

Navy and Marine Corps Public Health Center Technical Manual

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

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

#### ACKNOWLEDGEMENTS

The 2019 edition of the manual is an update of the 2010 edition, with additions to the main text and to the chemical, pharmacological, and biological hazards sections. Major contributors to this update include Roger Scott Akins, CAPT, MC, Douglas Talk, LCDR, MC, Robert Walton, LCDR, MC, James Smith, Jr., PhD, Amy Delong, PhD, and John Muller, MD, MPH (primary editor). Special thanks are given to CAPT Todd Wagner, MC, USN, for his leadership as Commander of Navy and Marine Corps Public Health Center (NMCPHC).

**Reviewed and Approved** 

T. L. Wagner, CAPT, MC, USN Commander

#### <u>PURPOSE</u>

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

#### 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 (OEM) Department, NMCPHC. 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 NMCPHC. Updating hyperlinks is an ongoing process. While effort has been made to verify that links are working at the time this document was published, it is readily acknowledged that hyperlinks may be outdated. If a hyperlink in this document is found to be functioning incorrectly, the reader is encouraged to search the Internet for the referenced document, as it may be available from a different Internet address.

#### USING THE MANUAL

This manual provides general guidance in the recognition, assessment, and control of reproductive and developmental (ReproDev) hazards to both male and female uniformed and civil service personnel. It primarily focuses on ReproDev hazards associated with the occupational exposures of workers. Strategies for managing individuals potentially exposed to ReproDev hazards in the workplace are presented. This manual promotes a consistent, scientific and evidence-based approach to the assessment and disposition of workplace ReproDev issues throughout the Navy.

The manual utilizes the policy and guidance from many regulatory and non-regulatory agencies, including OSHA, EPA, the Food and Drug Administration (FDA), the National Toxicology Program (NTP), and the Centers for Disease Control (CDC). Information from other sources regarding potential reproductive and developmental hazards may be incorporated into the manual, if considered appropriate and scientifically rigorous. This document is not intended as a guide to investigation of outbreaks or "clusters" of adverse effects. Providers and others dealing with environmental investigations are directed to the <u>NMCPHC web site</u> for additional resources.

Numerous references and hyperlinks to sources other than those maintained by the Navy are included in the manual. Hyperlinks are marked by colored text, and PubMed numbers are hyperlinked to abstracts (in the format <u>PMID 000000</u>). 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, including notification of broken links, are always appreciated and will assist in continual improvement of this manual. They may be sent to the OEM Department, Navy and Marine Corps Public Health Center, 620 John Paul Jones Circle Suite 1100, Portsmouth, VA 23708, or e-mail <u>usn.hampton-roads.navmcpubhlthcenpors.list.nmcphc-repro@mail.mil</u>.

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

ACGIH	American Conference of Governmental Industrial Hygienists (ACGIH <sup>®</sup> )
BUMED	Bureau of Medicine and Surgery
Cd	Cadmium
CFR	Code of Federal Regulations
DBCP	1,2-dibromo-3-chloropropane
DES	Diethylstilbestrol
DON	Department of the Navy
EPA	Environmental Protection Agency
ETO	Ethylene Oxide
FSH	Follicle-Stimulating Hormone
FDA	Food and Drug Administration
НСР	Health Care Practitioner
HCW	Health Care Worker
Нg	Mercury
HIV	Human Immunodeficiency Virus
ІН	Industrial Hygiene
IUGR	Intrauterine Growth Retardation
LH	Luteinizing Hormone
L/min	Liters per Minute
LMP	Last Menstrual Period
MTF	Medical Treatment Facility
NMCPHC	Navy and Marine Corps Public Health Center
NEPMU	Navy Environmental and Preventive Medicine Unit
NH	Naval Hospital
NHC	Naval Health Clinic
NIOSH	National Institute for Occupational Safety and Health
NAVMEDCEN	Naval Medical Center
NTP	National Toxicology Program
OEM	Occupational and Environmental Medicine
ОН	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
ppm	Parts of a substance per million parts
ppb	Parts of a substance per billion parts
PPE	Personal Protective Equipment

ReproDev	Reproductive and Developmental
RDA	Recommended Dietary Allowance
REL	Recommended Exposure Limits
SDS	Safety Data Sheet
TCDD	2,3,7,8-tetrachlorodibenzo-para-dioxin
TLV	Threshold Limit Value (TLV <sup>®</sup> )
TV	Tidal Volume
TWA	Time-Weighted Average
WBGT	Wet-Bulb Globe Temperature

## (II) INTRODUCTION

This manual provides general guidance to Navy medical department personnel in the recognition, assessment, and control of workplace reproductive and developmental (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.

Increasingly, Navy medical providers have had to respond to concerns related to contaminants in drinking water, groundwater, surface water, ambient air, soil, and sediment, and to vapor intrusion. In addition, the number of emerging contaminants (those without current standards) are growing. Occupational and environmental exposures to ReproDev hazards may be very different with regard to the exposure media (e.g., soil, water, ambient air), routes of exposure (e.g., inhalation, ingestion, direct contact), the populations exposed (civilian workers, military service members, civilian beneficiaries), the exposure scenarios (e.g., industrial, residential, recreational), and the acceptable exposure levels. Because environmental exposure levels of concern (EPA Screening Levels) tend to be much lower than occupational ones (OSHA Permissible Exposure Limits, PELs), different management strategies may be required. Investigating disease clusters (the manifestation or recognition of an adverse health effect) may include considering both occupational and environmental exposures. Sitespecific strategies are necessary for the scientific investigation (to exercise due diligence) and to address stakeholder's health risk concerns. Outbreak investigations are beyond the scope of this document. Providers and others dealing with environmental investigations are directed to the NMCPHC web site for additional resources.

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. Very early in pregnancy (up to week 3), developmental hazards generally either have no effect or cause fetal demise (miscarriage or "spontaneous abortion"). During the embryonic period (weeks 3-10), developmental hazards can disrupt organ systems and cause structural

birth defects. After the embryonic period, developmental hazards can affect the growth and development of the fetus, but do not typically cause structural defects.<sup>1</sup> <u>Table 1</u> 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), toxicologists and other occupational health (OH) professionals are necessary to appropriately identify ReproDev hazards so that they can 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.

Chromosome	A thread-like structure in the nucleus of a cell that is made up of
	coiled double-stranded DNA and histone proteins.
Deformity, birth	Malformation, present at birth, of the body or a body part.
Developmental toxicity	The potential to cause harmful effects on the developing child,
	whether before or after birth, up to adulthood. The
	manifestation of the effect may happen at any time during the
	person's life span.
DNA	Deoxyribonucleic acid. A carrier of genetic information for all
	organisms except the RNA viruses. <sup>†</sup> Deoxyribonucleic acid is a
	coiled, self replicating, double stranded molecule present in
	nearly all living organisms. It conferrs heritable genetic
	information from one generation to the next.
Embryo	The developing human from pregnancy weeks 3 to 10 based on
<b>–</b> • • • •	the menstrual cycle.
Embryotoxicity	Potential to cause adverse effects on the embryo, generally
	attributed to a substance that enters the mother and crosses the
	placental barrier or to an environmental or physical agent.
Fecundability	The probability of becoming pregnant in a single menstrual cycle.
Fecundity	The capability of a person or couple to produce offspring. When
	referring to populations, fecundity may be the reproductive rate
	of a population or the probability of achieving a live birth in a
	single menstrual cycle.
Fertility	The production of offspring or the ability to produce offspring.
Fetotoxicity	Adverse health effect on the fetus. Generally, this is applied to
	agents in the maternal circulation that cross the placenta and
	cause fetal demise, growth restriction, or other adverse health
<b>Fatura</b>	effect.
Fetus	The unborn baby in the post-embryonic period (week 10 of
Cono	pregnancy). A portion of chromosomal DNA consisting of a series of
Gene	nucleotides that codes for a specific trait and serves as the basic
	unit of heredity.
Histones	A group of simple proteins found in chromatin that confer
1113101123	structure to DNA in chromosomal regions.
Infertility	The failure to achieve a clinical pregnancy after 12 months or
mertinty	more of regular unprotected sexual intercourse. <sup>2</sup>
Mutagen	Anything (generally a chemical or a physical agent) that causes or
wintagen	leads to genetic change.

#### Table 1 – Definitions

Mutation	A change in the structure of a gene by alteration of single
	nucleotide bases within DNA, or the deletion, insertion, or
	rearrangement of DNA fragments, that may result in the
	transmission of a heritable changes in DNA sequence to
	subsequent generations.
Ovulation	The discharge (release) of the ova, or ovules, from the ovary.
Ovum	An egg (ova) or mature female reproductive cell that, once
	fertilized by a male cell, can divide to give rise to an embryo.
Reproductive toxicity	The potential to cause adverse effects on fertility and to cause
	developmental toxicity.
RNA	Ribonucleic acid, a single-stranded nucleic acid that principally
	functions as a messenger required in protein synthesis. Lesser
	RNA molecules may be important in the regulation of protein
	translation and transcription.
Spermatogenesis	The production or development of mature spermatozoa.
Spermatozoa	Mature motile male sex cell, typically having a head and one or
	more flagella for movement, which fertilizes the ovum.
Subfertility	A reduction in the expected birth rate due to factors other than
	choice. This includes a delay in time to conception.
Teratogen	Anything that causes physical defects in the developing embryo.
U	

## (III) 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 Safety Data Sheet (SDS) 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, 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 (VI) The Biology of Reproductive and Developmental Hazards 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 Department at the Navy and Marine Corps Public Health Center (NMCPHC) can provide a response that addresses the OEM considerations.

Chapters (VII) Occupational Chemical Reproductive and Developmental Hazards, (VIII) Drug Reproductive and Developmental Hazards, and (IX) Occupational Biological Reproductive and Developmental Hazards 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 criteria used to identify a hazard as a "known hazard" are the Occupational Safety and Health Administration (OSHA) criteria for reproductive toxicants category 1 (OSHA).<sup>3</sup> The chemicals and medications lists in Chapters (VII) and <u>(VIII)</u> were adopted from other similar lists, such as the <u>State of California's Reproductive</u> <u>and Developmental Toxicity List</u>.<sup>4</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 (VII) Occupational Chemical Reproductive and Developmental Hazards, (VIII) Drug Reproductive and Developmental Hazards, and (IX) Occupational Biological Reproductive and Developmental Hazards, 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 (NH)/Naval Health Clinic (NHC), Navy Environmental and Preventive Medicine Unit (NEPMU), or NMCPHC.

The identification and evaluation of potential reproductive and developmental hazards is an ongoing process. 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. Where stressor specific standards either do not exist, or were developed without consideration of reproductive health risk, local review in consultation with the OEM staff may be necessary.

Routine industrial hygiene assessments of workplaces should be focused to the toxic effects of the stressors present as based on some trigger of exposure. A ReproDev hazard "action level" (one half of the Occupational Exposure Limit), except for the physical stressors) can be used as a trigger for implementing "non-negative" assessment actions that would require hazard abatement with control recommendations and inclusion of specific training due to unknown risks, see Chapter (IV) Reproductive and Developmental Hazards in Occupational Safety and Health Administration Standards. If skin is a significant route of entry, dermal uptake should be included as part of the worksite assessment for all stressors.

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 <u>Navy Industrial Hygiene Field</u> <u>Operations Manual</u>).<sup>5</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.

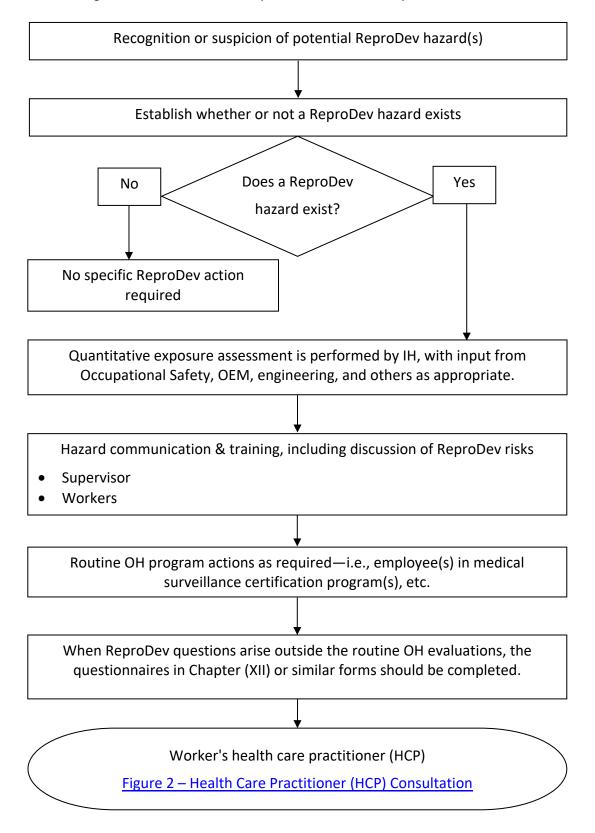
In this role, the OEM Department:

- 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 (VII) Occupational Chemical Reproductive and Developmental Hazards to Chapter (X) Occupational Physical Reproductive and Developmental Hazards—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 NHCs and most NHs) or NMCPHC.

#### **D) WORKER INQUIRIES**

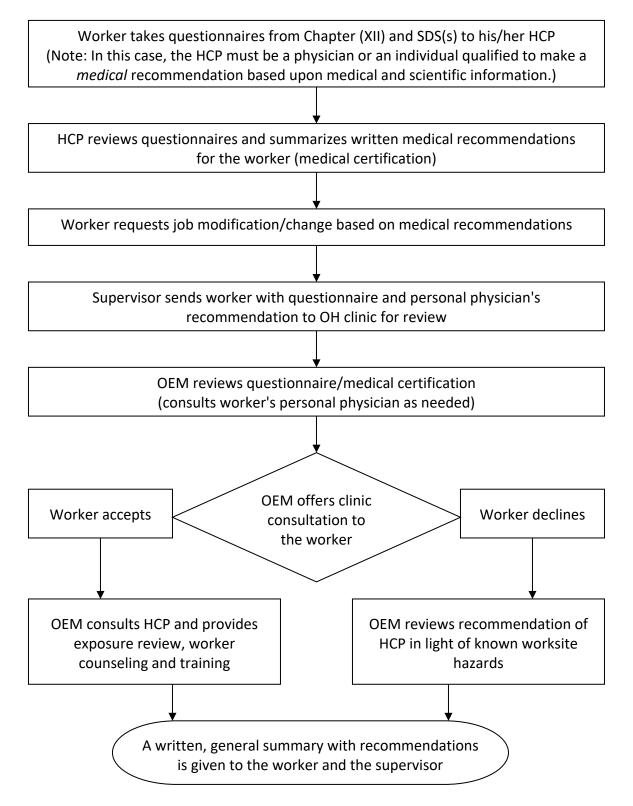
Workers, individually or through a collective group such as a union or rate/specialty association, may raise questions about the ReproDev risk of an agent or condition. Frequently, review of the agent or condition in light of the available literature or information, and discussion with the inquiring 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 (X) Occupational Physical Reproductive and Developmental Hazards is a summary of physical agents and conditions (hazards) that should be considered when reviewing potential ReproDev hazards in the workplace. Chapter (XII) Occupational Exposures of Reproductive and Developmental Concern - Supervisor's and Worker's Statements discusses questionnaires (forms) that may be used for any worker with ReproDev concerns, including the worker's self-assessment of his/her occupational/nonoccupational exposures to physical, chemical, biological, and environmental agents. These questionnaires and the pertinent SDSs 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. See Chapter (V) Evaluating and Managing the Pregnant Employee for further guidance about pregnant active duty members or civil service employees.



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





## 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>6</sup> The OEM Department has the expertise to determine 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 NMCPHC if needed.

The investigation process includes the following steps:

 Schedule an individual appointment with the OEM physician for each involved worker. In some cases, it is prudent to include the worker's spouse in such discussions, with the consent of the worker. 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. Consultation with another specialist, including but not limited to medical genetics, 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. If indicated and necessary to such investigations, medical records pertinent to the investigation should be obtained through standard request procedures, with signed consent from the worker for release of specific 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 (VI) The Biology of Reproductive and Developmental Hazards.
- 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 OEM Department cannot confidently rule out a cluster, it may request assistance from the cognizant epidemiology, risk assessment, or toxicology support (if any), or supplemental assistance from NMCPHC.
- 9. Complaints of infertility should be recorded (and handled as confidential) to alert both the OEM 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 issues will require a consultation with a specialist in toxicology, reproductive endocrinology, or other appropriate field.

## (IV) 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 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) (<u>29 CFR 1915.1047</u>),<sup>7</sup> lead (Pb) (<u>29 CFR 1910.1025</u><sup>8</sup> and <u>29 CFR 1926.62</u><sup>9</sup>), and 1,2-dibromo-3-chloropropane (DBCP)(<u>29 CFR 1910.1027</u>).<sup>12</sup> 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 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>13</sup> sperm motility [PMID 9987558],<sup>14</sup> and production of malformed sperm [PMID 1442789]<sup>15</sup> have been found at elevated blood Pb levels: 40 micrograms per deciliter (µg/dl)<sup>i</sup> has been noted in a review article[PMID 9764095].<sup>16</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>17</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>18</sup> Fetal blood Pb levels have been noted to increase with maternal occupational exposure [PMID 7448135].<sup>19</sup>

Fetal and infant/child neurological damage may occur at blood Pb levels above 5  $\mu$ g/dl [<u>CDC</u>],<sup>20</sup> and may be manifested by childhood learning difficulties [<u>PMID 7679348</u>].<sup>21</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  $\mu$ g/100g maximum permissible blood level in both males and females who wish to bear children.<sup>22</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  $\mu$ g/dl in older workers with previous Pb exposures or <10  $\mu$ g/dl in younger workers) easily attainable.

<sup>&</sup>lt;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.

Elevated blood Pb levels during pregnancy have been attributed to mobilized skeletal Pb stores [PMID 9242366].<sup>23</sup> It has been recommended that a woman with a blood Pb above 20  $\mu$ g/dl and desiring to become pregnant be advised to avoid uncontrolled Pb exposure for 1 to 2 years before attempting pregnancy.<sup>24</sup>

Although no threshold has been found to trigger the adverse health effects of lead, in nonpregnant adults blood lead levels less than 5  $\mu$ g/dl are considered normal, blood lead levels between 5  $\mu$ g/dL and 10  $\mu$ g/dl require follow-up, and blood lead levels greater than 10  $\mu$ g/dl are managed with environmental assessment and abatement of exposures. Chelation therapy is considered at blood lead levels greater than 40  $\mu$ g/dl for symptomatic individuals, and levels greater than 70  $\mu$ g/dl are considered a medical emergency. In children, treatment with chelation is recommended at blood lead levels of 45  $\mu$ g/dl (a level considered a critical health concern) or greater.<sup>25,26,27</sup> The CDC recommends that pregnant women with blood lead concentrations of 10  $\mu$ g/dL or higher be removed from occupational lead exposure [CDC].<sup>28</sup>

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>29</sup>

Lead appears in human breast milk (see <u>Breastfeeding</u>, page 25) [<u>PMID 9755144</u>],<sup>30</sup> and may be passed on to the child during breast feeding.

## D) 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>31</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

Cd 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, Cd is associated with decreased birth weight (with inhalation exposure, ATSDR),<sup>32</sup> placental toxicity (Miller),<sup>33</sup> preterm delivery (<u>PMID 8094678</u>),<sup>34</sup> and possibly with prostate cancer (<u>29 CFR 1910.1027 App D</u>).<sup>35</sup> OSHA requires that employers provide pre-placement and periodic detailed medical and work history, to include a reproductive history with an emphasis on reproductive dysfunction (<u>29 CFR 1910.1027</u>).<sup>36</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 current PELs for different glycol ethers vary widely depending on the specific chemical.

## (V) 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.<sup>37</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>38</sup> A National Institute for Occupational Safety and Health (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>40</sup>

	-
Lead	Pesticides
Mercury	Chlorinated hydrocarbons
Arsenic	Estrogenic substances
Cadmium	Infectious agents

#### Table 2 – Contaminants That Have Caused Health Effects Among Workers' Families

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) Occupational Exposures of Reproductive and Developmental Concern -Supervisor's and Worker's Statements discusses forms that may be used 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 (particulate matter, as measured by PM<sub>10</sub> have been associated with adverse pregnancy outcomes [PMID 18231086])<sup>41</sup>
- 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)

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.

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>42</sup> Most drugs with molecular weight < 500 Daltons cross the placenta, and most drugs with molecular weight > 1000 Daltons do not cross the placenta (e.g., heparin, protamine, insulin). For example, neither succinylcholine (low molecular weight but highly ionized) or non-depolarizing neuromuscular blocking drugs (high molecular weights) cross the placenta.

**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>43</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>44</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 decrease arterial pCO2 (32 mm Hg) and respiratory alkalosis partially compensated for by a decrease in plasma bicarbonate.<sup>45</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>46</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>47</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 herpetiformis 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. Dermatology should be consulted if needed 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 standingii 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>48,49,50</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. 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 in <u>OPNAVINST 6000.1D</u>.<sup>51</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.

- 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.
- Engineering controls (improving exhaust, enclosing processes, powered lift assistance),
- Administrative controls (rotation or reassignment) and, as a last choice,
- Personal protective equipment (PPE), such as aprons, gloves, or respirators.

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

## E) WOMEN ABOARD SUBMARINES

Historically, women have been excluded from permanent assignment aboard submarines. OPNAVINST 6420.1 excluded pregnant females from traveling aboard submarines.<sup>52</sup> The Navy Submarine Research Laboratory addressed the medical implications of stationing women as crew members aboard submarines, noting "Risks to the developing fetus are at present unknown. Categorical reassurance cannot be given that the submarine environment is safe for a developing fetus. Extensive animal research is needed."<sup>53</sup> It convened an Expert Panel to review Submarine Atmosphere Control Limits (SACLs) to protect mixed gender submarine crews. A submarine is a unique enclosed work environment that cannot easily be modified. Submariners are exposed to airborne contaminates 24 hours a day, 7 days a week, for up to 90

<sup>&</sup>lt;sup>ii</sup> One duration used in the literature is 3 or more hours per day (Ha E, Cho SI, Park H, Chen D, Chen C, Wang L, Xu X, Christiani DC. Does standing at work during pregnancy result in reduced infant birth weight? J Occup Environ Med. 2002 Sep;44(9):815-21).

days, in contrast to workers that have a respite from exposure after an 8 hour shift and a 5 day work week. Information applicable to other worksites also applies to submarines. Female officers began serving aboard submarines in 2011 and female enlisted began serving aboard submarines in 2016. This led to the rescinding of the 1994 Direct Combat Exclusion Act (restricting women from serving onboard submarines) and the Chairman of the Joint Chiefs of Staff directing Armed Forces to integrate women into occupational fields. As of 2017, a total of 18 crews and 11 boats have been integrated. More than 100 female officers have joined the submarine force and more than 40 have successfully completed submarine warfare qualifications.

#### 1) Oxygen

The partial pressure of oxygen in the air aboard a submerged submarine is likely to be lower than that of ambient air at sea level, and the resulting blood oxygenation (PaO<sub>2</sub>) may approximate that of living at higher altitudes, sometimes of 8000 feet or more above sea level (see <u>Altitude</u>, section (X)A), page 121). Such altitudes have known ReproDev effects, but the ReproDev effects of low oxygen at pressure (i.e., at 1 atmosphere barometric pressure), if any, have not been determined.

#### 2) Evacuation

While women are not to be assigned shipboard after 20 weeks gestation, complications of early pregnancy (such as tubal or ruptured ectopic pregnancy) are medical emergencies requiring care not available aboard submarines. Emergency medical evacuation from submarines is hazardous and risks discovery of the submarine's location.

#### 3) Chemical Hazards

The principles of determining the presence of chemicals and characterizing exposure are no different aboard submarines than aboard other ships, although methods may require modification. The atmosphere aboard submarines has been carefully studied in the past, and chemical stressors have been identified.<sup>54</sup> Of the chemicals identified, 26 compounds have been more extensively addressed.<sup>55</sup> As with other occupational exposures, current IH sampling data is necessary. While submarines have powerful atmosphere "scrubber" systems, the scrubber system must not be relied on to eliminate all chemical exposures. PPE may be required in the immediate vicinity of certain chemicals. However, chemical use (e.g., applying a solvent or machine oil) in one part of the submarine does not indicate the entire crew must use PPE.

#### 4) Ionizing Radiation

While PELs of chemical occupational hazards apply to pregnant and non-pregnant personnel, ionizing radiation exposure limits for pregnant workers are more strictly defined (see <u>lonizing Radiation</u>, <u>below</u>). Under most conditions, these would only need consideration aboard certain areas of nuclear submarines.

## F) 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.

## G) 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. Breastfeeding cessation is a risk factor for increased anxiety and depression [PMID 22621668].<sup>56</sup>

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>57</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>58</sup>

A 1997 <u>American Academy of Pediatrics policy statement</u> noted many advantages of breastfeeding, including "reduced employee absenteeism for care attributable to child illness." The same statement called for "employers to provide appropriate facilities and adequate time in the workplace for breast-pumping."<sup>59</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. Breastfeeding should be encouraged under most circumstances despite the presence of trace amounts of environmental toxins [PMID 7702761].<sup>60</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. While the usual methods and guidelines for minimizing worker exposure apply (administrative and engineering controls and use of PPE such as respirators), in certain situations specific controls may be helpful in minimizing both exposures and concerns (e.g., issuing non-lead bullets to breastfeeding personnel who carry weapons and temporarily lifting requirements to attend indoor shooting ranges).

