a>].<sup>92</sup> [NIOSH].<sup>93</sup></p> <p>Development: No human developmental data, teratogenic in several animal species [EPA].<sup>94</sup></p>
Carbendazim	37953-07-4	06/07/00	<p>Human data lacking, but reproductive/developmental effects are noted in several animal species:</p> <p>Male (rat): Testicular [<a href="#">PMID 9719423</a>].<sup>95</sup>/sperm toxicity [<a href="#">PMID 2227156</a>].<sup>96</sup> [<a href="#">PMID 9070363</a>].<sup>97</sup></p> <p>Embryotoxic [<a href="#">PMID 1601229</a>].<sup>98</sup> [<a href="#">PMID 1609414</a>].<sup>99</sup></p> <p>Teratogenic [Cummings/USEPA].<sup>100</sup></p>
Carbon disulfide	75-15-0	09/30/94	<p>Male: Spermatotoxic [Paul].<sup>101</sup> [<a href="#">PMID 5079601</a>],<sup>102</sup> decreased libido, impotence [Schardein].<sup>103</sup></p> <p>Female: Menstrual irregularities, decreased fertility, increased spontaneous abortion [Schardein].<sup>104</sup></p> <p>Pregnancy: 4 ppm (10 mg/m<sup>3</sup>) recommended as occupational exposure limit during pregnancy [OSHA],<sup>105</sup> birth defects reported [Bao],<sup>106</sup> children's intelligence hindered significantly when one or both of their parents were exposed to carbon disulfide at levels greater than 10 mg/m<sup>3</sup> (3 to 4 ppm), in addition to birth defects [Li].<sup>107</sup></p> <p>Breastfeeding: Can cross the placental barrier and be secreted into mothers' milk [<a href="#">PMID 7216838</a>].<sup>108</sup></p>

Agent	CAS Number	Date Added	Notes
Carbon monoxide	630-08-0	09/30/94	Pregnancy (fetal hemoglobin binds O <sub>2</sub> more avidly than adult hemoglobin): Low birth weight [ <a href="#">PMID 9872713</a> ], <sup>109</sup> CNS abnormalities reported [ <a href="#">PMID 2125322</a> ], <sup>110</sup> hyperbaric O <sub>2</sub> not contraindicated in pregnancy [ <a href="#">PMID 7772366</a> ] <sup>111</sup> Animal studies have shown immunological [ <a href="#">PMID 8115310</a> ] <sup>112</sup> and neurobehavioral [ <a href="#">PMID 7786165</a> ] <sup>113</sup> [ <a href="#">PMID 8711066</a> ] <sup>114</sup> effects
Chlordecone	143-50-0	09/30/94	Male: Oligospermia, decreased sperm motility, but no loss of fertility [ <a href="#">ATSDR</a> ] <sup>115</sup>
Cigarette smoke	---		(See Tobacco smoke - environmental)
Cigarette smoking	---		(See Tobacco smoke (primary))
Ciguatoxin	---		Category X [Briggs 4th] <sup>116</sup> (a case report of fetal agitation with neonatal facial palsy and meconium aspiration after preterm maternal ciguatoxin poisoning noted [ <a href="#">PMID 7070322</a> ]) <sup>117</sup> Breastfeeding: Excreted in breast milk [Briggs 4th] <sup>118</sup>
Cocaine	50-36-2	06/30/95	Category C [Briggs 4th] <sup>119</sup> Category X if nonmedicinal use [ <a href="#">Briggs</a> ][Briggs 4th] <sup>120</sup> (associated with fetal malformations, placental toxicity [ <a href="#">PMID 9434858</a> ]) <sup>121</sup> Breastfeeding: Contraindicated (may cause cocaine intoxication) [ <a href="#">AAP</a> ]
Cycloheximide	66-81-9	09/30/94	Human studies lacking, but cycloheximide is a known protein synthesis (meiosis) inhibitor [ <a href="#">PMID 9592729</a> ], <sup>122</sup> developmental defects in rats and mice, but not in rabbits [Schardein] <sup>123</sup>
2,4-D	94-75-7		(See 2,4-Dichlorophenoxy acetic acid)
DBCP	96-12-8		Male: Toxicity [ <a href="#">EPA</a> ] <sup>124</sup> (lowered number of sperm [ <a href="#">NIOSH</a> ]) <sup>125</sup>

Agent	CAS Number	Date Added	Notes
DDT (p,p'-Dichlorodiphenyl-trichloroethane)	50-29-3		Pregnancy: Possible association with spontaneous abortion, toxemia, and low birth weight [Schardein]. <sup>126</sup> Developmental: Little teratogenic potential [Schardein]. <sup>127</sup> However, there is concern about cumulative (over several generations) reproductive toxicity, due to bio-accumulation and widespread environmental exposure [EPA]. <sup>128</sup> Breastfeeding: Excreted in human milk [PMID 2551196], <sup>129</sup> no reported effects [AAP]. <sup>130</sup>
DEHP			(See di(2-ethylhexyl) Phthalate)
1,2-Dibromo-3-chloropropane	96-12-8		(See DBCP)
2,4-Dichlorophenoxy acetic acid	94-75-7	06/27/00	Male: Abnormal sperm shape, altered sperm transport [NIOSH]. <sup>131</sup> Pregnancy: Associated with spontaneous abortion and premature birth [Schardein]. <sup>132</sup> Developmental: One report of multiple congenital anomalies [Schardein], <sup>133</sup> teratogenic in several animal species [Schardein]. <sup>134</sup>
di(2-ethylhexyl) Phthalate	117-81-7	07/26/00	Developmental: "Concern" about developing male reproductive tract [NTP]. <sup>135</sup>
Dinocap (fungicide)	39300-45-3	09/30/94	Animal data: Developmental toxicity: Increased post-implantation mortality, reduced newborn viability, abnormalities of the musculoskeletal and hepatobiliary systems, craniofacial abnormalities, behavioral abnormalities, and delayed growth in mice [EPA]
Dinoseb (herbicide)	88-85-7	09/30/94	Male: Reduced fertility index in rats, decreased seminal vesicle weight, decreased sperm count and increased incidence of abnormal sperm [EPA] Developmental: Decreased pup weights, developmental malformations and/or anomalies, an increased incidence of an absence of ossification for a number of skeletal sites and supernumerary ribs neural tube defects [EPA]

Agent	CAS Number	Date Added	Notes
2,4-Dinitrotoluene	121-14-2	03/10/00	Male: Lowered number of sperm [NIOSH] <sup>136</sup>
2,6-Dinitrotoluene	606-20-2		(See 2,4-Dinitrotoluene)
Dioxin	1746-01-6		(See TCDD or specific compound)
Disodium cyanodithiomido-carbonate	138-93-2	03/10/00	Developmental: Both maternal and fetal effects in rabbits and rats [EPA] <sup>137</sup>
Ecstasy			(MDMA or N-Methyl-3,4-methylenedioxamphetamine) (See Amphetamines)
Epichlorohydrin	106-89-8	03/10/00	Male: Impaired fertility, however human data do not confirm animal data [PMID 2010350] <sup>138</sup> demonstrating impaired male fertility [EPA] <sup>139</sup>
Ethanol	64-17-5		Category D [Briggs 4th] <sup>140</sup> Category X [Briggs] (when used in large amounts or for prolonged periods [Briggs 4th]) <sup>141</sup> (developmental defects, which may include the fetal alcohol syndrome [PMID 9434858], <sup>142</sup> low birth weight, spontaneous abortion, growth retardation, congenital anomalies [Schardein], <sup>143</sup> placental toxicity [PMID 1621875]) <sup>144</sup> Breastfeeding: Minimal dose [Briggs], compatible [AAP], contraindicated [Briggs 1997] <sup>145</sup>
2-Ethoxyethanol	110-80-5		(See Ethylene glycol monoethyl ether)
Ethyl alcohol	64-17-5		(See Ethanol)
Ethyl carbamate	51-79-6		(See Urethane)
Ethylene dibromide	106-93-4	03/10/00	Male: Reproductive toxicity [PMID 2980345] <sup>146</sup> [PMID 3297130] <sup>147</sup> (lowered number of sperm, abnormal sperm shape, altered sperm transport [NIOSH]) <sup>148</sup>
Ethylene glycol monoethyl ether	110-80-5	09/30/94	Male: Lowered number of sperm [NIOSH] <sup>149</sup> Male and female reproductive effects in multiple animal species [NIOSH] <sup>150</sup>
Ethylene glycol monomethyl ether	109-86-4	09/30/94	Male and female reproductive effects in multiple animal species [NIOSH] <sup>151</sup>

Agent	CAS Number	Date Added	Notes
Ethylene glycol monomethyl ether acetate	110-49-6	09/30/94	Developmental: Hypospadias and other male genital abnormalities [ <a href="#">PMID 2357456</a> ] <sup>152</sup> [Johanson] <sup>153</sup> (See Ethylene glycol monomethyl ether-toxicological profile is almost identical [ <a href="#">PMID 2357456</a> ]) <sup>154</sup>
Ethylene oxide	75-21-8	03/10/00	Male: Appears in testes in higher concentrations than in blood, has been associated with sister chromatid exchanges in humans occupationally exposed, but effects on sperm were inconclusive [ <a href="#">NIOSH</a> ] <sup>155</sup> Developmental: Malformations in animals (mice) [Kimmel] <sup>156</sup>
Ethylene thiourea (Ethylenethiourea)	96-45-7	06/30/95	Developmental: Teratogen [ <a href="#">NIOSH</a> ] <sup>157</sup>
Ethylnitrosourea	759-73-9		Developmental: CNS tumors in rats born to rats exposed in the latter part of gestation [ <a href="#">PMID 4321468</a> ] <sup>158</sup> [ <a href="#">EPA</a> ] <sup>159,160,161</sup>
Fava beans	---	07/05/00	Breastfeeding: Hemolysis in patient with G-6-PD deficiency [ <a href="#">AAP</a> ] <sup>162</sup>
Gasoline	8006-61-9 ? or is it: 86290-81-5	07/10/00	Pregnancy: Fetal gasoline syndrome (narrow forehead, upslanting palpebral fissures, full cheeks, spastic positioning) with high levels of inhalation exposure ("sniffing") [Schardein] <sup>163</sup>
Heroin	561-27-3		Pregnancy: Preterm birth [ <a href="#">PMID 2304039</a> ], <sup>164</sup> neonatal withdrawal [Williams] <sup>165</sup> Breastfeeding: Contraindicated (tremors, restlessness, vomiting, poor feeding) [ <a href="#">AAP</a> ] <sup>166</sup> (excreted in milk [ <a href="#">PMID 9363416</a> ]) <sup>167</sup>
Hexachlorobenzene	118-74-1	06/30/95	Fetal death due to pembe yara <sup>ii</sup> [ <a href="#">PMID 7138315</a> ] <sup>168</sup> Breastfeeding: Possible association with porphyria cutanea tarda symptoms, reduced growth, and arthritic changes in the appendages [ <a href="#">EPA</a> ] <sup>169</sup> (excreted in human milk)[ <a href="#">PMID 2590490</a> ], <sup>170</sup> skin rash, diarrhea, vomiting, dark urine, neurotoxicity, death [ <a href="#">AAP</a> ] <sup>171</sup>

<sup>ii</sup> "Pink sore", a low grade cellulitis that quickly deteriorates into a limb- or life-threatening soft tissue infection.

Agent	CAS Number	Date Added	Notes
Hexamethylphosphoramide	680-31-9	06/30/95	Testicular atrophy and aspermia (rats), testicular development inhibition (cockerels) [EPA] <sup>172</sup>
Hexamethylphosphoric triamide	680-31-9		(See Hexamethylphosphoramide)
HMPA	680-31-9		(See Hexamethylphosphoramide)
Hormone pregnancy test tablets			Category X [Briggs 4th] <sup>173</sup> Breastfeeding: See Oral contraceptives
Iodides	---		(See Iodine)
Iodine	7553-56-2		Category D [Briggs 4th] <sup>174</sup> Breastfeeding: Not compatible (concentrated in breast milk, and long term use may adversely affect the nursing infant's thyroid activity) [Briggs 1997] <sup>175</sup>
Kepone®			(See Chlordecone)
Lead (Pb)	7439-92-1	09/30/94	Male: [PMID 6441528] <sup>176</sup> Lowered number of sperm, abnormal sperm shape, altered sperm transport [NIOSH] <sup>177</sup> Female: Premature membrane rupture and preterm births [PMID 1257615] <sup>178</sup> Developmental [PMID 6716624] <sup>179</sup> Breastfeeding: Possible neurotoxicity [AAP] <sup>180</sup>
Marijuana	---	06/28/00	Category C [Briggs 4th] <sup>181</sup> Breastfeeding: Contraindicated [Briggs 1997] <sup>182</sup> [AAP] <sup>183</sup>
MDMA			(Ecstasy or N-Methyl-3,4-methylenedioxyamphetamine) (See Amphetamines)
Mercury and mercury compounds (see specific compound)		09/30/94	Breastfeeding: May affect neurodevelopment [AAP] Present in breast milk [PMID 9098513] <sup>184</sup>
Mercury, elemental	7439-97-6	05/31/00	Male: Maternal spontaneous abortions [ATSDR] <sup>185</sup> Female: Reproductive failure [ATSDR] <sup>186</sup> Developmental: Decreased birth weight [ATSDR] <sup>187</sup> Breastfeeding: May affect neurodevelopment [AAP]
Mercury, inorganic	---	03/10/00	Spontaneous abortion [ATSDR] <sup>188</sup>
Mercury, organic	---	03/10/00	Developmental (CNS neurological impairment [ATSDR]) <sup>189</sup> Breastfeeding: May affect neurodevelopment [AAP] <sup>190</sup>

Agent	CAS Number	Date Added	Notes
2-Methoxyethanol			(See Ethylene glycol monomethyl ether)
Methyl benzimidazole-carbamate	10605-21-7		(See Carbendazim)
Methyl Cellosolve acetate			(See Ethylene glycol monomethyl ether acetate)
Methylene blue	61-73-4		Category C [Briggs 4th] <sup>191</sup> Category D if injected intra-amniotically [Briggs 4th] <sup>192</sup> (hemolytic anemia, jaundice, intestinal atresia with intra-amniotic injection [ <a href="#">PMID 9434858</a> ]) <sup>193</sup>
Methyl isocyanate	624-83-9	07/10/00	Pregnancy: Associated with spontaneous abortion and neonatal deaths [Schardein] <sup>194</sup>
Methyl mercury	22967-92-6	09/30/94	(See also Mercury, organic, and Mercury and mercury compounds) Pregnancy: Microcephaly, cerebral palsy, abnormal reflexes [ <a href="#">PMID 9434858</a> ], <sup>195</sup> abnormal dentition, neurological deficits [Schardein] <sup>196</sup> Breastfeeding: May affect neurodevelopment [ <a href="#">AAP</a> ]
Methylmethane sulfonate	66-27-3		Pregnancy: Embryo lethality and malformations in rats [Nagao] <sup>197</sup> [ <a href="#">PMID 2595598</a> ], <sup>198</sup> embryotoxicity in mice [ <a href="#">PMID 4349609</a> ] <sup>199</sup>
Methylnitrosourea	684-93-5		Animal data: Male: Malformed ribs in offspring of exposed males [ <a href="#">PMID 3821763</a> ] <sup>200</sup> Developmental: Teratogenic in rats (microcephaly [ <a href="#">PMID 8016749</a> ]) <sup>201</sup> and mice (in mice it was teratogenic and embryo-lethal one-half day before implantation [ <a href="#">PMID 2520503</a> ]) <sup>202</sup>
MIC			(See Methyl isocyanate)
Mirex	2385-85-5		Animal studies only [ATSDR] <sup>203</sup> Male: Decreased sperm counts and fertility <sup>204</sup> Female: Decreased litter size and number of offspring <sup>205</sup> Developmental: Increased resorptions and stillbirths, arrhythmias, and other anomalies <sup>206</sup> Breastfeeding: Appears in human milk [ATSDR] <sup>207</sup>

Agent	CAS Number	Date Added	Notes
$\alpha$ -Naphthyl-N-methylcarbamate	63-25-2		(See Carbaryl)
Nickel	7440-02-0	07/07/00	Pregnancy: Increased structural malformations and spontaneous abortions in occupationally exposed women who also lifted heavy weights and may have experienced heat stress [ATSDR] <sup>208</sup>
N-Methyl-3,4-methylene-dioxyamphetamine			(Ecstasy or MDMA) (See Amphetamines)
o,p'-DDT	789-02-6		(See DDT)
Oryzalen	19044-88-3	06/27/00	Male: One report of spontaneous abortion and heart defects born to spouses of occupationally exposed males [Schardein] <sup>209</sup>
Oxydemeton methyl	301-12-2	03/10/00	Developmental: Human case report (multiple cardiac defects, bilateral optic nerve colobomas, left eye microphthalmia, cerebral and cerebellar atrophy, and facial anomalies [PMID 2583071]) <sup>210</sup> Animals: Chick embryos [PMID 8248858] <sup>211</sup> , rats [WHO] <sup>212</sup>
p,p'-DDT	50-29-3		(See DDT)
p,p'-Dichlorodiphenyltrichloroethane	50-29-3		(See DDT)
PCBs	1336-36-3		(See Polychlorinated biphenyls)
Perchloroethylene	127-18-4	06/27/00	Male: Altered sperm transport [NIOSH] <sup>213</sup> Breastfeeding: Obstructive jaundice, dark urine [AAP] <sup>214</sup>
Phencyclidine	60124-79-0		Category X [Briggs 4th] <sup>215</sup> (hallucinogen with no legitimate use) Breastfeeding: Contraindicated [AAP] <sup>216</sup>

Agent	CAS Number	Date Added	Notes
Polychlorinated biphenyls (PCBs)	1336-36-3	09/30/94	Yusho Disease/Yu-Cheng Disease (hyperpigmentation [ <a href="#">PMID 3921364</a> ] <sup>217</sup> , low birth weight, nail and conjunctival abnormalities, neurobehavioral deficits, developmental delays [ <a href="#">PMID 3133768</a> ] <sup>218</sup> )[ <a href="#">EPA</a> ] <sup>219</sup> Breastfeeding: Discontinue (appears in human milk; exposures are higher in nursing infants than in utero [ <a href="#">PMID 2104928</a> ] <sup>220</sup> , may cause lack of endurance, hypotonia, sullen expressionless facies [ <a href="#">AAP</a> ]) <sup>221</sup>
Sevin®			(See Carbaryl)
TCE			(See Trichloroethylene)
TCDD	1746-01-6		Male: No known effects [ <a href="#">EPA</a> ] <sup>222</sup> , limited/ suggestive evidence of an association with spina bifida in offspring born to males exposed to Agent Orange, which also contained other substances [ <a href="#">IOM</a> ] <sup>223</sup> [ <a href="#">IOM 1998</a> ] Female: Inconclusive [ <a href="#">EPA</a> ] <sup>224</sup> , current study results of exposures in Seveso, Italy pending [ <a href="#">PMID 10739069</a> ] <sup>225</sup> Breastfeeding: Present in human milk [ <a href="#">PMID 9831540</a> ] <sup>226</sup>
Tetrachloroethylene	127-18-4		(See Perchloroethylene)
2,3,7,8-Tetrachlorodibenzo-para-dioxin	1746-01-6	09/30/94	(See TCDD)
Tobacco smoke - environmental (secondary/passive)	---	06/08/00	Males: Decreased fertility (fecundability) [ <a href="#">PMID 9829871</a> ] <sup>227</sup> Pregnancy/developmental: LBW at term, small-for-gestational-age [ <a href="#">PMID 9987784</a> ] <sup>228</sup> [ <a href="#">PMID 9772856</a> ] <sup>229</sup> , adverse effects on IQ in females [ <a href="#">Seidman</a> ] <sup>230</sup> , decreased fertility (fecundability) in adult females [ <a href="#">PMID 2705427</a> ] <sup>231</sup> , specifically including those who were exposed to tobacco smoke <i>in utero</i> and who currently smoke (as adults)[ <a href="#">PMID 9829871</a> ] <sup>232</sup>