A specific area requiring attention is exposure to surgical (medical, dental, or veterinary) anesthesia. When anesthetic gases (e.g., nitrous oxide, halothane, etc.) 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 parts per million (ppm) [PMID 986147].<sup>61</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>62</sup> NIOSH has published recommendations on controlling exposures to nitrous oxide during anesthetic administration [NIOSH].<sup>63</sup>

Breastfeeding women should not handle antineoplastics or work in areas where they are handled (McDiarmid).<sup>64</sup> These agents may contaminate surfaces in pharmacy drug preparation areas and drug administration areas [PMID 10428450]<sup>65</sup> and even occasionally penetrate gloves [PMID 10595805].<sup>66</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).

#### H) AVIATION

According to the Aeromedical Reference and Waiver Guide published by the Naval Aerospace Medical Institute, pregnancy is considered disqualifying for all aviation duties except for Air Traffic Controllers [NAMI].<sup>67</sup> Waivers in certain circumstances may be obtained (OPNAVINST 3710.7 and OPNAVINST 6000.1 series are referenced).

# (VI) 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 (also called spermatozoa) 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>68</sup> By puberty, approximately 400,000 oocytes exist, whereas after age 36 there are less than one-tenth that number.<sup>69</sup> There is no mechanism for the replacement of damaged oocytes. 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).

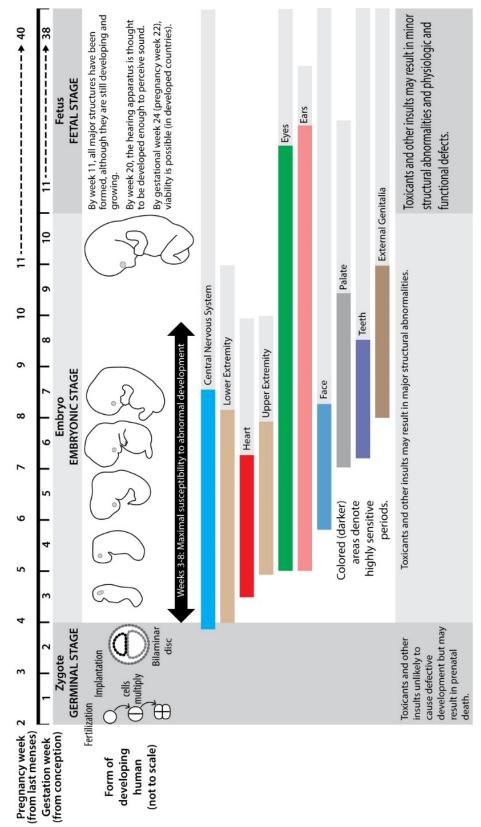
Estrogens are instrumental in the preparation of the uterus for the implantation of the fertilized ovum. Estrogens are also responsible for the development and maintenance of secondary sex characteristics (breast development, body fat pattern) and the changes in cervical mucus associated with the menstrual 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, and the fertilized ovum migrates to the uterus and implants in the uterine wall. After ovulation, the cells of the ovarian follicle produce 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>70</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. Consequently, it is the 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. There are critical periods of development for specific organs or body systems.



## Figure 3 - Critical Periods of Development

## 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 about 88 percent of the time.<sup>71</sup>

Up to 50 percent of embryos fail to survive the first 2 weeks following fertilization. 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 <u>Table 3</u>).

#### Table 3 – Rates of Reproductive Success

Reproductive or developmental event	Outcome
Couples attempting pregnancy	100
Positive serum hCG	90*
Unrecognized pregnancy loss	22*
Recognized pregnancy loss	9*
Stillbirth (after 16 weeks pregnancy)	1 <sup>+</sup>
Premature, postmature, growth retardation	10 <sup>‡</sup>
Term births	58**
Developmental abnormality	3 <sup>§</sup>
* Wilcox AJ, Weinberg CR, O'Connor JF, Baird DD, Schlatterer JP, Canfield F	RE, Armstrong EG, Nisula BC. Incidence
of early loss of pregnancy. N Engl J Med. 1988 Jul 28;319(4):189-94.	

<sup>+</sup> Rasmussen S, Irgens LM, Skjaerven R, Melve KK. Prior adverse pregnancy outcome and the risk of stillbirth. Obstet Gynecol. 2009 Dec;114(6):1259-70. doi: 10.1097/AOG.0b013e3181c22422.

<sup>+</sup> Vayssière C, Sentilhes L, Ego A, et al. Fetal growth restriction and intra-uterine growth restriction: guidelines for clinical practice from the French College of Gynaecologists and Obstetricians. Eur J Obstet Gynecol Reprod Biol. 2015 Oct;193:10-8.

<sup>§</sup> CDC. Update on Overall Prevalence of Major Birth Defects --- Atlanta, Georgia, 1978—2005. MMWR. January 11, 2008 / 57(01);1-5.

\*\* Calculated from above.

## 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". For example, women who have a spouse deployed during pregnancy are at increased risk for preterm birth and postpartum depression

[PMID: 26244533].<sup>72</sup> 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—can be critical for the development of adverse effects. 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>73</sup> Pb exposure causes decreased fecundity before pregnancy,<sup>74</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, or
- 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. For example, anticancer drugs have been associated with an excess of abnormalities of chromosome 5 [PMID: 20881619].<sup>75</sup> 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 (polycyclic aromatic hydrocarbon compounds)
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. In addition to gestational diabetes, hypertension, operative delivery, macrosomia, and birth trauma, a meta-analysis identified obesity (body mass index >30) as a risk factor for spina bifida, neural-tube defects, hydrocephaly, and overweight (body mass index 25-30) as a risk factor for neural-tube defects and cardiovascular anomalies [PMID 19211471].<sup>76</sup>

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

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

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

#### 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>77</sup>

#### Table 6 – Effects of Selected Occupational Exposures on Sperm Parameters

Lowered number of sperm	Altered sperm transfer	Abnormal sperm shape		
Bromine vapor	Bromine vapor	Bromine vapor		
DBCP	2,4-Dichlorophenoxy acetic	Carbaryl (Sevin™)		
Dinitrotoluene	acid (2,4-D)	2,4-Dichlorophenoxy acetic		
Ethylene dibromide	Ethylene dibromide	acid (2,4-D)		
Ethylene glycol monoethyl	Heat	Ethylene dibromide		
ether	Kepone	Pb		
Heat	Pb	Perchloroethylene		
Military radar	Perchloroethylene	Plastic production (styrene		
Pb	Radiation	and acetone)		
Radiation	Welding	Radiation		
Toluenediamine Welding				
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>78</sup> Semen Pb was not found to be a valuable adjunct to blood Pb monitoring [PMID 9787850].<sup>79</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>80</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>81</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>82</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>83</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>84</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.

General health	Social	history	Medical history		
Age (before age 17 or after	Substance abuse		Ethnicity ("race")		
35)	Tobacco use		Medication		
Nutrition	Economic statu	ıs (income,	Polycystic ovary syndrome		
Body weight (obesity or	wealth, pov	erty)	Endometriosis		
underweight)	Health insuran	ce	Pelvic inflammatory disease		
Exercise	Occupation (stress, exertion, shift duration and rotation) Occupational exposures Social network and support (family, friends) Education Paternal age, health, fertility, exposures		Chronic illness (hypertension, diabetes, HIV, renal, autoimmune, thyroid disease, cancer, epilepsy, etc.) HIV		
	Hobbies Pregnanc	y-specific			
Parity (nulliparity, grand multi		History of pre-	term birth		
Multiple gestation		Rh injection			
History of three or more misca	•		ortion		
History of late abortion	-		ic or systemic)		
History of stillbirth		Placental abno	rmalities		
Child with genetic problem		Gestational dia	abetes		
History of post-partum depression		Weight gain du	uring pregnancy		
Time since last pregnancy	-		auterine growth retardation)		
Toxemia (pre-eclampsia/eclam	npsia)				
	Soci	etal			
Life expectancy					
	Food (availability and quality)				
Availability of outpatient care (prenatal and follow-up of mother and baby)					
Access (transportation, cost) to medical care					
Availability of advanced medical care (maternal and neonatal)					
	Cultural norms (value of women, allowing women to receive medical care, allowing women				
to be examined by males, acceptance of women working outside the home, etc.)					
Ethnicity (member of marginalized group)					
Government policy (e.g., appr					
Environment (e.g., nutrition du	vironment (e.g., nutrition during the winter)				

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

# (VII) OCCUPATIONAL CHEMICAL REPRODUCTIVE AND DEVELOPMENTAL HAZARDS

## 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 (VIII) Drug Reproductive and Developmental Hazards. 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," currently in its third edition, 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. This list represents the drugs and chemicals that may be harmful to the developing fetus. This list is based on a literature review done in August 2017. As the data for drugs and chemicals is constantly updated, the reader is encouraged to review the current data for updates.

(For a description of the "categories" listed for some of the chemicals, please see Section (VIII)D) on Page 60.)

Agent	CAS Number	Date Added	Notes
lpha-Naphthyl-N-	63-25-2		(See <u>Carbaryl</u> )
methylcarbamate			
Acetaldehyde	75-07-0		Primary metabolite of ethanol
			[PMID 9105505] <sup>85</sup> [PMID
			<u>1789375</u> ] <sup>86</sup>
Acetylaminofluorene	53-96-3	11-1-2017	No human data, but skeletal
			defects and cleft lip in mice, and
			DNA adducts in vitro
			[PubChem] <sup>87</sup>
Alcohol			(See <u>Ethanol</u> )
Anesthetic gases			(See Drug Reproductive and
			<b>Developmental Hazards List</b> )
Antimony	7440-36-0	12/06/2017	Female: menstrual cycle
			disturbances, increased
			spontaneous abortion
			Developmental: decreases in infant
			body weight gain
			[ATSDR] <sup>88</sup>

Table 8 – Chemical Reproductive and Developmental Hazards List

Agent	CAS Number	Date Added	Notes
Arsenic	7440-38-2		Pregnancy: Occupational exposure
			to inhaled inorganic arsenic
			associated with increased
			incidence of congenital
			malformations and decreased
			birth weight [ATSDR]; <sup>89</sup> Ingested
			inorganic arsenic has been
			reported in association with
			premature delivery and
			subsequent neonatal death
			[ATSDR]. <sup>90</sup> Occupational
			exposure to high levels of
			inorganic arsenic (>50 ppb) in air
			and drinking water is associated
			with increased risk of
			spontaneous abortion, stillbirth
			and low birth weight. Further
			research is needed on the
			impact of low-moderate arsenic
			concentration exposures on
			pregnancy outcomes. <sup>91</sup>
			Placental toxicity
			Appears in cord blood in almost
			same levels as maternal blood
			[PMID 9742656] <sup>92</sup>
			Breastfeeding: Low concentrations
			in breast milk [PMID 9742656] <sup>93</sup>
Atrazine	1912-24-9	12/06/2017	Increased risk of pre-term delivery
			[ATSDR] <sup>94</sup>
Benzene	71-43-2	03/10/00	Pregnancy: Spontaneous abortion,
			premature births, neonatal
			complications [Schardein] <sup>95</sup>
Benzimidazoles			(See <u>Carbendazim</u> )
Bischloroethyl	154-93-8	09/30/94	Category D [USPDI] <sup>96,97</sup>
nitrosourea		-	Breastfeeding: Contraindicated
			[Briggs 1997] <sup>98</sup>
2-Bromopropane	75-26-3	12/06/2017	Male: decreased sperm count and
		-	sperm motility
			Female: failure to menstruate
			[NTP] <sup>99</sup>

Agent	CAS Number	Date Added	Notes
1,3-Butadiene	106-99-0	07/25/00	No human data. Animal data (inhalation exposure)[ATSDR]: <sup>100</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>101</sup>
Cadmium	7440-43-9	2-11-00	Males (inhalation exposure): No consistent effect [ATSDR]; <sup>102</sup> OSHA notes an increased risk of prostate cancer ( <u>29 CFR</u> <u>1910.1027 App D</u> ). <sup>103</sup> Disruption of the blood-testis barrier and oxidative stress have been noted, with onset of widespread necrosis at higher dosage exposures. <sup>104</sup> Pregnancy: Decreased birth weight (with inhalation exposure) [ATSDR], <sup>105</sup> placental toxicity [Miller], <sup>106</sup> associated with preterm [ <u>PMID 8094678</u> ] <sup>107</sup> Abnormalities in the embryo, depending on the stage of exposure and dose given: craniofacial, neurological, cardiovascular, gastrointestinal, genitourinary, and limb anomalies. <sup>108</sup> Breastfeeding: No reported effect [ <u>AAP</u> ] <sup>109</sup>
Carbarsone	121-59-5	03/06/00	Category D (contains 29% <u>Arsenic</u> ) [Briggs 4th] <sup>110</sup>

Agent	CAS Number	Date Added	Notes
Carbaryl	63-25-2	06/07/00	Males: Abnormal sperm shape
			[PMID 6791917] <sup>111</sup> [NIOSH] <sup>112</sup>
			Development: No human
			developmental data, teratogenic
			in several animal species
			[EPA] <sup>113</sup>
Carbendazim	37953-07-4	06/07/00	Human data lacking, but
			reproductive/ developmental
			effects are noted in several
			animal species.
			May influence the hypothalamus–
			pituitary–gonad axis [PMID
			24863245]. <sup>114</sup>
			Male (rat): Testicular [PMID
			9719423] <sup>115</sup> /sperm toxicity
			[PMID 2227156] <sup>116</sup> [PMID
			<u>9070363</u> ] <sup>117</sup>
			Embryotoxic [PMID
			<u>1601229</u> <sup>118</sup> [ <u>PMID 1609414</u> ] <sup>119</sup>
		44/04/0047	Teratogenic [Cummings/USEPA] <sup>120</sup>
Carbon dioxide	124-38-9	11/01/2017	Fetal resorption at 3% [NAMRU]. <sup>121</sup>
Carbon disulfide	75-15-0	09/30/94	Male: Spermatotoxic [Paul] <sup>122</sup>
			[ <u>PMID 5079601</u> ], <sup>123</sup> decreased
			libido, impotence [Schardein] <sup>124</sup>
			Female: Menstrual irregularities,
			decreased fertility, increased
			spontaneous abortion
			[Schardein] <sup>125</sup>
			Pregnancy: 4 ppm (10 mg/m <sup>3</sup> )
			recommended as occupational
			exposure limit during pregnancy
			[OSHA], <sup>126</sup> birth defects
			reported [Bao], <sup>127</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>128</sup>
			Breastfeeding: Can cross the
			placental barrier and be
			secreted into mothers' milk
			[PMID 7216838] <sup>129</sup>

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 [ <u>PMID 9872713</u> ], <sup>130</sup> CNS abnormalities reported [ <u>PMID</u> 2125322], <sup>131</sup> hyperbaric O <sub>2</sub> not contraindicated in pregnancy [ <u>PMID 7772366</u> ] <sup>132</sup> Animal studies have shown immunological [ <u>PMID</u> <u>8115310</u> ] <sup>133</sup> and neurobehavioral [ <u>PMID</u> <u>7786165</u> ] <sup>134</sup> [ <u>PMID 8711066</u> ] <sup>135</sup> effects
Chlordecone	143-50-0	09/30/94	Male: Oligospermia, decreased sperm motility, but no loss of fertility [ATSDR] <sup>136</sup>
Cigarette smoke			(See <u>Tobacco smoke -</u> environmental)
Ciguatoxin			Category X [Briggs 4th] <sup>137</sup> (a case report of fetal agitation with neonatal facial palsy and meconium aspiration after preterm maternal ciguatoxin poisoning noted [ <u>PMID</u> <u>7070322</u> ]) <sup>138</sup> Breastfeeding: Excreted in breast milk [Briggs 4th], <sup>139</sup> [Bagnis], <sup>140</sup> although not consistently reported [ <u>PMID 19325530</u> ] <sup>141</sup>
Cycloheximide	66-81-9	09/30/94	Human studies lacking, but cycloheximide is a known protein synthesis (meiosis) inhibitor [ <u>PMID 9592729</u> ]; <sup>142</sup> developmental defects in rats and mice, but not in rabbits [Schardein] <sup>143</sup>
2,4-D	94-75-7		(See <u>2,4-Dichlorophenoxy acetic</u> <u>acid</u> )
DBCP (1,2-dibromo-3- chloropropane)	96-12-8		Male: Toxicity [ <u>EPA</u> ] <sup>144</sup> (lowered number of sperm [ <u>NIOSH</u> ]) <sup>145</sup>

Agent	CAS Number	Date Added	Notes
DDT (p,p'-	50-29-3		Pregnancy: Possible association
Dichlorodiphenyl-			with spontaneous abortion,
trichloroethane)			toxemia, and low birth weight
			[Schardein]. <sup>146</sup>
			Developmental: Little teratogenic
			potential [Schardein]. <sup>147</sup>
			However, there is concern about
			cumulative (over several
			generations) reproductive
			toxicity, due to bio-
			accumulation and widespread
			environmental exposure
			[ <u>EPA</u> ]. <sup>148</sup>
			Breastfeeding: Excreted in human
			milk [ <u>PMID 2551196</u> ], <sup>149</sup> no
			reported effects [ <u>AAP</u> ] <sup>150</sup>
DEHP			(See <u>di(2-ethylhexyl) Phthalate</u> )
1,2-Dibromo-3-	96-12-8		(See <u>DBCP</u> )
chloropropane			
1,2-Dibromoethane	106-93-4	12/06/2017	Male: changes in sperm velocity
			and count, decreased sperm
			concentration and semen
			volume [ATSDR] <sup>151</sup>
2,4-Dichlorophenoxy	94-75-7	06/27/00	Male: Abnormal sperm shape,
acetic acid			altered sperm transport
			[NIOSH] <sup>152</sup>
			Pregnancy: Associated with
			spontaneous abortion and
			premature birth [Schardein] <sup>153</sup>
			Developmental: One report of
			multiple congenital anomalies
			[Schardein], <sup>154</sup> teratogenic in
			several animal species
			[Schardein] <sup>155</sup>

Agent	CAS Number	Date Added	Notes
di(2-ethylhexyl) Phthalate (DEHP)	117-81-7	07/26/00	Developmental: "Concern" about developing male reproductive
Philialate (DEHP)			tract <sup>156</sup> Mice exposure to DEHP
			at doses relevant to human
			exposure during sex
			determination significantly
			affected ovarian function in
			female adult offspring and
			carried through subsequent
			generations. <sup>157</sup>
			Pregnancy: Associated with pre-
			term birth [ <u>PMID24247736</u> ] <sup>158</sup>
Dimethylaminopropionitr	1738-25-6	02/12/2007	Male: Impotence, decreased libido
ile (DMAPN)			[PMID 6243374, <sup>159</sup> PMID
			<u>7330630</u> ] <sup>160</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]
2,4-Dinitrotoluene	121-14-2	03/10/00	Male: Lowered number of sperm
			[ <u>NIOSH</u> ] <sup>161</sup>
2,6-Dinitrotoluene	606-20-2		(See <u>2,4-Dinitrotoluene</u> )

Agent	CAS Number	Date Added	Notes
Dioxin	1746-01-6		(A group of dibeno-p-dioxins containing from 1 to 8 chlorine
			atoms of which the 2,3,7,8-
			isomer is the most toxic. See
			TCDD or specific compound)
Disodium cyanodithio- midocarbonate (DCDIC)	138-93-2	03/10/00	Developmental: Both maternal and fetal effects in rabbits and rats [ <u>EPA</u> ] <sup>162</sup>
Epichlorohydrin	106-89-8	03/10/00	Male: Impaired fertility, however
			human data do not confirm
			animal data [ <u>PMID 2010350</u> ] <sup>163</sup>
			demonstrating impaired male fertility [ <u>EPA</u> ] <sup>164</sup>
Ethanol	64-17-5		(See <u>Ethanol</u> under Drug Hazards)
2-Ethoxyethanol	110-80-5		(See <u>Ethylene glycol monoethyl</u> <u>ether</u> )
Ethyl alcohol	64-17-5		(See <u>Ethanol</u> under Drug Hazards)
Ethyl carbamate	51-79-6		(See <u>Urethane</u> )
Ethylene dibromide	106-93-4	03/10/00	Male: Reproductive toxicity
			[PMID 2980345] <sup>165</sup> [PMID
			<u>3297130</u> ] <sup>166</sup> (lowered number of
			sperm, abnormal sperm shape,
			altered sperm transport
			[ <u>NIOSH</u> ]) <sup>167</sup>
Ethylene glycol monoethyl ether	110-80-5	09/30/94	Male: Lowered number of sperm [NIOSH] <sup>168</sup>
			Male and female reproductive
			effects in multiple animal
			species [NIOSH] <sup>169</sup>
Ethylene glycol	109-86-4	09/30/94	Male and female reproductive
monomethyl ether			effects in multiple animal
			species [NIOSH] <sup>170</sup>
Ethylene glycol	110-49-6	09/30/94	Developmental: Hypospadias and
monomethyl ether			other male genital abnormalities
acetate			[ <u>PMID 2357456</u> ] <sup>171</sup> [Johanson] <sup>172</sup>
			(See Ethylene glycol monomethyl
			ether-toxicological profile is
			almost identical
			[ <u>PMID 2357456</u> ]) <sup>173</sup>

Agent	CAS Number	Date Added	Notes
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 [NIOSH] <sup>174</sup> Female: spontaneous abortion rates in ethylene oxide sterilizer personnel in hospitals in Finland were found to be significantly higher than those of non- exposed workers. <sup>175</sup> Developmental: Malformations in animals (mice) [Kimmel] <sup>176</sup>
Ethylene thiourea (Ethylenethiourea)	96-45-7	06/30/95	Developmental: Teratogen [NIOSH] <sup>177</sup>
Ethylnitrosourea	759-73-9		Developmental: CNS tumors in rats born to rats exposed in the latter part of gestation [PMID 4321468] <sup>178</sup> [EPA] <sup>179,180,181</sup> Induces congenital anomalies in fetuses and affects placenta when administered to pregnant animals. <sup>182</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>183</sup>
Hexachlorocyclohexane (Lindane <sup>®</sup> )	58-89-9	12/6/17	Increase in serum luteinizing hormone levels in men [ATSDR] <sup>184</sup>

Agent	CAS Number	Date Added	Notes
Hexachlorobenzene	118-74-1	06/30/95	Fetal death due to pembe yara <sup>iii</sup>
			[PMID 7138315] <sup>185</sup>
			Breastfeeding: Possible association
			with porphyria cutanea tarda
			symptoms, reduced growth, and
			arthritic changes in the
			appendages [ <u>EPA</u> ] <sup>186</sup> (excreted
			in human milk)[ <u>PMID</u>
			2590490], <sup>187</sup> skin rash, diarrhea,
			vomiting, dark urine,
			neurotoxicity, death [ <u>AAP</u> ] <sup>188</sup>
Hexamethylphosphorami	680-31-9	06/30/95	Testicular atrophy and aspermia
de			(rats), testicular development
			inhibition (cockerels) [ <u>NIOSH</u> ] <sup>189</sup>
Hexamethylphosphoric triamide	680-31-9		(See <u>Hexamethylphosphoramide</u> )
НМРА	680-31-9		(See <u>Hexamethylphosphoramide</u> )
Iodides			(See <u>lodine</u> )
lodine	7553-56-2		Iodine excess and iodine deficiency
			during pregnancy can have
			adverse effects on the fetal
			thyroid and possibly on brain
			development and hearing.
			Category D [Briggs 4th] <sup>190</sup>
			Breastfeeding: Not compatible
			(concentrated in breast milk,
			and long term use may
			adversely affect the nursing
			infant's thyroid activity) [Briggs
			1997] <sup>191</sup>
Kepone®			(See <u>Chlordecone</u> )

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

CAS Number	Date Added	Notes
7439-92-1	09/30/94	Male: [PMID 6441528] <sup>192</sup> Lowered
		number of sperm, abnormal
		sperm shape, altered sperm
		transport [ <u>NIOSH</u> ] <sup>193</sup>
		Female: Premature membrane
		rupture and preterm births
		[PMID 1257615] <sup>194</sup>
		Developmental [PMID 6716624] <sup>195</sup> .
		Prenatal lead exposure impairs
		children's neurodevelopment,
		placing them at increased risk
		for developmental delay,
		reduced IQ, and behavioral
		problems. <sup>196</sup>
		Breastfeeding: Possible
		neurotoxicity [ <u>AAP</u> ] <sup>197</sup> Not
		recommended if lead level is
		above 40 μg/dL. <sup>198</sup>
		-
Various	09/30/94	Exposure varies with the form of
		the mercury. Elemental
		mercury poses little oral
		exposure route risk (GI
		absorption is <0.01%), its vapors
		are highly toxic. In contrast,
		mercury salts (like that found
		naturally in soils) and organic
		mercury (like that in fish tissues) do not tend to be volatile. Each
		of these has its own relative
		bioavailability through the oral
		route. Their toxicity is largely a result of their oral availability.
		Historically, methyl mercury is
		associated with oral
		CONSUMPTION OF MARCUNV IN
		consumption of mercury in foods (fish and whale meat)
		foods (fish and whale meat).
		foods (fish and whale meat). Breastfeeding: May affect
		foods (fish and whale meat).
		7439-92-1 09/30/94

Agent	CAS Number	Date Added	Notes
Agent Mercury, elemental	CAS Number           7439-97-6	05/31/00	Male: Maternal spontaneous abortions [ATSDR] <sup>201</sup> Female: Reproductive failure [ATSDR] <sup>202</sup> adverse neurological outcomes in children. Mercury found in dental amalgams has not been shown to be associated with adverse outcomes. Developmental: Decreased birth weight [ATSDR] <sup>203</sup> Breastfeeding: May affect neurodevelopment [AAP] <sup>204</sup> Mercury is transferred to the milk from dental amalgams, but the amount that is transferred is small. Infants who are exclusively breastfed by women with mercury amalgam have been found to have low weight gain but did not have adverse neurological outcomes. The advantages of breast-feeding likely outweigh any potential risks in terms of dental amalgam
Mercury, inorganic		03/10/00	mercury. Spontaneous abortion [ATSDR] <sup>205</sup> May lead to an increased risk of stillbirth and fetal growth restriction, but there does not appear to be an increased risk of poor neurological outcomes
Mercury, organic		03/10/00	Developmental (CNS neurological impairment [ATSDR]) <sup>206</sup> microcephaly, cerebral palsy, seizures Breastfeeding: May affect neurodevelopment [ <u>AAP</u> ] <sup>207</sup>
2-Methoxyethanol			(See <u>Ethylene glycol monomethyl</u> <u>ether</u> )
Methyl benzimidazole- carbamate	10605-21-7		(See <u>Carbendazim</u> )

Agent	CAS Number	Date Added	Notes
Methyl Cellosolve			(See Ethylene glycol monomethyl
acetate			<u>ether acetate</u> )
Methylene blue	61-73-4		Category C [Briggs 4th] <sup>208</sup>
			Category D if injected intra-
			amniotically [Briggs 4th] <sup>209</sup>
			(hemolytic anemia, jaundice,
			intestinal atresia with intra-
			amniotic injection [PMID
			<u>9434858]</u> ) <sup>210</sup>
Methyl isocyanate	624-83-9	07/10/00	Pregnancy: Associated with
			spontaneous abortion and
			neonatal deaths [Schardein] <sup>211</sup>
Methyl mercury	22967-92-6	09/30/94	(See also <u>Mercury, organic</u> , and
			Mercury and mercury
			<u>compounds</u> )
			Pregnancy: Microcephaly, cerebral
			palsy, abnormal reflexes [PMID
			<u>9434858</u> ], <sup>212</sup> abnormal
			dentition, neurological deficits
			[Schardein] <sup>213</sup>
			Breastfeeding: May affect
			neurodevelopment [ <u>AAP</u> ] <sup>214</sup>
Methylmethane	66-27-3		Pregnancy: Embryo lethality and
sulfonate			malformations in rats [Nagao] <sup>215</sup>
			[ <u>PMID 2595598</u> ], <sup>216</sup>
			embryotoxicity in mice [PMID
			<u>4349609</u> ] <sup>217</sup>
Methylnitrosourea	684-93-5		Animal data:
			Male: Malformed ribs in offspring
			of exposed males [PMID
			<u>3821763</u> ] <sup>218</sup>
			Developmental: Teratogenic in rats
			(microcephaly [PMID
			8016749]) <sup>219</sup> and mice (in mice it
			was teratogenic and
			embryolethal one-half day
			before implantation [PMID
			<u>2520503</u> ]) <sup>220</sup>
MIC			(See <u>Methyl isocyanate</u> )

Agent	CAS Number	Date Added	Notes
Mirex	2385-85-5		Animal studies only [ATSDR] <sup>221</sup>
			Male: Decreased sperm counts and
			fertility <sup>222</sup>
			Female: Decreased litter size and
			number of offspring <sup>223</sup>
			Developmental: Increased
			resorptions and stillbirths,
			arrhythmias, and other
			anomalies <sup>224</sup> Edema and cardiac
			toxicity in the offspring of rats
			exposed during pregnancy
			Breastfeeding: Appears in human
			milk [ATSDR] <sup>225</sup>
lpha-Naphthyl-N-	63-25-2		(See <u>Carbaryl</u> )
methylcarbamate			
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>226</sup>
o,p'-DDT	789-02-6		(See <u>DDT</u> )
Oryzalin	19044-88-3	06/27/00	Male: One report of spontaneous
			abortion and heart defects born
			to spouses of occupationally
			exposed males [Schardein] <sup>227</sup>
			Based on experimental animal
			studies, oryzalin is not expected
			to increase the risk of congenital
			anomalies under typical
			exposure conditions.