Agent	CAS Number	Date Added	Notes
Tobacco smoke (primary)	---	06/30/95	<p>Males: Decreased sperm concentration and motility [<a href="#">PMID 9051418</a>]<sup>233</sup> and percentage of sperm with normal morphology [<a href="#">PMID 1521002</a>]<sup>234</sup></p> <p>Females: Decreased fertility [<a href="#">PMID 9829871</a>],<sup>235</sup> decreased fecundity, early mean age of menopause [<a href="#">PMID 9434858</a>]<sup>236</sup></p> <p>Pregnancy: IUGR [<a href="#">PMID 9131707</a>]<sup>237</sup> [<a href="#">PMID 9434858</a>]<sup>238</sup></p> <p>Increased blood pressure (which returns to normal within two years) [<a href="#">PMID 8648540</a>]<sup>239</sup></p> <p>Retinal vascular abnormalities (which resolve by age 6 months) [<a href="#">PMID 10839873</a>]<sup>240</sup></p> <p>Adverse lung function effects [<a href="#">PMID 9272918</a>]<sup>241</sup></p> <p>Breastfeeding: Conflicting studies finding decreased [<a href="#">PMID 9457000</a>]<sup>242</sup> or increased [<a href="#">PMID 8067348</a>]<sup>243</sup> infant growth</p>
Toluene	108-88-3	09/30/94	<p>Category X [<a href="#">Briggs</a>]</p> <p>Significant delays in fetal growth following chronic and excessive industrial accidents or intentional abuse [<a href="#">PMID 9143096</a>]<sup>244</sup></p> <p>Toluene embryopathy has been reported (motor and intellectual effects) [<a href="#">PMID 9294310</a>]<sup>245</sup> (developmental delay, CNS dysfunction, hydronephrosis, ventricular septal defects, craniofacial and limb anomalies including microcephaly [<a href="#">PMID 9434858</a>])<sup>246</sup></p> <p>Animal studies also suggest developmental toxicity with respiratory exposure [<a href="#">ATSDR</a>]<sup>247</sup></p>
Toluenediamine	95-80-7	06/27/00	Male: Lowered number of sperm [ <a href="#">NIOSH</a> ] <sup>248</sup>
Toluene-2,4-diamine	95-80-7		(See Toluenediamine)

Agent	CAS Number	Date Added	Notes
Trichlorfon	52-68-6	06/26/00	Male: One report of diminished seminal fluid volume, sperm count, motility, and viability, and increased number of abnormally-shaped sperm [ <a href="#">PMID 5932734</a> ] <sup>249</sup> Pregnancy: One report possibly associating consumption of contaminated fish with congenital abnormalities [ <a href="#">PMID 8094783</a> ], <sup>250</sup> skeletal abnormalities in several animal species [Schardein] <sup>251</sup>
Trichloroethylene	79-01-6	11/30/00	Male: impotence (occupational exposure) <sup>252</sup> Female: amenorrhea, irregular menses (after accidental exposure to high levels) <sup>253</sup>
Urethane (ethyl carbamate - NOT "polyurethane")	51-79-6	06/30/95	Animal data: Oncogenic in several mammalian species; crosses the placenta [ <a href="#">PMID 3050270</a> ], <sup>254</sup> genotoxic in mice [Platzek], <sup>255</sup> preconception exposure of male and female mice produced neoplasms in offspring [ <a href="#">PMID 10406931</a> ] <sup>256</sup>
VCM	75-01-4		(See Vinyl chloride)
Vinyl chloride (monomer— not polyvinyl chloride or PVC)	75-01-4	03/10/00	Fetal loss in wives of exposed males [ <a href="#">PMID 56545</a> ] <sup>257</sup> CNS defects in communities of polyvinyl chloride polymerization plants [ <a href="#">PMID 1069539</a> ] <sup>258</sup> Increased incidence of birth defects (not limited to a single organ system, association lacking substantiation) [ <a href="#">PMID 6879459</a> ] <sup>259</sup>
Xylenes	1330-20-7	03/10/00	Female: Menstrual disorders Pregnancy: Possible association with spontaneous abortion [ATSDR]; <sup>260</sup> "adverse effects" with high levels of maternal exposure [ATSDR]; <sup>261</sup> xylene has known neurological effects, but insufficient human data to confirm neurological effects from in utero exposure [ATSDR] <sup>262</sup>

## **(IX) DRUG REPRODUCTIVE AND DEVELOPMENTAL HAZARDS**

### **A) INTRODUCTION**

Several drugs (folate antagonists and alkylating agents) are known to induce spontaneous abortions as well as congenital malformations. However, compilations of drugs that cause ReproDev adverse effects are usually based upon drugs known to cause teratogenicity. Therapeutic agents known to have teratogenic effects in humans are thalidomide, androgenic hormones, progestogens, folate antagonists, anti-thyroid drugs, and diethylstilbestrol.

Estrogens, in high pharmacologic doses, are used as post-coital contraceptives and cause early pregnancy loss. Diethylstilbestrol (DES), a non-steroidal estrogen, causes adenocarcinoma of the vagina (but not other cancers, to date [[PMID 9718055](#)])<sup>263</sup> in female offspring of treated mothers and disorders of reproductive function in male and female offspring of treated mothers. Male disorders associated with DES include epididymal cysts, microphallus, cryptorchidism, testicular hypoplasia, diminished semen analyses, and decreased sperm penetration assays; however, impairment of fertility has not been demonstrated. Female abnormalities associated with DES include structural defects of the cervix, vagina, uterus, and fallopian tubes, and adverse pregnancy outcomes contributed to by increased rates of spontaneous abortion, ectopic pregnancy, premature delivery, and perinatal deaths [[PMID 6121486](#)].<sup>264</sup> Studies involving the self-reporting of immune system effects associated with the use of DES have been contradictory [[PMID 8606329](#), [PMID 9578280](#)].<sup>265,266</sup>

### **B) HEALTH CARE WORKERS AND HAZARDOUS OCCUPATIONAL EXPOSURES**

There are several potential ReproDev hazards to which HCWs are uniquely exposed. Although HCWs are often not thought of as working in typical “industrial” or manufacturing settings, HCWs routinely have close contact with hazards that directly impact human health. Females (for example, nurse-anesthetists) occupationally exposed to anesthetic gases were shown to have increased spontaneous abortions ([PMID 5114397](#),<sup>267</sup> [PMID 4414878](#)),<sup>268</sup> decreased fecundity ([PMID 4113412](#)),<sup>269</sup> fetal growth retardation ([PMID 63667](#)),<sup>270</sup> and congenital malformations ([PMID 4412215](#)).<sup>271</sup> Even spouses of males occupationally exposed to anesthetic gases have had increased rates of malformations ([PMID 620176](#)).<sup>272</sup> Dispensing pharmaceuticals (for example, those with ReproDev activity, such as antineoplastics or estrogens) may result in exposure via inhalation of vaporized medications ([PMID 10986478](#)),<sup>273</sup> percutaneous absorption, and hand-to-mouth ingestion of dust (shown to contaminate surfaces of both pharmacy drug preparation and drug administration areas, [PMID 10428450](#)).<sup>274</sup> HCWs using, removing (including housekeeping), or cleaning sharps (needles, scalpels, etc.) may be exposed to punctures and lacerations. Additionally, medical instruments may act as transport mechanisms for blood-borne or other body fluids-borne pathogens, such as hepatitis B or human immunodeficiency virus (HIV). Air and droplet spread of communicable disease may be a ReproDev hazard to which HCWs are occupationally exposed. Sterilization of medical supplies, whether by chemicals (for example, gas sterilization with ethylene oxide) or by heat, may expose HCWs to significant ReproDev hazards. Finally, while not unique to HCWs, rotating shifts are often associated with medical work. (Also see the section on Occupational Exposures and Breastfeeding.)

### **C) ANTINEOPLASTIC AGENTS**

The hazards of occupational exposure to antineoplastic agents were addressed by the National Study Commission on Cytotoxic Exposure. The following are excerpts from the Commission's

statement on the handling of cytotoxic agents by women who are attempting to conceive, are pregnant, or are breastfeeding:

*There are substantial data regarding the mutagenic, teratogenic and abortifacient properties of certain cytotoxic agents both in animals and humans who have received therapeutic doses of these agents. Additionally, the scientific literature suggests a possible association of occupational exposure to certain cytotoxic agents during the first trimester of pregnancy with fetal loss or malformation. These data suggest the need for caution when women who are pregnant or attempting to conceive, handle cytotoxic agents. . . . it is prudent that women who are breast feeding should exercise caution in handling cytotoxic agents. . . . Personnel should be provided with information to make an individual decision. This information should be provided in written form and it is advisable that a statement of understanding be signed. . . . It is essential to refer to individual state right-to-know laws to ensure compliance.*<sup>275</sup>

The 1995 OSHA Technical Manual, [Section VI: Chapter 2, Controlling Occupational Exposure To Hazardous Drugs](#), gives more detailed and current information dealing with occupational hazards of administering pharmaceuticals in general and addresses antineoplastics in particular.<sup>276</sup> These recommendations provide the best guidance available at this time.

#### D) DRUG PREGNANCY RISK CATEGORIES

The US Food and Drug Administration uses pregnancy risk categories for pharmaceuticals as set forth in the following table.<sup>277</sup>

**Table 9 - ReproDev Pregnancy Risk Category Key**<sup>278</sup>

Category	Description	Interpretation
<b>A</b>	Controlled human studies show no risk.	Adequate, well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester of pregnancy.
<b>B</b>	No evidence of risk in humans.	Adequate, well-controlled studies in pregnant women have not shown increased risk of fetal abnormalities despite adverse findings in animals, or, in the absence of adequate human studies, animal studies show no fetal risk. The chance of fetal harm is remote, but remains a possibility.
<b>C</b>	Risk cannot be ruled out.	Adequate, well-controlled human studies are lacking, and animal studies have shown a risk to the fetus or are lacking. There is a chance of fetal harm if the drug is administered during pregnancy; but the potential benefits may outweigh the potential risk.
<b>D</b>	Positive evidence of risk.	Studies in humans, or investigational or post-marketing data, have demonstrated fetal risk. Nevertheless, potential benefits from the use of the drug may outweigh the potential risk. For example, the drug may be acceptable if needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective.
<b>X</b>	Contraindicated in pregnancy.	Studies in animals or humans, or investigational or post-marketing reports, have demonstrated positive evidence of fetal abnormalities or risk which clearly outweighs any possible benefit to the patient.

## E) DRUG REPRODUCTIVE AND DEVELOPMENTAL HAZARDS LIST

The following table is a list that may be used as a guideline by health care professionals when dealing with pharmaceuticals or drugs of abuse.

**Table 10 – Drug and Pharmaceutical Reproductive and Developmental Toxicants List**

Drug/Substance	CAS Number	Date Added	Comments/Notes
1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea	13010-47-4	06/30/95	(See Lomustine)
1,25-Dihydrocholecalciferol		10/17/00	(See Calcitriol)
1,4-Butanediol dimethylsulfonate	55-98-1	06/30/95	(See Busulfan)
2-Chloro-2'-deoxyadenosine	4291-63-8		(See Cladribine)
2-Chloroadenosine		10/17/00	(See Cladribine)
4-Aminopteroylglutamic acid	54-62-6		(See Aminopterin)
5-Fluorouracil	51-21-8		(See Fluorouracil)
5-FU	51-21-8		(See Fluorouracil)
6-Mercaptopurine	50-44-2		(See Mercaptopurine)
8-Methoxypsoralen		10/20/00	(See Methoxsalen)
8-MOP		10/20/00	(See Methoxsalen)
Accupril®			(Quinapril) (See ACE Inhibitors)
Accutane®			(See Isotretinoin)
ACE Inhibitors	Captopril 62571-86-2 Enalapril 75847-73-3 Lisinopril 76547-98-3 Benazepril 86541-75-5 Fosinopril 98048-97-6 Quinapril 85441-61-8 Ramipril 87333-19-5		Category C–first trimester [USPDI] <sup>279</sup> (may be acceptable in first trimester [ <a href="#">PMID 10676826</a> ]) <sup>280</sup> Category D–second trimester [USPDI] <sup>281</sup> (ACE inhibitor fetopathy–characterized by fetal hypotension, anuria-oligohydranios, growth restriction, pulmonary hypoplasia, renal tubular dysplasia, and hypocalvaria [ <a href="#">PMID 8507813</a> ]) <sup>282</sup> Breastfeeding: Excretion into milk negligible, but authors differ as to advisability [ <a href="#">PMID 9673832</a> ] <sup>283</sup> [ <a href="#">PMID 9520613</a> ] <sup>284</sup>
Acetohydroxamic acid	546-88-3	06/30/95	Category X (may cause fetal harm) [#] <sup>285</sup> Breastfeeding: Discontinue [#] <sup>286</sup>
Acetyladriamycin	---		(See Daunorubicin citrate)
Achromycin®			(See Tetracycline hydrochloride)
Acitretin	55079-83-9	11/20/00	(See Isotretinoin and Etretinate [ <a href="#">TERIS</a> ]) <sup>287</sup> (Converted to Etretinate in the body [ <a href="#">TERIS</a> ]) <sup>288</sup>
Actinomycin D	50-76-0	06/30/95	(See Dactinomycin)
Adderall®			(See Amphetamines)
Adriamycin®			(See Doxorubicin hydrochloride)
Adrucil®			(See Fluorouracil)
Alfenta®		10/16/00	(See Alfentanil)

Drug/Substance	CAS Number	Date Added	Comments/Notes
Alfentanil	71195-58-9		Category C [#] <sup>289</sup> (D if used for prolonged periods or in high doses at term [Briggs 4th]) <sup>290</sup> Breastfeeding: Express and discard breast milk once before resuming nursing after use [#] <sup>291</sup>
Alkeran®		10/20/00	(See Melphalan)
All-transretinoic acid		10/20/00	(See Tretinoin)
Alprazolam	28981-97-7	06/30/95	Category D (may cause fetal harm and postnatal withdrawal) [#] <sup>292</sup> Breastfeeding: See Benzodiazepines
Altace®			(Ramipril) (See ACE Inhibitors)
Altretamine	645-05-6	08/20/99	Category D [#] <sup>293</sup> Breastfeeding: Discontinue [Facts and Comparisons] <sup>294</sup> [#] <sup>295</sup>
Amethopterin®		10/20/00	(See Methotrexate)
Amikacin	39831-55-5		(See Aminoglycosides)
Amikin®			(Amikacin) (See Aminoglycosides)
4-Aminopteroylglutamic acid	54-62-6		(See Aminopterin)
Aminoglutethimide	125-84-8	06/30/95	Category D [USPDI] <sup>296</sup> [Schardein] <sup>297</sup> (can cause fetal harm [Facts and Comparisons]) <sup>298</sup> Breastfeeding: Discontinue [Facts and Comparisons] <sup>299</sup>
Aminoglycosides	Amikacin 39831-55-5 Gentamicin 1403-66-3 Kanamycin 8063-07-8 Streptomycin 57-92-1 Tobramycin 32986-56-4	06/30/95	Category D (can cause fetal harm) [#] <sup>300</sup> Category C (gentamicin) [USPDI] <sup>301</sup> All cross placenta. <i>In utero</i> aminoglycoside ototoxicity has been reported to date with tobramycin and streptomycin, but not with amikacin, gentamicin, or kanamycin [USPDI]. <sup>302</sup> Breastfeeding: Compatible [Briggs][Briggs 1997] <sup>303</sup> (excreted in milk but are poorly absorbed and problems in nursing infants have not been documented [USPDI]) <sup>304</sup>
Aminopterin	54-62-6	09/30/94	Category X [Schardein] <sup>305</sup> (abortifacient [PMID 507011], <sup>306</sup> aminopterin embryopathy [PMID 10413333] <sup>307</sup> /syndrome [PMID 675555] <sup>308</sup> ) <i>Note: Currently used as a rodenticide.</i>
Amiodarone	1951-25-3	06/23/00	(See Amiodarone hydrochloride)
Amiodarone hydrochloride	19774-82-4	03/06/00	Category D [#] <sup>309</sup> Breastfeeding: Discontinue [#] <sup>310</sup>

Drug/Substance	CAS Number	Date Added	Comments/Notes
Amitriptyline	549-18-8		Category D [Briggs] [Briggs 4th] <sup>311</sup> Category C [#] <sup>312</sup> Breastfeeding: Discontinue (excreted in milk) [#] <sup>313</sup>
Amobarbital		10/17/00	(See Barbiturates)
Amphetamines (amphetamine, dextroamphetamine, methamphetamine)	---		Category C [Briggs 4th] <sup>314</sup> (illicit use is associated with IUGR, preterm labor, and fetal cerebrovascular accidents, withdrawal in infants born to amphetamine addicted mothers) [Briggs] Breastfeeding: Contraindicated [Briggs 1997] <sup>315</sup> (irritability, poor sleeping pattern [AAP]), <sup>316</sup> discontinue (excreted in breast milk) [Facts and Comparisons] <sup>317</sup>
Amytal®		10/17/00	(See Barbiturates) (Amobarbital)
Anabolic steroids (nandrolone, oxandrolone, oxymetholone, stanozolol)	---	03/10/00	Category X [Facts and Comparisons] <sup>318</sup> Breastfeeding: Discontinue [Facts and Comparisons] <sup>319</sup>
Anacufen®		10/20/00	(See Methandriol)
Anadrol®-50			(See Oxymetholone)
Andro LA 200®		10/17/00	(See Testosterone enanthate)
Androderm®			(See Testosterone)
Androgens (testosterone, methyltestosterone, fluoxymesterone)	---		Pregnancy: Contraindicated [Schardein], <sup>320</sup> masculinization (pseudohermaphroditism [Schardein], <sup>321</sup> virilization of female fetuses [Schardein]) <sup>322</sup>
Android®-10 & 25		10/17/00	(See Methyltestosterone)
Android-F®			(See Fluoxymesterone)
Andropository-200®		10/17/00	(See Testosterone enanthate)
Anesthetic gases	---	03/10/00	Female: Reduced fertility <sup>323</sup> Pregnancy: Spontaneous abortion, IUGR <sup>324</sup>
Angiotensin converting enzyme inhibitors	---	06/30/95	(See ACE Inhibitors)
Anisindione	117-37-3	06/30/95	Category D [Briggs 4th] <sup>325</sup> (congenital malformations have been reported) [USPDI] <sup>326</sup> Breastfeeding: Monitor nursing infant for evidence of hypoprothrombinemia [USPDI] <sup>327</sup>
Antabuse®		10/20/00	(See Disulfiram)

Drug/Substance	CAS Number	Date Added	Comments/Notes
Antihistamines (brompheniramine, diphenhydramine)	---		Breastfeeding: Contraindicated [#] <sup>328,329</sup> (first generation antihistamines may inhibit lactation through anticholinergic actions; use not recommended as small amounts are distributed into breast milk with risk to infant of unusual excitement or irritability [USPDI]) <sup>330</sup>
Antineoplastics (cancer chemotherapeutic drugs in general)		07/27/00	Male: Infertility [DLI] <sup>331</sup> Female: Infertility [DLI] <sup>332</sup> Pregnancy: Spontaneous abortion, birth defects, growth retardation [DLI] <sup>333</sup>
ARA-C		10/17/00	(See Cytarabine)
Aspirin	50-78-2	06/30/95	Category C dose < 150 mg/day [Briggs][Briggs 4th] <sup>334</sup> Category D if full-dose aspirin used in 3 <sup>rd</sup> trimester [Briggs][Briggs 4th] <sup>335</sup> (avoid in the last trimester, especially 1 week prior to and during delivery [#]) <sup>336</sup> Breastfeeding: Avoid (excreted in breast milk) [#], <sup>337</sup> compatible but use with caution (one reported case of metabolic acidosis [AAP]) <sup>338</sup> [Briggs 1997] <sup>339</sup>
Atenolol	29122-68-7	03/10/00	Category D (can cause fetal harm) [#] <sup>340</sup> Breastfeeding: Compatible [AAP], <sup>341</sup> with caution (excreted in human milk, may cause bradycardia in nursing infants) [#] <sup>342</sup>
Ativan®		10/17/00	(See Lorazepam)
Atromid-S®		10/17/00	(See Clofibrate)
Azathioprine	446-86-6		Category D [Briggs 4th] <sup>343</sup> Breastfeeding: Discontinue (drug and its metabolites transmitted in breast milk at low level [Facts and Comparisons]) <sup>344</sup>
Bactrim®			(See Sulfonamides)
Barbiturates (amobarbital, butalbital, mephobarbital, metharbital, pentobarbital, phenobarbital, secobarbital)	---	06/30/95	Category D [Briggs] (can cause fetal damage [Briggs 4th]) <sup>345</sup> Breastfeeding: With caution [AAP] <sup>346</sup> (small amounts excreted in breast milk [Briggs 4th]) <sup>347</sup>
BCNU	154-93-8		(See Carmustine)
Benadryl®		10/17/00	(See Diphenhydramine)
Benazepril	86541-75-5	4/25/00	Category D [Briggs][Briggs 4th] <sup>348</sup> Breastfeeding: See ACE Inhibitors (distributed into breast milk [USPDI]) <sup>349</sup>
Bentyl®		10/17/00	(See Dicyclomine)

Drug/Substance	CAS Number	Date Added	Comments/Notes
Benzodiazepines (alprazolam, chlorazepate, chlordiazepoxide, diazepam, estazolam, flunitrazepam, flurazepam, halazepam, lorazepam, midazolam, oxazepam, quazepam, temazepam, triazolam)	---	06/30/95	Category X (as a class [Schardein]), <sup>350</sup> or see specific agents Breastfeeding: Occasional use compatible, use with caution [Briggs 1997], <sup>351</sup> excreted in breast milk [Facts and Comparisons]; <sup>352</sup> since neonates metabolize benzodiazepines more slowly than adults, accumulation of the drug and its metabolites may occur [USPDI] <sup>353</sup>
Benzphetamine hydrochloride	5411-22-3	06/30/95	(See Amphetamines)
Betadine®			(See Povidone-iodine)
BiCNU®	154-93-8		(See Carmustine)
Blenoxane®		10/17/00	(See Bleomycin)
Bleomycin	11056-06-7		Category D [Briggs 4th] <sup>354</sup> Breastfeeding: Contraindicated [Briggs 1997] <sup>355</sup>
Bromides (anticonvulsant/sedative)	---		Category D [Briggs][Briggs 4th] <sup>356</sup> Breastfeeding: Compatible with breastfeeding [AAP], <sup>357</sup> not recommended [Briggs 4th] <sup>358</sup>
Bromocriptine	25614-03-3		Category C [Briggs][Briggs 4th] <sup>359</sup> Breastfeeding: Contraindicated [AAP], <sup>360</sup> suppresses lactation [Briggs][Briggs 1997] <sup>361</sup>
Brompheniramine	86-22-6		Category C [Briggs][Briggs 4th] <sup>362</sup> Breastfeeding: Contraindicated [#] <sup>363</sup>
Bumetanide	---		Category D [Briggs] [Briggs 5th] <sup>364</sup> Breastfeeding: Contraindicated [Briggs][Briggs 5th] <sup>365</sup>
Bumex®		10/17/00	(See Bumetanide)
Busulfan	55-98-1	06/30/95	Category D (may cause fetal harm) [#] <sup>366</sup> Breastfeeding: Discontinue [#] <sup>367</sup>
Butalbital		10/17/00	(See Barbiturates)
1,4-Butanediol dimethylsulfonate	55-98-1	06/30/95	(See Busulfan)
Butazone®	50-33-9	07/10/00	(See Phenylbutazone)
Calcijex®		10/17/00	(See Calcitriol)
Calcitriol	32222-06-3	07/10/00	Category A [Briggs 4th] <sup>368</sup> Category D if recommended dietary allowance (RDA) exceeded [Briggs 4th] <sup>369</sup> [Schardein] <sup>370</sup>
Capoten®		10/17/00	(See Captopril)

Drug/Substance	CAS Number	Date Added	Comments/Notes
Captopril	62571-86-2	03/06/00	Category C (first trimester) [#] <sup>371</sup> Category D (second trimester) (may cause fetal harm or death) [#] <sup>372</sup> Breastfeeding: Discontinue (excreted in human milk and may cause adverse reactions in nursing infants) [#] <sup>373</sup>
Carbamazepine	298-46-4	03/10/00	Category D (can cause fetal harm) [#] <sup>374</sup> Breastfeeding: Discontinue [#], <sup>375</sup> compatible [AAP] <sup>376</sup>
Carbatrol®			(See Carbamazepine)
Carbimazole	22232-54-8		Category D [Briggs] (associated with scalp abnormalities [PMID 1885895]) <sup>377</sup> Breastfeeding: Compatible [AAP] <sup>378</sup>
Carboplatin	41575-94-4	09/30/94	Category D (may cause fetal harm) [#] <sup>379</sup> Breastfeeding: Discontinue [#] <sup>380</sup>
Carmustine	154-93-8	06/28/00	Category D [#] <sup>381</sup> Breastfeeding: Discontinue [#] <sup>382</sup>
CCNU	13010-47-4		(See Lomustine)
Cd A		10/17/00	(See Cladribine)
CDDP®		10/17/00	(See Cisplatin)
CeeNu®		10/17/00	(See Lomustine)
Cerubidine®			(See Daunorubicin hydrochloride)
Chenix®		10/17/00	(See Chenodiol)
Chenodeoxycholic acid	474-25-9		(See Chenodiol)
Chenodiol	474-25-9	06/30/95	Category X [USPDI] <sup>383</sup>
Chlorambucil	305-03-3	09/30/94	Males: Reversible sterility, permanent sterility, azoospermia [#] <sup>384</sup> Females: Reversible sterility, permanent sterility, amenorrhea [#] <sup>385</sup> Category D (can cause fetal harm) [#] <sup>386</sup> Breastfeeding: Discontinue [#] <sup>387</sup>
Chloramphenicol	56-75-7		Category C [Briggs][Briggs 4th] <sup>388</sup> Not recommended in pregnancy at term (neonatal "gray baby" disease or "gray syndrome," bone marrow suppression) [USPDI] <sup>389</sup> Breastfeeding: Use with caution [Briggs 1997] <sup>390</sup> (excreted in breast milk [USPDI], <sup>391</sup> possible idiosyncratic bone marrow suppression [AAP]) <sup>392</sup>
Chlorazepate		10/17/00	(See Benzodiazepines)
Chlordiazepoxide	58-25-3	06/30/95	Category D [Briggs][Briggs 4th] <sup>393</sup> Breastfeeding: See Benzodiazepines
Chlordiazepoxide hydrochloride	438-41-5	06/30/95	(See Chlordiazepoxide)
2-Chloroadeoxyadenosine		10/17/00	(See Cladribine)
2-Chloro-2'-deoxyadenosine	4291-63-8		(See Cladribine)
1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea	13010-47-4	06/30/95	(See Lomustine)

Drug/Substance	CAS Number	Date Added	Comments/Notes
Chloromycetin®			(See Chloramphenicol)
Chlorothiazide	58-94-6	04/25/00	Category D [Briggs][Briggs 4 <sup>th</sup> ] <sup>394</sup> Breastfeeding: Discontinue [#] <sup>395</sup> (excreted in breast milk in low concentrations [Briggs 4th]), <sup>396</sup> compatible [AAP] <sup>397</sup>
Chlorotrianisene	569-57-3		Category X [USPDI] <sup>398</sup> Breastfeeding: Not recommended (distributed into breast milk) [USPDI] <sup>399</sup>
Chlorpropamide	94-20-2		Category D [Briggs][Briggs 4th] <sup>400</sup> Breastfeeding: Not recommended (excreted in human milk) [#] <sup>401</sup>
Chlortetracycline	57-62-5		Pregnancy: Available only for ophthalmic use, in which problems in humans have not been documented [USPDI] <sup>402</sup> Breastfeeding: Available only for ophthalmic use, in which problems in humans have not been documented [USPDI] <sup>403</sup> (See Tetracycline hydrochloride for consideration of other exposures)
Cholecalciferol	67-97-0	07/10/00	Category A [Briggs 4th] <sup>404</sup> Category D if RDA exceeded [Briggs 4th] <sup>405</sup> [Schardein] <sup>406</sup>
Cidofovir	149394-66-1	03/10/00	Males: Inhibition of spermatogenesis in rats and monkeys [#] <sup>407</sup> Category C [#] <sup>408</sup> Breastfeeding: Should not be administered to nursing mothers [#] <sup>409</sup>
Cinobac®		10/17/00	(See Cinoxacin)
Cinoxacin	28657-80-9		Category C (crosses the placenta) [USPDI] <sup>410</sup> Breastfeeding: Not recommended (unknown if excreted in milk, but has caused arthropathy in immature animals) [USPDI] <sup>411</sup>
Cipro®			(See Ciprofloxacin)
Ciprofloxacin	85721-33-1		Pregnancy: Category C [#] <sup>412</sup> Breastfeeding: Discontinue (excreted in human milk) [#] <sup>413</sup> (do not resume breastfeeding before 48 hours after last dose [Briggs][Briggs 4th]) <sup>414</sup> (See also Fluoroquinolones)
Cisplatin	15663-27-1		Category D (can cause fetal harm) [#] <sup>415</sup> Breastfeeding: Controversy exists— Do not breastfeed (found in human milk) [#], <sup>416</sup> Compatible (not found in milk) [AAP] <sup>417</sup>

Drug/Substance	CAS Number	Date Added	Comments/Notes
Cladribine	4291-63-8	03/10/00	Category D [#] <sup>418</sup> Breastfeeding: Discontinue [#] <sup>419</sup>
Clinoril®			(See Sulindac)
Clofibrate	---	06/28/00	Category C [Briggs 4th] <sup>420</sup> Breastfeeding: Contraindicated [Briggs 1997] <sup>421</sup>
Clomid®			(See Clomiphene)
Clomiphene	911-45-5		Category X [#] <sup>422</sup> Breastfeeding: Exercise caution [#] <sup>423</sup>
Clomocycline	1181-54-0		Category D [Briggs 4th] <sup>424</sup> (case report of multiple fetal abnormalities and neonatal death exists [ <a href="#">PMID 143981</a> ]) <sup>425</sup> Breastfeeding: See Tetracycline hydrochloride
Clorazepate dipotassium	57109-90-7	06/30/95	Pregnancy: Use during pregnancy should almost always be avoided [#] <sup>426</sup> Breastfeeding: See Benzodiazepines
Cocaine	50-36-2	06/30/95	Category C [Briggs 4th] <sup>427</sup> Category X if nonmedicinal use [ <a href="#">Briggs</a> ][Briggs 4th] <sup>428</sup> (associated with fetal malformations, placental toxicity [ <a href="#">PMID 9434858</a> ]) <sup>429</sup> Breastfeeding: Contraindicated (may cause cocaine intoxication) [ <a href="#">AAP</a> ]
Colchicine	64-86-8	06/30/95	Category D [ <a href="#">Briggs 4th</a> ] <sup>430</sup> Breastfeeding: Compatible [ <a href="#">AAP</a> ] <sup>431</sup>
Conjugated estrogens	12126-59-9		Category X [Facts and Comparisons] <sup>432</sup> Breastfeeding: Administer only when clearly needed (may be excreted in breast milk; decrease the quantity and quality of breast milk [Facts and Comparisons]) <sup>433</sup>
Copper <sup>64</sup> (64Cu)	13981-25-4		Breastfeeding: Discontinue temporarily (radioactivity in milk present at 50 hours) [ <a href="#">AAP</a> ] <sup>434</sup>
Cordarone®			(See Amiodarone hydrochloride)
Cortisone	53-06-5	07/10/00	Category D [Briggs 4th] <sup>435</sup> Breastfeeding: Appears in breast milk [Facts and Comparisons] <sup>436</sup>
Cosmegen®			(See Dactinomycin)
Coumadin®			(See Warfarin)
Cuprimine®			(See Penicillamine)

Drug/Substance	CAS Number	Date Added	Comments/Notes
Cyclophosphamide	50-18-0		Category D [ <a href="#">Briggs</a> ] [USPDI] <sup>437</sup> Breastfeeding: Contraindicated [ <a href="#">Briggs</a> ][Briggs 1997], <sup>438</sup> (possible immune suppression, association with carcinogenesis, neutropenia [ <a href="#">AAP</a> ]), <sup>439</sup> not recommended (distributed into breast milk) [USPDI] <sup>440</sup>
Cyclosporin	79217-60-0		Category C (crosses the placenta, associated with preterm births and low birth weight) [USPDI] <sup>441</sup> Breastfeeding: Contraindicated [Briggs 1997] <sup>442</sup> (possible immune suppression [ <a href="#">AAP</a> ]), <sup>443</sup> compatibility with breastfeeding not established [ <a href="#">PMID 7847911</a> ], <sup>444</sup> not recommended (distributed into breast milk) [USPDI] <sup>445</sup>
Cyclosporine	79217-60-0		(See Cyclosporin)
Cyproterone acetate	427-51-0		Contraindicated [#] <sup>446</sup> [Jahn] <sup>447</sup> Breastfeeding: Contraindicated (transferred into breast milk) [#] <sup>448</sup>
Cytadren®			(See Aminoglutethimide)
Cytarabine	147-94-4	09/30/94	Category D (can cause fetal harm) [#] <sup>449</sup> Breastfeeding: Discontinue [#] <sup>450</sup>
Cytosar-U®			(See Cytarabine)
Cytosine arabinosine		10/17/00	(See Cytarabine)
Cytotec®			(See Misoprostol)
Cytovene®			(See Ganciclovir)
Cytoxan®			(See Cyclophosphamide)
D.H.E.®		10/20/00	(See Dihydroergotamine mesylate)
Dacarbazine	4342-03-4	06/28/00	Category C [Briggs 4th] <sup>451</sup> Breastfeeding: Contraindicated [Briggs 1997] <sup>452</sup>
Dactinomycin	50-76-0	06/30/95	Category C (can cause malformations and embryotoxicity in animals) [#] <sup>453</sup> Breastfeeding: Discontinue [#] <sup>454</sup>
Dalmane®		10/17/00	(See Flurazepam)
Danacrine®			(See Danazol)
Danazol	1723-88-5	06/30/95	Category X (contraindicated, may result in androgenic effects on the female fetus) [#] <sup>455</sup> Breastfeeding: Contraindicated [#] <sup>456</sup>
Daraprim®			(See Pyrimethamine)
Daunorubicin	20830-81-3		(See Daunorubicin citrate)
Daunorubicin citrate	20830-81-3	05/04/00	Category D (can cause fetal harm) [#] <sup>457</sup>
Daunorubicin hydrochloride	23541-50-6	09/30/94	Category D (may cause fetal harm) [#] <sup>458</sup> Breastfeeding: Discontinue [#] <sup>459</sup>
DaunoXome®	20830-81-3		(See Daunorubicin citrate)
Declomycin®			(See Demeclocycline hydrochloride)
Delatestryl®			(See Testosterone enanthate)

Drug/Substance	CAS Number	Date Added	Comments/Notes
Delta-D®		10/17/00	(See Cholecalciferol)
Demeclocycline hydrochloride (internal use)	64-73-3	06/30/95	Category D [Briggs][Briggs 4th] <sup>460</sup> Breastfeeding: See Tetracycline hydrochloride
Depacon®			(See Valproate sodium)
Depakene®			(See Valproic acid)
Depakote®		10/20/00	(See Valproate sodium)
Depandro®		10/17/00	(See Testosterone cypionate)
Depen®			(See Penicillamine)
Depotest®		10/17/00	(See Testosterone cypionate)
Depo-testosterone®		10/17/00	(See Testosterone cypionate)
DES	56-53-1		(See Diethylstilbestrol)
Desoxyn®			(Methamphetamine) (See Amphetamines)
Diabinese®			(See Chlorpropamide)
Diacetylmorphine	561-27-3		(See Heroin)
Diazepam	439-14-5	06/30/95	Category D [Briggs][Briggs 4th] <sup>461</sup> Breastfeeding: May be of concern [AAP], <sup>462</sup> not recommended (excreted in breast milk and may accumulate in breast-fed infants) [Briggs 4th] <sup>463</sup>
Dicumarol	66-76-2	06/30/95	Category D [Briggs] [Briggs 4th] <sup>464</sup> Breastfeeding: Compatible [AAP] <sup>465</sup>
Dicyclomine	67-92-5		Category B [#] <sup>466</sup> Breastfeeding: Contraindicated (excreted in human milk) [#] <sup>467</sup>
Dicycloverine hydrochloride	67-92-5		(See Dicyclomine)
Didrex®		10/17/00	(See Amphetamines) (Benzphetamine hydrochloride)
Dienestrol	84-17-3		Category X [#] <sup>468</sup> Breastfeeding: With caution [#] <sup>469</sup>
Diethyldithiocarbamate	148-18-5	07/26/00	No data, but is metabolized to disulfiram (See Disulfiram)
Diethylstilbestrol (DES)	56-53-1	06/30/95	Category X [USPDI] <sup>470</sup> (see Introduction to this section, above) Breastfeeding: Compatible [Briggs 1997] <sup>471</sup>
Diflunisal	22494-42-4	07/05/00	Category C [Briggs 4th] <sup>472</sup> Category D if used in the 3 <sup>rd</sup> trimester [Briggs 4th] <sup>473</sup> Breastfeeding: Discontinue (excreted in breast milk in concentrations 2%-7% of those in plasma) [#] <sup>474</sup>
1,25-Dihydrocholecalciferol		10/17/00	(See Calcitriol)
Dihydroergotamine mesylate	6190-39-2	03/10/00	Category X [#] <sup>475</sup> Breastfeeding: Contraindicated [#] <sup>476</sup>
Dilantin®			(See Diphenylhydantoin)
Dimetane®			(See Brompheniramine)
Dimetapp®		10/17/00	(See Brompheniramine)