Agent	CAS Number	Date Added	Notes
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 [ <u>PMID 2583071</u> ]) <sup>228</sup>
			Based on experimental animal
			studies, oxydemeton is not
			associated with an increased the
			risk of congenital anomalies
			with normal use. The case
			report of a fetus with multiple
			anomalies but also exposure to
			other agents.
			Animals: Chick embryos [PMID
			8248858], <sup>229</sup> rats [WHO] <sup>230</sup>
p,p'-DDT	50-29-3		(See <u>DDT</u> )
p,p'-Dichlorodiphenyltri-	50-29-3		(See <u>DDT</u> )
chloroethane			
PCBs	1336-36-3		(See <u>Polychlorinated biphenyls</u> )
Perchloroethylene (PCE)	127-18-4	06/27/00	Male: Altered sperm transport
			[ <u>NIOSH</u> ] <sup>231</sup>
			Based on human and animal
			studies, there is no increased
			risk for birth defects. There may
			be an increased risk of
			miscarriage, but only for highly-
			exposed workers in the dry-
			cleaning business.
			Breastfeeding: Obstructive
			jaundice, dark urine [AAP] <sup>232</sup>
Phthalates			Several associated with pre-term
			labor.
			(See <u>di(2-ethylhexyl) Phthalate</u> )

Agent	CAS Number	Date Added	Notes
Polychlorinated	1336-36-3	09/30/94	Yusho Disease/Yu-Cheng Disease
biphenyls (PCBs)			(hyperpigmentation [PMID
			<u>3921364</u> ], <sup>233</sup> low birth weight,
			nail and conjunctival
			abnormalities, neurobehavioral
			deficits, developmental delays
			[PMID 3133768] <sup>234</sup> )[EPA] <sup>235</sup>
			Breastfeeding: Discontinue
			(appears in human milk;
			exposures are higher in nursing
			infants than in utero [ <u>PMID</u>
			2104928], <sup>236</sup> may cause lack of
			endurance, hypotonia, sullen
			expressionless facies [AAP] <sup>237</sup>
			Polychlorinated biphenyls are a
			large group of 209 unique
			biphenyl compounds containing
			1 to 10 chlorine atoms.
			Environmental fate of these
			compounds is dictated by their
			chlorine content. While the
			more chlorinated compounds
			tent to be more toxic, perhaps
			as a result of their greater
			persistence in the body, the
			toxicityof individual compounds
			can vary greatly and include
			both dioxin-like toxicity as well
			as non-dioxin toxicity. Some of
			the more toxic PCB compounds
			with regard to reproductive
			effects have non-dioxin-like
			characteristics.
Sevin®			(See <u>Carbaryl</u> )
TCE			(See <u>Trichloroethylene</u> )

Agent	CAS Number	Date Added	Notes
TCDD	1746-01-6		Male: No known effects [EPA], <sup>238</sup>
			limited/ suggestive evidence of
			an association with spina bifida
			in offspring born to males
			exposed to Agent Orange, which
			also contained other substances
			[IOM] <sup>239</sup> [ <u>IOM 1998]</u>
			Female: Inconclusive [EPA], <sup>240</sup>
			current study results of
			exposures in Seveso, Italy
			pending [ <u>PMID 10739069</u> ] <sup>241</sup>
			There are no human data that
			suggest risk of birth defects.
			There are limited data
			suggesting an increased risk of
			sex selection (females over
			males in Seveso Italy exposed
			individuals) and spina bifida in
			offspring of Vietnam veterans,
			but this is not consistent.
			Animal studies showed an
			increased risk of multiple birth
			defects, some of which (cleft
			palate in mice) may have little
			relevance in humans.
			Breastfeeding: Present in human
			milk [ <u>PMID 9831540</u> ] <sup>242</sup>
Tetrachloroethylene	127-18-4		(See <u>Perchloroethylene</u> )
2,3,7,8-	1746-01-6	09/30/94	(See <u>TCDD</u> )
Tetrachlorodibenzo-p-			
dioxin			

Agent	CAS Number	Date Added	Notes
Tobacco smoke -		06/08/00	Males: Decreased fertility
environmental			(fecundability) [ <u>PMID</u>
(secondary/passive)			9829871] <sup>243</sup>
			Pregnancy/developmental: LBW at
			term, small-for-gestational-age
			[PMID 9987784] <sup>244</sup> [PMID
			9772856], <sup>245</sup> adverse effects on
			IQ in females [Seidman], <sup>246</sup>
			decreased fertility
			(fecundability) in adult females
			[PMID 2705427], <sup>247</sup> specifically
			including those who were
			exposed to tobacco smoke in
			utero and who currently smoke
			(as adults)[ <u>PMID 9829871]<sup>248</sup></u>
			Discontinuing smoking by 15 weeks
			gestation reduces risk [PMID
			19325177] <sup>249</sup>
Toluene	108-88-3	09/30/94	Significant delays in fetal growth
			following chronic and excessive
			industrial accidents or
			intentional abuse [PMID
			<u>9143096]</u> <sup>250</sup>
			Toluene embryopathy has been
			reported (motor and intellectual
			effects) [ <u>PMID 9294310</u> ] <sup>251</sup>
			(developmental delay, CNS
			dysfunction, hydronephrosis,
			ventricular septal defects,
			craniofacial and limb anomalies
			including microcephaly [PMID
			<u>9434858]</u> ) <sup>252</sup>
			Breastfeeding: Toluene is found in
			milk but no adverse
			neurobehavioral outcomes have
			been found in animal data.
			Animal studies also suggest
			developmental toxicity with
			respiratory exposure [ <u>ATSDR</u> ] <sup>253</sup>
Toluenediamine	95-80-7	06/27/00	Male: Lowered number of sperm
			[ <u>NIOSH</u> ] <sup>254</sup>
Toluene-2,4-diamine	95-80-7		(See <u>Toluenediamine</u> )

8094783],256 skeletal abnormalities in several animal species [Schardein]257Trichloroethylene (TCE)79-01-611/30/00Male: impotence (occupational exposure)258Female: amenorrhea, irregular menses (after accidental exposure to high levels)259Female: amenorrhea, irregular menses (after accidental exposure to high levels)259TCE exposure in rats is associated with cardiac defects, which US EPA suggests ocurrs during gestational exposure. Similar cardiac effects are observed for TCE metabolites dichloroacetic acid (DCA) and trichloroacetic acid (TCA).Urethane (ethyl carbamate - NOT "polyurethane")51-79-606/30/95Animal data: Oncogenic in severa mammalian species; crosses th placenta [PMID 3050270],260 genotoxic in mice [Platzek],261 preconception exposure of ma and female mice produced	Agent	CAS Number	Date Added	Notes
Image: Second	Trichlorfon	52-68-6	06/26/00	seminal fluid volume, sperm count, motility, and viability, and increased number of abnormally-shaped sperm [PMID 5932734] <sup>255</sup> Pregnancy: One report possibly associating consumption of contaminated fish with congenital abnormalities [PMID <u>8094783</u> ], <sup>256</sup> skeletal abnormalities in several animal
carbamate - NOT "polyurethane") genotoxic in mice [Platzek], <sup>261</sup> preconception exposure of ma and female mice produced	Trichloroethylene (TCE)	79-01-6	11/30/00	Male: impotence (occupational exposure) <sup>258</sup> Female: amenorrhea, irregular menses (after accidental exposure to high levels) <sup>259</sup> TCE exposure in rats is associated with cardiac defects, which US EPA suggests ocurrs during gestational exposure. Similar cardiac effects are observed for TCE metabolites dichloroacetic acid (DCA) and trichloroacetic
Neoplasms in offspring [PIVIID           10406931] <sup>262</sup> VCM         75-01-4           (See Vinyl chloride)	carbamate - NOT "polyurethane")		06/30/95	genotoxic in mice [Platzek], <sup>261</sup> preconception exposure of male and female mice produced neoplasms in offspring [PMID 10406931] <sup>262</sup>

Agent	CAS Number	Date Added	Notes
Vinyl chloride	75-01-4	03/10/00	This has not been shown to
(monomer—not			consistently be associated with
polyvinyl chloride or			adverse reproductive outcomes.
PVC)			Fetal loss in wives of exposed
			males [ <u>PMID 56545</u> ] <sup>263</sup>
			CNS defects in communities of
			polyvinyl chloride
			polymerization plants [PMID
			<u>1069539</u> ] <sup>264</sup>
			Increased incidence of birth defects
			(not limited to a single organ
			system, association lacking
			substantiation) [PMID
			<u>6879459</u> ] <sup>265</sup>
Xylenes	1330-20-7	03/10/00	Female: Menstrual disorders
			Pregnancy: Possible association
			with spontaneous abortion
			[ATSDR]; <sup>266</sup> "adverse effects"
			with high levels of maternal
			exposure [ATSDR]; <sup>267</sup> xylene has
			known neurological effects, but
			insufficient human data to
			confirm neurological effects
			from in utero exposure
			[ATSDR] <sup>268</sup>

## (VIII) 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, 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>269</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>270</sup> Studies involving the self-reporting of immune system effects associated with the use of DES have been contradictory [PMID 8606329, PMID 9578280].<sup>271,272</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, 273 PMID 4414878), 274 decreased fecundity (PMID 4113412),<sup>275</sup> fetal growth retardation (PMID 63667),<sup>276</sup> and congenital malformations (PMID 4412215).<sup>277</sup> Even spouses of males occupationally exposed to anesthetic gases have had increased rates of malformations (PMID 620176).<sup>278</sup> Dispensing pharmaceuticals (for example, those with ReproDev activity, such as antineoplastics) may result in exposure via inhalation of vaporized medications (PMID 10986478),<sup>279</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>280</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 exposure HCWs to significant ReproDev hazards. Finally, while not unique to HCWs, rotating shifts are often associated with medical work. (Also see the section on Shift Work and Extended Hours of Duty.)

## 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>281</sup>

The 2016 OSHA Technical Manual, <u>Controlling Occupational Exposure to Hazardous Drugs</u>, gives more detailed and current information dealing with occupational hazards of administering pharmaceuticals in general and addresses antineoplastics in particular.<sup>282</sup> These recommendations provide the best guidance available at this time.

## D) DRUG PREGNANCY RISK CATEGORIES

The US Food and Drug Administration began using pregnancy risk categories in 1979 for pharmaceuticals as set forth in the <u>Table 9</u>.<sup>283</sup> In 2015, the FDA replaced the A, B, C, D and X risk categories with text summarizing risk and discussing use related to pregnancy and lactation. While that is generally more useful than simply a category designation, information on specific drugs often continues to refer to category, and narrative text would be unwieldly in this document. Therefore, in many cases the use of those categories is continued here. For further information, the information supplied in the new format by the drug manufacturer should be consulted first.<sup>284</sup>

Category	Description	Interpretation
А	Controlled	Adequate, well-controlled studies in pregnant women have
	human studies	failed to demonstrate a risk to the fetus in any trimester of
	show no risk.	pregnancy.
В	No evidence of	Adequate, well-controlled studies in pregnant women have
	risk in humans.	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 heart is remote, but remains a possibility.
С	Risk cannot be	Adequate, well-controlled human studies are lacking, and
	ruled out.	animal studies have shown a risk to the fetus or are lacking
		is well. There is a chance of fetal harm if the drug is
		administered during pregnancy; but the potential benefits
		may outweigh the potential risk.
D	Positive evidence	Studies in humans, or investigational or post-marketing
	of risk.	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.
x	Contraindicated	Studies in animals or humans, or investigational or post-
	in pregnancy.	marketing reports, have demonstrated positive evidence of
		fetal abnormalities or risk which clearly outweighs any
		possible benefit to the patient.

Table 9 –	ReproDev	Pregnancy	Risk	Category	v Kev <sup>285</sup>

## 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.

Drug/Substance	CAS Number	Date Added	Comments/Notes
1-(2-Chloroethyl)-3- cyclohexyl-1- nitrosourea	13010-47-4	06/30/95	(See <u>Lomustine</u> )
1,25- Dihydrocholecalciferol		10/17/00	(See <u>Calcitriol</u> )
1,4-Butanediol dimethylsulfonate	55-98-1	06/30/95	(See <u>Busulfan</u> )
2-Chloro-2'- deoxyadenosine	4291-63-8		(See <u>Cladribine</u> )

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

Drug/Substance	CAS	Date	Comments/Notes
	Number	Added	
2-Chloroadeoxyadenosine		10/17/00	(See <u>Cladribine</u> )
4-Aminopteroylglutamic	54-62-6		(See <u>Aminopterin</u> )
acid			
5-Fluorouracil	51-21-8		(See <u>Fluorouracil</u> )
5-FU	51-21-8		(See <u>Fluorouracil</u> )
6-Mercaptopurine	50-44-2		(See <u>Mercaptopurine</u> )
8-Methoxypsoralen		10/20/00	(See <u>Methoxsalen</u> )
8-MOP		10/20/00	(See <u>Methoxsalen</u> )
Accupril®			(Quinapril, see <u>ACE Inhibitors</u> )
Accutane®			(See <u>Isotretinoin</u> )
ACE Inhibitors	Captopril		Pregnancy: Not recommended during
	62571-86-2		pregnancy. Use in any trimester
	Enalapril		associated with oligohydramnios
	75847-73-3		resulting fetal lung hypoplasia and
	Lisinopril		skeletal malformations. Use in
	76547-98-3		pregnancy is also associated with
	Benazepril		anuria, hypotension, renal failure,
	86541-75-5		skull hypoplasia, and death in the
	Fosinopril		fetus/neonate [ <u>PMID: 24150027</u> ]. <sup>286</sup>
	98048-97-6		Renin Angiotensin System Blockade
	Quinapril		Fetopathy (also called ACE inhibitor
	85441-61-8		fetopathy), renal, pulmonary,
	Ramipril		cardiac, skeletal, and central
	87333-19-5		nervous system abnormalities,
			characterized by fetal hypotension,
			anuria-oligohydramnios, growth
			restriction, pulmonary hypoplasia,
			renal tubular dysplasia, and
			hypocalvaria [PMID 26130112] <sup>287</sup>
			[PMID 8507813] <sup>288</sup> [PMID
			<u>22753220</u> ]) <sup>289</sup>
			Breastfeeding: Excretion into milk
			negligible, but authors differ as to
			advisability [PMID 9673832] <sup>290</sup>
			[PMID 9520613] <sup>291</sup> Acceptable for
			use in breastfeeding women.
			Monitoring of the nursing child's
			weight for the first 4 weeks is
Acotobydrovamic acid	546-88-3	06/30/95	recommended [PMID: 24150027]. <sup>292</sup>
Acetohydroxamic acid	540-08-5	00/30/93	Category X (may cause fetal harm) <sup>293</sup>
			Breastfeeding: Discontinue <sup>294</sup>

Drug/Substance	CAS Number	Date Added	Comments/Notes
Acetyladriamycin			(See <u>Daunorubicin citrate</u> )
Achromycin®			(See <u>Tetracycline hydrochloride</u> )
Acitretin	55079-83-9	11/20/00	(See <u>Isotretinoin</u> and <u>Etretinate</u>
			[ <u>TERIS</u> ]) <sup>295</sup>
			(Converted to Etretinate in the body
			[ <u>TERIS</u> ]) <sup>296</sup>
Actinomycin D	50-76-0	06/30/95	(See <u>Dactinomycin</u> )
Adderall®			(See <u>Amphetamines</u> )
Adriamycin®			(See <u>Doxorubicin hydrochloride</u> )
Adrucil®			(See <u>Fluorouracil</u> )
Alfenta®		10/16/00	(See <u>Alfentanil</u> )
Alfentanil	71195-58-9		Pregnancy: Adverse events have been
			observed in some animal
			reproduction studies. Use during
			labor and immediately prior to labor
			is not recommended by the
			manufacturer [ <u>PMID: 12100826</u> ]. <sup>297</sup>
			Category C <sup>298</sup> (D if used for prolonged
			periods or in high doses at term
			[Briggs 4th]) <sup>299</sup>
			Breastfeeding: Express and discard
			breast milk once before resuming
			nursing after use <sup>300</sup> Decision to
			continue or discontinue breast-
			feeding during therapy should
			weigh infant risk/benefit. Breast-
			feeding infants should be monitored
			for apnea and sedation[PMID:
			<u>12100826</u> ]. <sup>301</sup>
Alkeran®		10/20/00	(See <u>Melphalan</u> )
All-transretinoic acid		10/20/00	(See <u>Tretinoin</u> )
Alprazolam	28981-97-7	06/30/95	Category D (may cause fetal harm and
			postnatal withdrawal) <sup>302</sup>
			Breastfeeding: See <u>Benzodiazepines</u>
Altace®			(Ramipril)
			(See <u>ACE Inhibitors</u> )
Altretamine	645-05-6	08/20/99	Category D <sup>303</sup>
			Breastfeeding: Discontinue [Facts and
			Comparisons] <sup>304,305</sup>
Amethopterin®		10/20/00	(See <u>Methotrexate</u> )
Amikacin	39831-55-5		(See <u>Aminoglycosides</u> )

Drug/Substance	CAS Number	Date Added	Comments/Notes
Amikin®			(Amikacin)
			(See <u>Aminoglycosides</u> )
4-Aminopteroylglutamic acid	54-62-6		(See <u>Aminopterin</u> )
Aminoglutethimide	125-84-8	06/30/95	Category D [USPDI] <sup>306</sup> [Schardein] <sup>307</sup> (can cause fetal harm [Facts and Comparisons]) <sup>308</sup> Breastfeeding: Discontinue [Facts and Comparisons] <sup>309</sup>
Aminoglycosides	Amikacin 39831-55-5 Gentamicin 1403-66-3 Kanamycin 8063-07-8 Streptomyc in 57-92-1 Tobramycin 32986-56-4	06/30/95	Category D (can cause fetal harm) <sup>310</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>311</sup> However, kanamycin causes deafness in fetal sheep [PMID 12297800]. <sup>312</sup> Breastfeeding: Compatible [Briggs 1997] <sup>313</sup> (excreted in milk but are poorly absorbed and problems in nursing infants have not been documented [USPDI]) <sup>314</sup>
Aminopterin	54-62-6	09/30/94	Category X [Schardein] <sup>315</sup> (abortifacient [ <u>PMID 507011</u> ], <sup>316</sup> aminopterin embryopathy [ <u>PMID 10413333</u> ] <sup>317</sup> /syndrome [ <u>PMID 675555</u> ] <sup>318</sup> ) Note: Currently used as a rodenticide.
Amiodarone	1951-25-3	06/23/00	(See Amiodarone hydrochloride)
Amiodarone hydrochloride	19774-82-4	03/06/00	Pregnancy: May cause fetal harm when administered to a pregnant woman. Oral or IV amiodarone should be used in pregnant women only to treat arrhythmias refractory to other treatments or when other treatments are contraindicated [PMID: 21873418]. <sup>319</sup> Breastfeeding: Discontinue <sup>320</sup>

Drug/Substance	CAS Number	Date Added	Comments/Notes
Amitryptyline	549-18-8		Category D [Briggs 4th] <sup>321</sup> Category C <sup>322</sup> Breastfeeding: Discontinue (excreted in milk) <sup>323</sup>
Amobarbital		10/17/00	(See <u>Barbiturates</u> )
Amphetamines (amphetamine, dextroamphetamine, methamphetamine)			Category C [Briggs 4th] <sup>324</sup> (illicit use is associated with IUGR, preterm labor [ <u>PMID 2240103</u> ], <sup>325</sup> and fetal cerebrovascular accidents, withdrawal in infants born to amphetamine addicted mothers [Briggs 6 <sup>th</sup> ]) <sup>326</sup> Breastfeeding: Contraindicated [Briggs 1997] <sup>327</sup> (irritability, poor sleeping pattern [ <u>AAP</u> ]), <sup>328</sup> discontinue (excreted in breast milk) [Facts and Comparisons] <sup>329</sup> (concentrated in breast milk) [Briggs 6 <sup>th</sup> ] <sup>330</sup>
Amytal®		10/17/00	(See <u>Barbiturates</u> ) (Amobarbital)
Anabolic steroids (nandrolone, oxandrolone, oxymetholone, stanozolol)		03/10/00	Category X [Facts and Comparisons] <sup>331</sup> Breastfeeding: Discontinue [Facts and Comparisons] <sup>332</sup>
, Anacufen <sup>®</sup>		10/20/00	(See <u>Methandriol</u> )
Anadrol <sup>®</sup> -50			(See Oxymetholone)
Andro LA 200 <sup>®</sup>		10/17/00	(See <u>Testosterone enanthate</u> )
Androderm®			(See <u>Testosterone</u> )
Androgens (testosterone, methyltestosterone, fluoxymesterone)			Pregnancy: Contraindicated [Schardein], <sup>333</sup> masculinization (pseudohermaphroditism [Schardein], <sup>334</sup> virilization of female fetuses [Schardein]) <sup>335</sup>
Android <sup>®</sup> -10 & 25		10/17/00	(See <u>Methyltestosterone</u> )
Android-F <sup>®</sup>		-	(See <u>Fluoxymesterone</u> )
Andropository-200®		10/17/00	(See <u>Testosterone enanthate</u> )
Anesthetic gases		03/10/00	Female: Reduced fertility <sup>336</sup> Pregnancy: Spontaneous abortion, IUGR <sup>337</sup>