Drug/Substance	CAS Number	Date Added	Comments/Notes
Dindevan®		10/20/00	(See Phenindione)
Diphenhydramine	58-73-1		Category C [Briggs 4th] <sup>477</sup> Breastfeeding: Contraindicated [#] <sup>478</sup> (See also Antihistamines)
Diphenylhydantoin	57-41-0	06/30/95	(See Phenytoin)
Disulfiram	97-77-8	07/10/00	Controversy exists as to category— Category X [Schardein] <sup>479</sup> Category C (noted reports of malformations but unknown relationship to disulfiram; noted embryotoxicity) [Briggs 4th] <sup>480</sup>
Diuril®		10/17/00	(See Chlorothiazide)
dl-Penicillamine	52-66-4		(See Penicillamine)
Dolobid®		10/20/00	(See Diflunisal)
Doral®		10/20/00	(See Quazepam)
Doxorubicin	23214-92-8		(See Doxorubicin hydrochloride)
Doxorubicin hydrochloride	25316-40-9		Category D [#] <sup>481</sup> [Briggs][Briggs 4th] <sup>482</sup> Breastfeeding: Contraindicated (concentrated in human milk, possible immune suppression) [AAP], <sup>483</sup> avoid [#] <sup>484</sup>
Doxycycline	564-25-0	06/30/95	Category D (after 12 weeks of pregnancy [Briggs]) (second half of pregnancy [#]) <sup>485</sup> Breastfeeding: Excreted in human milk. Not recommended [#]. <sup>486</sup>
Drisdol®			(See Ergocalciferol)
Durabolin®		10/17/00	(See Anabolic steroids) (Nandrolone)
Duratest®		10/17/00	(See Testosterone cypionate)
Durathate-200®		10/17/00	(See Testosterone enanthate)
Ecstasy			(See MDMA)
Elavil®		10/17/00	(See Amitriptyline)
Enalapril	75847-73-3		Category D (second and third trimesters) [#] <sup>487</sup> Category C (first trimester) [#] <sup>488</sup> Breastfeeding: Not recommended. Excreted in human milk [#]. <sup>489</sup>
Endoxan®			(See Cyclophosphamide)
Enovid®		10/20/00	(See Norethynodrel)
Enoxacin		10/20/00	(See Fluoroquinolones)
Equanil®		10/20/00	(See Meprobamate)
Ergocalciferol	50-14-6	07/10/00	Category A [Briggs 4th] <sup>490</sup> Category D in doses above the RDA [Briggs 4th] <sup>491</sup>
Ergostat®		10/20/00	(See Ergotamine tartrate)

Drug/Substance	CAS Number	Date Added	Comments/Notes
Ergotamine	113-15-5	06/30/95	Category X [#] <sup>492</sup> [Briggs] Category D [Briggs 5th] <sup>493</sup> Breastfeeding: Contraindicated [Briggs 1997] <sup>494</sup> (vomiting, diarrhea, convulsions at doses used in migraine medications [AAP]) <sup>495</sup>
Ergotamine tartrate	379-79-3		(See Ergotamine)
Esidrix®		10/20/00	(See Hydrochlorothiazide)
Eskalith®			(See Lithium carbonate)
Estazolam	29975-16-4		Category X [USPDI] <sup>496</sup> Breastfeeding: See Benzodiazepines (human studies lacking, but appears in animal breast milk [USPDI]) <sup>497</sup>
Estinyl®		10/20/00	(See Ethinyl estradiol)
Estrace®		10/20/00	(See Estradiol)
Estradiol	50-28-2		Category X [#] <sup>498</sup> Breastfeeding: Decreased quantity and quality of milk [#], <sup>499</sup> but compatible [Briggs 1997] <sup>500</sup>
Estrogens	---		Category X [Briggs 4th] <sup>501</sup> Breastfeeding: Compatible [Briggs 1997] <sup>502</sup>
Estropipate	7280-37-7	03/10/00	Category X [#] <sup>503</sup> Breastfeeding: Decreased quantity and quality of milk [#] <sup>504</sup>
Ethanol	64-17-5		Category D [Briggs 4th] <sup>505</sup> Category X [Briggs] (when used in large amounts or for prolonged periods [Briggs 4th]) <sup>506</sup> (developmental defects, which may include the fetal alcohol syndrome [PMID 9434858], <sup>507</sup> low birth weight, spontaneous abortion, growth retardation, congenital anomalies [Schardein], <sup>508</sup> placental toxicity [PMID 1621875]) <sup>509</sup> Breastfeeding: Minimal dose [Briggs], compatible [AAP], contraindicated [Briggs 1997] <sup>510</sup>
Ethinyl estradiol	57-63-6		Category X [#] <sup>511</sup> Breastfeeding: Excreted in milk; decreased quantity and quality of milk [#], <sup>512</sup> but compatible [Briggs 1997] <sup>513</sup>
Ethisterone	434-03-7	07/10/00	Category D [Briggs 4th] <sup>514</sup> (case reports of female masculinization [Schardein]) <sup>515</sup> Breastfeeding: See Oral contraceptives
Ethyl biscoumacetate	548-00-5	06/29/00	Category D [Briggs 4th] <sup>516</sup> Breastfeeding: Avoid (possible adverse effects on nursing infants [Briggs 4th]) <sup>517</sup>

Drug/Substance	CAS Number	Date Added	Comments/Notes
Ethynodiol diacetate	297-76-7	07/10/00	Category D [Briggs 4th] <sup>518</sup> Breastfeeding: See Oral contraceptives
Etodolac	41340-25-4	03/10/00	Category C [#] <sup>519</sup> Possible closure of ductus arteriosus—avoid during late pregnancy [#] <sup>520</sup>
Etoposide	33419-42-0	09/30/94	Category D [#] <sup>521</sup> Breastfeeding: Avoid [#], <sup>522</sup> contraindicated [Briggs 1997] <sup>523</sup>
Etretinate	54350-48-0	06/30/95	Category X [Briggs][Briggs 4th] <sup>524</sup> (small amounts detected more than 2 years after treatment concluded [Facts and Comparisons]) <sup>525</sup> Breastfeeding: Not recommended [USPDI] <sup>526</sup>
Eulexin®		10/20/00	(See Flutamide)
Everone 200®		10/17/00	(See Testosterone enanthate)
Famciclovir	104227-87-4	06/28/00	Category B [Facts and Comparisons] <sup>527</sup> Breastfeeding: Not recommended [Briggs 1997] <sup>528</sup>
Famvir®		10/20/00	(See Famciclovir)
Fertinex®			(See Urofollitropin)
Finasteride	98319-26-7	06/02/00	Category X [Facts and Comparisons] <sup>529</sup> (risk to male fetus) [#], <sup>530</sup> women should not handle crushed or broken tablets when pregnant or may potentially be pregnant [#] <sup>531</sup> Breastfeeding: Not indicated for use in women [#] <sup>532</sup> (not known if excreted in breast milk [Facts and Comparisons]) <sup>533</sup>
Flagyl®			(See Metronidazole)
Floxin®			(See Ofloxacin)
Fludara®		10/20/00	(See Fludarabine)
Fludarabine	21679-14-1	06/28/00	Category D [Facts and Comparisons] <sup>534</sup> Breastfeeding: Contraindicated [Briggs 1997] <sup>535</sup>
Flunitrazepam		10/17/00	(See Benzodiazepines)
5-Fluorouracil	51-21-8		(See Fluorouracil)
Fluoroquinolones (ciprofloxacin, levofloxacin, norfloxacin, enoxacin, ofloxacin, gatifloxacin, lomefloxacin)	---		Category C (do not use in pregnant women [Facts and Comparisons]) <sup>536</sup> Breastfeeding: Discontinue [Facts and Comparisons] <sup>537</sup>
Fluorouracil	51-21-8	09/30/94	Category X [#] <sup>538</sup> Breastfeeding: Contraindicated [#] <sup>539</sup>

Drug/Substance	CAS Number	Date Added	Comments/Notes
Fluoxymesterone	76-43-7	06/30/95	Male: Fertility effects [ <a href="#">PMID 137913</a> ] <sup>540</sup> (may be dose dependent [ <a href="#">PMID 3435196</a> ]) <sup>541</sup> Genotoxic effects [ <a href="#">PMID 7715612</a> ] <sup>542</sup> Category X [Facts and Comparisons] <sup>543</sup> Breastfeeding: Discontinue [Facts and Comparisons] <sup>544</sup>
Flurazepam hydrochloride	1172-18-5	06/30/95	Contraindicated in pregnancy [#] <sup>545</sup> (crosses the placenta, benzodiazepines may cause fetal damage when administered during pregnancy [Facts and Comparisons]) <sup>546</sup> Breastfeeding: Safety not established [Facts and Comparisons] <sup>547</sup>
Flutamide	13311-84-7	06/30/95	Male: Reduced sperm counts and spermatogenesis [#] <sup>548</sup> Category D [#] <sup>549</sup> Breastfeeding: Product only indicated for use in males
Fluvastatin	93957-54-1	06/28/00	Category X [Facts and Comparisons] <sup>550</sup> Breastfeeding: Contraindicated [Briggs 1997] <sup>551</sup>
Folex®		10/20/00	(See Methotrexate)
5-FU	51-21-8		(See Fluorouracil)
Furadantin®			(See Nitrofurantoin)
Gallium <sup>67</sup> (67Ga)	7440-55-3		Category C [USPDI] <sup>552</sup> Breastfeeding: Discontinue temporarily (radioactivity in milk present for 2 weeks) [ <a href="#">AAP</a> ] <sup>553</sup>
Ganciclovir	82410-32-0	03/10/00	Category C (may be teratogenic or embryotoxic) [#] <sup>554</sup> Breastfeeding: Discontinue use [#] <sup>555</sup>
Garamycin®			(Gentamicin) (See Aminoglycosides)
Gatifloxacin		10/20/00	(See Fluoroquinolones)
Gemfibrozil	25812-30-0	03/10/00	Category C [#] <sup>556</sup> Breastfeeding: Discontinue [Facts and Comparisons] <sup>557</sup>
Gentamicin	1403-66-3		(See Aminoglycosides)
Goserelin acetate	65807-02-5	03/10/00	Category X (avoid pregnancy for 12 weeks after discontinuing use) [#] <sup>558</sup> Breastfeeding: Contraindicated [#] <sup>559</sup>
Halazepam	23092-17-3	06/30/95	Category D [Drug Information Handbook] <sup>560</sup> Breastfeeding: See Benzodiazepines
Halcion®			(See Triazolam)
Halotestin®		10/17/00	(See Fluoxymesterone)
HCTZ		10/20/00	(See Hydrochlorothiazide)

Drug/Substance	CAS Number	Date Added	Comments/Notes
Heroin	561-27-3		Pregnancy: Preterm birth [ <a href="#">PMID 2304039</a> ], <sup>561</sup> neonatal withdrawal [Williams] <sup>562</sup> Breastfeeding: Contraindicated (tremors, restlessness, vomiting, poor feeding) [ <a href="#">AAP</a> ] <sup>563</sup> (excreted in milk [ <a href="#">PMID 9363416</a> ]) <sup>564</sup>
Hexalen®			(See Altretamine)
Histerone 100®		10/17/00	(See Testosterone)
Histrelin	76712-82-8		(See Histrelin acetate)
Histrelin acetate	---	03/10/00	Category X [Facts and Comparisons] <sup>565</sup> Breastfeeding: Do not use [Facts and Comparisons] <sup>566</sup>
HN <sub>2</sub>		10/20/00	(See Mechllorethamine)
Hormone pregnancy test tablets			Category X [Briggs 4th] <sup>567</sup> Breastfeeding: See Oral contraceptives
Hydrea®		10/20/00	(See Hydroxyurea)
Hydriodic acid	10034-85-2		(See Potassium iodide) (Iodide is the active ingredient) [Briggs 4th] <sup>568</sup>
Hydrochlorothiazide	58-93-5	07/10/00	(See Chlorothiazide)
HydroDiuril®		10/20/00	(See Hydrochlorothiazide)
Hydrogen iodide		10/20/00	(See Hydriodic acid)
Hydroxyprogesterone	68-96-2	07/10/00	Category D [Briggs 4th] <sup>569</sup> Breastfeeding: Not recommended (distributed into breast milk) [USPDI] <sup>570</sup>
Hydroxyurea	127-07-1		Male: Testicular atrophy, impaired spermatogenesis [#] <sup>571</sup> Category D (embryotoxic, fetal malformations) [#] <sup>572</sup> Breastfeeding: Incompatible (excreted in human milk) [#], <sup>573</sup> contraindicated [Briggs 1997] <sup>574</sup>
Hylutin®		10/20/00	(See Hydroxyprogesterone)
Hyprogest 250®		10/20/00	(See Hydroxyprogesterone)
Ibuprofen	15687-27-1	05/30/00	Category B [#] <sup>575</sup> Category D at end of pregnancy (may cause premature closure of ductus arteriosus and delay parturition) [ <a href="#">Briggs</a> ][Briggs 4th] <sup>576</sup> Breastfeeding: Compatible [ <a href="#">AAP</a> ] <sup>577</sup>
Idamycin®		10/20/00	(See Idarubicin hydrochloride)
Idarubicin hydrochloride	57852-57-0	03/10/00	Category D (embryotoxic and teratogenic in rats) [#] <sup>578</sup> Breastfeeding: Discontinue prior to taking drug [#], <sup>579</sup> contraindicated [Briggs 1997] <sup>580</sup>
Ifex®		10/20/00	(See Ifosfamide)

Drug/Substance	CAS Number	Date Added	Comments/Notes
Ifosfamide	3778-73-2	09/30/94	Category D [#] <sup>581</sup> Breastfeeding: Incompatible [#], <sup>582</sup> contraindicated [Briggs 1997] <sup>583</sup>
Imuran®		10/17/00	(See Azathioprine)
Imuthiol®		10/20/00	(See Diethyldithiocarbamate)
Indium <sup>111</sup> (111In)	7440-74-6		Category C [USPDI] <sup>584</sup> Breastfeeding: Discontinue temporarily (very small amount present at 20 hours) [AAP] <sup>585</sup>
Indocin®		10/17/00	(See Indomethacin)
Indomethacin	53-86-1		Category B [Briggs][Briggs 4th] <sup>586</sup> Category D if used for longer than 48 hours or after 34 weeks gestation [Briggs 4th] <sup>587</sup> (may cause premature closure of ductus arteriosus and delay parturition [Briggs], associated with fetal anuria, oligohydramnios, persistent pulmonary hypertension [PMID 9434858]) <sup>588</sup> Breastfeeding: Not recommended (excreted in milk) [#] <sup>589</sup>
Iodides	---		(See Iodine)
Iodinated glycerol (anti-tussive/expectorant)	5634-39-9		Category X [Briggs 4th] <sup>590</sup> Breastfeeding: Concentrated in breast milk [Briggs 4th], <sup>591</sup> but compatible [AAP] <sup>592</sup>
Iodine	7553-56-2		Category D [Briggs 4th] <sup>593</sup> Breastfeeding: Not compatible (concentrated in breast milk, and long term use may adversely affect the nursing infant's thyroid activity) [Briggs 1997] <sup>594</sup>
Iodine <sup>123</sup> (I <sup>123</sup> )	15715-08-9		Breastfeeding: Discontinue temporarily (radioactivity in milk present up to 36 hours) [AAP] <sup>595</sup>
Iodine <sup>125</sup> (I <sup>125</sup> )	14158-31-7		Category X [Briggs] Breastfeeding: Contraindicated (radioactivity in milk for 12 days) [AAP] <sup>596</sup>
Iodine <sup>131</sup> (I <sup>131</sup> )	100043-66-0	03/10/00	Category X [Briggs] Breastfeeding: Contraindicated (radioactivity in milk for 2 to 14 days) [AAP] <sup>597</sup>
Isoretinoin	4759-48-2		(See Isotretinoin)
Isotretinoin	4759-48-2	06/30/95	Category X (spontaneous abortions and fetal malformations) [Briggs] [Briggs 4th] <sup>598</sup> [#] <sup>599</sup> Breastfeeding: Do not give [Facts and Comparisons] <sup>600</sup>

Drug/Substance	CAS Number	Date Added	Comments/Notes
Kanamycin sulfate	8063-07-8		Category D [Briggs][Briggs 4 <sup>th</sup> ] <sup>601</sup> Breastfeeding: Compatible [AAP] <sup>602</sup> (excreted in breast milk) [Briggs 4th] <sup>603</sup> (See also Aminoglycosides)
Kannasyn®			(See Kanamycin)
Kantrex®		10/17/00	(See Kanamycin)
Lescol®		10/20/00	(See Fluvastatin)
Leukeran®			(See Chlorambucil)
Leuprolide acetate	74381-53-6	03/06/00	Category X [#] <sup>604</sup> Breastfeeding: Do not use [#] <sup>605</sup>
Leustatin®			(See Cladribine)
Levofloxacin		10/20/00	(See Fluoroquinolones)
Levonorgestrel implants	797-63-7	03/10/00	Category X [#] <sup>606</sup> Breastfeeding: Excreted in breast milk [#] <sup>607</sup>
Levaquin®			(See Levofloxacin)
Librium®			(See Chlordiazepoxide)
Lithium	7439-93-2		(See Lithium carbonate)
Lithium carbonate	554-13-2	06/30/95	Category D [Briggs][Briggs 4th] <sup>608</sup> (cardiac anomalies) [#] <sup>609</sup> Breastfeeding: Contraindicated [Briggs][Briggs 1997] <sup>610</sup> [AAP] (excreted in human milk) [#] <sup>611</sup>
Lithium citrate	919-16-4	06/30/95	(See Lithium carbonate)
Lithostat®		10/16/00	(See Acetohydroxamic acid)
Lodine®		10/20/00	(See Etodolac)
Lomustine	13010-47-4		Category D (embryotoxic and teratogenic in rats) [#] <sup>612</sup> Breastfeeding: Not recommended (unknown if excreted in human milk) [#] <sup>613</sup>
Lopid®		10/20/00	(See Gemfibrozil)
Lorazepam	846-49-1	06/30/95	Category D [Briggs][Briggs 4th] <sup>614</sup> Breastfeeding: With caution [Briggs] (excreted in breast milk in low concentrations [Briggs 4th], <sup>615</sup> effect may be of concern [AAP]) <sup>616</sup>
Lomefloxacin		10/20/00	(See Fluoroquinolones)
Lotensin®			(Benazepril) (See ACE Inhibitors)
Lovastatin	75330-75-5	06/30/95	Category X [#] <sup>617</sup> Breastfeeding: Contraindicated [#] <sup>618</sup>
L-PAM		10/20/00	(See Melphalan)
L-Phenylalanine Mustard		10/20/00	(See Melphalan)
L-Sarcosylsin		10/20/00	(See Melphalan)
Macrochantin	67-20-9		(See Nitrofurantoin)
Marcoumar®		10/20/00	(See Phenprocoumon)

Drug/Substance	CAS Number	Date Added	Comments/Notes
Marijuana	---	06/28/00	Category C [Briggs 4th] <sup>619</sup> Breastfeeding: Contraindicated [Briggs 1997] <sup>620</sup> [AAP] <sup>621</sup>
Matulane®		10/20/00	(See Procarbazine hydrochloride)
Maxaquin®			(See Lomefloxacin)
MDMA			(See N-Methyl-3,4-methylenedioxy-amphetamine)
Measles vaccine, live	---		Category C, but contraindicated in pregnancy, and pregnancy should be avoided for 3 months after vaccination (natural measles is associated with spontaneous abortion, stillbirth, congenital defects, premature delivery) [#] <sup>622</sup> Breastfeeding: With caution [#] <sup>623</sup>
Mebaral®		10/17/00	(See Barbiturates) (Mephobarbital)
Mechlorethamine	51-75-2		Category D (can cause fetal harm) [#] <sup>624</sup> Breastfeeding: Incompatible [#] <sup>625</sup>
Medroxyprogesterone acetate	71-58-9	06/30/95	Category D [Briggs][Briggs 4th] <sup>626</sup> (may cause hypospadias) [#] <sup>627</sup> Breastfeeding: Compatible [AAP] <sup>628</sup>
Megace®		10/20/00	(See Megestrol acetate)
Megestrol acetate	595-33-5	06/30/95	Category X (genital abnormalities) [#] <sup>629</sup> Breastfeeding: Discontinue [#] <sup>630</sup>
Melphalan	148-82-3	06/30/95	Category D [#] <sup>631</sup> Breastfeeding: Discontinue [#] <sup>632</sup>
Menadiol	---		(See Menadione)
Menadiol sodium diphosphate	---		(See Menadione)
Menadione	58-27-5		Category C [Briggs 4th] <sup>633</sup> Category X (in third trimester or close to delivery) [Briggs 5th] <sup>634</sup> Breastfeeding: Vitamin K <sub>1</sub> preferred (may produce newborn toxicity) [Briggs 5th] <sup>635</sup> [Drug Information Handbook] <sup>636</sup>
Menotropins	9002-68-0	06/30/95	Category X [#] <sup>637</sup> Breastfeeding: With caution [#] <sup>638</sup>
Mephobarbital		10/17/00	(See Barbiturates)
Meprobamate	57-53-4	06/30/95	Category D [Briggs][Briggs 4th] <sup>639</sup> Breastfeeding: Concentrated in milk [Briggs][Briggs 4th], <sup>640</sup> may cause sedation in the nursing infant [USPDI] <sup>641</sup>
6-Mercaptopurine	50-44-2		(See Mercaptopurine)
Mercaptopurine	6112-76-1	06/30/95	Category D (can cause fetal harm, including spontaneous abortion and possibly death in utero) [#] <sup>642</sup> Breastfeeding: Discontinue [#] <sup>643</sup>

Drug/Substance	CAS Number	Date Added	Comments/Notes
Meruvax® II			(See Rubella vaccine, live)
Mestranol	72-33-3		Category X [#] <sup>644</sup> Breastfeeding: Discouraged (excreted in milk, may cause jaundice and breast enlargement in nursing children) [#] <sup>645</sup>
Methacycline hydrochloride	3963-95-9	06/30/95	Category D [Briggs 5th] <sup>646</sup> [Briggs 4th] <sup>647</sup> Breastfeeding: See Tetracycline hydrochloride (excreted in milk in low concentration; theoretical dental staining and inhibition of bone growth)
Methandriol	521-10-8	07/10/00	(See Androgens)
Metharbital		10/17/00	(See Barbiturates)
Methimazole	60-56-0	06/30/95	Category D [Briggs][Briggs 4th] <sup>648</sup> (may cause fetal harm and congenital defects [#]) <sup>649</sup> Breastfeeding: Contraindicated (appears in human milk) [#] <sup>650</sup>
Methotrexate	59-05-2	09/30/94	Category D [Briggs][Briggs 4th] <sup>651</sup> Breastfeeding: Contraindicated [Briggs][Briggs 1997] <sup>652</sup> (possible immune suppression [AAP]) <sup>653</sup>
Methotrexate sodium	15475-56-6	06/30/95	(See Methotrexate)
Methoxsalen	298-81-7	06/28/00	Category C [Facts and Comparisons] <sup>654</sup> [Briggs 5th] <sup>655</sup> Breastfeeding: Contraindicated [Briggs 1997] <sup>656</sup>
8-Methoxypsoralen		10/20/00	(See Methoxsalen)
Methylene blue	61-73-4		Category C Category D if injected intra-amniotically [Briggs 4th] <sup>657</sup> (hemolytic anemia, jaundice, intestinal atresia with intra-amniotic injection [PMID 9434858]) <sup>658</sup>
N-Methyl-3,4-methylenedioxymphetamine		07/27/00	(See Amphetamines)
Methyltestosterone	58-18-4	06/30/95	Category X [#] <sup>659</sup> Breastfeeding: Contraindicated [#] <sup>660</sup>
Methylthiouracil	56-04-2	07/10/00	Pregnancy: Malformations, including one report of retarded ossification [Schardein] <sup>661</sup>
Metrodin®			(See Urofollitropin)
Metronidazole	443-48-1	06/09/00	Category B [#] <sup>662</sup> Contraindicated in first trimester [#] <sup>663</sup> Breastfeeding: Discontinue [#] <sup>664</sup> (excreted in breast milk [Briggs 4th]) <sup>665</sup>
Mevacor®		10/20/00	(See Lovastatin)
Midazolam hydrochloride	59467-96-8	06/30/95	Category D [#] <sup>666</sup> Breastfeeding: With caution (excreted in human milk) [#] <sup>667</sup>

Drug/Substance	CAS Number	Date Added	Comments/Notes
Mifepristone	84371-65-3		Category X [Briggs 5th] <sup>668</sup> (abortifacient) [PMID 6744860] <sup>669</sup> Breastfeeding: Minimally excreted in primate milk [PMID 8314974] <sup>670</sup>
MIH		10/20/00	(See Procarbazine hydrochloride)
Miltown®		10/20/00	(See Meprobamate)
Minocin®			(See Minocycline hydrochloride)
Minocycline	10118-90-8		(See Minocycline hydrochloride)
Minocycline hydrochloride (internal use)	13614-98-7	06/30/95	Category D [#] <sup>671</sup> Breastfeeding: Discontinue (excreted in human milk) [#] <sup>672</sup>
Miradon®		10/17/00	(See Anisindione)
Misoprostol	59122-46-2	06/30/95	Category X [Briggs] (abortifacient, may cause congenital anomalies) [#] <sup>673</sup> Breastfeeding: Contraindicated [Briggs 1997] <sup>674</sup> [#] <sup>675</sup>
Mithracin®			(See Plicamycin)
Mitomycin	50-07-7	06/28/00	Pregnancy: Safety not established (teratological changes in animals) [Facts and Comparisons] <sup>676</sup> Breastfeeding: Contraindicated [Briggs 1997] <sup>677</sup>
Mitomycin-C		10/20/00	(See Mitomycin)
Mitoxantrone hydrochloride	70476-82-3	09/30/94	Category D (may cause fetal harm) [#] <sup>678</sup> Breastfeeding: Discontinue [#] <sup>679</sup>
Modrastane®			(See Trilostane)
Monopril®			(Fosinopril) (See ACE Inhibitors)
8-MOP		10/20/00	(See Methoxsalen)
Motrin®		10/20/00	(See Ibuprofen)
MTC		10/20/00	(See Mitomycin)
MTX®		10/20/00	(See Methotrexate)
Mumps vaccine, live	---		Category C, but contraindicated in pregnancy, and pregnancy should be avoided for 3 months after vaccination [#] <sup>680</sup> Breastfeeding: With caution [#] <sup>681</sup>
Mustargen®			(See Mechlorethamine)
Mutamycin®		10/20/00	(See Mitomycin)
Mycifradin®		10/20/00	(See Neomycin sulfate)
Myleran®			(See Busulfan)
Mysoline®		10/20/00	(See Primidone)
Nadrobolic®		10/17/00	(See Anabolic steroids) (Nandrolone)
Nafarelin acetate	86220-42-0	06/30/95	Category X (may cause fetal harm) [#] <sup>682</sup> Breastfeeding: Contraindicated [#] <sup>683</sup>
Nandrolone		10/17/00	(See Anabolic steroids)

Drug/Substance	CAS Number	Date Added	Comments/Notes
Narcotic analgesics	---		Breastfeeding: Discouraged (morphine is excreted in milk) [#] <sup>684</sup> (Also see Heroin, Alfentanil)
Nebcin®			(See Tobramycin sulfate)
Nembutal®			(See Pentobarbital sodium)
Neo-mens®			(See Ethisterone)
Neomycin sulfate (oral)	1405-10-3	06/30/95	Category D [Facts and Comparisons] <sup>685</sup> Breastfeeding: Discontinue [Facts and Comparisons], <sup>686</sup> compatible [Briggs 1997] <sup>687</sup>
Neoral®		10/17/00	(See Cyclosporin)
Neotigason®		11/20/2000	(See Acitretin)
Netilmicin sulfate	56391-57-2	06/30/95	Category D (can cause fetal harm) [#] <sup>688</sup> Breastfeeding: Discontinue [#] <sup>689</sup>
Netromycin®			(See Netilmicin sulfate)
Neutrexin®			(See Trimetrexate glucuronate)
Nicotine	54-11-5	06/30/95	Category X [Briggs] (nicotine polacrilex [Facts and Comparisons]) <sup>690</sup> Category D (nasal spray; can cause fetal harm [#], <sup>691</sup> transdermal nicotine [Facts and Comparisons]) <sup>692</sup> Breastfeeding: Contraindicated (shock, vomiting, diarrhea, rapid heart rate, restlessness; decreased milk production) [AAP], <sup>693</sup> use with caution (excreted in milk) [#] <sup>694</sup> [Briggs 1997], <sup>695</sup> discontinue [Facts and Comparisons] <sup>696</sup>
Nicotrol®			(See Nicotine)
Nipent®			(See Pentostatin)
Nitrofurantoin	67-20-9	06/30/95	Category B [#] <sup>697</sup> Contraindicated at term (38-42 weeks gestation), during labor and delivery, or when the onset of labor is imminent [#] <sup>698</sup> Breastfeeding: Discontinue in infants under one month of age (excreted in trace amounts in human milk) [#] <sup>699</sup>
Nitrogen mustard	51-75-2	09/30/94	(See Mechlorethamine)
Nitrogen mustard hydrochloride	55-86-7	06/30/95	(See Mechlorethamine)
N-Methyl-3,4-methylenedioxyamphetamine			(See listing alphabetically under "Methyl" as N-Methyl-3,4-methylenedioxyamphetamine)
N-Methylhydrazine		10/20/00	(See Procarbazine hydrochloride)
Nolvadex®			(See Tamoxifen citrate)
Non-steroidal anti-inflammatory indene derivatives			(See NSAIDs)

Drug/Substance	CAS Number	Date Added	Comments/Notes
Norethindrone/ethinyl estradiol	68-22-4/ 57-63-6	06/30/95	Category X [#] <sup>700</sup> Breastfeeding: Discouraged (appears in human milk and may cause adverse effects in the child) [#] <sup>701</sup>
Norethindrone/mestranol	68-22-4/ 72-33-3	06/30/95	Category X [#] <sup>702</sup> Breastfeeding: Discouraged (appears in human milk and may cause adverse effects in the child) [#] <sup>703</sup>
Norethynodrel	68-23-5		Category X [Briggs 4th] <sup>704</sup> Breastfeeding: See Oral contraceptives
Norfloxacin		10/20/00	(See Fluoroquinolones)
Norgestimate/ethinyl estradiol	35189-28-7/ 57-63-6	06/01/00	Category X [#] <sup>705</sup> Breastfeeding: Discouraged (appears in human milk and may cause adverse effects in the child) [#] <sup>706</sup>
Norgestrel/ethinyl estradiol	797-63-7/ 57-63-6	06/30/95	Category X [#] <sup>707</sup> Breastfeeding: Discouraged (appears in human milk and may cause adverse effects in the child) [#] <sup>708</sup>
Norinyl 1+35®		10/20/00	(See Norethindrone/ethinyl estradiol)
Norinyl 1+50®		10/20/00	(See Norethindrone/mestranol)
Normethandrone		07/10/00	(See Androgens)
Noroxin®			(See Ofloxacin)
Norplant® System		10/20/00	(See Levonorgestrel implants)
Nortriptyline hydrochloride	894-71-3		Category D [Briggs 4th] <sup>709</sup> (safe use not established, transferred through human placenta, case reports of fetal harm—decreased muscle tone, decreased sensitivity to painful stimuli, abnormal EKG in an infant born to a mother who had taken 1.5 to 1.75 grams [ <a href="#">PMID 5017806</a> ], <sup>710</sup> urinary retention [ <a href="#">PMID 5049831</a> ], <sup>711</sup> lower limb deformity with therapeutic doses [ <a href="#">PMID 4129246</a> ] <sup>712</sup> ) [#] <sup>713</sup> Breastfeeding: Safe use not established [#] <sup>714</sup> (excreted into breast milk [Briggs 4th]) <sup>715</sup>
Novantrone®			(See Mitoxantrone hydrochloride)

Drug/Substance	CAS Number	Date Added	Comments/Notes
NSAIDs (ibuprofen, indomethacin, sulindac)	---		Category B (ketoprofen, naproxen, flurbiprofen, diclofenac) [Facts and Comparisons] <sup>716</sup> Category C (etodolac, ketorolac, mefenamic acid, nabumetone, oxaprozin, tolmetin) [Facts and Comparisons] <sup>717</sup> Use during the third trimester of pregnancy may cause fetal harm (including constriction of the ductus arteriosus prenatally, tricuspid incompetence, pulmonary hypertension, platelet dysfunction, intracranial bleeding, renal dysfunction, gastrointestinal bleeding) [#] <sup>718</sup> Breastfeeding: Do not use in nursing mothers [Facts and Comparisons] <sup>719</sup>
Ofloxacin		10/20/00	(See Fluoroquinolones)
Ogen®		10/20/00	(See Estropipate)
Omeprazole	73590-58-6	06/28/00	Category C [Briggs 4th] <sup>720</sup> Breastfeeding: Contraindicated [Briggs 1997] <sup>721</sup>
Oncovin®			(See Vincristine sulfate)
Oral contraceptives	---		Category X [Briggs 4th] <sup>722</sup> Breastfeeding: Compatible [AAP] <sup>723</sup>
Oretic®		10/20/00	(See Hydrochlorothiazide)
Oretonmethyl®		10/17/00	(See Methyltestosterone)
Ortho-Cyclen®			(See Norgestimate/ethinyl estradiol)
Ortho-Dienestrol®		10/17/00	(See Dienestrol)
Ortho-Est®		10/20/00	(See Estropipate)
Ortho-Novum 1/35®		10/20/00	(See Norethindrone/ethinyl estradiol)
Ortho-Novum 1/50®		10/20/00	(See Norethindrone/mestranol)
Ortho-Tri-Cyclen®			(See Norgestimate/ethinyl estradiol)
Ovcon®		10/20/00	(See Norethindrone/ethinyl estradiol)
Ovral®		10/20/00	(See Norgestrel/ethinyl estradiol)
Oxandrin®		10/17/00	(See Anabolic steroids) (Oxandrolone)
Oxandrolone		10/17/00	(See Anabolic steroids)
Oxazepam		10/17/00	(See Benzodiazepines)
Oxazolidinedione anticonvulsants (paramethadione, trimethadione)	---	07/10/00	Category X [Schardein] <sup>724</sup>
Oxsoralen®		10/20/00	(See Methoxsalen)
Oxymetholone	434-07-1	03/10/00	Category X (can cause fetal harm) [#] <sup>725</sup> Breastfeeding: Discontinue [#] <sup>726</sup> (Also see Anabolic steroids)

Drug/Substance	CAS Number	Date Added	Comments/Notes
Oxytetracycline	79-57-2		Category D [Briggs 4th] <sup>727</sup> (use in the last half of pregnancy may permanently discolor the teeth of the fetus) [#] <sup>728</sup> Breastfeeding: See Tetracycline hydrochloride (present in human milk) [#] <sup>729</sup>
Oxytetracycline hydrochloride (internal use)	2058-46-0	06/30/95	(See Oxytetracycline)
Paclitaxel	33069-62-4	03/10/00	Category D (can cause fetal harm) [#] <sup>730</sup> Breastfeeding: Discontinue [#] <sup>731</sup>
L-PAM		10/20/00	(See Melphalan)
Pamelor®			(See Nortriptyline)
Paradione®		10/20/00	(See Oxazolidinedione anticonvulsants ) (Paramethadione)
Paradione®		10/20/00	(See Paramethadione)
Paramethadione	115-67-3	06/30/95	Category D [Briggs 4th] <sup>732</sup> (fetal methadione syndrome [ <a href="#">PMID 50427</a> ] <sup>733</sup> [ <a href="#">PMID 412416</a> ] <sup>734</sup> ) (See also Oxazolidinedione anticonvulsants )
Paraplatin®	41575-94-4		(See Carboplatin)
Parlodel®		10/17/00	(See Bromocriptine)
Paxipam®		10/20/00	(See Halazepam)
PBZ®		10/20/00	(See Tripeleminamine)
PCP	60124-79-0		(See Phencyclidine)
Pelamine®		10/20/00	(See Tripeleminamine)
Penetrex®			(See Enoxacin)
dl-Penicillamine	52-66-4		(See Penicillamine)
Penicillamine (dl-Penicillamine)	52-66-4		Category X (except in treatment of Wilson's Disease or certain cases of cystinuria) [#] <sup>735, 736</sup> Category D [Briggs 5th] <sup>737</sup> (in treatment of Wilson's Disease and certain cases of cystinuria) [#] <sup>738, 739</sup> Breastfeeding: Contraindicated [#] <sup>740, 741</sup>
Pentobarbital sodium	57-33-0	06/30/95	Category D (can cause fetal damage and withdrawal symptoms) [#] <sup>742</sup> Breastfeeding: With caution (small amounts excreted in milk) [#] <sup>743</sup> (See also Barbiturates)
Pentostatin	53910-25-1	03/10/00	Category D [Facts and Comparisons] <sup>744</sup> (can cause fetal harm) [#] <sup>745</sup> Breastfeeding: Discontinue [#] <sup>746</sup> [Facts and Comparisons] <sup>747</sup>
Pertix®		10/20/00	(See Menadione)
Phenacemide	63-98-9	06/30/95	Category D [Facts and Comparisons] <sup>748</sup> Breastfeeding: Discontinue [Facts and Comparisons] <sup>749</sup>