Drug/Substance	CAS	Date	Comments/Notes
	Number	Added	
Angiotensin converting enzyme inhibitors		06/30/95	(See <u>ACE Inhibitors</u> )
Anisindione	117-37-3	06/30/95	Category D [Briggs 4th] <sup>338</sup> (congenital malformations have been reported) [USPDI] <sup>339</sup> Breastfeeding: Monitor nursing infant for evidence of hypoprothrombinemia [USPDI] <sup>340</sup>
Antabuse®		10/20/00	(See <u>Disulfiram</u> )
Antihistamines (brompheniramine, diphenhydramine)			Breastfeeding: Contraindicated <sup>341,342</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>343</sup>
Antineoplastics (cancer		07/27/00	Male: Infertility [DLI] <sup>344</sup>
chemotherapeutic drugs in general)			Female: Infertility [DLI] <sup>345</sup> Pregnancy: Spontaneous abortion, birth defects, growth retardation [DLI] <sup>346</sup>
ARA-C		10/17/00	(See Cytarabine)
Aspirin	50-78-2	06/30/95	Category C dose ≤ 150 mg/day [Briggs 4 <sup>th</sup> , <sup>347</sup> PMID: 27640943] <sup>348</sup> Category D if full-dose aspirin used in 3 <sup>rd</sup> trimester [Briggs 4th] <sup>349</sup> (avoid in the last trimester, especially 1 week prior to and during delivery) <sup>350</sup> Breastfeeding: Avoid (excreted in breast milk), <sup>351</sup> compatible but use with caution (one reported case of metabolic acidosis [AAP] <sup>352</sup> [Briggs 1997] <sup>353</sup>
Atenolol	29122-68-7	03/10/00	Category D (can cause fetal harm) <sup>354</sup> Breastfeeding: Cyanosis, bradycardia [ <u>AAP</u> ] <sup>355</sup> with caution (excreted in human milk, may cause bradycardia in nursing infants) <sup>356</sup>
Ativan®		10/17/00	(See Lorazepam)
Atromid-S <sup>®</sup>		10/17/00	(See <u>Clofibrate</u> )

Drug/Substance	CAS	Date	Comments/Notes
	Number	Added	
Azathioprine	446-86-6		Category D [Briggs 4th] <sup>357</sup> Breastfeeding: Discontinue (drug and its metabolites transmitted in breast milk at low level [Facts and
			Comparisons]) <sup>358</sup>
Bactrim <sup>®</sup>			(See <u>Sulfonamides</u> )
Barbiturates (amobarbital, butalbital, mephobarbital, metharbital, pentobarbital, phenobarbital, secobarbital)		06/30/95	Category D (can cause fetal damage [Briggs 4th]) <sup>359</sup> Breastfeeding: With caution (sedation, infantile spasms after weaning from milk containing phenobarbital, methemoglobinemia [AAP] <sup>360</sup> small amounts excreted in breast milk [Briggs 4th]) <sup>361</sup>
BCNU	154-93-8		(See Carmustine)
Benadryl®		10/17/00	(See Diphenhydramine)
Benazepril	86541-75-5	4/25/00	Pregnancy: Adverse fetal events well documented with exposure in pregnancy. ACE inhibitor use in pregnant women is not recommended [PMID: 24150027]. <sup>362</sup> Category C in 1 <sup>st</sup> trimester, Category D in 2 <sup>nd</sup> and 3 <sup>rd</sup> trimesters [Briggs 6 <sup>th</sup> ] <sup>363</sup> Breastfeeding: See <u>ACE Inhibitors</u> (distributed into breast milk [USPDI]) <sup>364</sup>
Bentyl®		10/17/00	(See <u>Dicyclomine</u> )
Benzodiazepines (alprazolam, chlorazepate, chlordiazepoxide, diazepam, estazolam,flunitrazepa m, flurazepam,halazepam, lorazepam, midazolam, oxazepam, quazepam, temazepam, triazolam)		06/30/95	Category X (as a class [Schardein]), <sup>365</sup> or see specific agents. If used lorazepam preferred. Breastfeeding: Not recommended. Occasional use compatible, use with caution [Briggs 1997], <sup>366</sup> excreted in breast milk [Facts and Comparisons]; <sup>367</sup> since neonates metabolize benzodiazepines more slowly than adults, accumulation of the drug and its metabolites may occur [USPDI] <sup>368</sup>

Drug/Substance	CAS Number	Date Added	Comments/Notes
Benzphetamine hydrochloride	5411-22-3	06/30/95	(See <u>Amphetamines</u> )
Betadine <sup>®</sup>			(See <u>Povidone-iodine</u> )
BiCNU®	154-93-8		(See <u>Carmustine</u> )
Blenoxane®		10/17/00	(See <u>Bleomycin</u> )
Bleomycin	11056-06-7		Category D [Briggs 4th] <sup>369</sup> Breastfeeding: Contraindicated [Briggs 1997] <sup>370</sup>
Bromides (anticonvulsant/sedativ e)			Category D [Briggs 4th] <sup>371</sup> Breastfeeding: Potential absorption and bromide transfer into milk [ <u>AAP</u> ] <sup>372</sup> not recommended [Briggs 4th] <sup>373</sup>
Bromocriptine	25614-03-3		Category C [Briggs 4th] <sup>374</sup> Breastfeeding: With caution (suppresses lactation; may be hazardous to the mother [ <u>AAP</u> ] <sup>375</sup> suppresses lactation [Briggs 1997] <sup>376</sup>
Brompheniramine	86-22-6		Category C [Briggs 4th] <sup>377</sup> Breastfeeding: Contraindicated <sup>378</sup>
Bumetanide			Category D [Briggs 5th] <sup>379</sup> Breastfeeding: Contraindicated [Briggs 5th] <sup>380</sup>
Bumex®		10/17/00	(See <u>Bumetanide</u> )
Busulfan	55-98-1	06/30/95	Category D (may cause fetal harm) <sup>381</sup> Breastfeeding: Discontinue <sup>382</sup>
Butalbital		10/17/00	(See <u>Barbiturates</u> )
1,4-Butanediol dimethylsulfonate	55-98-1	06/30/95	(See <u>Busulfan</u> )
Butazone®	50-33-9	07/10/00	(See <u>Phenylbutazone</u> )
Calcijex <sup>®</sup>		10/17/00	(See <u>Calcitriol</u> )

Drug/Substance	CAS Number	Date Added	Comments/Notes
Calcitriol	32222-06-3	07/10/00	CAT C Adverse effects observed in some animal reproduction studies. Mild hypercalcemia has been reported in a newborns following maternal use of calcitriol during pregnancy [PMID: 20926527]. <sup>383</sup> Category A [Briggs 4th] <sup>384</sup> Category D if recommended dietary allowance (RDA) exceeded [Briggs 4th] <sup>385</sup> [Schardein] <sup>386</sup> Breastfeeding: CAT B [PMID:
			<u>20926527</u> ]. <sup>387</sup>
Capoten®		10/17/00	(See <u>Captopril</u> )
Captopril	62571-86-2	03/06/00	Pregnancy: Not recommended during pregnancy. Use in any trimester associated with oligohydramnios resulting fetal lung hypoplasia and skeletal malformations. Use in pregnancy is also associated with anuria, hypotension, renal failure, skull hypoplasia, and death in the fetus/neonate [PMID: 24150027]. <sup>388</sup> Category C (first trimester) <sup>389</sup> Category D (second trimester) (may cause fetal harm or death) <sup>390</sup> Breastfeeding: Acceptable for use in breastfeeding women. Monitoring of the nursing child's weight for the first 4 weeks is recommended [PMID: 24150027] <sup>391</sup> (excreted in human milk and may cause adverse reactions in nursing infants) <sup>392</sup>
Carbamazepine	298-46-4	03/10/00	Category D (can cause fetal harm) <sup>393</sup> Breastfeeding: Discontinue, <sup>394</sup> compatible [AAP] <sup>395</sup>
Carbatrol®			(See <u>Carbamazepine</u> )

Drug/Substance	CAS Number	Date Added	Comments/Notes
Carbimazole	22232-54-8	Added	Category D [Briggs 6 <sup>th</sup> ] <sup>396</sup> (associated
Carbinazoie	22252-54-0		with scalp abnormalities [PMID
			1885895]) <sup>397</sup>
			Breastfeeding: Compatible, but has
			been associated with goiter [AAP] <sup>398</sup>
			Possible choanal atresia,
			tracheoesophageal fistula and
			clinodactyly [PMID 21807695] <sup>399</sup>
Carboplatin	41575-94-4	09/30/94	Category D (may cause fetal harm) <sup>400</sup>
	41373 54 4	05/50/54	Breastfeeding: Discontinue <sup>401</sup>
Carmustine	154-93-8	06/28/00	Category D <sup>402</sup>
Carmustine	134-33-8	00/28/00	Breastfeeding: Discontinue <sup>403</sup>
CCNU	13010-47-4		(See Lomustine)
Cd A	13010-47-4	10/17/00	(See Cladribine)
CDDP®		10/17/00	(See <u>Cisplatin</u> )
CeeNu®		10/17/00	(See Lomustine)
Cerubidine®		10/17/00	(See Daunorubicin hydrochloride)
Celexa®	59729-33-8	09/28/20	Septal heart defects [PMID
Celexa	59729-55-8	09/28/20	<u>19776103</u> <sup>404</sup>
Chenix®		10/17/00	(See <u>Chenodiol</u> )
Chenodeoxycholic acid	474-25-9	10/1/00	(See <u>Chenodiol</u> )
Chenodiol	474-25-9	06/30/95	Category X [USPDI] <sup>405</sup>
Chlorambucil	305-03-3	09/30/94	Males: Reversible sterility, permanent
		03/00/31	sterility, azoospermia <sup>406</sup>
			Females: Reversible sterility,
			permanent sterility, amenorrhea <sup>407</sup>
			Category D (can cause fetal harm) <sup>408</sup>
			Breastfeeding: Discontinue <sup>409</sup>
Chloramphenicol	56-75-7		Category C [Briggs 4th] <sup>410</sup>
			Not recommended in pregnancy at
			term (neonatal "gray baby" disease
			or "gray syndrome," bone marrow
			suppression) [USPDI] <sup>411</sup>
			Breastfeeding: Use with caution [Briggs
			1997] <sup>412</sup> (excreted in breast milk
			[USPDI]), <sup>413</sup> especially with preterm
			and young infants (<1 month)
			[PMID: 3292101] <sup>414</sup>
Chlorazepate		10/17/00	(See <u>Benzodiazepines</u> )
Chlordiazepoxide	58-25-3	06/30/95	Category D [Briggs 4th] <sup>415</sup>
			Breastfeeding: See <u>Benzodiazepines</u>

Drug/Substance	CAS Number	Date Added	Comments/Notes
Chlordiazepoxide	438-41-5	06/30/95	(See <u>Chlordiazepoxide</u> )
hydrochloride			
2-Chloroadeoxyadenosine		10/17/00	(See <u>Cladribine</u> )
2-Chloro-2'-	4291-63-8		(See <u>Cladribine</u> )
deoxyadenosine			
1-(2-Chloroethyl)-3-	13010-47-4	06/30/95	(See <u>Lomustine</u> )
cyclohexyl-1-			· · · · · · · · · · · · · · · · · · ·
nitrosourea			
Chloromycetin®			(See <u>Chloramphenicol</u> )
Chlorothiazide	58-94-6	04/25/00	Pregnancy: Use may cause may cause fetal or neonatal jaundice, thrombocytopenia, or other adverse events observed in adults. Women who required thiazide diuretics for the treatment of hypertension prior to pregnancy may continue their use [PMID: 24150027]. <sup>416</sup> Category D [Briggs 4 <sup>th</sup> ] <sup>417</sup> Breastfeeding: Discontinue <sup>418</sup> (excreted in breast milk in low concentrations [Briggs 4th]), <sup>419</sup> has potential to decrease milk volume and suppress lactation[PMID: 24150027] <sup>420</sup>
Chlorotrianisene	569-57-3		Category X [USPDI] <sup>421</sup> Breastfeeding: Not recommended (distributed into breast milk) [USPDI] <sup>422</sup>
Chlorpropamide	94-20-2		Pregnancy: Category C: If chlorpropamide is used during pregnancy, it should be discontinued at least 1 month before the expected delivery date [PubMed 15738045, <sup>423</sup> PubMed 23969827] <sup>424</sup> Breastfeeding: Not recommended (excreted in human milk) <sup>425</sup> Discontinue [PubMed 15738045, <sup>426</sup> PubMed 23969827]. <sup>427</sup>

Drug/Substance	CAS	Date	Comments/Notes
	Number	Added	
Chlortetracycline	57-62-5		<ul> <li>Pregnancy: Available only for ophthalmic use, in which problems in humans have not been documented [USPDI]<sup>428</sup></li> <li>Breastfeeding: Available only for ophthalmic use, in which problems in humans have not been documented [USPDI]<sup>429</sup></li> <li>(See <u>Tetracycline hydrochloride</u> for consideration of other exposures)</li> </ul>
Cholecalciferol	67-97-0	07/10/00	Category A [Briggs 4th] <sup>430</sup> Category D if RDA exceeded [Briggs 4th] <sup>431</sup> [Schardein] <sup>432</sup>
Cidofovir	149394-66- 1	03/10/00	<ul> <li>Males: Inhibition of spermatogenesis in rats and monkeys<sup>433</sup></li> <li>Category C<sup>434</sup> Possibly carcinogenic and teratogenic based on animal data. May cause hypospermia. Women of childbearing potential should use effective contraception during therapy and for 1 month following treatment. Males should use a barrier contraceptive during therapy and for 3 months following treatment.<sup>435</sup></li> <li>Breastfeeding: Should not be administered to nursing mothers<sup>436</sup></li> </ul>
Cinobac®		10/17/00	(See Cinoxacin)
Cinoxacin	28657-80-9		Category C (crosses the placenta) [USPDI] <sup>437</sup> Breastfeeding: Not recommended (unknown if excreted in milk, but has caused arthropathy in immature animals) [USPDI] <sup>438</sup>
Cipro®			(See <u>Ciprofloxacin</u> )
Ciprofloxacin	85721-33-1		Pregnancy: Category C <sup>439</sup> Breastfeeding: Discontinue (excreted in human milk) <sup>440</sup> (do not resume breastfeeding before 48 hours after last dose [Briggs 4th]) <sup>441</sup> (See also <u>Fluoroquinolones</u> )

Drug/Substance	CAS Number	Date Added	Comments/Notes
Ciaplatia	-	Added	Catagory D (and any fatal have) <sup>442</sup>
Cisplatin	15663-27-1		Category D (can cause fetal harm) <sup>442</sup>
			May cause fetal ototoxicity [PMID
			<u>25004323</u> ] <sup>443</sup>
			Breastfeeding: Controversy exists—
			Do not breastfeed (found in human milk), <sup>444</sup>
			Compatible (not found in milk) [AAP] <sup>445</sup>
Citalopram	59729-33-8	09/28/20	Category C: Risk of cardiovascular
		09	defects, Serotonin syndrome and
			Persistent pulmonary hypertension
			of the newborn (PPHN) reported
			with SSRI exposure [PMID:
			18378767] <sup>446</sup> Septal heart defects
			[PMID 19776103] <sup>447</sup>
			Breastfeeding: Exercise Caution, can
			cause sedation [PMID: 18378767] <sup>448</sup>
Cladribine	4291-63-8	03/10/00	Category D <sup>449</sup>
			Breastfeeding: Discontinue <sup>450</sup>
Clinoril®			(See <u>Sulindac</u> )
Clofibrate		06/28/00	Category C [Briggs 4th] <sup>451</sup>
			Breastfeeding: Contraindicated [Briggs 1997] <sup>452</sup>
Clomid®			(See <u>Clomiphene</u> )
Clomiphene	911-45-5		Category X <sup>453</sup>
F			Breastfeeding: Exercise caution <sup>454</sup>
Clomocycline	1181-54-0		Category D [Briggs 4th] <sup>455</sup> (case report
			of multiple fetal abnormalities and
			neonatal death exists [PMID
			143981]) <sup>456</sup>
			Breastfeeding: See <u>Tetracycline</u>
			hydrochloride
Clorazepate dipotassium	57109-90-7	06/30/95	Pregnancy: Use during pregnancy
			should almost always be avoided <sup>457</sup>
			Breastfeeding: See <u>Benzodiazepines</u>

Drug/Substance	CAS	Date	Comments/Notes
Casaina	Number	Added	
Cocaine	50-36-2	06/30/95	Category C [Briggs 4th] <sup>458</sup>
			Category X if nonmedicinal use [Briggs
			4th] <sup>459</sup> (associated with fetal
			malformations, placental toxicity
			[PMID 9434858]) <sup>460</sup>
			Breastfeeding: Contraindicated (may
			cause cocaine intoxication:
			irritability, vomiting, diarrhea,
Calabiai a	64.06.0	00/20/05	tremulousness, seizures) [ <u>AAP</u> ] <sup>461</sup>
Colchicine	64-86-8	06/30/95	Category D [Briggs 4th] <sup>462</sup>
			Breastfeeding: Compatible [AAP] <sup>463</sup>
Conjugated estrogens	12126-59-9		Category X [Facts and Comparisons] <sup>464</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>465</sup>
Copper <sup>64</sup> (64Cu)	13981-25-4		Breastfeeding: Discontinue temporarily
			(radioactivity in milk present at 50
			hours) [ <u>AAP</u> ] <sup>466</sup>
Cordarone®			(See <u>Amiodarone hydrochloride</u> )
Cortisone	53-06-5	07/10/00	Category C: Should be avoided in
			pregnancy, especially in first
			trimester or in high doses[PMID:
			<u>20977425</u> ] <sup>467</sup>
			Breastfeeding: Appears in breast milk
			[Facts and Comparisons <sup>468</sup> PMID:
			<u>20977425</u> ] <sup>469</sup>
Cosmegen®			(See <u>Dactinomycin</u> )
Coumadin®			(See <u>Warfarin</u> )
Cuprimine®			(See <u>Penicillamine</u> )
Cyclophosphamide	50-18-0		Category D [Briggs 6 <sup>th</sup> ] <sup>470</sup> [USPDI] <sup>471</sup>
			Breastfeeding: Contraindicated [Briggs
			1997], <sup>472</sup> (possible immune
			suppression, association with
			carcinogenesis, neutropenia
			[AAP] <sup>473</sup> not recommended
			(distributed into breast milk)
			[USPDI] <sup>474</sup>

Drug/Substance	CAS	Date	Comments/Notes
	Number	Added	
Cyclosporin	79217-60-0		Category C (crosses the placenta,
			associated with preterm births and
			low birth weight) [USPDI] <sup>475</sup>
			Breastfeeding: Contraindicated [Briggs
			1997] <sup>476</sup> (possible immune
			suppression [ <u>AAP</u> ] <sup>477</sup> compatibility
			with breastfeeding not established
			[ <u>PMID 7847911</u> ], <sup>478</sup> not
			recommended (distributed into
			breast milk) [USPDI] <sup>479</sup>
Cyclosporine	79217-60-0		(See <u>Cyclosporin</u> )
Cyproterone acetate	427-51-0		Contraindicated <sup>480</sup> [Jahn] <sup>481</sup>
			Breastfeeding: Contraindicated
			(transferred into breast milk) <sup>482</sup>
Cytadren®			(See <u>Aminoglutethimide</u> )
Cytarabine	147-94-4	09/30/94	Category D (can cause fetal harm) <sup>483</sup>
			Breastfeeding: Discontinue <sup>484</sup>
Cytosar-U <sup>®</sup>			(See <u>Cytarabine</u> )
Cytosine arabinosine		10/17/00	(See <u>Cytarabine</u> )
Cytotec <sup>®</sup>			(See <u>Misoprostol</u> )
Cytovene®			(See <u>Ganciclovir</u> )
Cytoxan®			(See <u>Cyclophosphamide</u> )
D.H.E.®		10/20/00	(See <u>Dihydroergotamine mesylate</u> )
Dacarbazine	4342-03-4	06/28/00	Category C [Briggs 4th] <sup>485</sup>
			Breastfeeding: Contraindicated [Briggs 1997] <sup>486</sup>
Dactinomycin	50-76-0	06/30/95	Category C (can cause malformations
			and embryotoxicity in animals) <sup>487</sup>
			Breastfeeding: Discontinue <sup>488</sup>
Dalmane®		10/17/00	(See <u>Flurazepam</u> )
Danacrine®			(See <u>Danazol</u> )
Danazol	1723-88-5	06/30/95	Category X (contraindicated, may
			result in androgenic effects on the
			female fetus) <sup>489</sup>
			Breastfeeding: Contraindicated <sup>490</sup>
Daraprim®			(See <u>Pyrimethamine</u> )
Daunorubicin	20830-81-3		(See <u>Daunorubicin citrate</u> )
Daunorubicin citrate	20830-81-3	05/04/00	Category D (can cause fetal harm) <sup>491</sup>
Daunorubicin	23541-50-6	09/30/94	Category D (may cause fetal harm) <sup>492</sup>
hydrochloride			Breastfeeding: Discontinue <sup>493</sup>
DaunoXome®	20830-81-3		(See <u>Daunorubicin citrate</u> )

Drug/Substance	CAS	Date	Comments/Notes
	Number	Added	
Declomycin®			(See <u>Demeclocycline hydrochloride</u> )
Delatestryl®			(See <u>Testosterone enanthate</u> )
Delta-D®		10/17/00	(See <u>Cholecalciferol</u> )
Demeclocycline	64-73-3	06/30/95	Category D [Briggs 4th] <sup>494</sup>
hydrochloride (internal			Breastfeeding: See <u>Tetracycline</u>
use)			<u>hydrochloride</u>
Depacon®			(See <u>Valproate sodium</u> )
Depakene®			(See <u>Valproic acid</u> )
Depakote®		10/20/00	(See <u>Valproate sodium</u> )
Depandro <sup>®</sup>		10/17/00	(See <u>Testosterone cypionate</u> )
Depen®			(See <u>Penicillamine</u> )
Depotest <sup>®</sup>		10/17/00	(See Testosterone cypionate)
Depo-testosterone <sup>®</sup>		10/17/00	(See Testosterone cypionate)
DES	56-53-1		(See Diethylstilbestrol)
Desoxyn <sup>®</sup>			(Methamphetamine)
·			(See <u>Amphetamines</u> )
Diabinese®			(See <u>Chlorpropamide</u> )
Diacetylmorphine	561-27-3		(See <u>Heroin</u> )
Diazepam	439-14-5	06/30/95	Category D [Briggs 4th] <sup>495</sup> If
·			Benzodiazepines used lorazepam
			preferred [PMID: 11773648] <sup>496</sup>
			Breastfeeding: May be of concern
			[AAP] <sup>497</sup> not recommended [PMID:
			<u>11773648</u> ] <sup>498</sup> (excreted in breast
			milk and may accumulate in breast-
			fed infants) [Briggs 4th] <sup>499</sup>
Diazoxide	364-98-7	February	Category C pulmonary hypertension
		27,	[FDA] <sup>500</sup>
		2001	Breastfeeding: Contraindicated [Briggs
			1997] <sup>501</sup>
			Neonatal hyperglycemia [Briggs
			1997] <sup>502</sup>
Dicumarol	66-76-2	06/30/95	Category D [Briggs 6 <sup>th</sup> ] <sup>503</sup>
			Breastfeeding: Compatible [AAP] <sup>504</sup>
Dicyclomine	67-92-5		Category B <sup>505</sup>
			Breastfeeding: Contraindicated
			(excreted in human milk) <sup>506</sup>
Dicycloverine	67-92-5		(See <u>Dicyclomine</u> )
hydrochloride			
Didrex®		10/17/00	(See <u>Amphetamines</u> )
			(Benzphetamine hydrochloride)

Drug/Substance	CAS Number	Date Added	Comments/Notes
Dienestrol	84-17-3		Category X <sup>507</sup>
			Breastfeeding: With caution <sup>508</sup>
Diethyldithiocarbamate	148-18-5	07/26/00	No data, but is metabolized to
			disulfiram (See <u>Disulfiram</u> )
Diethylstilbestrol (DES)	56-53-1	06/30/95	Category X [USPDI] <sup>509</sup> (see
			Introduction to this section, above)
			Breastfeeding: Compatible [Briggs
			1997] <sup>510</sup>
Diflucan®		09/27/00	(See <u>Fluconazole</u> )
Diflunisal	22494-42-4	07/05/00	Category C [Briggs 4th] <sup>511</sup> Should be avoided in pregnancy, especially during 1st and 3rd trimester [ <u>PMID:</u> <u>24663106</u> ] <sup>512</sup>
			Category D if used in the 3 <sup>rd</sup> trimester [Briggs 4th] <sup>513</sup>
			Breastfeeding: Discontinue (excreted
			in breast milk in concentrations 2%-
			7% of those in plasma) <sup>514</sup> Not
			recommended [ <u>PMID: 24663106</u> ] <sup>515</sup>
1,25-		10/17/00	(See <u>Calcitriol</u> )
Dihydrocholecalciferol			
Dihydroergotamine	6190-39-2	03/10/00	Category X <sup>516</sup>
mesylate			Breastfeeding: Contraindicated <sup>517</sup>
Dilantin®			(See <u>Diphenylhydantoin</u> )
Diltiazem hydrochloride	33286-22-5	10/28/03	Category C (excreted in breast milk in
(CARDIZEM <sup>®</sup> )			concentrations approximating
			maternal serum levels) <sup>518</sup> Should be
			avoided in pregnancy. Women with
			heart disease who are controlled
			with diltiazem prior to pregnancy
			may continue therapy [PMID:
			<u>22068434</u> ]. <sup>519</sup>
			Breastfeeding: Not recommended
Dimatana®			[PMID: 22068434]. <sup>520</sup>
Dimetane <sup>®</sup>		10/17/00	(See Brompheniramine)
Dimetapp <sup>®</sup>		10/17/00	(See <u>Brompheniramine</u> )
Dindevan <sup>®</sup>		10/20/00	(See <u>Phenindione</u> )