Drug/Substance	CAS Number	Date Added	Comments/Notes
Phencyclidine	60124-79-0		Category X [Briggs 4th] <sup>750</sup> (hallucinogen with no legitimate use) Breastfeeding: Contraindicated [AAP] <sup>751</sup>
Phenindione	83-12-5	06/30/00	Category D [Briggs 4th] <sup>752</sup> Breastfeeding: Contraindicated (increased prothrombin and partial thromboplastin time in one infant)[AAP] <sup>753</sup>
Phenobarbital	50-06-6		Category D [Briggs][Briggs 4th] <sup>754</sup> (manufacturer notes Category C [#]) <sup>755</sup> Breastfeeding: With caution [#] <sup>756</sup> (sedation, infantile spasms after weaning from milk containing phenobarbital, one reported case of methemoglobinemia [AAP]) <sup>757</sup> (See also Barbiturates)
Phenprocoumon	435-97-2	06/30/95	Category D [Briggs 4th] <sup>758</sup> (may cause fetal harm, including CNS malformations and hearing disorder [PMID 8147045]) <sup>759</sup> Breastfeeding: Avoid [Briggs 4th] <sup>760</sup>
Phenurone®			(See Phenacemide)
L-Phenylalanine mustard		10/20/00	(See Melphalan)
Phenylbutazone	50-33-9	07/10/00	Category C [Briggs 4th] <sup>761</sup> Category D if used in the third trimester [Briggs 4th] <sup>762</sup> Breastfeeding: Compatible [AAP] <sup>763</sup> (excreted in breast milk [Briggs 4th]) <sup>764</sup>
Phenytoin	57-41-0		Category D [Briggs] (possible fetal hydantoin syndrome [#]) <sup>765</sup> Breastfeeding: Not recommended (secreted in low concentrations in human milk) [#] <sup>766</sup>
Phenytoin sodium	630-93-3		(See Diphenylhydantoin)
Pindione®		10/20/00	(See Phenindione)
Piperazine estrone sulfate	7280-37-7		(See Estropipate)
Pipobroman	54-91-1	06/30/94	(Antimetabolite) Animal data: Developmental: [PMID 4504975] <sup>767</sup> Breastfeeding: Contraindicated [Briggs 1997] <sup>768</sup>
Platinol®-AQ			(See Cisplatin)
Plicamycin	18378-89-7	09/30/94	Category X (may cause fetal harm) [#] <sup>769</sup> Breastfeeding: Discontinue [#] <sup>770</sup>
Potassium iodide	7681-11-0		Category D (can cause fetal harm) [#] <sup>771</sup> Breastfeeding: Compatible [AAP] <sup>772</sup> (excreted in breast milk, may cause skin rash and thyroid suppression in the infant [#]) <sup>773</sup>

Drug/Substance	CAS Number	Date Added	Comments/Notes
Povidone-iodine	25655-41-8		Category D [Briggs 4th] <sup>774</sup> (do not use vaginally or in broken skin during pregnancy, may be used as a surgical prep for C-section[#], <sup>775</sup> can cause fetal harm [PMID 7431610] <sup>776</sup> ) Breastfeeding: Compatible [AAP]; <sup>777</sup> do not use vaginally or in broken skin (can cause fetal harm) [#] <sup>778</sup>
Pravachol®			(See Pravastatin sodium)
Pravastatin sodium	81131-70-6	03/10/00	Category X [#] <sup>779</sup> Breastfeeding: Contraindicated (small amount excreted in human milk) [#] <sup>780</sup>
Premarin®			(See Conjugated estrogens)
Prilosec®		10/20/00	(See Omeprazole)
Primidone	125-33-7		Category D [Briggs 4th] <sup>781</sup> (minor dysmorphic features—possibly a “fetal primidone syndrome” [PMID 9434858], <sup>782</sup> neonatal hemorrhage; prophylactic vitamin K <sub>1</sub> advised for one month prior to and during delivery [#]) <sup>783</sup> Breastfeeding: Discontinue nursing in the presence of undue somnolence and drowsiness in nursing newborns [#] <sup>784</sup> (appears in breast milk in substantial quantities [Facts and Comparisons]), <sup>785</sup> use with caution [AAP] <sup>786</sup>
Prinivil®			(Lisinopril) (See ACE Inhibitors)
Procarbazine	671-16-9		(See Procarbazine hydrochloride)
Procarbazine hydrochloride	366-70-1	06/30/95	Male: Azoospermia [#] <sup>787</sup> Category D (can cause fetal harm) [#] <sup>788</sup> Breastfeeding: Do not nurse [#] <sup>789</sup>
Progesterone	57-83-0	07/10/00	(See Hydroxyprogesterone)
Propecia®			(See Finasteride)
Propylthiouracil	51-52-5	06/30/95	Category D (can cause fetal harm) [#] <sup>790</sup> Breastfeeding: Contraindicated (excreted in human milk) [#] <sup>791</sup>
Proscar®		10/20/00	(See Finasteride)
Prosom®		10/20/00	(See Estazolam)
Provera®		10/20/00	(See Medroxyprogesterone acetate)
PTU		10/20/00	(See Propylthiouracil)
Purinethol®			(See Mercaptopurine)

Drug/Substance	CAS Number	Date Added	Comments/Notes
Pyrimethamine	58-14-0	03/10/00	Category C (concurrent administration of folic acid strongly recommended when used for the treatment of toxoplasmosis during pregnancy; teratogenic in rats) [#] <sup>792</sup> Breastfeeding: Discontinue (excreted in human milk) [#] <sup>793</sup>
Quazepam	36735-22-5	03/10/00	Category X [Facts and Comparisons] <sup>794</sup> [USPDI] <sup>795</sup> Breastfeeding: See Benzodiazepines
Quinine	130-95-0		(See Quinine sulfate)
Quinine sulfate			Category X [#] <sup>796</sup> (uterine contraction activity with doses higher than recommended, malformations with large doses) [Facts and Comparisons] <sup>797</sup> Breastfeeding: With caution (excreted in breast milk in small amounts) [#], <sup>798</sup> infants with G-6-PD should not breastfeed [Briggs 1997] <sup>799</sup>
Radioactive sodium		06/28/00	Breastfeeding: Contraindicated [Briggs 1997] <sup>800</sup> (radioactivity in milk present 96 hours) [AAP] <sup>801</sup>
Restoril®		10/17/00	(See Temazepam)
Retinoic acid	302-79-4		Category C (applied to skin) [Facts and Comparisons] <sup>802</sup> Pregnancy: Oral (internal) exposure teratogenic (Retinoic acid embryopathy [PMID 3162101] <sup>803</sup> [PMID 1438063]) <sup>804</sup> Breastfeeding: With caution [Facts and Comparisons] <sup>805</sup> (See also Isotretinoin, Tretinoin)
Retinol	68-26-8	06/30/95	(See Vitamin A)
Retinyl esters			(See Vitamin A)
Ribavirin	36791-04-5	09/30/94	Category X (may cause fetal harm) [#] <sup>806</sup> Breastfeeding: Discontinue [#] <sup>807</sup>
Rocaltrol®		10/17/00	(See Calcitriol)
Rohypnol®			(See Flunitrazepam)
Randomycin®		10/20/00	(See Methacycline hydrochloride)
RU-486®		10/20/00	(See Mifepristone)
Rubella vaccine, live			Contraindicated (Category C) [#] <sup>808</sup> Breastfeeding: With caution (live virus secreted in milk and may be transmitted to breast-fed infant) [#] <sup>809</sup>
Sandimmune®		10/17/00	(See Cyclosporin)
L-Sarcosylsin		10/20/00	(See Melphalan)
Secobarbital	309-43-3	06/30/95	(See Barbiturates)
Seconal®		10/17/00	(See Barbiturates) (Secobarbital)

Drug/Substance	CAS Number	Date Added	Comments/Notes
Septra®			(See Sulfonamides)
Serax®		10/17/00	(See Benzodiazepines) (Oxazepam)
Simvastatin	79902-63-9	06/07/00	Category X [#] <sup>810</sup> [Briggs] (skeletal abnormalities in animals) [Facts and Comparisons] <sup>811</sup> Breastfeeding: Contraindicated [#] <sup>812</sup>
Smallpox vaccine		07/10/00	Category X [Schardein] <sup>813</sup>
Sodium (radioactive)		06/28/00	(See Radioactive sodium)
Sodium iodide	7681-82-5		(See Iodine)
Sodium iodide I <sup>125</sup>			(See Iodine125)
Sodium iodide I <sup>131</sup>			(See Iodine131)
Soriatane®		11/20/2000	(See Acitretin)
Stanozolol	10418-03-8	06/08/00	Category X (can cause fetal harm) [#] <sup>814</sup> Breastfeeding: Discontinue [#] <sup>815</sup>
Streptomycin	57-92-1	06/07/00	(See Streptomycin sulfate)
Streptomycin sulfate	3810-74-0	06/30/95	Category D (can cause fetal harm) [#] <sup>816</sup> Breastfeeding: Discontinue [#] <sup>817</sup> (See also Aminoglycosides)
Streptozocin (streptozotocin)	18883-66-4	03/10/00	Category D [#] <sup>818</sup> Breastfeeding: Discontinue [#] <sup>819</sup>
Styptobion®		10/20/00	(See Menadione)
Sulfamethoxazole			(See Sulfonamides)
Sulfonamides	---		Contraindicated (Category C) (may cause kernicterus) [#] <sup>820</sup> Breastfeeding: Contraindicated (excreted in milk and may cause kernicterus) [#] <sup>821</sup>
Sulindac	38194-50-2	03/10/00	(See NSAIDs) Not recommended [#] <sup>822</sup> Breastfeeding: Should not be undertaken [#] <sup>823</sup>
Supprelin®			(See Histrelin acetate)
Synarel®			(See Nafarelin acetate)
Synkavite®		10/20/00	(See Menadione)
Tabloid®			(See Thioguanine)
TACE®			(See Chlorotrianisene)
Tamoxifen citrate	54965-24-1	06/30/95	Category D (may cause fetal harm) [#] <sup>824</sup> Breastfeeding: Discontinue [#] <sup>825</sup>
Tapazole®			(See Methimazole)
Technitium <sup>99</sup>			Category X [Briggs] Breastfeeding: Contraindicated [Briggs 1997] <sup>826</sup> (radioactivity in milk for 15 hours to 3 days [AAP]) <sup>827</sup>
Tegison®		10/20/00	(See Etreinate)
Tegretol®		10/17/00	(See Carbamazepine)
Temazepam	846-50-4	06/30/95	Category X (contraindicated) [#] <sup>828</sup> Breastfeeding: With caution [#] <sup>829</sup> (See also Benzodiazepines)

Drug/Substance	CAS Number	Date Added	Comments/Notes
Teniposide	29767-20-2		Category D (may cause fetal harm) [#] <sup>830</sup> Breastfeeding: Discontinue [#] <sup>831</sup>
Tenoretic®			(See Atenolol and Chlorothiazide) (Atenolol and Hydrochlorothiazide)
Tenormin®			(See Atenolol)
Terramycin®			(See Oxytetracycline)
Tesanone®		10/17/00	(See Testosterone)
Testandro®		10/17/00	(See Testosterone)
Testoderm®			(See Testosterone)
Testosterone	58-22-0	06/07/00	Category X (may cause fetal harm) [#] <sup>832</sup> Breastfeeding: Contraindicated [#] <sup>833</sup>
Testosterone cypionate	58-20-8	06/30/95	Contraindicated (may cause virilization of the external genitalia of the female fetus) [#] <sup>834</sup> Breastfeeding: Contraindicated [#] <sup>835</sup>
Testosterone enanthate	315-37-7	06/30/95	Category X (contraindicated, may cause virilization of the external genitalia of the female fetus) [#] <sup>836</sup> Breastfeeding: Discontinue [#] <sup>837</sup>
Testosterone propionate		10/17/00	(See Testosterone)
Testred®		10/17/00	(See Methyltestosterone)
Tetracycline	60-54-8		(See Tetracycline hydrochloride)
Tetracycline hydrochloride (internal use)	64-75-5	06/30/95	Category D [Briggs] (may cause fetal harm) [#] <sup>838</sup> Breastfeeding: Compatible [AAP] <sup>839</sup> (present in the milk of lactating women [#], <sup>840</sup> but negligible absorption by infant [Briggs][Briggs 4th]) <sup>841</sup>
Tequin®			(See Gatifloxacin)
Thalidomide	50-35-1	06/30/95	Category X (may cause fetal harm) [#] <sup>842</sup> Males: Contraindicated in males having intercourse with fertile females without barrier protection (i.e., males must use latex condoms to prevent exposing pregnant or potentially pregnant females to thalidomide in semen) [#] <sup>843</sup> Breastfeeding: Discontinue [#] <sup>844</sup>
Thalomid®			(See Thalidomide)
Thioguanine	154-42-7	06/30/95	Category D (may cause fetal harm) [#] <sup>845</sup> Breastfeeding: Discontinue [#] <sup>846</sup>
Thioplex®			(See Thiotepa)
Thiotepa	52-24-4		Category D (can cause fetal harm) [#] <sup>847</sup> Breastfeeding: Discontinue [#] <sup>848</sup>
Thiouracil	141-90-2	07/10/00	(See Propylthiouracil)
Thyreostat®		10/20/00	(See Methylthiouracil)
Tobramycin	32986-56-4		(See Tobramycin sulfate)
Tobramycin sulfate	49842-07-1	06/30/95	Category D [#] <sup>849</sup> (See Aminoglycosides)
Toxol®			(See Paclitaxel)

Drug/Substance	CAS Number	Date Added	Comments/Notes
Tranxene®		10/17/00	(See Benzodiazepines) (Chlorazepate)
Tretinoin	302-79-4		(See Isotretinoin)
Triazolam	28911-01-5	06/30/95	Category X [#] <sup>850</sup> Breastfeeding: Not recommended [#] <sup>851</sup> (See also Benzodiazepines)
Tridione®		10/20/00	(See Oxazolinedione anticonvulsants ) (Trimethadione)
Tridione®		10/20/00	(See Trimethadione)
Trilostane	13647-35-3	06/30/95	Fertility: Reversible gonadal function [USPDI] <sup>852</sup> Category X (reduces circulating progesterone, produces cervical dilation, may terminate pregnancy) [USPDI] <sup>853</sup> Breastfeeding: Problems have not been documented [USPDI] <sup>854</sup>
Trimethadione	127-48-0	06/30/95	Category D [Briggs 4th] <sup>855</sup> (fetal trimethadione syndrome [ <a href="#">PMID 50427</a> ] <sup>856</sup> ; growth retardation, microcephaly, cleft lip/palate, unusual facies, cardiovascular malformations [ <a href="#">PMID 9434858</a> ]) <sup>857</sup> (See Oxazolinedione anticonvulsants )
Trimetrexate glucuronate	82952-64-5	03/10/00	Category D (can cause fetal harm) [#] <sup>858</sup> Breastfeeding: Discontinue [#] <sup>859</sup>
Tripelennamine	91-81-6		Category B [Briggs 4th] <sup>860</sup> Breastfeeding: Contraindicated [Briggs 4th] <sup>861</sup> (excreted in breast milk [Facts and Comparisons]) <sup>862</sup>
Tromexane®			(See Ethyl biscoumacetate)
Uracil mustard	66-75-1	06/30/95	Male: Azoospermia [USPDI] <sup>863</sup> Female: Amenorrhea [USPDI] <sup>864</sup> Pregnancy: Avoid [USPDI] <sup>865</sup> Breastfeeding: Not recommended (risks of adverse effects, mutagenicity, carcinogenicity) [USPDI] <sup>866</sup>
Uramustine®		10/20/00	(See Uracil mustard)
Urofollitropin	26995-91-5	06/30/95	Category X (may cause fetal harm) [#] <sup>867</sup> Breastfeeding: With caution [#] <sup>868</sup>
Urolene Blue®		10/20/00	(See Methylene blue)
Vaccine (live measles)			(See Measles vaccine, live)
Vaccine (live mumps)			(See Mumps vaccine, live)
Valium®			(See Diazepam)
Valproate sodium	1069-66-5	06/30/95	Category D (can produce teratogenic effects) [#] <sup>869</sup> Breastfeeding: Consider discontinuing nursing (excreted in breast milk) [#] <sup>870</sup>

Drug/Substance	CAS Number	Date Added	Comments/Notes
Valproic acid	99-66-1		Category D (may produce teratogenic effects) [#] <sup>871</sup> Breastfeeding: With caution (excreted in breast milk) [#] <sup>872</sup>
Vasotec®		10/17/00	(See Enalapril)
Velban®			(See Vinblastine sulfate)
VePesid®		10/20/00	(See Etoposide)
Vercite®			(See Pipobroman)
Vercyte®		10/20/00	(See Pipobroman)
Versanoin®		10/20/00	(See Tretinoin)
Versed®		10/17/00	(See Midazolam)
Vibramycin®			(See Doxycycline)
Vibra-tabs®			(See Doxycycline)
Vinblastine	865-21-4		(See Vinblastine sulfate)
Vinblastine sulfate	143-67-9	06/30/95	Category D (can cause fetal harm) [#] <sup>873</sup> Breastfeeding: Discontinue [#] <sup>874</sup>
Vincristine	57-22-7		(See Vincristine sulfate)
Vincristine sulfate	2068-78-2	06/30/95	Category D (can cause fetal harm) [#] <sup>875</sup> Breastfeeding: Discontinue [#] <sup>876</sup>
Virilon®		10/20/00	(See Methyltestosterone)
Virilon®			(See Testosterone cypionate)
Vistide®			(See Cidofovir)
Vitamin A	68-26-8		Category A Category X (if used in does above the RDA [Briggs 4th], <sup>877</sup> may cause fetal harm; safety of amounts exceeding 6,000 Units of Vitamin A daily during pregnancy has not been established [#] <sup>878</sup> Essential for normal reproduction (US RDA = 8,000 IU; Institute of Medicine advocates an RDA = 2667 IU in pregnant females [ <a href="#">Institute of Medicine</a> ][ <a href="#">USDA</a> ]) <sup>879</sup> Breastfeeding: US RDA of 5,000 Units is recommended for nursing mothers [#] <sup>880</sup> (USDA references 1300 µg for lactating women [ <a href="#">USDA</a> ])
Vitamin A acid		10/20/00	(See Tretinoin)
Vitamin D <sub>2</sub>			(See Ergocalciferol)
Vitamin D <sub>3</sub>			(See Cholecalciferol)
VP-16-213		10/20/00	(See Etoposide)
Vumon®			(See Teniposide)

Drug/Substance	CAS Number	Date Added	Comments/Notes
Warfarin	81-81-2	06/30/95	Category X (may cause fatal fetal hemorrhage <i>in utero</i> or birth malformations) [#] <sup>881</sup> (See Dicumarol) Breastfeeding: Compatible [AAP], <sup>882</sup> no restrictions (appears in human milk in an inactive form) [#] <sup>883</sup>
Winstrol®			(See Stanozolol)
Xanax®		10/17/00	(See Alprazolam)
Yellow fever vaccine		07/10/00	Category D [Schardein] <sup>884</sup>
Zanosar®			(See Streptozocin)
Zesteril®			(Lisinopril) (See ACE Inhibitors)
Zocor®		10/20/00	(See Simvastatin)
Zoladex®			(See Goserelin acetate)

## (X) OCCUPATIONAL BIOLOGICAL REPRODUCTIVE AND DEVELOPMENTAL HAZARDS

### A) INTRODUCTION

Biologic ReproDev hazards include microorganisms (including bacteria, protozoa, viruses, and fungi), vaccines, and hyperpyrexia—fever > 102.2°F or 39°C—a possible response to infection or vaccination.<sup>iii</sup> Although numerous biological hazardous agents exist, many of these are transmitted only under unusual circumstances, or are a risk primarily in specialized occupations (e.g., veterinary medicine, laboratory medicine, meat processing and packaging, hunting). In addition, agents that cause adverse fetal effects indirectly have been omitted (e.g., bacterial infections that may result in spontaneous abortions due to sepsis). The listed biologic hazards produce adverse reproductive or developmental effects through transmission from the mother to the fetus during pregnancy, or to the neonate during delivery or shortly after birth. Many of these agents are associated with health care, day care, or school settings. However, any given agent may not carry the same degree of risk of transmission in all settings. Accordingly, the clinician should assess a given worker's risk from biologic hazards through a review of his/her status, the frequency and duration of exposure, and current exposure control methods including personal protective equipment.

Prevention of infection is accomplished by prevention of exposure, or through immunization or acquired immunity where applicable. Proper engineering controls, work practices, and personal protective equipment must be used. Worker education on ReproDev hazards and preventive protective practices is essential.

**Table 11 –Occupational Biological Reproductive and Developmental Hazards List**

Category	Agent	Notes
Bacteria	Group B Streptococcus	Early-onset (neonatal) group B streptococcus [MMWR] <sup>885</sup>
	Leprosy	<i>Mycobacteria leprae</i> Hansen's Disease. Fetal and placental infection is rare, <sup>886</sup> but transmission from an infected, untreated mother to infant is not uncommon <sup>887</sup> (apparently from skin-to-skin or droplet transmission). <sup>888</sup>
	<i>Listeria monocytogenes</i>	<i>Granulomatosis infantiseptica</i> Listeriosis symptoms during pregnancy may mimic those of influenza and coincide with bacteremic phase of infection. Management of pregnant women with febrile illness may include blood cultures to rule out listeriosis. <sup>889</sup>

<sup>iii</sup> This is not to imply that hyperpyrexia is only due to infections. For example, elevated body temperature has been associated with use of hot tubs.

Category	Agent	Notes
	Lyme disease	<i>Borrelia burgdorferi</i> [ <a href="#">PMID 2423719</a> ] <sup>890</sup> Timely maternal antibiotic treatment appears to eliminate risks to the fetus of adverse Lyme disease sequelae [ <a href="#">PMID 10666804</a> ] <sup>891</sup> [ <a href="#">PMID 8362948</a> ]. <sup>892</sup>
	Syphilis	Severe infection may cause fetal demise with hydrops; mild infection may cause detectable abnormalities of skin, teeth, and bones [ <a href="#">PMID 921549</a> ] <sup>893</sup> High risk of spontaneous abortion, stillbirth, or infected infant when untreated maternal infection occurs at any time during pregnancy; recognizable features of congenital syphilis rarely occur before 16 <sup>th</sup> week of gestation [ <a href="#">PMID 6551148</a> ] <sup>894</sup>
	Tuberculosis	(TB)
	Typhoid fever	Spontaneous abortion, premature delivery [ <a href="#">PMID 3832761</a> ] <sup>895</sup>
Protozoa	Malaria	<i>Plasmodium vivax</i> , <i>P. ovale</i> , <i>P. falciparum</i> , <i>P. malariae</i> Prophylactic antimalarials may pose some risk, but it is generally felt that their use is preferred to the risk to the fetus and mother of contracting malaria.
	Toxoplasmosis	Domestic cats are a potential source.
Virus	Coxsackievirus	First & second trimesters: Low risk of transmission; certain strains associated with prematurity, congenital abnormalities, spontaneous abortion Term: Some risk of transmission and severely infected infant [ <a href="#">PMID 6551148</a> ] <sup>896</sup>
	Cytomegalovirus	Human herpesvirus 5
	Ebola virus	Spontaneous abortions among pregnant women with Ebola Hemorrhagic Fever. <sup>897</sup>
	Echovirus	Term: High risk of transmission and severely infected infant [ <a href="#">PMID 6551148</a> ] <sup>898</sup>

Category	Agent	Notes
	Hepatitis B virus	First & second trimesters: Some risk of transmission; Third trimester: High risk of transmission; High risk of transmission from asymptomatic HBeAg carrier mothers; Some risk of transmission from HBsAg carrier (HBeAg negative) mothers [ <a href="#">PMID 6551148</a> ] <sup>899</sup>
	Human immunodeficiency virus	HIV, AIDS
	Human parvovirus B19	Erythema infectiosa or Fifth disease
	Mumps virus	Mumps orchitis uncommonly may cause sterility
	Poliovirus	Early pregnancy: prematurity, low birth weight, stillbirth, spontaneous abortion; Term: Some risk of transmission and severely infected infant [ <a href="#">PMID 6551148</a> ] <sup>900</sup>
	Rubella virus	German measles <i>Congenital rubella syndrome</i> may include: heart malformations (patent ductus arteriosus, intraventricular septal defect, and pulmonic stenosis), ocular lesions (cataracts, microphthalmos, and chorioretinitis), CNS abnormalities (mental retardation, microcephaly, and deafness), malformation of bone metaphyses, hepatosplenomegaly, thrombocytopenia, interstitial pneumonitis, myocarditis, thrombocytopenic purpura, small size, and subacute sclerosing panencephalitis, a rare complication. Diabetes mellitus may be a late complication. <sup>901</sup>
	Varicella/herpes zoster virus	human herpesvirus 3, early in pregnancy or 5 days before delivery
Vaccine	Mumps	Live attenuated vaccine—avoid pregnancy for 3 months after vaccination [ <a href="#">Briggs</a> ]

Category	Agent	Notes
	Rubella	Live attenuated vaccine—avoid pregnancy for 3 months after vaccination [Briggs]. “No cases of congenital rubella syndrome or abnormalities attributable to a rubella vaccine virus infection have been observed in infants born to susceptible mothers who received rubella vaccine during pregnancy” [MMWR] <sup>902</sup>
	Varicella/herpes zoster virus vaccine	Category C (contraindicated during pregnancy) [#] <sup>903</sup> Avoid pregnancy for 3 months following vaccination [#] <sup>904</sup> Live attenuated vaccine. It is indicated for young adults not previously infected, especially HCWs and close contacts of immunocompromised persons. It produces detectable varicella antibodies in 97% of recipients and reduces the likelihood of clinical illness by 70% after exposure. No immune globulins, including varicella-zoster immune globulin, should be given within 5 mo before or 2 mo after vaccination. This vaccine may be given concomitantly with measles-mumps-rubella. Recipients should avoid salicylates for 6 wk because of the possibility of Reye's syndrome. <sup>905</sup>
	Venezuelan equine encephalitis TC-83 vaccine	Category X [Briggs] Live attenuated vaccine—avoid pregnancy for 3 months after vaccination [Briggs]
	Yellow fever	Live attenuated vaccine Category D (evidence of fetal risk, but benefits outweigh risks). <sup>906</sup> Avoid in first trimester if possible [Briggs], but administer if a pregnant female must travel to endemic areas [MMWR] <sup>907</sup>
Miscellaneous	Hyperpyrexia [PMID 4014176] <sup>908</sup>	Effect of infection or immunization that can be a related ReproDev hazard

Category	Agent	Notes
Biologicals not commonly encountered	Biowarfare agents (potential)	Q-fever Ebola hemorrhagic fever (spontaneous abortion, stillbirth) [ <a href="#">PMID 9988157</a> ] <sup>909</sup> Lassa fever (fetal and neonatal loss)[ <a href="#">PMID 3139220</a> ] <sup>910</sup>

## (XI) OCCUPATIONAL PHYSICAL REPRODUCTIVE AND DEVELOPMENTAL HAZARDS

**Table 12 - Occupational Physical Reproductive and Developmental Hazards List**

AGENT	DATE ADDED
Excessive heat (thermal stress)	06/30/1995
Heaving lifting	
Impact	
Ionizing radiation	06/30/1995
Noise	
Postures, such as standing in military formations (attention or parade rest), and other prolonged periods without movement)	
Respirator use	
Shift work	
Vibration	01/24/2000

### A) PHYSICAL EXERTION – GENERAL

Normal physiological changes in pregnancy result in increased resting heart rate, respiratory tidal volume, and oxygen debt incurred by performing a given task. Some epidemiological studies suggest an increased risk of adverse pregnancy outcomes, such as premature labor or spontaneous abortion, with activities that result in increased physical exertion. Other studies do not show such an association.

Although the healthy pregnant worker generally will be able to do most of her work up until the time of delivery,<sup>911</sup> some reduction in exertion requirements may be needed in the last trimester. [Table 13 – American Medical Association Guidelines for Continuation of Various Levels of Work During Pregnancy](#) gives general guidance for physical work restrictions based on the week of gestation. Recommendations regarding limitations on physically strenuous work **must be individualized**<sup>912</sup> because physical capabilities vary greatly among women. Limitations should reflect the percent of maximal exertion required to complete the task before pregnancy. In general, a maximum pre-pregnancy load should be decreased by 20-25 percent during the third trimester. At no time during the pregnancy should the physical demands be increased over what the employee was accustomed to before becoming pregnant. Excessive or chronic fatigue should be avoided.

Generally, the medical professional best suited to make a determination regarding work load restrictions/allowances during pregnancy is a person knowledgeable in the woman's' medical status, pregnancy status, and job requirements. Often, this determination should be made by more than one medical or health professional working in concert with the woman's' supervisory chain of command or authority. The overall requirements of the job (with respect to physical effort, frequency, duration, and the availability of spontaneous at lib rest periods) and ongoing

obstetrical evaluation of each worker must be considered in periodically making recommendations for restrictions on exertion as the pregnancy progresses. The pregnant worker's physical capabilities and the possibility of work limitation(s) should be addressed at each appointment with a HCP. A written medical recommendation should be provided by the HCP managing the pregnancy.

**Table 13 – American Medical Association Guidelines for Continuation of Various Levels of Work During Pregnancy**

<b>JOB FUNCTION</b>	<b>WEEK OF GESTATION</b>
Secretarial and light clerical	40
Professional and managerial	40
Sitting with light tasks	
Prolonged (>4 hr)	40
Intermittent	40
Standing	
Prolonged (>4 hr)	24
Intermittent (>30 min/hr)	32
Intermittent (≤30 min/hr)	40
Stooping and bending below knee level	
Repetitive (>10 times/hr)	20
Intermittent (≤10 and >2 times/hr)	28
Intermittent (≤2 times/hr)	40
Climbing	
Vertical ladders and poles	
Repetitive (≥4 times/8-hr shift)	20
Intermittent (<4 times/8-hr shift)	28
Stairs	
Repetitive (≥4 times/8-hr shift)	28
Intermittent (<4 times/8-hr shift)	40
Lifting	
Repetitive	
>23 kg	20
≤23 kg and >11 kg	24
≤11 kg	40
Intermittent	
>23 kg	30
≤23 kg and >11 kg	40
≤11 kg	40

Adapted from the American Medical Association Council on Scientific Affairs Report: Effects of Pregnancy on Work Performance. JAMA 251:15, April 20, 1984, 1995-1997, copyrighted 1984, American Medical Association. Used with permission.

## B) LIFTING

There are two primary concerns regarding lifting in pregnancy: protecting the worker from injury (primarily back injury), and protecting the pregnancy until term. It is biologically plausible that heavy physical exertion may have an influence on the course and outcome of pregnancy. The epidemiologic evidence is strongest for possibly increasing the risk of preterm delivery. Although not supported by all studies [[PMID 2617257](#)],<sup>913</sup> the risk of impeded fetal growth or spontaneous abortion appears to be associated with maternal heavy lifting in the occupational setting [[PMID 3806263](#)],<sup>914</sup> although bending, rather than lifting itself, may be the main cause [[PMID 8282467](#)].<sup>915</sup> It can, however, be recommended that female workers avoid extremely heavy physical exertion (close to the individual's maximal capacity). The [AMA 1999 "Report of the Council On Scientific Affairs"](#) recommendations include "minimizing heavy lifting."<sup>916</sup>

Although specific lifting restrictions should be individualized as described in the preceding paragraph, nationally recognized lifting guidelines can be used to supplement the AMA recommendations provided in [Table 13](#). The National Institute for Occupational Safety and Health (NIOSH) Publications [Work Practices Guide for Manual Lifting](#)<sup>917</sup> and [Applications Manual for the Revised NIOSH Lifting Equation](#)<sup>918</sup> provide guidance only for workers in general and do not provide specific recommendations for pregnant women.

Based on the general guidelines given above, if a woman was able to perform a non-maximal effort task to which she is accustomed prior to pregnancy, then she will likely be able to continue that task during an uncomplicated pregnancy at least up to the third trimester. The worker and her supervisors should be advised that changes in lifting biomechanics occur as the pregnant abdomen increases the horizontal distance away from the axial skeleton at which objects must be held. Additional training may be required.

Additional restrictions in the third trimester of pregnancy include limiting or prohibiting work requiring balance (climbing ladders) and lifting weights that are bulky or awkward or that approach the woman's maximal (prior to pregnancy) lifting capacity. As pregnancy progresses, it is wise to reduce the physical workload and ensure rest periods of adequate frequency and duration. In late pregnancy, a pregnant woman should not do any task that may require a Valsalva (bearing down) maneuver.

## C) SHIFT WORK AND EXTENDED HOURS OF DUTY

Based on animal studies, it is thought that the biological rhythms of the unborn child follow those of the mother. Time shifts experienced by shift workers lead to disruption of their biological rhythms with varying degrees of associated fatigue and health complaints, such as general malaise and gastrointestinal disorders [[PMID 2203158](#)].<sup>919</sup> Most "swing shift" and "graveyard" workers experience some degree of sleep deprivation and disruption of their normal biological rhythm. Workers with young children at home are particularly apt to be sleep deprived. Studies of workers in general have found increased fatigue after about nine hours of duty as evidenced by performance deficits and decreased alertness.

The degree of risk to pregnancy outcome from extended hours and shift work is not known. It is prudent at this time, and required for Navy servicewomen in the last trimester ([OPNAVINST 6000.1A](#)), to limit the number of total hours worked per week to 40, unless longer hours are requested by the employee and approved by her HCP.<sup>920</sup> Shift work, especially rotating shift

work, should be considered an added stressor for the pregnancy. Overtime work in conjunction with shift work should be avoided during pregnancy [[PMID 2203158](#)].<sup>921</sup>

**Table 14 - Occupational Physical Factors Associated with Low Birth Weight or Preterm Deliveries**

<b>Factor</b>	<b>Notes</b>
Fatigue	
Standing	Standing > 8 hours/day also associated with spontaneous abortion
Working > 41 hours/week	Working > 46 hours/week also associated with spontaneous abortion
Work + fatigue	
Heavy lifting	Heavy lifting > 15 times/day also associated with spontaneous abortion
Rotating shiftwork	Also associated with spontaneous abortion
Unemployment and decrease in income	

From pp. 280-283 of Scott A, Ladou J. Shiftwork: Effects on Sleep and Health. In: Scott A, ed. Occupational Medicine: State of the Art Reviews. 1990;5:273-299.

#### D) HEAT STRESS (ENVIRONMENTAL CONDITIONS) AND HEAT STRAIN (PHYSIOLOGIC RESPONSE)

##### 1) Effects on Fertility

Men who work in hot environments may have an associated lowering of sperm counts [[PMID 9756281](#)].<sup>922</sup> This reversible effect may result in infertility until the heat exposure ceases and the sperm count is restored to normal levels. Male workers should be advised of this potential heat effect upon sperm counts. An appropriate specialist should evaluate men who have been trying unsuccessfully to father children. If a low sperm count is determined to be the cause of infertility in a man who works in a hot environment, temporary reassignment to a job without heat stress should be considered.

##### 2) Effects on Pregnancy

Physiological changes that occur in pregnancy make the pregnant worker more susceptible to the effects of heat stress. The plasma volume increases and causes a relative anemia; the resting heart rate increases, and the cardiac output increases with much of the increase shunted to the placenta. There is also a 10-15 mm Hg fall in diastolic blood pressure. Uterine enlargement encroaches on the inferior vena cava and slows venous return from the lower extremities. Together, these cardiovascular changes increase the risk of heat syncope or fainting—and the associated risk of injury to the woman or the developing fetus. Varicosities of the lower extremity may be aggravated. Pedal edema is common in the last trimester and is aggravated by heat stress conditions. A decrease in appetite may occur with exposure to heat and lead to poor weight gain. The extra weight of the pregnant abdomen increases metabolic load resulting in

increased generation of heat and an increased oxygen debt incurred from physical exertion. Finally, the fetal temperature is about 0.5°C higher than normal maternal temperature. This adds to the increased thermal load of pregnancy. Other sources of heat that contribute to a “heat stress environment” include fever [[PMID 4014176](#)]<sup>923</sup> and hot tub or hot bath use [[PMID 1640616](#)],<sup>924</sup> in addition to occupational heat exposure.

### 3) Effects on Development

Few studies specifically address the epidemiological relationship between heat exposure and pregnancy outcome. Evidence from animal studies clearly indicates that elevation of core body temperature of sufficient degree and duration during specific gestational age intervals induces spontaneous abortion, fetal malformations, and postnatal developmental abnormalities. (For example, intrauterine growth retardation in lambs is a known effect of heat stressing pregnant ewes [[PMID 2030175](#)].)<sup>925</sup> Human studies of pregnancy complicated by significant febrile episodes (maternal core temperature > 38.9°C—such as during influenza) at different stages of pregnancy suggest an association with adverse developmental outcomes,<sup>926</sup> including neural tube defects [[PMID 6446171](#)].<sup>927</sup> However, other human studies have failed to show any significant increase in specified developmental abnormalities.<sup>928</sup>

The American Conference of Governmental Industrial Hygienists (ACGIH) TLVs, NIOSH recommended exposure limits (RELs), and the Navy Physiological Heat Exposure Limits (PHELs) curves take into account the wet bulb globe temperature (WBGT) index and metabolic heat produced by work. However, these exposure limits apply to healthy, non-pregnant individuals and specifically do not apply to pregnant women. There is no accepted heat exposure standard to follow during pregnancy. NIOSH suggests that it is “prudent to monitor the body temperature of a pregnant worker exposed to total heat loads above the REL, every hour or so to ensure that the body temperature<sup>iv</sup> does not exceed 39°–39.5°C (102°–103°F) during the first trimester of pregnancy.”<sup>929</sup> However, measuring core temperatures hourly during work may be difficult or impossible, and using a cut-off value of 102° may not be adequately protective. Clearly, maximum allowable WBGT levels for physical exertion must be lower and work times must be reduced for pregnant women in hot environments. As in all heat stress exposures, adequate replacement of lost fluids is essential. Supervisors must be especially responsive to early signs and/or symptoms of heat exhaustion in pregnant women (confusion, agitation, dizziness, visual disturbances, numbness, weakness, muscle cramping, involuntary muscle contractions, swelling/edema, nausea, vomiting, abdominal cramping, and uncontrollable shivering). (NOTE: The Navy uses an *aspirated wet bulb* in the determination of the WBGT index; the ACGIH and NIOSH recommended criteria use a *natural wet bulb*, which has no fan-assisted air movement across the wick. Care should be employed when using these criteria, especially when using different criteria and Navy-specific WBGT index meters.)

Standing times should also be reduced. [OPNAVINST 6000.1A](#)<sup>930</sup> exempts pregnant women from standing at parade rest or at attention for longer than 15 minutes. In hot conditions, this time should be decreased and, preferably, standing at attention should be allowed only momentarily.