Drug/Substance	CAS	Date	Comments/Notes
	Number	Added	
Diphenhydramine	58-73-1		Pregnancy: Category B - May be used
			for the treatment of allergic
			conditions in pregnant women
			when a first generation
			antihistamine is indicated [PMID:
			<u>23914886</u> ] <sup>521</sup>
			Breastfeeding:Avoid. Second
			generation antihistamines preferred
			[PMID: 23914886] <sup>522</sup>
			(See also <u>Antihistamines</u> )
Diphenylhydantoin	57-41-0	06/30/95	(See <u>Phenytoin</u> )
Disulfiram	97-77-8	07/10/00	Controversy exists as to category—
			Category X [Schardein] <sup>523</sup>
			Category C (noted reports of
			malformations but unknown
			relationship to disulfiram; noted
			embryotoxicity) [Briggs 4th] <sup>524</sup>
Diuril®		10/17/00	(See <u>Chlorothiazide</u> )
dl-Penicillamine	52-66-4		(See <u>Penicillamine</u> )
Dolobid®		10/20/00	(See <u>Diflunisal</u> )
Doral <sup>®</sup>		10/20/00	(See <u>Quazepam</u> )
Doxorubicin	23214-92-8		(See <u>Doxorubicin hydrochloride</u> )
Doxorubicin hydrochloride	25316-40-9		Category D <sup>525</sup> [Briggs 4th] <sup>526</sup>
			Breastfeeding: Contraindicated
			(concentrated in human milk,
			possible immune suppression
			[AAP] <sup>527</sup> avoid <sup>528</sup>
Doxycycline	564-25-0	06/30/95	Category D Should be avoided during
			pregnancy [PMID: 20814687] <sup>529</sup>
			Breastfeeding: Excreted in human milk.
			Not recommended, <sup>530</sup> [ <u>PMID:</u>
			<u>20814687</u> ]. <sup>531</sup>
Drisdol®			(See <u>Ergocalciferol</u> )
Durabolin®		10/17/00	(See <u>Anabolic steroids</u> )
			(Nandrolone)
Duratest <sup>®</sup>		10/17/00	(See <u>Testosterone cypionate</u> )
Durathate-200 <sup>®</sup>		10/17/00	(See <u>Testosterone enanthate</u> )
Ecstasy			(See <u>MDMA</u> )
Elavil®		10/17/00	(See <u>Amitryptyline</u> )

Drug/Substance	CAS	Date	Comments/Notes
	Number	Added	
Enalapril	75847-73-3		Pregnancy: Not recommended during
			pregnancy. Use in any trimester
			associated with oligohydramnios
			resulting fetal lung hypoplasia and
			skeletal malformations. Use in
			pregnancy is also associated with
			anuria, hypotension, renal failure,
			skull hypoplasia, and death in the
			fetus/neonate [PMID: 24150027].532
			Breastfeeding: Acceptable for use in
			breastfeeding women. Monitoring
			of the nursing child's weight for the
			first 4 weeks is
			recommended.[PMID: 24150027].533
			Excreted in human milk. <sup>534</sup>
Endoxan®			(See <u>Cyclophosphamide</u> )
Enovid®		10/20/00	(See <u>Norethynodrel</u> )
Enoxacin		10/20/00	(See <u>Fluoroquinolones</u> )
Equanil®		10/20/00	(See <u>Meprobamate</u> )
Ergocalciferol	50-14-6	07/10/00	Pregnancy: Category C - current
			guidelines recommend a total of
			1000 to 2000 units/day until more
			safety data is available. In women
			not at risk for deficiency, doses
			larger than the RDA should be
			avoided during pregnancy [PMID:
			<u>21691184</u> ]. <sup>535</sup>
			Category D in doses above the RDA
			[Briggs 4th] <sup>536</sup>
			Breastfeeding: Can be detected in
			breast milk. Recommend caution
			be used if administered to nursing
			women. Hypercalcemia has been
			noted in a breast-feeding infant
			following maternal use of large
			amounts of vitamin D; calcium
			serum concentrations should be
			monitored in nursing infants
			exposed to large doses [PMID:
			<u>21691184</u> ]. <sup>537</sup>
Ergostat®		10/20/00	(See <u>Ergotamine tartrate</u> )

Drug/Substance	CAS Number	Date Added	Comments/Notes
Ergotamine	113-15-5	06/30/95	Category X <sup>538</sup> [Briggs 6 <sup>th</sup> ] <sup>539</sup>
			Breastfeeding: Contraindicated [Briggs
			1997], <sup>540</sup> should not be given
			(vomiting, diarrhea, convulsions at
			doses used in migraine medications
			[ <u>AAP</u> ] <sup>541</sup>
Ergotamine tartrate	379-79-3		(See <u>Ergotamine</u> )
Erismodegib			(See <u>Sonidegib</u> )
Esidrix®		10/20/00	(See <u>Hydrochlorothiazide</u> )
Eskalith®			(See <u>Lithium carbonate</u> )
Estazolam	29975-16-4		Pregnancy: Category D. If
			Benzodiazepines used lorazepam
			preferred [PMID: 11773648].542
			Breastfeeding: Not recommended
			[ <u>PMID: 11773648</u> ]. <sup>543</sup> See
			Benzodiazepines (human studies
			lacking, but appears in animal
			breast milk [USPDI]) <sup>544</sup>
Estinyl®		10/20/00	(See <u>Ethinyl estradiol</u> )
Estrace <sup>®</sup>		10/20/00	(See <u>Estradiol</u> )
Estradiol	50-28-2		Category X <sup>545</sup>
			Breastfeeding: Decreased quantity and
			quality of milk, <sup>546</sup> but compatible
			[Briggs 1997] <sup>547</sup>
Estrogens			Category X [Briggs 4th] <sup>548</sup>
			Breastfeeding: Compatible [Briggs
			1997] <sup>549</sup>
Estropipate	7280-37-7	03/10/00	Category X <sup>550</sup>
			Breastfeeding: Decreased quantity and
			quality of milk <sup>551</sup>

Drug/Substance	CAS	Date	Comments/Notes
	Number	Added	
Ethanol	64-17-5		Category D [Briggs 6 <sup>th</sup> ] <sup>552</sup>
			Category X (when used in large
			amounts or for prolonged periods
			[Briggs 4th]) <sup>553</sup> (developmental
			defects, which may include the fetal
			alcohol syndrome [PMID
			<u>9434858</u> ], <sup>554</sup> low birth weight,
			spontaneous abortion, growth
			retardation, congenital anomalies
			[Schardein], <sup>555</sup> placental toxicity
			[PMID 1621875]) <sup>556</sup> Alcohol is a
			teratogen with the potential to
			cause deleterious effects at all
			stages of gestation and at any level
			of consumption. The most severe
			consequences of prenatal alcohol
			exposure are stillbirth and fetal
			alcohol spectrum disorder (FASD),
			which encompasses the physical,
			mental, behavioral, and cognitive
			effects associated with in utero
			alcohol exposure [PMID:
			<u>28586842</u> ]. <sup>557</sup>
			Breastfeeding: Not Recommended
			[PMID: 28586842]. <sup>558</sup>
Ethinyl estradiol	57-63-6		Category X <sup>559</sup>
			Breastfeeding: Excreted in milk;
			decreased quantity and quality of
			milk, <sup>560</sup> but compatible [Briggs
			1997] <sup>561</sup>
Ethisterone	434-03-7	07/10/00	Category D [Briggs 4th] <sup>562</sup> (case reports
			of female masculinization
			[Schardein]) <sup>563</sup>
			Breastfeeding: See Oral contraceptives
Ethyl biscoumacetate	548-00-5	06/29/00	Category D [Briggs 4th] <sup>564</sup>
			Breastfeeding: Avoid (possible adverse
			effects on nursing infants [Briggs
			4th]) <sup>565</sup>
Ethynodiol diacetate	297-76-7	07/10/00	Category D [Briggs 4th] <sup>566</sup>
			Breastfeeding: See Oral contraceptives

Drug/Substance	CAS Number	Date Added	Comments/Notes
Etodolac	41340-25-4	03/10/00	Category C <sup>567</sup>
			Possible closure of ductus arteriosus-
			avoid during late pregnancy <sup>568</sup>
Etoposide	33419-42-0	09/30/94	Category D <sup>569</sup>
			Breastfeeding: Avoid, 570
			contraindicated [Briggs 1997] <sup>571</sup>
Etretinate	54350-48-0	06/30/95	Category X [Briggs 4th] <sup>572</sup> (small
			amounts detected more than 2
			years after treatment concluded
			[Facts and Comparisons]) <sup>573</sup>
			Breastfeeding: Not recommended
			[USPDI] <sup>574</sup>
Eulexin®		10/20/00	(See <u>Flutamide</u> )
Everone 200 <sup>®</sup>		10/17/00	(See <u>Testosterone enanthate</u> )
Famciclovir	104227-87-	06/28/00	Category B [Facts and Comparisons] <sup>575</sup>
	4		Breastfeeding: Not recommended
			[Briggs 1997] <sup>576</sup>
Famvir®		10/20/00	(See Famciclovir)
Fertinex®			(See <u>Urofollitropin</u> )
Finasteride	98319-26-7	06/02/00	Category X [Facts and Comparisons] <sup>577</sup>
			(risk to male fetus); <sup>578</sup> women
			should not handle crushed or
			broken tablets when pregnant or
			may potentially be pregnant <sup>579</sup>
			Breastfeeding: Not indicated for use in
			women <sup>580</sup> (not known if excreted in
			breast milk [Facts and Compari-
			sons]) <sup>581</sup>
Flagyl®			(See Metronidazole)
Floxin <sup>®</sup>			(See <u>Ofloxacin</u> )
Fluconazole	86386-73-4	09/27/20	Category D when used in high doses
		11	(category C for single 150 mg dose).
			Brachycephaly, abnormal facies,
			abnormal calvarial development,
			cleft palate, femoral bowing, thin
			ribs and long bones, arthrogryposis,
			and congenital heart disease
			[FDA]. <sup>582</sup>
Fludara®		10/20/00	(See <u>Fludarabine</u> )

Drug/Substance	CAS Number	Date Added	Comments/Notes
Fludarabine	21679-14-1	06/28/00	Category D [Facts and Comparisons] <sup>583</sup> Breastfeeding: Contraindicated [Briggs 1997] <sup>584</sup>
Flunitrazepam		10/17/00	(See <u>Benzodiazepines</u> )
5-Fluorouracil	51-21-8		(See <u>Fluorouracil</u> )
Fluoroquinolones (ciprofloxacin, levofloxacin, norfloxacin, enoxacin, ofloxacin, gatifloxacin, lomefloxacin)			Category C Fluoroquinolones should be used during pregnancy only if a safer alternative is not available [PMID: 19181435]. <sup>585</sup> Breastfeeding: Avoid [PMID: 19181435]. <sup>586</sup>
Fluorouracil	51-21-8	09/30/94	Category X <sup>587</sup> Breastfeeding: Contraindicated <sup>588</sup>
Fluoxetine	56296-78-7	11/01/20 17	Ventricular septal defects, right ventricular outflow tract obstruction cardiac defects, and craniosynostosis [BMJ]. <sup>589</sup>
Fluoxymesterone	76-43-7	06/30/95	Pregnancy: Category X - Use is contraindicated in women who are or may become pregnant. May cause androgenic effects to the female fetus; clitoral hypertrophy, labial fusion, urogenital sinus defect, vaginal atresia, and ambiguous genitalia have been reported [NIOSH]. <sup>590</sup> Male: Fertility effects [PMID 137913] <sup>591</sup> (may be dose dependent [PMID <u>3435196</u> ]) <sup>592</sup> Genotoxic effects [PMID 7715612] <sup>593</sup> Category X [Facts and Comparisons] <sup>594</sup> Breastfeeding: Avoid [NIOSH]. <sup>595</sup>

Drug/Substance	CAS	Date	Comments/Notes
	Number	Added	
Flurazepam hydrochloride	1172-18-5	06/30/95	Contraindicated in pregnancy <sup>596</sup>
			(crosses the placenta,
			benzodiazepines may cause fetal
			damage when administered during
			pregnancy [Facts and
			Comparisons]) <sup>597</sup> If Benzodiazepines
			used lorazepam preferred[PMID:
			<u>11773648</u> ]. <sup>598</sup>
			Breastfeeding: Safety not established
			[Facts and Comparisons] <sup>599</sup> Not
			recommended [PMID: 11773648].600
Flutamide	13311-84-7	06/30/95	Male: Reduced sperm counts and
			spermatogenesis <sup>601</sup>
			Category D <sup>602</sup>
			Breastfeeding: Product only indicated
			for use in males
Fluvastatin	93957-54-1	06/28/00	Category X [Facts and Comparisons] <sup>603</sup>
			Breastfeeding: Contraindicated [Briggs
			1997] <sup>604</sup>
Folex®		10/20/00	(See <u>Methotrexate</u> )
5-FU	51-21-8		(See <u>Fluorouracil</u> )
Furadantin <sup>®</sup>			(See <u>Nitrofurantoin</u> )

Drug/Substance	CAS	Date	Comments/Notes
<u> </u>	Number	Added	
Gallium <sup>67</sup> (67Ga)	7440-55-3		Pregnancy: Category C. No data.
Gallium <sup>68</sup> (68Ga)			Recommend treat 68Ga as 67Ga
			[Netspot, <sup>605</sup> USPDI]. <sup>606</sup> Category D:
			Use may suppress fertility in
			females, inhibit spermatogenesis in
			males, and cause birth defects if
			used in pregnant women. Female
			patients should undergo pregnancy
			testing prior to initiation and use
			effective contraception during and
			for at least 30 days after therapy.
			Male patients should use a barrier
			contraceptive during and for at least
			90 days after therapy [ <u>NIOSH</u> ]. <sup>607</sup>
			Breastfeeding: Recommend breast-
			feeding be interrupted and breast
			milk discarded for 12 hours after
			administration [Netspot].608
			Discontinue temporarily
			(radioactivity in milk present for 2
			weeks) [ <u>AAP</u> ]. <sup>609</sup> Not Recommended
			[ <u>NIOSH</u> ]. <sup>610</sup>
Ganciclovir	82410-32-0	03/10/00	Category C (may be teratogenic or
			embryotoxic) <sup>611</sup>
			Breastfeeding: Discontinue use <sup>612</sup>
Garamycin <sup>®</sup>			(Gentamicin)
			(See <u>Aminoglycosides</u> )
Gatifloxacin		10/20/00	(See <u>Fluoroquinolones</u> )
Gemfibrozil	25812-30-0	03/10/00	Category C <sup>613</sup>
			Breastfeeding: Discontinue [Facts and
			Comparisons] <sup>614</sup>
Gentamicin	1403-66-3		(See <u>Aminoglycosides</u> )
Goserelin acetate	65807-02-5	03/10/00	Category X (avoid pregnancy for 12
			weeks after discontinuing use) <sup>615</sup>
			Breastfeeding: Contraindicated <sup>616</sup>
Halazepam	23092-17-3	06/30/95	Category D Category D. If
			Benzodiazepines used lorazepam
			preferred [PMID: 11773648].617
			Breastfeeding: Not recommended
			[ <u>PMID: 11773648</u> ]. <sup>618</sup>
Halcion®			(See <u>Triazolam</u> )

Drug/Substance	CAS	Date	Comments/Notes
Halotestin <sup>®</sup>	Number	Added	(See Elucyumosterene)
		10/17/00	(See <u>Fluoxymesterone</u> )
HCTZ	561-27-3	10/20/00	(See <u>Hydrochlorothiazide</u> )
Heroin	501-27-3		Pregnancy: Preterm birth [ <u>PMID</u> 2304039], <sup>619</sup> neonatal withdrawal
			[Williams] <sup>620</sup>
			Breastfeeding: Contraindicated
			(tremors, restlessness, vomiting,
			poor feeding [AAP] <sup>621</sup> (excreted in
			milk [PMID 9363416]) <sup>622</sup>
Hexalen®			(See <u>Altretamine</u> )
Histerone 100®		10/17/00	(See <u>Testosterone</u> )
Histrelin	76712-82-8	10/1/00	(See <u>Histrelin acetate</u> )
Histrelin acetate		03/10/00	Category X [Facts and Comparisons] <sup>623</sup>
		00, 10, 00	Breastfeeding: Do not use [Facts and
			Comparisons] <sup>624</sup>
HN <sub>2</sub>		10/20/00	(See <u>Mechlorethamine</u> )
Hormone pregnancy test			Category X [Briggs 4th] <sup>625</sup>
tablets			Breastfeeding: See <u>Oral contraceptives</u>
Hydrea <sup>®</sup>		10/20/00	(See Hydroxyurea)
Hydriodic acid	10034-85-2		(See <u>Potassium iodide</u> )
,			(lodide is the active ingredient) [Briggs
			4th] <sup>626</sup>
Hydrochlorothiazide	58-93-5	07/10/00	(See <u>Chlorothiazide</u> )
HydroDiuril®		10/20/00	(See <u>Hydrochlorothiazide</u> )
Hydrogen iodide		10/20/00	(See <u>Hydriodic acid</u> )
Hydroxyprogesterone	68-96-2	07/10/00	Category Category C – Indicated for
			use in the prevention of preterm
			birth. Avoid in first trimester
			[ <u>PMID: 26921136</u> ]. <sup>627</sup>
			Breastfeeding: Not recommended
			[PMID: 26921136] <sup>628</sup> (distributed
			into breast milk) [USPDI] <sup>629</sup>
Hydroxyurea	127-07-1		Male: Testicular atrophy, impaired
			spermatogenesis <sup>630</sup>
			Category D (embryotoxic, fetal
			malformations) <sup>631</sup>
			Breastfeeding: Incompatible (excreted
			in human milk), <sup>632</sup> contraindicated
			[Briggs 1997] <sup>633</sup>
Hylutin®		10/20/00	(See <u>Hydroxyprogesterone</u> )
Hyprogest 250 <sup>®</sup>		10/20/00	(See <u>Hydroxyprogesterone</u> )

Drug/Substance	CAS	Date	Comments/Notes
	Number	Added	
Ibuprofen	15687-27-1	05/30/00	Category B <sup>634</sup>
			Category D at end of pregnancy (may
			cause premature closure of ductus
			arteriosus and delay parturition)
			[Briggs 4th] <sup>635</sup>
			Breastfeeding: Compatible [AAP] <sup>636</sup>
Idamycin <sup>®</sup>		10/20/00	(See Idarubicin hydrochloride)
Idarubicin hydrochloride	57852-57-0	03/10/00	Category D (embryotoxic and
			teratogenic in rats)637
			Breastfeeding: Discontinue prior to
			taking drug, <sup>638</sup> contraindicated
			[Briggs 1997] <sup>639</sup>
lfex®		10/20/00	(See Ifosfamide)
Ifosfamide	3778-73-2	09/30/94	Category D <sup>640</sup>
			Breastfeeding: Incompatible, 641
			contraindicated [Briggs 1997] <sup>642</sup>
Imuran <sup>®</sup>		10/17/00	(See <u>Azathioprine</u> )
Imuthiol®		10/20/00	(See Diethyldithiocarbamate)
Indium <sup>111</sup> (111In)	7440-74-6		Category C [USPDI] <sup>643</sup>
			Breastfeeding: Discontinue temporarily
			(very small amount present at 20
			hours) [AAP] <sup>644</sup>
Indocin®		10/17/00	(See Indomethacin)
Indomethacin	53-86-1		Category B [Briggs 4th] <sup>645</sup>
			Category Category C – indicated for
			preterm labor. Category D if used
			for longer than 48 hours or after 30
			weeks gestation or close to delivery
			(may cause premature closure
			of ductus arteriosus, is associated with
			fetal anuria, oligohydramnios,
			persistent pulmonary hypertension
			[PMID: 27661654]. <sup>646</sup> associated
			with fetal anuria, oligohydramnios,
			persistent pulmonary hypertension
			[PMID 9434858] <sup>647</sup>
			Breastfeeding: Not recommended
			[PMID: 27661654], <sup>648</sup> (excreted in
			milk) <sup>649</sup>
Iodides			(See lodine)

Drug/Substance	CAS Number	Date Added	Comments/Notes
lodinated glycerol (anti- tussive/expectorant)	5634-39-9		Category X [Briggs 6 <sup>th</sup> ] <sup>650</sup> Breastfeeding: Concentrated in breast milk [Briggs 4th], <sup>651</sup> but compatible [AAP] <sup>652</sup>
lodine	7553-56-2		Category D [Briggs 4th] <sup>653</sup> Breastfeeding: Not compatible (concentrated in breast milk, and long term use may adversely affect the nursing infant's thyroid activity) [Briggs 1997] <sup>654</sup>
lodine <sup>123</sup> (l <sup>123</sup> )	15715-08-9		Breastfeeding: Discontinue temporarily (radioactivity in milk present up to 36 hours) [AAP] <sup>655</sup>
lodine <sup>125</sup> (l <sup>125</sup> )	14158-31-7		Contraindicated [ <u>Merck</u> ] <sup>656</sup> Breastfeeding: Contraindicated (radioactivity in milk for 12 days) [ <u>AAP</u> ] <sup>657</sup>
lodine <sup>131</sup> (l <sup>131</sup> )	100043-66- 0	03/10/00	Contraindicated [ <u>Merck</u> ] <sup>658</sup> Breastfeeding: Contraindicated (radioactivity in milk for 2 to 14 days) [ <u>AAP</u> ] <sup>659</sup>
Isoretinoin	4759-48-2		(See <u>Isotretinoin</u> )
Isotretinoin	4759-48-2	06/30/95	Category X (spontaneous abortions and fetal malformations) [Briggs 4th <sup>660,661</sup> Breastfeeding: Do not give [Facts and Comparisons] <sup>662</sup>
Kanamycin sulfate	8063-07-8		Category D [Briggs 4 <sup>th</sup> ]. <sup>663</sup> May cause fetal ototoxicity (based on a case report of high dose kanamycin in pregnancy) [ <u>PMID: 4702131</u> ]. <sup>664</sup> As with any aminoglycoside, can also cause kidney damage. Breastfeeding: Compatible [ <u>AAP</u> ] <sup>665</sup> (excreted in breast milk) [Briggs 4th] <sup>666</sup> (See also <u>Aminoglycosides</u> )
Kannasyn®			(See <u>Kanamycin</u> )
Kantrex®		10/17/00	(See <u>Kanamycin</u> )
LDE225			(See <u>Sonidegib</u> )
Lescol®		10/20/00	(See <u>Fluvastatin</u> )

Drug/Substance	CAS Number	Date Added	Comments/Notes
Leukeran®			(See <u>Chlorambucil</u> )
Leuprolide acetate (GnRH analogue)	74381-53-6	03/06/00	Category X <sup>667</sup> (but not expected to cause birth defects) Breastfeeding: Do not use <sup>668</sup> although no reports of toxicity. Also, GnRH is normally excreted in the milk of humans.
Leustatin <sup>®</sup>			(See <u>Cladribine</u> )
Levofloxacin		10/20/00	(See <u>Fluoroquinolones</u> )
Levonorgestrel implants (also known as Jadelle and is not available in the US)	797-63-7	03/10/00	Category X <sup>669</sup> Breastfeeding: Excreted in breast milk <sup>670</sup>
Levaquin <sup>®</sup>			(See <u>Levofloxacin</u> )
Librium®			(See <u>Chlordiazepoxide</u> )
Lithium	7439-93-2		(See <u>Lithium carbonate</u> )
Lithium carbonate	554-13-2	06/30/95	Category D [Briggs 4th] <sup>671</sup> (cardiac anomalies) <sup>672</sup> Breastfeeding: Contraindicated [Briggs 1997]; <sup>673</sup> with caution (one-third to one-half therapeutic blood levels in infants [ <u>AAP</u> ] <sup>674</sup> (excreted in human milk) <sup>675</sup>
Lithium citrate	919-16-4	06/30/95	(See <u>Lithium carbonate</u> )
Lithostat®		10/16/00	(See <u>Acetohydroxamic acid</u> )
Lodine®		10/20/00	(See <u>Etodolac</u> )
Lomustine	13010-47-4		Category D (embryotoxic and teratogenic in rats) <sup>676</sup> Breastfeeding: Not recommended (unknown if excreted in human milk) <sup>677</sup>
Lopid®		10/20/00	(See <u>Gemfibrozil</u> )

Drug/Substance	CAS	Date	Comments/Notes
	Number	Added	
Lorazepam	846-49-1	06/30/95	Category D [Briggs 4th]. Does not
			appear to be associated with any
			risk of birth defects. If administered
			near delivery, may lead to sedation,
			decreased tone, and respiratory
			depression in the
			infant.Breastfeeding: Excreted in
			breast milk in low concentrations
			[Briggs 4th], <sup>678</sup> effect may be of
			concern [ <u>AAP</u> ] <sup>679</sup> Probably safe. This
			is secreted in the milk but at lower
			doses than through the placenta.
			May lead to poor feeding or
			drowsiness.
Lomefloxacin		10/20/00	(See <u>Fluoroquinolones</u> )
Lotensin <sup>®</sup>			(Benazepril)
			(See <u>ACE Inhibitors</u> )
Lovastatin	75330-75-5	06/30/95	Category X <sup>680</sup> (Based on human data,
			there is no increased risk of birth
			defects. However, due to a
			theoretical concern for the effects
			of preventing cholesterol formation
			(as the fetus is completely
			dependent on maternal cholesterol)
			as well as lack of benefit for treating
			maternal hyperlipidemia while
			pregnant, this drug is generally not
			given in pregnancy. Note: There are
			research protocols ongoing now
			looking at statin use for prevention
			of preeclampsia in pregnancy, so
			this class of medicine may be more
			widely used in the future.)
			Breastfeeding: Contraindicated <sup>681</sup>
L-PAM		10/20/00	(See <u>Melphalan</u> )
L-Phenylalanine Mustard		10/20/00	(See <u>Melphalan</u> )
L-Sarcolysin		10/20/00	(See <u>Melphalan</u> )
Macrodantin	67-20-9		(See <u>Nitrofurantoin</u> )
Marcoumar®		10/20/00	(See <u>Phenprocoumon</u> )