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<sup>iv</sup> Core body temperature is usually assessed by somewhat “invasive” means, such as measuring rectal, vaginal, or esophageal temperature (but not by measuring oral temperature). The modern tympanic thermometer is a practical method for this application. (*Footnote not in original quoted text*)

The healthcare practitioner should issue medical recommendations for decreased working hours and exertion for pregnant women with complaints of excessive fatigue, swelling of the feet and ankles, lightheadedness, and poor appetite. Pregnant women should not be required to do work during their pregnancy that is more demanding than that to which they were accustomed to before pregnancy. Abrupt increases in environmental temperatures will increase the metabolic demands of physical activity for all workers. In order to avoid increasing the metabolic requirements for the pregnant worker, the exertion and/or the hours of work required should be appropriately decreased for work that must be done in hot environments. In most instances, proper administrative actions should be the result of close coordination between the managing HCP and the professional OH staff.

## E) SOUND AND VIBRATION

### 1) Fetal Sound Exposure

Environmental or workplace sound is transmitted to the fetus through body tissues and uterine fluids, and probably within the fetus by bone conduction [[PMID 8944295](#)].<sup>931</sup> Sound intensity in amniotic fluid was found to be about 4000 times less than at a sound source in air 2 cm from the abdomen [[PMID 1547171](#)].<sup>932</sup> Low frequency noise poses the greatest risk since it penetrates to the fetal cochlea more effectively than high frequencies. Most studies suggest attenuation at the cochlea of about 10 to 20 dB less than 250 Hz, and over 40 dB at 2000 Hz [[PMID 8899910](#)].<sup>933</sup> However, one study reported sound enhancement at 125 Hz [[PMID 1635729](#)].<sup>934</sup> Based on animal (sheep) data, sound levels within the uterus resulting from direct physical contact with a sound source decrease as the point of contact moves away from the abdomen [[PMID 3394740](#)].<sup>935</sup> If a pregnant woman leans against a noise source with her abdomen, her fetus would be exposed to a greater sound level than if she leans against the same sound source with her shoulder.

### 2) Fetal Sound Response

The fetal cochlea first demonstrates consistent auditory responsiveness in the 20<sup>th</sup> week of gestation. There have been no indications of behavioral auditory responses before 19 weeks gestation.<sup>936</sup> Fetal effects of sound may vary with gestational age. Mammalian studies indicate increased susceptibility to damage from sound during the final functional and structural stages of development in young animal cochleas.<sup>937</sup> While there are no data for humans, children *in utero* could theoretically suffer hearing loss at lower sound levels and after a shorter duration of sound exposure than mature adults. The current auditory risk criteria were formulated for non-pregnant adults.<sup>938</sup>

### 3) Sound Exposure Effects

Studies linking maternal sound exposure during pregnancy to increased incidence of hearing loss in neonates and young children are inconclusive due to inability to control all variables [[PMID 3788986](#)].<sup>939</sup> After the development of the fetal ear (mid-pregnancy), the fetus is able to perceive, and even respond to, external sounds. Sound attenuation from external air to within the uterus has been demonstrated ([PMID 1635729](#)).<sup>940</sup> Exact levels of attenuation have differed (and one study even suggested low frequency sound level augmentation within the uterus), but high frequency sound levels (those thought to pose the most significant hazard to adult hearing) are consistently diminished more than low frequency. Concern remains, however, as to whether maternal exposure to high sound levels, even of low frequencies, may be harmful to the hearing

of the fetus, because the fetus cannot be protected (for example, by earplugs) from the direct effects of such sounds ([PMID 2237460](#)).<sup>941</sup> A significantly increased rate of loss of hearing at 4000 Hz has been noted in children whose mothers were exposed to high sound levels with both low and high (rather than only high) frequency components. (However, other risk factors may have been confounders.) The same study identified a three-fold increase in childhood high-frequency hearing loss among children whose mothers were exposed to occupational sound levels of 85 to 95 dB compared to those whose mothers had lower occupational sound level exposures during pregnancy. The authors recommended setting a temporary 85 dBA 8 hour sound limit for pregnant women until further research verifies the safety of higher sound level exposures ([PMID 3788986](#)).<sup>942</sup> Some authors feel that any sustained exposure of the developing auditory system to high sound levels represents an increase in the risk of noise-induced hearing loss ([PMID 2237460](#)),<sup>943</sup> although this has not been proven in humans. At least one Navy medical officer has advised that pregnant women not be subjected to noise in excess of 90 dB for an 8 hour work day (Moore).<sup>944</sup> Currently, definitive cut-off levels of hazardous (or non-hazardous) of sound remain not identified.

Low birth weight is the most common non-auditory consequence associated with maternal sound exposure; however, this finding is not consistent across studies summarized by Nurminen in 1995 [[PMID 8520958](#)].<sup>945</sup> There has been extended discussion of possible non-auditory consequences to maternal sound exposure, related to stress-induced increase of catecholamine levels and placental vasoconstriction. Shift work in a “noisy” environment was associated with pregnancy-induced hypertension in one study [[PMID 2772574](#)].<sup>946</sup> Whether sound-related, stress-induced increases of catecholamine levels and placental vasoconstriction are causally related to preterm births is unproven [[PMID 8520958](#)].<sup>947</sup> In one study of sound exposure during the first trimester of pregnancy, there was no association with selected structural malformations in infants (orofacial cleft or structural defect of the central nervous system, skeleton, or heart and great vessels) [[PMID: 2772573](#)].<sup>948</sup>

#### 4) Vibration Effects

While not specifically “noise-related”, vibration has also been explored as a possible reproductive or developmental hazard. There is currently no conclusive evidence that whole body vibration poses maternal or fetal risk.<sup>949</sup> Segmental vibration of the maternal abdomen, such as would be caused by vibrating tools or objects contacting the abdomen, has been documented in mammalian (sheep) studies to alter fetal sleep [[PMID 7963297](#)].<sup>950</sup>

#### 5) Maternal Noise and Vibration Exposure Guidelines

The ACGIH Physical Agents TLV Committee has noted that an 8-hour TWA exposure of 115 dBC or a peak exposure of 155 dBC to the abdomen of a pregnant worker beyond the fifth month of pregnancy may cause hearing loss in the fetus.<sup>951</sup> This peak level equates to noise exposures generated by discharging firearms with larger than a .22 caliber round.

The following recommendations are based on current knowledge. They are not requirements or regulations.

1. Pregnant workers should be vigilant in wearing hearing protectors whenever environmental noise exceeds 84 dBA, to minimize potentially unhealthy maternal cardiovascular and endocrine effects on the growing fetus.

2. Extended exposures (more than 12 minutes) above 104 dBA should be avoided, even with the use of maternal hearing protection.
3. Impact/impulse noise exposure sufficient to require personal hearing protection should be avoided.
4. Although there is currently no conclusive data defining safe-for-the-fetus noise levels after 20 weeks gestation, it is prudent to avoid unnecessary exposure to loud sounds. It is recommended that for noise at levels of 84 dBA or higher, the potential for risk (as contrasted to the actual known risk) to fetal hearing should be discussed with the mother. The aforementioned exposure limit of 90 dB recommended by Moore<sup>952</sup> provides good guidance and may be used as a starting point for those without specific expertise. If there is a question, then a team approach with an OB/GYN, OEM, pediatrics, and IH may be needed.
5. The ACGIH 115 dBC TWA and peak 155 dBC noise notations should be observed as exclusion criteria starting at 20 weeks gestation. Excluding pregnant women from discharging firearms after 20 weeks gestation would be consistent with those criteria.
6. Consider job rotation after the twentieth week of pregnancy for women working around intense sound levels.<sup>953</sup>
7. Care should be taken to avoid contact between the abdomen and vibrating tools or objects.
8. Determination as to the advisability of continuing work at a given sound level is deferred to the attending physician.

#### F) IONIZING RADIATION

Exposure limits for ionizing radiation are contained in NAVMED P-5055 (1990), Radiation Health Protection Manual.<sup>954</sup>

## **(XII) OCCUPATIONAL EXPOSURES OF REPRODUCTIVE AND DEVELOPMENTAL CONCERN - SUPERVISOR'S AND WORKER'S STATEMENTS**

The following pages contain copies of forms that may be used to help evaluate workers for potential ReproDev hazard exposures. As necessary, they may be modified to suit the needs of a particular worksite. THE NECESSITY TO MAINTAIN CONFIDENTIALITY IN MATTERS OF PERSONAL HEALTH MUST BE EMPHASIZED.

Page [97](#) is Occupational Exposures of Reproductive or Developmental Concern - Supervisor's Statement.

Page [98](#) is Occupational Exposures of Reproductive or Developmental Concern - Worker's Statement.

## Occupational Exposures of Reproductive or Developmental Concern - Supervisor's Statement

To be completed by the supervisor for any worker with concerns regarding workplace reproductive or developmental hazards. This form should then be forwarded to appropriate medical personnel such as Occupational Medicine, OB/GYN, etc. Please attach material safety data sheets (MSDS) for any substances to which this worker is exposed.

Revised  
11-2000

### PLEASE PRINT.

Worker's Name    SSN    -   -

*Last First m.i.*

Rank/Rate/Job Code  Date

*Day Month Year*

Supervisor

Command/Shop  Supervisor's Telephone  Worker's Telephone

Job Duties (not job title)

### Check all boxes that apply

Workplace:  Shipboard  Shop  Office  Outdoors  
 Other (describe):

Is the worker exposed to:

#### Chemical Agents

- Inorganic chemicals
- Organic solvents and fuels
- Metals - lead, cadmium, mercury, etc. (specify below)
- Pesticides (specify below)
- Pharmaceuticals/drugs (specify below)
- Other hazards (specify below)

#### Physical Agents

- Ionizing radiation
- Microwave and other RF radiation
- "Noise" (intense sound)
- Thermal stress (heat or cold)
- Vibration
- Other hazards (specify below)

#### Biological Agents

- Bacteria  Animal danders
- Fungi  Endotoxins
- Viruses  Enzymes & other proteins
- Protozoa  Other hazards (specify below)

#### Physical Conditions

- Irregular or shift work
- Strenuous work
- Other hazards (specify below)

Specify agents or conditions here

Personal Protective Equipment required:  None  Hearing protection  Gloves  Protective clothing  Respirator

Is the worker required to work shifts?  No  Yes

If yes, which one(s)?

Is the worker in a medical surveillance program?  No  Yes  Don't know

Has the worksite had an Industrial Hygiene survey in the last two years?  No  Yes

*Day Month Year*

Are there Industrial Hygiene sampling data for the involved worker?  No  Yes

Did the Industrial Hygiene survey reveal reproductive or developmental hazards?  No  Yes Specify

Has the worker reported an occupational illness or injury in the last year?  No  Yes Specify

Has a detailed evaluation of the worksite(s) and/or process(s) with which the worker is involved been performed?  No  Yes

\_\_\_\_\_  
Supervisor's Signature

# Occupational Exposures of Reproductive or Developmental Concern - Worker's Statement Revised 11-2000

After your supervisor has completed the other side, please fill this out and have it with you when you see the health care professional who will help with your evaluation. **PLEASE PRINT.**

Worker's Name    SSN    -   -

*Last. First M.i.*

Rank/Rate/Job Code  Today's Date

*Day Month Year*

Age  Sex  Phone (work) (  ) -  Phone (home) (  ) -

### Females only

Are you pregnant? Yes  No  Number of previous pregnancies  How many were: Live births

Date last menstrual period began       Stillbirths

*Day Month Year*

### Males only

How many children have you fathered (ever)?  Miscarriages

Abortions

### All workers

How many years have you had your current job?

What did you do at your previous job?

What does your spouse or mate do at work?

Have you ever gotten sick or injured because of your job? No  Yes  *Give details of any "yes" answers here*

Have any of your children had birth defects? No  Yes

Do you have any illnesses you see the doctor for regularly? No  Yes

Do you take medications regularly? No  Yes

Do you use any other drugs, including tobacco? No  Yes

How much alcohol do you usually drink per week?  < 6 drinks  6 to 14  15 to 21  22 or more

Reason for consultation

What reproductive or developmental hazards are you most concerned about?

In your activities at home, recreation, hobbies, second job, etc., are you exposed to any of the following? (check all that apply)

<b>Chemical Agents</b>	<b>Physical Agents</b>	<b>Biological Agents</b>
<input type="checkbox"/> Inorganic chemicals	<input type="checkbox"/> Ionizing radiation	<input type="checkbox"/> Bacteria <input type="checkbox"/> Animal danders
<input type="checkbox"/> Organic solvents and fuels	<input type="checkbox"/> Microwave and other RF radiation	<input type="checkbox"/> Fungi <input type="checkbox"/> Endotoxins
<input type="checkbox"/> Metals (lead, cadmium, etc.)	<input type="checkbox"/> "Noise" (intense sound)	<input type="checkbox"/> Viruses <input type="checkbox"/> Enzymes & other proteins
<input type="checkbox"/> Pesticides	<input type="checkbox"/> Thermal stress (heat or cold)	<input type="checkbox"/> Protozoa
<input type="checkbox"/> Pharmaceuticals/drugs	<input type="checkbox"/> Vibration	<b>Physical Conditions</b>
<input type="checkbox"/> Other hazards (specify) _____		<input type="checkbox"/> Irregular or shift work <input type="checkbox"/> Strenuous work
<input type="checkbox"/> None of the above	Worker's Signature _____	

## **(XIII) FEDERAL AND NAVY REGULATIONS RELATED TO PREGNANCY**

### **A) GENERAL PRINCIPLES**

Federal regulations prohibit discrimination from employment on the basis of pregnancy, childbirth or related medical conditions [[29 CFR 1604.10](#)].<sup>955</sup> The principle is that women affected by pregnancy and related medical conditions must be treated the same as other applicants and employees on the basis of their ability or inability to work.

If an employee is temporarily unable to perform the functions of her job because of a pregnancy-related condition, the employer is required to treat her in the same manner as it treats other temporarily disabled employees, such as providing modified tasks, alternative assignments or disability leave.

An employer cannot refuse to hire a woman because of her pregnancy-related condition so long as she is able to perform the major functions necessary to the job.

A woman is protected against being fired or refused a job or promotion merely because of pregnancy. She usually cannot be forced to go on leave as long as she can work. If a worker is absent on leave because of pregnancy or related conditions, the employer must hold her job open for her return on the same basis as jobs held open for workers on sick or disability leave for other reasons.

### **B) REGULATIONS CONCERNING PREGNANT FEDERAL CIVIL SERVICE PERSONNEL**

[29 CFR 1604.10, Employment Policies Relating to Pregnancy and Childbirth](#),<sup>956</sup>

#### [OPNAVINST 5100.23E](#)

The Pregnancy Discrimination Act<sup>957</sup> clarifies employment practices related to pregnancy or related conditions. [29 CFR 1610 Appendix](#)<sup>958</sup> further clarifies and gives answers to questions about the Act.

If a worker requests a change of duties or assignments after consulting her personal physician, the employing agency should make a reasonable effort to accommodate her. The personal physician should give her a written statement indicating the medical necessity of the recommended limitations. The OEM physician will review the recommendation. The OEM physician may consult with the personal physician to mutually determine the appropriate work restrictions for the worker. (It is to be noted that the worker's personal physician may require a signed release before discussing the case.)

### **C) REGULATIONS CONCERNING PREGNANT SERVICEWOMEN**

[SECNAVINST 1000.10](#)<sup>959</sup> and [OPNAVINST 6000.1A](#)<sup>960</sup> together provide comprehensive policy about issues related to pregnant servicewomen;

[OPNAVINST 6000.1A](#) (101.c.)<sup>961</sup> prohibits diving by pregnant servicewomen. [BUMEDINST 6200.15, Suspension of Diving Duty During Pregnancy](#),<sup>962</sup> provides guidance on suspension of diving duty of pregnant servicewomen.

D) REGULATIONS CONCERNING THE DEFINITION OF HEALTH CARE PRACTITIONERS

[BUMEDINST 6320.66B: Credentials Review and Privileging Program, Section 5: Definitions](#)

Health Care Practitioners (Licensed Independent Practitioners). Licensed Military (active duty and Reserve) and DON civilian providers (Federal civil service, foreign national hire, contract, or partnership) required by reference (a) to be granted clinical privileges to independently diagnose, initiate, alter, or terminate health care treatment regimens within the scope of his or her licensure, certification, or registration. This includes physicians, dentists, marriage and family therapists, nurse practitioners, nurse midwives, nurse anesthetists, clinical psychologists, optometrists, clinical dietitians, podiatrists, clinical social workers, clinical pharmacists, physical therapists, occupational therapists, audiologists, speech pathologists, and physician assistants. Individuals enrolled in training programs leading to qualification for clinical privileges and American Red Cross volunteers in any of these disciplines are also considered health care practitioners, for purposes of this instruction.

## (XIV) REFERENCES

*For ease of use, references are given in their entirety each time they are listed, even when listed multiple times, and World Wide Web addresses are given in selected cases.*

- 
- <sup>1</sup> California Proposition 65.  
[http://www.oehha.org/prop65/prop65\\_list/Newlist.html](http://www.oehha.org/prop65/prop65_list/Newlist.html)  
[http://www.oehha.org/prop65/prop65\\_list/42401LSTB.html](http://www.oehha.org/prop65/prop65_list/42401LSTB.html)
  - <sup>2</sup> Technical Manual NEHC-TM6290.91-2 Rev. B. Navy Industrial Hygiene Field Operations Manual. Navy Environmental Health Center. March 1999:2-1.
  - <sup>3</sup> Riggan WB, Manton KG, Creason JP, Woodbury MA, Stallard E. Assessment of spatial variation of risks in small populations. *Environ Health Perspect.* 1991 Dec;96:223-38.
  - <sup>4</sup> 29 CFR 1910.1047 – Ethylene oxide.  
[http://www.osha-slc.gov/OshStd\\_data/1910\\_1047.html](http://www.osha-slc.gov/OshStd_data/1910_1047.html)
  - <sup>5</sup> 29 CFR 1910.1025 – Lead.  
[http://www.osha-slc.gov/OshStd\\_data/1910\\_1025.html](http://www.osha-slc.gov/OshStd_data/1910_1025.html)
  - <sup>6</sup> 29 CFR 1910.1025 Appendix A.  
[http://www.osha-slc.gov/OshStd\\_data/1910\\_1025\\_APP\\_A.html](http://www.osha-slc.gov/OshStd_data/1910_1025_APP_A.html)
  - <sup>7</sup> 29 CFR 1910.1025 Appendix B.  
[http://www.osha-slc.gov/OshStd\\_data/1910\\_1025\\_APP\\_B.html](http://www.osha-slc.gov/OshStd_data/1910_1025_APP_B.html)
  - <sup>8</sup> 29 CFR 1926.62 – Lead  
[http://www.osha-slc.gov/OshStd\\_data/1926\\_0062.html](http://www.osha-slc.gov/OshStd_data/1926_0062.html)
  - <sup>9</sup> 29 CFR 1910.1044 – 1,2-dibromo-3-chloropropane.  
[http://www.osha-slc.gov/OshStd\\_data/1910\\_1044.html](http://www.osha-slc.gov/OshStd_data/1910_1044.html)
  - <sup>10</sup> 29 CFR 1910.1044 – Appendix A – Substance safety data sheet for DBCP.  
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Page: 10

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