Drug/Substance	CAS Number	Date Added	Comments/Notes
Marijuana		06/28/00	Pregnancy: "Because of concerns regarding impaired neurodevelopment, as well as maternal and fetal exposure to the adverse effects of smoking, women who are pregnant or contemplating pregnancy should be encouraged to discontinue marijuana use" [PMID: 28937574]. <sup>682</sup> Breastfeeding: "There are insufficient data to evaluate the effects of marijuana use on infants during lactation and breastfeeding, and in the absence of such data, marijuana use is discouraged" [PMID: 28937574]. <sup>683</sup>
Matulane®		10/20/00	(See Procarbazine hydrochloride)
Maxaquin®			(See Lomefloxacin)
MDMA			(See <u>N-Methyl-3,4-methylenedioxy-</u> 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>684</sup> Breastfeeding: With caution <sup>685</sup>
Mebaral®		10/17/00	(See <u>Barbiturates</u> ) (Mephobarbital)
Mechlorethamine	51-75-2		Category D (can cause fetal harm) <sup>686</sup> Breastfeeding: Incompatible <sup>687</sup>
Medroxyprogesterone acetate	71-58-9	06/30/95	Category D [Briggs 4th] <sup>688</sup> (may cause hypospadias) <sup>689</sup> Breastfeeding: Compatible [ <u>AAP</u> ] <sup>690</sup>
Megace®		10/20/00	(See Megestrol acetate)
Megestrol acetate	595-33-5	06/30/95	Category X (genital abnormalities) <sup>691</sup> Breastfeeding: Discontinue <sup>692</sup>
Melphalan	148-82-3	06/30/95	Category D <sup>693</sup> Breastfeeding: Discontinue <sup>694</sup>
Menadiol			(See <u>Menadione</u> )

Drug/Substance	CAS	Date	Comments/Notes
	Number	Added	
Menadiol sodium diphosphate			(See <u>Menadione</u> )
Menadione	58-27-5		Category C [Briggs 4th] <sup>695</sup> Category X (in third trimester or close to delivery) [Briggs 5th] <sup>696</sup> Breastfeeding: Vitamin K <sub>1</sub> preferred (may produce newborn toxicity) [Briggs 5th] <sup>697</sup> [Drug Information Handbook] <sup>698</sup>
Menotropins	9002-68-0	06/30/95	Category X <sup>699</sup> Breastfeeding: With caution <sup>700</sup>
Mephobarbital		10/17/00	(See <u>Barbiturates</u> )
Meprobamate	57-53-4	06/30/95	Category D [Briggs 4th] <sup>701</sup> Breastfeeding: Concentrated in milk [Briggs 4th], <sup>702</sup> may cause sedation in the nursing infant [USPDI] <sup>703</sup>
6-Mercaptopurine	50-44-2		(See <u>Mercaptopurine</u> )
Mercaptopurine	6112-76-1	06/30/95	Category D (can cause fetal harm, including spontaneous abortion and possibly death in utero) <sup>704</sup> Breastfeeding: Discontinue <sup>705</sup>
Meruvax <sup>®</sup> II			(See <u>Rubella vaccine, live</u> )
Mestranol	72-33-3		Category X <sup>706</sup> Breastfeeding: Discouraged (excreted in milk, may cause jaundice and breast enlargement in nursing children) <sup>707</sup>
Methacycline hydrochloride	3963-95-9	06/30/95	Category D [Briggs 5th] <sup>708</sup> [Briggs 4th] <sup>709</sup> Breastfeeding: See <u>Tetracycline</u> <u>hydrochloride</u> (excreted in milk in low concentration; theoretical dental staining and inhibition of bone growth)
Methandriol	521-10-8	07/10/00	(See <u>Androgens</u> )
Metharbital		10/17/00	(See <u>Barbiturates</u> )
Methimazole	60-56-0	06/30/95	Category D [Briggs 4th] <sup>710</sup> (may cause fetal harm and congenital defects) <sup>711</sup> Breastfeeding: Contraindicated (appears in human milk) <sup>712</sup>

Drug/Substance	CAS Number	Date Added	Comments/Notes
Methotrexate	59-05-2	09/30/94	Category D [Briggs 4th] <sup>713</sup> Breastfeeding: Contraindicated [Briggs 1997] <sup>714</sup> (possible immune suppression [AAP] <sup>715</sup>
Methotrexate sodium	15475-56-6	06/30/95	(See <u>Methotrexate</u> )
Methoxsalen	298-81-7	06/28/00	Category C [Facts and Comparisons] <sup>716</sup> [Briggs 5th] <sup>717</sup> Breastfeeding: Contraindicated [Briggs 1997] <sup>718</sup>
8-Methoxypsoralen		10/20/00	(See <u>Methoxsalen</u> )
Methylene blue	61-73-4		Category C Category D if injected intra- amniotically [Briggs 4th] <sup>719</sup> (hemolytic anemia, jaundice, intestinal atresia with intra-amniotic injection [PMID 9434858]) <sup>720</sup>
N-Methyl-3,4-methylene- dioxyamphetamine		07/27/00	(See <u>Amphetamines</u> )
Methyltestosterone	58-18-4	06/30/95	Category X <sup>721</sup> Breastfeeding: Contraindicated <sup>722</sup>
Methylthiouracil	56-04-2	07/10/00	Pregnancy: Malformations, including one report of retarded ossification [Schardein] <sup>723</sup>
Metrodin®			(See Urofollitropin)
Metronidazole	443-48-1	06/09/00	Category B <sup>724</sup> per manufacturer: Contraindicated in first trimester <sup>725</sup> . However, an investigation found "no association between metronidazole treatment during the first or later trimesters of pregnancy and preterm birth, low birth weight, or congenital anomalies" [PMID: 22751543]. <sup>726</sup> Breastfeeding: Discontinue <sup>727</sup> (excreted in breast milk [Briggs 4th]) <sup>728</sup> Some investigators believe it may be safely used in lactation [PMID: 10845129]. <sup>729</sup>
Mevacor®		10/20/00	(See <u>Lovastatin</u> )

Drug/Substance	CAS	Date	Comments/Notes
	Number	Added	720
Midazolam hydrochloride	59467-96-8	06/30/95	Category D <sup>730</sup>
			Breastfeeding: With caution (excreted
			in human milk) <sup>731</sup>
Mifepristone	84371-65-3		Category X [Briggs 5th] <sup>732</sup>
			(abortifacient) [ <u>PMID 6744860</u> ] <sup>733</sup>
			Fetal malformations [PMID:
			<u>27865944</u> ]. <sup>734</sup>
			Breastfeeding: Minimally excreted in
			primate milk [ <u>PMID 8314974</u> ] <sup>735</sup>
			Probably can be used during
			lactation [ <u>PMID: 20367522</u> ]. <sup>736</sup>
MIH		10/20/00	(See Procarbazine hydrochloride)
Miltown <sup>®</sup>		10/20/00	(See <u>Meprobamate</u> )
Minocin <sup>®</sup>			(See Minocycline hydrochloride)
Minocycline	10118-90-8		(See Minocycline hydrochloride)
Minocycline hydrochloride	13614-98-7	06/30/95	Category D <sup>737</sup>
(internal use)			Breastfeeding: Discontinue (excreted
			in human milk) <sup>738</sup>
Miradon®		10/17/00	(See <u>Anisindione</u> )
Misoprostol	59122-46-2	06/30/95	Category X [Briggs 6 <sup>th</sup> ] <sup>739</sup> (abortifacient,
			may cause congenital anomalies) <sup>740</sup>
			Breastfeeding: Contraindicated [Briggs
			1997] <sup>741,742</sup>
Mithracin®			(See <u>Plicamycin</u> )
Mitomycin	50-07-7	06/28/00	Pregnancy: Safety not established
			(teratological changes in animals)
			[Facts and Comparisons] <sup>743</sup>
			Breastfeeding: Contraindicated [Briggs
			1997] <sup>744</sup>
Mitomycin-C		10/20/00	(See <u>Mitomycin</u> )
Mitoxantrone	70476-82-3	09/30/94	Category D (may cause fetal harm) <sup>745</sup>
hydrochloride			Breastfeeding: Discontinue <sup>746</sup>
			Contraindicated [PMID:
			<u>22926165</u> ]. <sup>747</sup>
Modrastane®			(See <u>Trilostane</u> )
Monopril®			(Fosinopril)
			(See <u>ACE Inhibitors</u> )
8-MOP		10/20/00	(See <u>Methoxsalen</u> )
Motrin®		10/20/00	(See <u>lbuprofen</u> )
MTC		10/20/00	(See <u>Mitomycin</u> )
MTX <sup>®</sup>		10/20/00	(See <u>Methotrexate</u> )

Drug/Substance	CAS Number	Date Added	Comments/Notes
Mumps vaccine, live			Category C, but contraindicated in
			pregnancy, and pregnancy should
			be avoided for 3 months after
			vaccination <sup>748</sup>
			Breastfeeding: With caution <sup>749</sup>
Mustargen®			(See Mechlorethamine)
Mutamycin®		10/20/00	(See Mitomycin)
Mycifradin <sup>®</sup>		10/20/00	(See <u>Neomycin sulfate</u> )
Myleran®			(See <u>Busulfan</u> )
Mysoline®		10/20/00	(See <u>Primidone</u> )
Nadrobolic®		10/17/00	(See <u>Anabolic steroids</u> )
			(Nandrolone)
Nafarelin acetate	86220-42-0	06/30/95	Category X (may cause fetal harm) <sup>750</sup>
			Breastfeeding: Contraindicated <sup>751</sup>
Nandrolone		10/17/00	(See <u>Anabolic steroids</u> )
Narcotic analgesics			Pregnancy: Associated with neonatal
			withdrawal syndrome.
			Breastfeeding: Discouraged (morphine
			is excreted in milk) <sup>752</sup> may cause
			sedation.
			(Also see <u>Heroin</u> , <u>Alfentanil</u> )
Nebcin®			(See <u>Tobramycin sulfate</u> )
Nembutal®			(See Pentobarbital sodium)
Neo-mens <sup>®</sup>			(See <u>Ethisterone</u> )
Neomycin sulfate (oral)	1405-10-3	06/30/95	Category D [Facts and Comparisons] <sup>753</sup>
			Breastfeeding: Discontinue [Facts and
			Comparisons], <sup>754</sup> compatible [Briggs
			1997] <sup>755</sup>
			See also <u>Kanamycin</u> .
Neoral®		10/17/00	(See <u>Cyclosporin</u> )
Neotigason <sup>®</sup>		11/20/20	(See <u>Acitretin</u> )
		00	
Netilmicin sulfate	56391-57-2	06/30/95	Category D (can cause fetal harm) <sup>756</sup>
			Breastfeeding: Discontinue <sup>757</sup>
Netromycin®			(See <u>Netilmicin sulfate</u> )
Neutrexin®			(See <u>Trimetrexate glucuronate</u> )

Drug/Substance	CAS Number	Date Added	Comments/Notes
Nicotine	54-11-5	06/30/95	<ul> <li>Inconsistent ratings. "If you are pregnant or breast-feeding, only use this medicine on the advice of your health care provider. Smoking can seriously harm your child. Try to stop smoking without using any nicotine replacement medicine. This medicine is believed to be safer than smoking." (Glaxo).<sup>758</sup></li> <li>Category X (nicotine polacrilex [Facts and Comparisons])<sup>759</sup></li> <li>Category D (nasal spray; can cause fetal harm,<sup>760</sup> transdermal nicotine [Facts and Comparisons])<sup>761</sup></li> <li>Breastfeeding: Use with caution (excreted in milk)<sup>762</sup> [Briggs 1997],<sup>763</sup> (decrease in milk production and weight gain in the infant [AAP],<sup>764</sup> discontinue [Facts and Comparisons]<sup>765</sup></li> </ul>
Nicotrol®			(See <u>Nicotine</u> )
Nipent®			(See <u>Pentostatin</u> )
Nitrofurantoin	67-20-9	06/30/95	Category B <sup>766</sup> Contraindicated at term (38-42 weeks gestation), during labor and delivery, or when the onset of labor is imminent <sup>767</sup> Breastfeeding: Discontinue in infants under one month of age (excreted in trace amounts in human milk) <sup>768</sup>
Nitrogen mustard	51-75-2	09/30/94	(See <u>Mechlorethamine</u> )
Nitrogen mustard hydrochloride	55-86-7	06/30/95	(See <u>Mechlorethamine</u> )
N-Methyl-3,4-methylene- dioxyamphetamine			(See listing alphabetically under "Methyl" as <u>N-Methyl-3,4-methyl-</u> <u>enedioxyamphetamine</u> )
N-Methylhydrazine		10/20/00	(See Procarbazine hydrochloride)
Nolvadex®			(See <u>Tamoxifen citrate</u> )
Non-steroidal anti- inflammatory indene derivatives			(See <u>NSAIDs</u> )

Drug/Substance	CAS	Date	Comments/Notes
	Number	Added	700
norethindrone/ethinyl	68-22-4/	06/30/95	Category X <sup>769</sup>
estradiol	57-63-6		Breastfeeding: Discouraged (appears in
			human milk and may cause adverse
			effects in the child) <sup>770</sup>
			(See also <u>Mestranol</u> )
norethindrone/mestranol	68-22-4/	06/30/95	Category X <sup>771</sup>
	72-33-3		Breastfeeding: Discouraged (appears in
			human milk and may cause adverse
			effects in the child) <sup>772</sup>
			(See also <u>Mestranol</u> )
Norethynodrel	68-23-5		Category X [Briggs 4th] <sup>773</sup>
			Breastfeeding: See Oral contraceptives
			(See also <u>Mestranol</u> )
Norfloxacin		10/20/00	(See <u>Fluoroquinolones</u> )
Norgestimate/ethinyl	35189-28-	06/01/00	Category X <sup>774</sup>
estradiol	7/		Breastfeeding: Discouraged (appears in
	57-63-6		human milk and may cause adverse
			effects in the child) <sup>775</sup>
			(See also <u>Mestranol</u> )
Norgestrel/ethinyl	797-63-7/	06/30/95	Category X <sup>776</sup>
estradiol	57-63-6		Breastfeeding: Discouraged (appears in
			human milk and may cause adverse
			effects in the child) <sup>777</sup>
			(See also <u>Mestranol</u> )
Norinyl 1+35 <sup>®</sup>		10/20/00	(See <u>NORETHINDRONE/ETHINYL</u>
			<u>estradiol</u> )
Norinyl 1+50®		10/20/00	(See <u>NORETHINDRONE/MESTRANOL</u> )
Normethandrone		07/10/00	(See <u>Androgens</u> )
Noroxin®			(See <u>Ofloxacin</u> )
Norplant <sup>®</sup> System		10/20/00	(See <u>Levonorgestrel implants</u> )

Drug/Substance	CAS Number	Date Added	Comments/Notes
Nortriptyline hydrochloride	894-71-3		<ul> <li>Pregnancy: Can probably be used <ul> <li>[PMID: 22283766], <sup>778</sup> although</li> <li>previously designated as Category D</li> <li>[Briggs 4th]<sup>779</sup> (safe use not</li> <li>established, transferred through</li> <li>human placenta, case reports of</li> <li>fetal harm–decreased muscle tone,</li> <li>decreased sensitivity to painful</li> <li>stimuli, abnormal EKG in an infant</li> <li>born to a mother who had taken 1.5</li> <li>to 1.75 grams [PMID 5017806],<sup>780</sup></li> <li>urinary retention [PMID</li> <li>5049831],<sup>781</sup> lower limb deformity</li> <li>with therapeutic doses [PMID</li> <li>4129246]<sup>782</sup>)<sup>783</sup></li> </ul> </li> <li>Breastfeeding: Can probably be used <ul> <li>[PMID: 22283766],<sup>784</sup> although</li> <li>excreted into breast milk [Briggs 4th]<sup>785</sup></li> </ul> </li> </ul>
Novantrone®			(See <u>Mitoxantrone hydrochloride</u> )
NSAIDs (ibuprofen, indomethacin, sulindac)			Category B (ketoprofen, naproxen, flurbiprofen, diclofenac) [Facts and Comparisons] <sup>786</sup> Category C (etodolac, ketorolac, mefenamic acid, nabumetone, oxaprozin, tolmetin) [Facts and Comparisons] <sup>787</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>788</sup> Breastfeeding: Do not use in nursing mothers [Facts and Comparisons] <sup>789</sup>
Odomzo <sup>®</sup>			(See <u>Sonidegib</u> )
Ofloxacin		10/20/00	(See <u>Fluoroquinolones</u> )
Ogen®		10/20/00	(See <u>Estropipate</u> )

Drug/Substance	CAS	Date	Comments/Notes
	Number	Added	
Omeprazole	73590-58-6	06/28/00	Category C [Briggs 4th] <sup>790</sup>
			Breastfeeding: Contraindicated [Briggs
			1997] <sup>791</sup>
Oncovin®			(See <u>Vincristine sulfate</u> )
Oral contraceptives			Category X [Briggs 4th] <sup>792</sup>
			Breastfeeding: Compatible (rare breast
			enlargement; decrease in milk
			production and protein content
			[ <u>AAP</u> ] <sup>793</sup>
Oretic <sup>®</sup>		10/20/00	(See <u>Hydrochlorothiazide</u> )
Oretonmethyl®		10/17/00	(See <u>Methyltestosterone</u> )
Ortho-Cyclen®			(See <u>Norgestimate/ethinyl estradiol</u> )
Ortho-Dienestrol®		10/17/00	(See <u>Dienestrol</u> )
Ortho-Est <sup>®</sup>		10/20/00	(See <u>Estropipate</u> )
Ortho-Novum 1/35®		10/20/00	(See <u>NORETHINDRONE/ETHINYL</u>
			estradiol)
Ortho-Novum 1/50 <sup>®</sup>		10/20/00	(See <u>NORETHINDRONE/MESTRANOL</u> )
Ortho-Tri-Cyclen®			(See <u>Norgestimate/ethinyl estradiol</u> )
Ovcon <sup>®</sup>		10/20/00	(See <u>NORETHINDRONE/ETHINYL</u>
			estradiol)
Ovral®		10/20/00	(See <u>Norgestrel/ethinyl estradiol</u> )
Oxandrin <sup>®</sup>		10/17/00	(See <u>Anabolic steroids</u> )
			(Oxandrolone)
Oxandrolone		10/17/00	(See <u>Anabolic steroids</u> )
Oxazepam		10/17/00	(See <u>Benzodiazepines</u> )
Oxazolidinedione		07/10/00	Category X [Schardein] <sup>794</sup>
anticonvulsants			
(paramethadione,			
trimethadione)		40/20/00	
Oxsoralen®		10/20/00	(See <u>Methoxsalen</u> )
Oxymetholone	434-07-1	03/10/00	Category X (can cause fetal harm) <sup>795</sup>
			Breastfeeding: Discontinue <sup>796</sup>
			(Also see <u>Anabolic steroids</u> )
Oxytetracycline	79-57-2		Category D [Briggs 4th] <sup>797</sup> (use in the
			last half of pregnancy may
			permanently discolor the teeth of
			the fetus) <sup>798</sup> Broastfooding: Soo Totracueling
			Breastfeeding: See <u>Tetracycline</u>
			hydrochloride (present in human
			milk) <sup>799</sup>

Drug/Substance	CAS Number	Date Added	Comments/Notes
Oxytetracycline hydrochloride (internal use)	2058-46-0	06/30/95	(See <u>Oxytetracycline</u> )
Paclitaxel	33069-62-4	03/10/00	Category D (can cause fetal harm) <sup>800</sup> Breastfeeding: Discontinue <sup>801</sup>
L-PAM		10/20/00	(See <u>Melphalan</u> )
Pamelor®			(See <u>Nortriptyline</u> )
Paradione®		10/20/00	(See <u>Oxazolidinedione anticonvulsants</u> ) (Paramethadione)
Paradione®		10/20/00	(See Paramethadione)
Paramethadione	115-67-3	06/30/95	Category D [Briggs 4th] <sup>802</sup> (fetal methadione syndrome [PMID 50427] <sup>803</sup> [PMID 412416] <sup>804</sup> ) (See also <u>Oxazolidinedione</u> anticonvulsants)
Paraplatin <sup>®</sup>	41575-94-4		(See Carboplatin)
Parlodel®		10/17/00	(See <u>Bromocriptine</u> )
Paroxetine	78246-49-8	11/01/20 17	Anencephaly, atrial septal defects, right ventricular outflow tract obstruction cardiac defects, gastroschisis, and omphalocele [BMJ]. <sup>805</sup>
Paxipam <sup>®</sup>		10/20/00	(See <u>Halazepam</u> )
PBZ®		10/20/00	(See Tripelennamine)
РСР	60124-79-0		(See <u>Phencyclidine</u> )
Pelamine <sup>®</sup>		10/20/00	(See Tripelennamine)
Penetrex <sup>®</sup>			(See <u>Enoxacin</u> )
dl-Penicillamine	52-66-4		(See <u>Penicillamine</u> )
Penicillamine (dl- Penicillamine)	52-66-4		Category X (except in treatment of Wilson's Disease or certain cases of cystinuria) <sup>806, 807</sup> Category D [Briggs 5th] <sup>808</sup> (in treatment of Wilson's Disease and certain cases of cystinuria) <sup>809, 810</sup> Breastfeeding: Contraindicated <sup>811, 812</sup>
Pentobarbital sodium	57-33-0	06/30/95	Category D (can cause fetal damage and withdrawal symptoms) <sup>813</sup> Breastfeeding: With caution (small amounts excreted in milk) <sup>814</sup> (See also <u>Barbiturates</u> )

Drug/Substance	CAS Number	Date Added	Comments/Notes
Pentostatin	53910-25-1	03/10/00	Category D [Facts and Compari- sons] <sup>815</sup> (can cause fetal harm) <sup>816</sup> Breastfeeding: Discontinue <sup>817</sup> [Facts and Comparisons] <sup>818</sup>
Pertix®		10/20/00	(See <u>Menadione</u> )
Phenacemide	63-98-9	06/30/95	Category D [Facts and Comparisons] <sup>819</sup> Breastfeeding: Discontinue [Facts and Comparisons] <sup>820</sup>
Phencyclidine	60124-79-0		Category X [Briggs 4th] <sup>821</sup> (hallucinogen with no legitimate use) Breastfeeding: Contraindicated [AAP] <sup>822</sup>
Phenindione	83-12-5	06/30/00	Category D [Briggs 4th] <sup>823</sup> Breastfeeding: Contraindicated (increased prothrombin and partial thromboplastin time in one infant; not use in United States) [AAP] <sup>824</sup>
Phenobarbital	50-06-6		Category D [Briggs 4th] <sup>825</sup> (manufacturer notes Category C) <sup>826</sup> Breastfeeding: With caution; <sup>827</sup> should not be given (sedation, infantile spasms after weaning from milk containing phenobarbital, one reported case of methemoglobinemia [ <u>AAP</u> ] <sup>828</sup> (See also <u>Barbiturates</u> )
Phenprocoumon	435-97-2	06/30/95	Category D [Briggs 4th] <sup>829</sup> (may cause fetal harm, including CNS malformations and hearing disorder [ <u>PMID 8147045</u> ]) <sup>830</sup> Breastfeeding: Avoid [Briggs 4th] <sup>831</sup>
Phenurone®			(See <u>Phenacemide</u> )
L-Phenylalanine mustard		10/20/00	(See <u>Melphalan</u> )
Phenylbutazone	50-33-9	07/10/00	Category C [Briggs 4th] <sup>832</sup> Category D if used in the third trimester [Briggs 4th] <sup>833</sup> Breastfeeding: Compatible [AAP] <sup>834</sup> (excreted in breast milk [Briggs 4th]) <sup>835</sup>

Drug/Substance	CAS	Date	Comments/Notes
	Number	Added	
Phenytoin	57-41-0		Category D [Briggs 6 <sup>th</sup> ] <sup>836</sup> (possible fetal
			hydantoin syndrome) <sup>837</sup>
			Breastfeeding: Not recommended
			(secreted in low concentrations in
			human milk), <sup>838</sup> usually compatible
			(one case of methemoglobinemia
			reported [ <u>AAP</u> ] <sup>839</sup>
Phenytoin sodium	630-93-3		(See <u>Diphenylhydantoin</u> )
Pindione®		10/20/00	(See <u>Phenindione</u> )
Piperazine estrone sulfate	7280-37-7		(See Estropipate)
Pipobroman	54-91-1	06/30/94	(Antimetabolite)
			Animal data:
			Developmental: [PMID 4504975] <sup>840</sup>
			Breastfeeding: Contraindicated [Briggs
			1997] <sup>841</sup>
Platinol <sup>®</sup> -AQ			(See <u>Cisplatin</u> )
Plicamycin	18378-89-7	09/30/94	Category X (may cause fetal harm) <sup>842</sup>
		,, -	Breastfeeding: Discontinue <sup>843</sup>
Potassium iodide	7681-11-0		Category D (can cause fetal harm) <sup>844</sup>
			Breastfeeding: Compatible [AAP] <sup>845</sup>
			(excreted in breast milk, may cause
			skin rash and thyroid suppression in
			the infant) <sup>846</sup>
Povidone-iodine	25655-41-8		Category D [Briggs 4th] <sup>847</sup> (do not use
			vaginally or in broken skin during
			pregnancy, may be used as a
			surgical prep for C-section; <sup>848</sup> can
			cause fetal harm [PMID
			7431610]) <sup>849</sup>
			Breastfeeding: Compatible [AAP] <sup>850</sup> do
			not use vaginally or in broken skin
			(can cause fetal harm) <sup>851</sup>
Pravachol®			(See <u>Pravastatin sodium</u> )
Pravastatin sodium	81131-70-6	03/10/00	Category X <sup>852</sup>
			Breastfeeding: Contraindicated (small
			amount excreted in human milk) <sup>853</sup>
Premarin®			(See <u>Conjugated estrogens</u> )
Prilosec®		10/20/00	(See <u>Omeprazole</u> )

Drug/Substance	CAS	Date	Comments/Notes
	Number	Added	
Primidone	125-33-7		Category D [Briggs 4th] <sup>854</sup> (minor
			dysmorphic features-possibly a
			"fetal primidone syndrome" [PMID
			<u>9434858</u> ], <sup>855</sup> neonatal hemorrhage;
			prophylactic vitamin K <sub>1</sub> advised for
			one month prior to and during
			delivery) <sup>856</sup>
			Breastfeeding: Discontinue nursing in
			the presence of undue somnolence
			and drowsiness in nursing
			newborns <sup>857</sup> (appears in breast milk
			in substantial quantities [Facts and
			Comparisons]), <sup>858</sup> use with caution
			(sedation, feeding problems
			[ <u>AAP</u> ] <sup>859</sup>
Prinivil®			(Lisinopril)
			(See <u>ACE Inhibitors</u> )
Procarbazine	671-16-9		(See Procarbazine hydrochloride)
Procarbazine	366-70-1	06/30/95	Male: Azoospermia <sup>860</sup>
hydrochloride			Category D (can cause fetal harm) <sup>861</sup>
			Breastfeeding: Do not nurse <sup>862</sup>
Progesterone	57-83-0	07/10/00	(See <u>Hydroxyprogesterone</u> )
Propecia®			(See <u>Finasteride</u> )
Propylthiouracil	51-52-5	06/30/95	Category D (can cause fetal harm) <sup>863</sup>
			Breastfeeding: Contraindicated
			(excreted in human milk) <sup>864</sup>
Proscar <sup>®</sup>		10/20/00	(See <u>Finasteride</u> )
Prosom®		10/20/00	(See <u>Estazolam</u> )
Provera®		10/20/00	(See <u>Medroxyprogesterone acetate</u> )
Prozac <sup>®</sup>			(See <u>Fluoxetine</u> )
PTU		10/20/00	(See <u>Propylthiouracil</u> )
Purinethol®			(See <u>Mercaptopurine</u> )
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>865</sup>
			Breastfeeding: Discontinue (excreted
			in human milk) <sup>866</sup>

Drug/Substance	CAS Number	Date Added	Comments/Notes
Quazepam	36735-22-5	03/10/00	Category X [Facts and Comparisons] <sup>867</sup> [USPDI] <sup>868</sup>
			Breastfeeding: See <u>Benzodiazepines</u>
Quinine	130-95-0		(See <u>Quinine sulfate</u> )
Quinine sulfate			Category X <sup>869</sup> (uterine contraction activity with doses higher than
			recommended, malformations with large doses) [Facts and Compari- sons] <sup>870</sup>
			Breastfeeding: With caution (excreted in breast milk in small amounts), <sup>871</sup> infants with G-6-PD should not
			breastfeed [Briggs 1997] <sup>872</sup>
Radioactive sodium		06/28/00	Breastfeeding: Contraindicated [Briggs 1997] <sup>873</sup> (radioactivity in milk present 96 hours [AAP] <sup>874</sup>
Restoril®		10/17/00	(See <u>Temazepam</u> )
Retinoic acid	302-79-4	10/1//00	Category C (applied to skin) [Facts and
	502 75 4		Comparisons] <sup>875</sup>
			Pregnancy: Oral (internal) exposure
			teratogenic (Retinoic acid
			embryopathy [PMID 3162101] <sup>876</sup>
			[PMID 1438063]) <sup>877</sup>
			Breastfeeding: With caution [Facts and
			Comparisons] <sup>878</sup>
			(See also <u>Isotretinoin</u> , <u>Tretinoin</u> )
Retinol	68-26-8	06/30/95	(See <u>Vitamin A</u> )
Retinyl esters			(See <u>Vitamin A</u> )
Ribavirin	36791-04-5	09/30/94	Category X (may cause fetal harm) <sup>879</sup>
			Breastfeeding: Discontinue <sup>880</sup>
Rocaltrol <sup>®</sup>		10/17/00	(See <u>Calcitriol</u> )
Rohypnol <sup>®</sup>			(See Flunitrazepam)
Rondomycin®		10/20/00	(See Methacycline hydrochloride)
RU-486 <sup>®</sup>		10/20/00	(See <u>Mifepristone</u> )
Rubella vaccine, live			Contraindicated (Category C) <sup>881</sup>
			Breastfeeding: With caution (live virus
			secreted in milk and may be
			transmitted to breast-fed infant) <sup>882</sup>
Sandimmune®		10/17/00	(See <u>Cyclosporin</u> )
L-Sarcolysin		10/20/00	(See <u>Melphalan</u> )
Secobarbital	309-43-3	06/30/95	(See <u>Barbiturates</u> )

Drug/Substance	CAS Number	Date Added	Comments/Notes
Seconal®		10/17/00	(See <u>Barbiturates</u> )
		,,	(Secobarbital)
Selective serotonin		09/28/20	Septal heart defects with sertaline and
reuptake inhibitors		09	citalopram (but not other SSRIs)
(SSRIs)			[PMID 19776103] <sup>883</sup>
Septra®			(See <u>Sulfonamides</u> )
Serax <sup>®</sup>		10/17/00	(See <u>Benzodiazepines</u> )
			(Oxazepam)
Sertaline	79617-96-2	09/28/20	Septal heart defects [PMID
		09	<u>19776103</u> ] <sup>884</sup>
Simvastatin	79902-63-9	06/07/00	Category X <sup>885</sup> [Briggs 6 <sup>th</sup> ] <sup>886</sup> (skeletal
			abnormalities in animals) [Facts and
			Comparisons] <sup>887</sup>
			Breastfeeding: Contraindicated <sup>888</sup>
Smallpox vaccine		07/10/00	Category X [Schardein] <sup>889</sup>
Sonidegib	1218778-	07/28/20	Potential risk for severe birth defects
	77-8	15	or death to fetuses. Embryo-fetal
			death or severe birth defects when
			administered to a pregnant woman.
			In animal reproduction studies, oral
			administration of sonidegib during
			organogenesis at doses below the
			recommended human dose of 200
			mg resulted in embryotoxicity,
			fetotoxicity, and teratogenicity in
			rabbits. Teratogenic effects
			observed included severe midline
			defects, missing digits, and other irreversible malformations [FDA]. <sup>890</sup>
Sodium (radioactive)		06/28/00	(See <u>Radioactive sodium</u> )
Sodium (radioactive)	7681-82-5	00/28/00	(See Iodine)
Sodium iodide I <sup>125</sup>	7001-02-5		
Sodium iodide I <sup>131</sup>			(See <u>lodine<sup>125</sup></u> ) (See <u>lodine<sup>131</sup></u> )
	1010770		
Sonidegib	1218778- 77-8		
Soriatane®		11/20/20	(See <u>Acitretin</u> )
		00	
Stanozolol	10418-03-8	06/08/00	Category X (can cause fetal harm) <sup>891</sup>
			Breastfeeding: Discontinue <sup>892</sup>
Streptomycin	57-92-1	06/07/00	(See <u>Streptomycin sulfate</u> )

Drug/Substance	CAS	Date	Comments/Notes
	Number	Added	
Streptomycin sulfate	3810-74-0	06/30/95	Category D (can cause fetal harm) <sup>893</sup>
			Breastfeeding: Discontinue <sup>894</sup>
			(See also <u>Aminoglycosides</u> )
Streptozocin	18883-66-4	03/10/00	Category D <sup>895</sup>
(streptozotocin)			Breastfeeding: Discontinue <sup>896</sup>
Styptobion®		10/20/00	(See <u>Menadione</u> )
Sulfamethoxazole			(See <u>Sulfonamides</u> )
Sulfonamides			Contraindicated (Category C) (may
			cause kernicterus) <sup>897</sup>
			Breastfeeding: Contraindicated
			(excreted in milk and may cause
			kernicterus) <sup>898</sup>
Sulindac	38194-50-2	03/10/00	(See <u>NSAIDs</u> )
			Not recommended <sup>899</sup>
			Breastfeeding: Should not be
			undertaken <sup>900</sup>
Supprelin®			(See <u>Histrelin acetate</u> )
Synarel®			(See <u>Nafarelin acetate</u> )
Synkavite <sup>®</sup>		10/20/00	(See <u>Menadione</u> )
Tabloid®			(See <u>Thioguanine</u> )
TACE®			(See <u>Chlorotrianisene</u> )
Tamoxifen citrate	54965-24-1	06/30/95	Category D (may cause fetal harm) <sup>901</sup>
			Breastfeeding: Discontinue <sup>902</sup>
Tapazole®			(See <u>Methimazole</u> )
Technitium <sup>99</sup>			Category X
			Breastfeeding: Contraindicated [Briggs
			1997] <sup>903</sup> (radioactivity in milk for 15
			hours to 3 days [ <u>AAP</u> ] <sup>904</sup>
Tegison®		10/20/00	(See <u>Etretinate</u> )
Tegretol®		10/17/00	(See <u>Carbamazepine</u> )
Temazepam	846-50-4	06/30/95	Category X (contraindicated) <sup>905</sup>
			Breastfeeding: With caution <sup>906</sup>
			(See also <u>Benzodiazepines</u> )
Teniposide	29767-20-2		Category D (may cause fetal harm) <sup>907</sup>
			Breastfeeding: Discontinue <sup>908</sup>
Tenoretic <sup>®</sup>			(See <u>Atenolol</u> and <u>Chlorothiazide</u> )
			(Atenolol and Hydrochlorothiazide)
Tenormin <sup>®</sup>			(See <u>Atenolol</u> )
Terramycin <sup>®</sup>			(See <u>Oxytetracycline</u> )
Tesanone®		10/17/00	(See <u>Testosterone</u> )
Testandro®		10/17/00	(See <u>Testosterone</u> )

Drug/Substance	CAS Number	Date Added	Comments/Notes
Testoderm <sup>®</sup>			(See <u>Testosterone</u> )
Testosterone	58-22-0	06/07/00	Category X (may cause fetal harm) <sup>909</sup> Breastfeeding: Contraindicated <sup>910</sup>
Testosterone cypionate	58-20-8	06/30/95	Contraindicated (may cause virilization of the external genitalia of the female fetus) <sup>911</sup> Breastfeeding: Contraindicated <sup>912</sup>
Testosterone enanthate	315-37-7	06/30/95	Category X (contraindicated, may cause virilization of the external genitalia of the female fetus) <sup>913</sup> Breastfeeding: Discontinue <sup>914</sup>
Testosterone propionate		10/17/00	(See <u>Testosterone</u> )
Testred®		10/17/00	(See <u>Methyltestosterone</u> )
Tetracycline	60-54-8		(See <u>Tetracycline hydrochloride</u> )
Tetracycline hydrochloride (internal use)	64-75-5	06/30/95	Category D [Briggs 6 <sup>th</sup> ] <sup>915</sup> (may cause fetal harm) <sup>916</sup> Breastfeeding: Compatible [ <u>AAP</u> ] <sup>917</sup> (present in the milk of lactating women, <sup>918</sup> but negligible absorption by infant [Briggs 4th]) <sup>919</sup>
Tequin <sup>®</sup>			(See Gatifloxacin)
Thalidomide	50-35-1	06/30/95	Category X (may cause fetal harm) <sup>920</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>921</sup> Breastfeeding: Discontinue <sup>922</sup>
Thalomid <sup>®</sup>			(See <u>Thalidomide</u> )
Thioguanine	154-42-7	06/30/95	Category D (may cause fetal harm) <sup>923</sup> Breastfeeding: Discontinue <sup>924</sup>
Thioplex®			(See <u>Thiotepa</u> )
Thiotepa	52-24-4		Category D (can cause fetal harm) <sup>925</sup> Breastfeeding: Discontinue <sup>926</sup>
Thiouracil	141-90-2	07/10/00	(See Propylthiouracil)
Thyreostat®		10/20/00	(See Methylthiouracil)
Tobramycin	32986-56-4		(See <u>Tobramycin sulfate</u> )
Tobramycin sulfate	49842-07-1	06/30/95	Category D <sup>927</sup> (See <u>Aminoglycosides</u> )

Drug/Substance	CAS Number	Date Added	Comments/Notes
Topiramate	97240-79-4	02/26/20 14	Category D (cleft lip and/or palate) [Janssen] Low birth weight (PMID 24463659) <sup>928</sup>
Toxol®			(See <u>Paclitaxel</u> )
Tranxene®		10/17/00	(See <u>Benzodiazepines</u> ) (Chlorazepate)
Tretinoin	302-79-4		(See <u>Isotretinoin</u> )
Triazolam	28911-01-5	06/30/95	Category X <sup>929</sup> Breastfeeding: Not recommended <sup>930</sup> (See also <u>Benzodiazepines</u> )
Tridione®		10/20/00	(See <u>Oxazolidinedione anticonvulsants</u> ) (Trimethadione)
Tridione®		10/20/00	(See Trimethadione)
Trilostane	13647-35-3	06/30/95	Fertility: Reversible gonadal function [USPDI] <sup>931</sup> Category X (reduces circulating progesterone, produces cervical dilation, may terminate pregnancy) [USPDI] <sup>932</sup> Breastfeeding: Problems have not been documented [USPDI] <sup>933</sup>
Trimethadione	127-48-0	06/30/95	Category D [Briggs 4th] <sup>934</sup> (fetal trimethadione syndrome [PMID <u>50427</u> ]: <sup>935</sup> growth retardation, microcephaly, cleft lip/palate, unusual facies, cardiovascular malformations [PMID 9434858]) <sup>936</sup> (See <u>Oxazolidinedione anticonvulsants</u> )
Trimetrexate glucuronate	82952-64-5	03/10/00	Category D (can cause fetal harm) <sup>937</sup> Breastfeeding: Discontinue <sup>938</sup>
Tripelennamine	91-81-6		Category B [Briggs 4th] <sup>939</sup> Breastfeeding: Contraindicated [Briggs 4th] <sup>940</sup> (excreted in breast milk [Facts and Comparisons]) <sup>941</sup>
Tromexane®			(See <u>Ethyl biscoumacetate</u> )

Drug/Substance	CAS	Date	Comments/Notes
	Number	Added	
Uracil mustard	66-75-1	06/30/95	Male: Azoospermia [USPDI] <sup>942</sup>
			Female: Amenorrhea [USPDI] <sup>943</sup>
			Pregnancy: Avoid [USPDI] <sup>944</sup>
			Breastfeeding: Not recommended
			(risks of adverse effects,
			mutagenicity, carcinogenicity)
			[USPDI] <sup>945</sup>
Uramustine®		10/20/00	(See <u>Uracil mustard</u> )
Urofollitropin	26995-91-5	06/30/95	Category X (may cause fetal harm) <sup>946</sup>
			Breastfeeding: With caution <sup>947</sup>
Urolene Blue®		10/20/00	(See <u>Methylene blue</u> )
Vaccine (live measles)			(See Measles vaccine, live)
Vaccine (live mumps)			(See <u>Mumps vaccine, live</u> )
Valium®			(See <u>Diazepam</u> )
Valproate sodium	1069-66-5	06/30/95	Category X (can produce teratogenic
			effects) <sup>948</sup> , decreased cognitive
			functioning at age 3 years [PMID
			<u>19369666</u> ] <sup>949</sup> and at age 6 years
			[ <u>FDA</u> ]. <sup>950</sup>
			Breastfeeding: Consider discontinuing
			nursing (excreted in breast milk) <sup>951</sup>
Valproic acid	99-66-1		Category X [Briggs 6 <sup>th</sup> ] <sup>952</sup> (may produce
			teratogenic effects) <sup>953</sup> and
			decreased IQ at age 6 years
			[ <u>FDA</u> ]. <sup>954</sup>
			Breastfeeding: With caution (excreted
			in breast milk) <sup>955</sup>
Vasotec®		10/17/00	(See <u>Enalapril</u> )
Velban®			(See <u>Vinblastine sulfate</u> )
VePesid®		10/20/00	(See <u>Etoposide</u> )
Vercite®			(See <u>Pipobroman</u> )
Vercyte®		10/20/00	(See <u>Pipobroman</u> )
Versanoin®		10/20/00	(See <u>Tretinoin</u> )
Versed®		10/17/00	(See <u>Midazolam</u> )
Vibramycin®			(See <u>Doxycycline</u> )
Vibra-tabs <sup>®</sup>			(See <u>Doxycycline</u> )
Vinblastine	865-21-4		(See Vinblastine sulfate)
Vinblastine sulfate	143-67-9	06/30/95	Category D (can cause fetal harm) <sup>956</sup>
			Breastfeeding: Discontinue <sup>957</sup>
Vincristine	57-22-7		(See <u>Vincristine sulfate</u> )

Drug/Substance	CAS Number	Date Added	Comments/Notes
Vincristine sulfate	2068-78-2	06/30/95	Category D (can cause fetal harm) <sup>958</sup> Breastfeeding: Discontinue <sup>959</sup>
Virilon®		10/20/00	(See <u>Methyltestosterone</u> )
Virilon®		10/20/00	(See <u>Testosterone cypionate</u> )
Vistide®			(See Cidofovir)
Vitamin A	68-26-8		Category A Category X (if used in does above the RDA [Briggs 4th], <sup>960</sup> may cause fetal harm; safety of amounts exceeding 6,000 Units of Vitamin A daily during pregnancy has not been established) <sup>961</sup> Essential for normal reproduction (US RDA = 8,000 IU; Institute of Medicine advocates an RDA = 2667 IU in pregnant females [Institute of Medicine]) <sup>962</sup> Breastfeeding: US RDA of 5,000 Units is recommended for nursing mothers <sup>963</sup>
Vitamin A acid		10/20/00	(See <u>Tretinoin</u> )
Vitamin D <sub>2</sub>		10/20/00	(See Ergocalciferol)
Vitamin D <sub>3</sub>			(See <u>Cholecalciferol</u> )
VP-16-213		10/20/00	(See <u>Etoposide</u> )
Vumon <sup>®</sup>		10/20/00	(See <u>Teniposide</u> )
Warfarin	81-81-2	06/30/95	Category X (may cause fatal fetal hemorrhage <i>in utero</i> or birth malformations) <sup>964</sup> (See <u>Dicumarol</u> ) Breastfeeding: Compatible [ <u>AAP</u> ], <sup>965</sup> no restrictions (appears in human milk in an inactive form) <sup>966</sup>
Winstrol®			(See <u>Stanozolol</u> )
Xanax®		10/17/00	(See <u>Alprazolam</u> )
Yellow fever vaccine		07/10/00	Category D [Schardein] <sup>967</sup>
Zanosar®		- *	(See <u>Streptozocin</u> )
Zesteril®			(Lisinopril) (See <u>ACE Inhibitors</u> )
Zocor®		10/20/00	(See <u>Simvastatin</u> )
Zoladex®			(See <u>Goserelin acetate</u> )

Drug/Substance	CAS	Date	Comments/Notes
	Number	Added	
Zoloft®	79617-96-2	09/28/20	Septal heart defects [PMID
		09	<u>19776103</u> ] <sup>968</sup>
Zonisamide	68291-97-4	02/26/20	Teratogenic in multiple animal species
		14	[Rxlist] <sup>969</sup>
			Low birth weight ( <u>PMID 24463659</u> ) <sup>970</sup>
			Breastfeeding: excreted in human milk
			[ <u>Rxlist]</u> <sup>971</sup>

# (IX) OCCUPATIONAL BIOLOGICAL REPRODUCTIVE AND DEVELOPMENTAL HAZARDS

## A) INTRODUCTION

Biologic ReproDev hazards include microorganisms (including bacteria, protozoa, viruses, and fungi), vaccines, and hyperpyrexia—fever greater than 102.2°F or 39°C—a possible response to infection or vaccination.<sup>iv</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 ReproDev 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.

Category	Agent or Disease	Notes
Bacteria	Brucellosis	Brucella species (b. abortus, b. melitensis,
		b. suis, b. canis)
		Clinically symptomatic disease (not just
		exposure to or sub-clinical infection
		with brucella) has been associated with
		first trimester spontaneous abortion,
		third trimester fetal death and pre-term
		labor, although brucellosis is not
		commonly the reproductive hazard to
		humans that it is to animals, possibly
		due to the absence of erythritol in the
		human placenta [PMID 11283806], <sup>972</sup>
		[PMID 11770592], <sup>973</sup>
		[PMID 10909521]. <sup>974</sup>
		Congenital brucellosis [PMID 17597440] <sup>975</sup>

Table 11 Occupations	Dialogical Depreductive	and Davidon montal Hazarda List
Table II – Occupationa	i Biological Reproductive	and Developmental Hazards List

<sup>&</sup>lt;sup>iv</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 or Disease	Notes
	Ehrlichiosis	Human granulocytic ehrlichiosis [PMID 9691104]. <sup>976</sup> Treatment with tetracycline or doxycycline (preferably [PMID 4180868, <sup>977</sup> NEJM]), <sup>978</sup> both potentially harmful, or rifampin [PMID 9675481] <sup>979</sup> may need to be considered.
	Group B Streptococcus	Early-onset (neonatal) group B streptococcus [MMWR] <sup>980</sup>
	Invasive Hemophilus influenza	Increased susceptibility to invasive <i>H.</i> <i>influenza</i> during pregnancy, fetal loss and premature birth [PMID 24643602] <sup>981</sup>
	Leprosy	Mycobacteria leprae Hansen's Disease. Fetal and placental infection is rare, <sup>982</sup> but transmission from an infected, untreated mother to infant is not uncommon <sup>983</sup> (apparently from skin-to-skin or droplet transmission). <sup>984</sup>
	Listeriosis	Listeria monocytogenes Granulomatosis infantisepticemia, spontaneous abortion [PMID <u>15824987</u> ], <sup>985</sup> stillbirth [PMID <u>12437035</u> ], <sup>986</sup> premature labor [PMID <u>18646305</u> ], <sup>987</sup> chorioamnionitis with multiple placental abscesses [PMID <u>12389339</u> ] <sup>988</sup> 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 [MMWR]. <sup>989</sup>
	Lyme disease	Borrelia burgdorferi [PMID 2423719] <sup>990</sup> Timely maternal antibiotic treatment appears to eliminate risks to the fetus of adverse Lyme disease sequelae [PMID 10666804] <sup>991</sup> [PMID 8362948]. <sup>992</sup>

Category	Agent or Disease	Notes
	Relapsing fever	Borrelia hermsii, transmitted by the soft
		tick Ornithodoros hermsi [PMID
		<u>15004063</u> ] <sup>993</sup>
		High perinatal mortality, premature
		delivery, spontaneous abortion [PMID
		<u>9351408</u> ], <sup>994</sup> [PMID 3416842] <sup>995</sup>
	Syphilis	Severe infection may cause fetal demise
		with hydrops; mild infection may cause
		detectable abnormalities of skin, teeth,
		and bones [PMID 921549] <sup>996</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 [PMID 6551148] <sup>997</sup>
	Tuberculosis	(TB)
	Typhoid fever	Spontaneous abortion, premature delivery
		[PMID 3832761] <sup>998</sup>
		Neonatal typhoid (intrauterine
		transmission from an infected mother)
		[ <u>PMID 7808844</u> ] <sup>999</sup>
Protozoa	Leishmaniasis	Leishmania donovani
		Visceral leishmaniasis or Kala Azar
		Transplacental transmission may occur in
		asymptomatic women [PMID
		<u>10545591</u> ] <sup>1000</sup>
	Malaria	Plasmodium vivax, P. ovale, P. falciparum,
		P. malariae
		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.

Category	Agent or Disease	Notes
	Toxoplasmosis	Domestic cats are a potential source.
		Risk dependent on gestational age at the
		time of maternal seroconversion:
		intracranial hyperechogenic foci or
		calcifications and ventricular dilatation
		(generally bilateral and symmetrical),
		intrahepatic densities, increased
		thickness and hyperdensity of the
		placenta, ascites, pericardial and pleural
		effusions, cerebral palsy, microcephaly,
		bilateral blindness, hydrocephalus,
		epilepsy [PMID: 1566716]. <sup>1001</sup>
		Pregnant women who become infected
		during pregnancy are generally treated
		immediately with spiramycin.
	Trypanosomiasis	Trypanosoma cruzi
		American trypanosomiasis or Chagas'
		disease
		May infect the placenta with or without
		fetal transmission (congenital
		trypanosomiasis) [PMID 3938649] <sup>1002</sup>
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 [PMID
		<u>6551148]</u> <sup>1003</sup>

Category	Agent or Disease	Notes
	Cytomegalovirus	Human herpesvirus 5
		Sensoryneural hearing loss & vestibular
		disorders [PMID 26347442] <sup>1004</sup> Maternal
		viremia can result in transplacental
		infection (placental cytotrophoblasts
		are permissive to CMV replication);
		congenital infection from antepartum
		cervical/vaginal viral shedding is
		thought to be rare. Postnatal infection
		can occur via intrapartum exposure to
		cervical/vaginal viral shedding or via
		consumption of infected breast milk
		and is unlikely to cause severe disease
		in healthy full-term neonates. Clinical
		findings in symptomatic newborns
		include small for gestational age,
		microcephaly, ventriculomegaly,
		chorioretinitis, jaundice,
		hepatosplenomegaly,
		thrombocytopenia, and petechiae. The
		mortality rate among symptomatic
		newborns is approximately 5 percent,
		and 50 to 60 percent of survivors
		develop serious long-term neurologic
		morbidity [PMID: 8160023]. <sup>1005</sup>
	Ebola virus	Spontaneous abortions & stillbirth among
		pregnant women with Ebola
		Hemorrhagic Fever <sup>1006</sup> [PMID
		<u>9988157</u> ] <sup>1007</sup>
		Labor and Delivery has high risk of
		exposure to bodily fluids, including
		amniotic fluid [PMID 28383378] <sup>1008</sup>
	Echovirus	Term: High risk of transmission and
		severely infected infant [PMID
		<u>6551148</u> ] <sup>1009</sup>
	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 [PMID
		<u>6551148</u> ] <sup>1010</sup>

Category	Agent or Disease	Notes
	Hepatitis E virus	Maternal and fetal death, abortion, premature delivery, neonatal mortality [PMID 11307901], <sup>1011</sup> [PMID 7959147], <sup>1012</sup> icteric and anicteric hepatitis, hypothermia, hypoglycemia [PMID 7723501] <sup>1013</sup>
	Human immunodeficiency virus	HIV, AIDS
	Human parvovirus B19	Erythema infectiosa or Fifth disease, fetal anemia, fetal hydrops, death <sup>1014</sup>
	Human T-cell leukemia virus type 1	Possible transmission from breastfeeding [PMID 2512396] <sup>1015</sup> Intra-uterine infection [PMID 2332671] <sup>1016</sup>
	Influenza H1N1	Spontaneous abortion, premature rupture of membranes [MMWR] <sup>1017</sup>
		Fetal distress, premature delivery, emergency cesarean delivery, fetal death [ <u>PMID 20498414</u> ] <sup>1018</sup>
	Lymphocytic choriomeningitis virus	Congenital hydrocephalus, microcephaly, macrocephaly, intracranial calcifications, chorioretinitis, hydrops [PMID 11004296, <sup>1019</sup> PMID 11438904, <sup>1020</sup> PMID 662624] <sup>1021</sup> A potential risk for those handling rodents [MMWR]. <sup>1022</sup>
	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 [PMID 6551148] <sup>1023</sup>

Category	Agent or Disease	Notes
	Rubella virus	German measles
		Congenital rubella syndrome 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>1024</sup>
	Varicella/herpes zoster virus	human herpesvirus 3, congenital varicella
		if infected in first trimester, neonatal
		varicella if infected near delivery (5 days
		before to 2 days after delivery) <sup>1025</sup>
	West Nile Virus	Developmental (chorioretinitis, temporal
		and occipital white-matter loss)
		[ <u>MMWR</u> ] <sup>1026</sup>
		Breastfeeding has been associated with
		seropositivity, and virus has been
		identified in human breast milk
		[ <u>MMWR</u> , <sup>1027</sup> <u>MMWR</u> ] <sup>1028</sup>
	Zika Virus	Congenital Zika Syndrome <sup>1029,1030</sup>
		(microcephaly, <sup>1031</sup> decreased brain
		tissue and subcortical calcifications, eye
		abnormalities including macular
		scarring and retinal pigment changes,
		congenital contractures, such as
		clubfoot or arthrogryposis, and
		hypertonia, and may include
		microphthalmos and macular
		chorioretinal atrophy, <sup>1032</sup> and
		dysphagia <sup>1033</sup> )

Category	Agent or Disease	Notes
Vaccine	Mumps	Live attenuated vaccine—avoid pregnancy
		for 30 days after vaccination [ <u>CDC</u> ] <sup>1034</sup>
		(some authorities recommend avoiding
		pregnancy for 3 months)
		Category C [Briggs 6th] <sup>1035</sup>
	Rubella	Live attenuated vaccine—avoid pregnancy
		for 3 months after vaccination [CDC]. <sup>1036</sup>
		"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 1994]. <sup>1037</sup> "No evidence
		indicates that administration of rubella-
		containing vaccine virus to a pregnant
		woman presents a risk for her fetus,
		although such a risk cannot be excluded
		on theoretical grounds" [CDC]. <sup>1038</sup>
	Vaccinia	Category X [Briggs 6th] <sup>1039</sup>
		Fetal vaccinia (developmental) (very rare)
		Reported in women vaccinated in all three
		trimesters [MMWR] <sup>1040</sup>
	Varicella/herpes zoster virus	Category C (contraindicated during
	vaccine	pregnancy) <sup>1041</sup>
		Avoid pregnancy for 3 months following vaccination <sup>1042</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>1043</sup>

Category	Agent or Disease	Notes
	Venezuelan equine encephalitis	Category X [Briggs 6 <sup>th</sup> ] <sup>1044</sup>
	TC-83 vaccine	Live attenuated vaccine—avoid pregnancy
		for in the immediate future after vaccination [Briggs 6 <sup>th</sup> ] <sup>1045</sup>
	Yellow fever	Live attenuated vaccine
		Category D [Briggs 6 <sup>th</sup> ] <sup>1046</sup> (contraindicated
		in pregnancy except if exposure is
		unavoidable) (administer if a pregnant
		female must travel to endemic areas
		[ <u>MMWR 1994</u> ]) <sup>1047</sup>
Miscellaneous	Hyperpyrexia [PMID	Effect of infection or immunization that
	<u>4014176</u> ] <sup>1048</sup>	can be a related ReproDev hazard
	Fava beans	Breastfeeding: Hemolysis in patient with
		G-6-PD deficiency [AAP] <sup>1049</sup>
	Aflatoxin	Growth faltering [PMID 17576701] <sup>1050</sup>
		(mycotoxins have been detected in
		human milk [ <u>PMID 18338407]</u> ), <sup>1051</sup>
		limited evidence for IUGR [PMID
		2741679], <sup>1052</sup> [PMID 9814089] <sup>1053</sup>
<b>Biologicals not</b>	Biowarfare agents (potential)	Q-fever
commonly		Lassa fever (fetal and neonatal loss)[PMID
encountered		<u>3139220</u> <sup>1054</sup>

# (X)OCCUPATIONAL PHYSICAL REPRODUCTIVE AND DEVELOPMENTAL HAZARDS

Table 12 – Occupational Physical Reproductive and Developmental Hazards List

AGENT	DATE ADDED
Altitude	06/24/2003
Excessive heat (thermal stress)	06/30/1995
Heavy 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) ALTITUDE

High altitudes (8,000 feet or more above sea level) have been associated with diminished birth weight (approximately 25 grams or more decrease per 1,000 feet increase in elevation) and with preeclampsia and gestational hypertension [PMID 10329872,<sup>1055</sup> PMID 12700368].<sup>1056</sup> Aircraft flight at high altitude is accompanied by a decrease in partial pressure of oxygen and by increased exposure to cosmic radiation [PMID 12107289,<sup>1057</sup> PMID 12455507].<sup>1058</sup> The level (or dose) of those stresses is related to the duration of the flight [PMID 11973496].<sup>1059</sup> Physical exertion during initial exposure to high altitude may present increased risk of adverse health effects. Initial (short-term, i.e., 4 to 5 days, rather than a few hours or the duration of a flight) exposures to high altitude should be limited to 8,250 feet (2,500 meters) [PMID 8888456].<sup>1060</sup>

## **B) 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. However, physical activity in pregnancy has minimal risks and has been shown to benefit most women, although some modification to exercise routines may be necessary because of these normal anatomic and physiologic changes and fetal requirements. Women with uncomplicated pregnancies should be encouraged to engage in aerobic and strength-conditioning exercises before, during, and after pregnancy.

Obstetric care providers should carefully evaluate women with medical or obstetric complications before making recommendations on physical activity participation during pregnancy. Although frequently prescribed, bed rest is only rarely indicated and, in most cases, allowing ambulation should be considered. Regular physical activity during pregnancy improves or maintains physical fitness, helps with weight management, reduces the risk of gestational

diabetes in obese women, and enhances psychologic well-being. An exercise program that leads to an eventual goal of moderate-intensity exercise for at least 20–30 minutes per day on most or all days of the week should be developed with the patient and adjusted as medically indicated [PMID 26595585].<sup>1061</sup>

Although the healthy pregnant worker generally will be able to do most of her work up until the time of delivery,<sup>1062</sup> some reduction in exertion requirements may be needed in the last trimester. The American Medical Association Guidelines for Continuation of Various Levels of Work During Pregnancy was published in 1984 and gives general guidance for physical work restrictions based on the week of gestation. NIOSH has published and revised guidelines that take into account horizontal reach, vertical height, and frequency-duration pattern.<sup>1063</sup> NLE Calc is an app based on the Revised NIOSH Lifting Equation.<sup>1064</sup> Recommendations regarding limitations on physically strenuous work **must be individualized**<sup>1065</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 prepregnancy 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.

Guidelines can be summarized as follows.<sup>1066</sup>

- General office work, standing intermittently, stooping or bending below knee level 2 or fewer times per hour, going up stairs less than 4 times per shift, and repetitive lifting of up to 24 lbs. can be continued throughout pregnancy.
- Standing for more than 30 minutes at a time can be continued up to the 8th month.
- Stooping and bending below knee level more than 2 times per hour, going up stairs 4 or more times per shift, and vertical climbing (e.g., ladders) less than 4 times per shift can be continued until the 7th month.
- Standing for more than 4 hours can be continued until into the 6th month.

Stooping and bending below knee level more than 10 times per hour and vertical climbing 4 or more times per shift can be continued until the 5th month.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.

## C) 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>1067</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>1068</sup> although bending, rather than lifting itself, may be the main cause [PMID 8282467]. <sup>1069</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>1070</sup>

Specific lifting restrictions should be individualized as described in the preceding paragraph.NIOSH Publications *Work Practices Guide for Manual Lifting*<sup>1071</sup> and <u>Applications</u> <u>Manual for the Revised NIOSH Lifting Equation</u><sup>1072</sup> provide guidance only for workers in general and do not provide specific recommendations for pregnant women. Lifting involving awkward body mechanics (such as lifting during advanced pregnancy, in confined spaces, lifting large objects, lifting while twisting or using one hand or pushing, lifting unstable objects, high speed lifting, lifting on a slippery or uneven floor) are not covered by the NIOSH guidelines, and additional restrictions should be considered [PMID 23467051].<sup>1073,1074</sup>

Based on the general guidelines given above, if a woman was able to perform a nonmaximal 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.

## D) RESPIRATOR USE IN PREGNANCY

Pregnancy is a common disqualifying reason in physicals done to clear workers for respirator use [PMID 10086199],<sup>1075</sup> although there is little support for this in the scientific literature. The type of respirator (e.g., simple dust mask or solvent-exposure canister), size and habitus of the pregnant worker, and stage of pregnancy (e.g., 3 months or 8 months gestation) are all factors that may be considered.

## E) 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>1076</sup> Most "swing shift" and "graveyard shift" 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 (<u>OPNAVINST</u> 6000.1D),<sup>1077</sup> 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. 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>1078</sup>

## F) PSYCHOLOGICAL AND PERCEIVED STRESS

A study using questionnaire data found that women undergoing fertility treatments who perceived their job as more demanding were less likely to conceive, and that likelihood to deliver after fertility treatment was associated with less working hours [PMID 16404210].<sup>1079</sup>

## G) 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>1080</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>1081</sup> and hot tub or hot bath use [PMID 1640616],<sup>1082</sup> in addition to occupational heat exposure. High-risk pregnancies (specifically, hypertensive patients) have significantly increased uterine vascular resistance during short-term heat exposure. Thus, safe short-term heat stress in uncomplicated pregnancies may be detrimental in high-risk pregnancies [PMID 7993506].<sup>1083</sup>

#### 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>1084</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>1085</sup> including neural tube defects [PMID 6446171].<sup>1086</sup> However, other human studies have failed to show any significant increase in specified developmental abnormalities.<sup>1087</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>v</sup> does not exceed 39°–39.5°C (102°–103°F) during the first trimester of pregnancy."<sup>1088</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-

<sup>&</sup>lt;sup>v</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)* 

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. <u>OPNAVINST 6000.1D</u> exempts pregnant women from standing at parade rest or at attention for longer than 15 minutes.<sup>1089</sup> In hot conditions, this time should be decreased and, preferably, standing at attention should be allowed only momentarily.

The HCP 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.

#### H) 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>1090</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>1091</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 for frequencies less than 250 Hz, and over 40 dB at 2000 Hz [PMID 8899910].<sup>1092</sup> However, one study reported sound enhancement at 125 Hz [PMID 1635729].<sup>1093</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>1094</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.

While a fetus may be vulnerable to loud noise, the mother may have decreased hearing while she is pregnant; one study found a significant decrease in hearing levels for 125, 250 and 500 Hz, beginning in the first trimester and increasing in the second and third trimesters, and returning to normal in the post-partum period [PMID 11535140].<sup>1095</sup> Whether this would result in the mother being less likely to avoid loud sounds during pregnancy is unclear.

#### 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>1096</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>1097</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>1098</sup>

#### 3) Sound Exposure Effects

According to the American Academy of Pediatrics, studies suggest exposure to excessive noise during pregnancy may result in high-frequency hearing loss in newborns, and may be associated with prematurity and intrauterine growth retardation [PMID 9836852].<sup>1099</sup> 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>1100</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>1101</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>1102</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 threefold 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>1103</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>1104</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>1105</sup> This is the guideline recommended for general consideration, and is without respect to maternal hearing protection, as neither ear plugs nor ear muffs offer any fetal hearing protection.<sup>vi</sup> Currently, definitive cut-off levels of hazardous (or non-hazardous) 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>1106</sup> There has been extended discussion of possible non-auditory consequences to maternal sound exposure, related to stress-induced increase of

<sup>&</sup>lt;sup>vi</sup> Providers may advise pregnant workers to be alert to noise beyond the workplace, as hazardous noise levels may be found outside the work or industrial setting.

catecholamine levels and placental vasoconstriction. Shift work in a "noisy" environment was associated with pregnancy-induced hypertension in one study [PMID 2772574].<sup>1107</sup> Whether sound-related, stress-induced increases of catecholamine levels and placental vasoconstriction are causally related to preterm births is unproven [PMID 8520958].<sup>1108</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>1109</sup>

#### 4) Combined Fetal Exposures to Noise and Toxicants

Whether maternal occupational exposure to noise in combination with exposure to other occupational hazards poses an increased risk of fetal ototoxicity (i.e., an additive or synergistic response) has not been established. Data from studies investigating human populations exposed to both noise and industrial chemicals have been felt to be inadequate for assessing the combined effects of noise and chemical exposures on hearing [PMID 9284647].<sup>1110</sup> In most cases, exposure to chemical toxicants would be the primary concern. Non-occupational exposures are likely also to have a role, as prenatal maternal smoking has been associated with hearing loss in adolescents [PMID 23788030].<sup>1111</sup>

#### 5) 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>1112</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>1113</sup>

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

The ACGIH Physical Agents TLV Committee has noted that an 8-hour TWA exposure of 115 dBC (as distinct from dBA) 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>1114</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. 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.
- 2. 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.
- 3. Extended exposures (more than 12 minutes) above 104 dBA should be avoided after 20 weeks gestation, even with the use of maternal hearing protection.

- 4. Impact/impulse noise exposure sufficient to require personal hearing protection should be avoided.
- 5. 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 <u>Moore</u><sup>1115</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.
- 6. Consider job rotation after the twentieth week of pregnancy for women working around intense sound levels.<sup>1116</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.

### I) IONIZING RADIATION

Exposure limits for ionizing radiation are contained in NAVMED P-5055 (Feb 2011),<sup>1117</sup> Radiation Health Protection Manual, and <u>10 CFR 20</u>; pregnant females may not receive more than 500 mrem (i.e., 0.5 rem or 5 mSv) of ionizing radiation during the course of a pregnancy (<u>10 CFR 20.1208</u>),<sup>1118</sup> and may not receive more than 50 mrem/month during that time (NAVMED P-5055).<sup>1119</sup>

# (XI) SUMMARY TABLE AND MISCELLANEOUS REPRODUCTIVE AND DEVELOPMENTAL HAZARDS

## A) SUMMARY OF REPRODEV HAZARDS

The following is a summary listing of the chemical, biological, and physical ReproDev hazards. It is taken entirely from the preceding tables, contains no details, and is given only to provide a concise list for use at worksites.

#### **Chemical Agents**

 $\alpha$ -Naphthyl-Nmethylcarbamate 1,2-Dibromo-3chloropropane 1,2-Dibromoethane 1,3-Butadiene 2,3,7,8-Tetrachlorodibenzo-pdioxin 2,4-D 2,4-Dichlorophenoxy acetic acid 2.4-Dinitrotoluene 2,6-Dinitrotoluene 2-Bromopropane 2-Ethoxyethanol 2-Methoxyethanol Acetaldehyde Acetylaminofluorene Alcohol Anesthetic gases Antimonv Arsenic Atrazine Benzene **Benzimidazoles** Bischloroethyl nitrosourea **Butiphos** Cadmium Carbarsone Carbaryl Carbendazim Carbon dioxide Carbon disulfide Carbon monoxide Chlordecone Cigarette smoke Ciguatoxin Cycloheximide DBCP

DDT (p,p'-Dichlorodiphenyltrichloroethane) DEHP di(2-ethylhexyl) Phthalate (DEHP) Dimethylaminopropionitrile (DMAPN) Dinocap (fungicide) Dinoseb (herbicide) Dioxin Disodium cvanodithiomidocarbonate Epichlorohydrin Ethanol Ethyl alcohol Ethyl carbamate Ethylene dibromide Ethylene glycol monoethyl ether Ethylene glycol monomethyl ether Ethylene glycol monomethyl ether acetate Ethylene oxide Ethylene thiourea (Ethylenethiourea) Ethylnitrosourea Gasoline Hexachlorobenzene Hexachlorocyclohexane (Lindane<sup>®</sup>) Hexamethylphosphoramide Hexamethylphosphoric triamide HMPA Iodides lodine Kepone<sup>®</sup>

Lead (Pb) Lindane Mercury and mercury compounds Mercury, elemental Mercury, inorganic Mercury, organic Methyl benzimidazolecarbamate Methyl Cellosolve acetate Methyl isocyanate Methyl mercury Methylene blue Methylmethane sulfonate Methylnitrosourea MIC Mirex Nickel o,p'-DDT Oryzalin Oxydemeton methyl p,p'-DDT p,p'-Dichlorodiphenyltrichloroethane PCBs Perchloroethylene (PCE) Phthalates Polychlorinated biphenyls (PCBs) Sevin® TCDD TCE Tetrachloroethylene Tobacco smoke environmental (secondary/passive) Toluene Toluene-2,4-diamine Toluenediamine Trichlorfon Trichloroethylene (TCE)

Urethane (ethyl carbamate - NOT "polyurethane") VCM Vinyl chloride (monomer, not polyvinyl chloride or PVC) Xylenes

#### **Biological Agents**

Aflatoxin **Biowarfare agents Brucellosis** Coxsackievirus Cytomegalovirus Ebola virus Echovirus Ehrlichiosis Fava beans **Group B Streptococcus** Hepatitis B virus Hepatitis E virus Human immunodeficiency virus Human parvovirus B19 Human T-cell leukemia virus type 1 Hyperpyrexia Influenza H1N1 **Invasive Hemophilus** influenza Leishmaniasis Leprosy Listeriosis Lyme disease Lymphocytic choriomeningitis virus Malaria Mumps Mumps virus Poliovirus **Relapsing fever** Rubella Rubella virus Syphilis Toxoplasmosis Trypanosomiasis Tuberculosis Typhoid fever Vaccinia Varicella/herpes zoster virus

Varicella/herpes zoster virus vaccine Venezuelan equine encephalitis TC-83 vaccine West Nile Virus Yellow fever Zika Virus

#### **Physical Agents**

Altitude Excessive heat (thermal stress) Heavy lifting Impact Ionizing radiation Noise Postures, such as standing in military formations (attention or parade rest), and other prolonged periods without movement) Respirator use Shift work Vibration

## B) OTHE REPRODEV HAZARDS

The following table is included separately for completeness. Hazards include certain drugs of abuse as well as other substances unlikely to be considered in routine workplace evaluation.

Alcohol	64-17-5		(See <u>Ethanol</u> under Drug Hazards)
Aspartame	22839-47-0	07/05/00	Category B [Briggs 4th] <sup>1120</sup>
			Category C in women with
			phenylketonuria [Briggs 4th] <sup>1121</sup>
			Breastfeeding: With caution if
			mother or infant has
			phenylketonuria [ <u>AAP</u> ] <sup>1122</sup>
Cigarette smoking			(See <u>Tobacco smoke (primary)</u> )
Cocaine	50-36-2	06/30/95	Category C [Briggs 4th] <sup>1123</sup>
			Category X if nonmedicinal use
			[Briggs 4th] <sup>1124</sup> (associated with
			fetal malformations, placental
			toxicity [ <u>PMID 9434858</u> ]) <sup>1125</sup>
			Breastfeeding: Adverse effects
			reported (may cause cocaine
			intoxication) [ <u>AAP</u> ] <sup>1126</sup>
Ecstasy	ACX number		(MDMA or N-Methyl-3,4-methyl-
	X1008014-7		enedioxyamphetamine)
			(See <u>Amphetamines</u> )
Ethanol	64-17-5		(See <u>Ethanol</u> under Drug Hazards)
Ethyl alcohol	64-17-5		(See <u>Ethanol</u> under Drug Hazards)
Fava beans		07/05/00	Breastfeeding: Hemolysis in patient
			with G-6-PD deficiency [ <u>AAP</u> ] <sup>1127</sup>
Heroin	561-27-3		Pregnancy: Preterm birth [PMID
			2304039], <sup>1128</sup> neonatal
			withdrawal [Williams] <sup>1129</sup>
			Breastfeeding: Contraindicated
			(tremors, restlessness, vomiting,
			poor feeding) [ <u>AAP</u> ] <sup>1130</sup> (excreted
			in milk [ <u>PMID 9363416</u> ]) <sup>1131</sup>
MDMA	ACX number		(Ecstasy or N-Methyl-3,4-methyl-
	X1008014-7		enedioxyamphetamine)
			(See <u>Amphetamines</u> )
N-Methyl-3,4-methylene-	ACX number		(Ecstasy or MDMA)
dioxyamphetamine	X1008014-7		(See <u>Amphetamines</u> )

 Table 13 – Miscellaneous Reprodev Hazards Not Generally Considered

Tobacco smoke (primary)	 06/30/95	Males: Decreased sperm
(see <u>Tobacco smoke -</u>	00,00,00	concentration and motility [PMID
environmental for		<u>9051418</u> ] <sup>1132</sup> and percentage of
second hand tobacco)		sperm with normal morphology
		[ <u>PMID 1521002</u> ] <sup>1133</sup>
		Females: Decreased fertility [PMID
		<u>9829871</u> ], <sup>1134</sup> decreased
		fecundity, early mean age of
		menopause [PMID 9434858] <sup>1135</sup>
		Pregnancy: IUGR [PMID 9131707] <sup>1136</sup>
		[PMID 9434858] <sup>1137</sup>
		Increased blood pressure (which
		returns to normal within two
		years) [PMID 8648540] <sup>1138</sup>
		Retinal vascular abnormalities
		(which resolve by age 6 months)
		[PMID 10839873] <sup>1139</sup>
		Adverse lung function effects [PMID
		9272918] <sup>1140</sup>
		Breastfeeding: Conflicting studies
		finding decreased [PMID
		9457000] <sup>1141</sup> or increased [PMID
		8067348] <sup>1142</sup> infant growth

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

Two forms (NAVMED 6260/8 and NAVMED 6260/9) have previously been used to help evaluate workers for potential ReproDev hazard exposures. At the time of this update, those forms have expired and are no longer valid. Until updated versions are released, locally developed forms may be used to assist in managing workers with occupational exposures of ReproDev concern. Any form developed locally should follow the appropriate guidelines for creating medical forms and to ensure the protections of personal identifiers and health information.

The necessity to maintain confidentiality in matters of personal health must be emphasized.

## (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>1143</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>1144</sup> and <u>OPNAVINST 5100.23 series</u>, Navy Safety and Occupational Health Program Manual CH1, 21 July 2011<sup>1145</sup> pertain to Navy employees.

The Pregnancy Discrimination Act<sup>1146</sup> clarifies employment practices related to pregnancy or related conditions. <u>29 CFR 1610 Appendix</u><sup>1147</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. (The worker's personal physician may require a signed release before discussing the case.)

## C) REGULATIONS CONCERNING PREGNANT SERVICEWOMEN

<u>SECNAVINST 1000.10A</u><sup>1148</sup> and <u>OPNAVINST 6000.1D</u><sup>1149</sup> together provide comprehensive policy about issues related to pregnant servicewomen.

<u>OPNAVINST 6000.1D</u><sup>1150</sup> prohibits diving as part of physical training by pregnant servicewomen. <u>BUMEDINST 6200.15A</u>, <u>Suspension of Diving Duty During Pregnancy</u>,<sup>1151</sup> provides guidance on suspension of diving duty of pregnant servicewomen.

## (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.

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<sup>907</sup> Bristol-Myers Squibb Oncology/Immunology Division, PO Box 4500, Princeton, NJ 08543-4500. Phone 800-426-7644, 609-818-3737.

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<sup>909</sup> Alza Pharmaceuticals, 1900 Charleston Rd., Mountain View, CA 94043. Phone 800-634-8944, 800-506-4959, 800-227-9953. Fax 650-962-2488, 888-261-8045.

<sup>910</sup> Alza Pharmaceuticals, 1900 Charleston Rd., Mountain View, CA 94043. Phone 800-634-8944, 800-506-4959, 800-227-9953. Fax 650-962-2488, 888-261-8045.

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<sup>914</sup> BTG Pharmaceuticals Corp., Iselin, NJ 08830. Delatestryl Wholesale Network, 7345 Airport Freeway, Fort Worth, TX 76118. Phone 800-741-2698. Fax 800-741-2696.

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<sup>925</sup> Immunex Corporation, 51 University Street, Seattle, WA 98101. Phone: 800-466-8639. Fax 800-221-6820, 206-223-5525.

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