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Reproductive Risks Associated with Hazardous Drug Exposures in Healthcare Workers and Recommendations for Reducing Exposures

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Foreword

The purpose of this Current Intelligence Bulletin is to increase awareness among healthcare workers and their employers about the potential adverse reproductive health effects from working with antineoplastic and other hazardous drugs. In addition, it will provide measures for protecting the reproductive health of workers and the health of their offspring. Healthcare workers who prepare or administer hazardous drugs or who work in areas where these drugs are used can be exposed when these agents are in the air or on work surfaces, drug vials and containers, contaminated clothing, medical equipment, and patient excreta. Workplace exposures to hazardous drugs have been associated with health effects such as skin disorders, adverse reproductive outcomes (including infertility, miscarriage, and congenital malformations), and possibly leukemia and other cancers. Of these, reproductive health is one of the most vulnerable endpoints, because many hazardous drugs used for cancer treatment target rapidly dividing cells in the same way teratogens target rapidly dividing embryonic cells. The risk can be influenced by the timing of the exposure and the potency and toxicity of the hazardous drug.

The production, distribution, clinical preparation, administration, and disposal of pharmaceutical products are widespread and essential to the healthcare industry. New areas of pharmaceutical development are continually bringing new drugs and fundamental changes to methods for treating and preventing or minimizing diseases. At the same time, a large number of medications or mixed exposures can be hazardous to healthcare workers who handle them and to their fetuses or nursing offspring. This NIOSH *Current Intelligence Bulletin* will help make workers and employers more aware of these hazards and provide recommendations for preventing exposures.

This *Current Intelligence Bulletin* applies to all healthcare workers who might handle hazardous drugs, such as pharmacists and pharmacy technicians, registered nurses, advanced practice registered nurses, licensed practical/vocational nurses, nurses' aides, physicians, physicians' assistants, operating

room personnel, shipping and receiving personnel, waste handlers, maintenance workers, laundry workers, laboratory personnel, and workers in veterinary practices. The current number of healthcare workers in the United States potentially exposed to hazardous drugs exceeds 8 million. However, not all of these workers will be exposed to hazardous drugs, and only a fraction of those who are exposed will be at reproductive risk. Workers in the drug manufacturing sector may also be exposed to hazardous drugs. However, the primary focus of this *Current Intelligence Bulletin* is workers in healthcare settings because of their unique potential to be in an environment of multiple exposures.

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Abstract

Healthcare workers who handle, compound (prepare), administer, or dispose of hazardous drugs can incur risks to their health, including reproductive harm. This document describes the vulnerability of workers, fetuses, and nursing infants of exposed workers to reproductive and health hazards and reviews human and animal studies of exposure to hazardous drugs. On the basis of a review of published data, the National Institute for Occupational Safety and Health (NIOSH) recommends steps to reduce employee exposure to hazardous drugs for all healthcare workers and especially those at reproductive risk. Special consideration may be needed for those workers with underlying medical conditions that may put a worker at exceptional risk of harm. These steps involve adhering to established industrial hygiene procedures, education and training for employees and employers on the safe handling of hazardous drugs, and including the implementation of an alternative duty program when exposure cannot be eliminated. Employers and all workers in healthcare settings (including employees and nonemployees such as contractors and credentialed providers) can work together to establish a program to provide a safe working environment for all healthcare workers, especially those who are at reproductive risk if exposed to hazardous drugs.

Contents

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Abbreviations

AHFS	American Hospital Formulary Service
ANA	American Nurses Association
ASHP	American Society of Health System-Pharmacists (Formerly known as American Society of Hospital Pharmacy)
BSC	Biological safety cabinet
CACI	Compounding aseptic containment isolator
CAPhO	Canadian Association of Pharmacy in Oncology
CFR	Code of Federal Regulations
CSTD	Closed system drug-transfer device
HSE	Health and Safety Executive
IARC	International Agency for Research on Cancer
NIOSH	National Institute for Occupational Safety and Health
NRC	Nuclear Regulatory Commission
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
ONS	Oncology Nursing Society
PPE	Personal protective equipment
SDS	Safety Data Sheet (Formally Material Safety Data Sheet)
USP	United States Pharmacopeial Convention

Glossary

Alternative duty: Temporary reassignment of duties, often within the same job, to avoid hazardous situations or agents (in this case, exposure to hazardous drugs).

Antineoplastic drug: A chemotherapeutic agent that controls or kills cancer cells. Drugs used in the treatment of cancer are cytotoxic but are generally more damaging to dividing cells than to resting cells.

Carcinogenicity: The ability or tendency to produce cancer.

Chemotherapy drug: A chemical agent used to treat diseases. The term usually refers to a drug used to treat cancer. Similar drugs are also known as antineoplastic and cytotoxic.

Closed system drug-transfer devices (CDTDs): A drug transfer device that mechanically prohibits the transfer of environmental contaminants into the system and the escape of hazardous drug or vapor concentrations outside the system.

Cytotoxic: A pharmacologic compound that is detrimental or destructive to cells within the body.

Engineering controls: Devices designed to eliminate or reduce worker exposures to chemical, biological, radiological, ergonomic, or physical hazards. Examples of those used in healthcare include laboratory fume hoods, glove bags, needleless systems, closed system transfer devices, biological safety cabinets, containment isolators, and robotic systems.

Genotoxicity: The ability to damage or mutate DNA. Genotoxic substances are not necessarily carcinogenic.

Hazardous drug: Any drug identified by at least one of the following criteria: carcinogenicity; teratogenicity or developmental toxicity; reproductive toxicity in humans; organ toxicity at low doses in humans or animals; genotoxicity; or new drugs that mimic existing hazardous drugs in structure or toxicity.

Healthcare workers: All workers who are involved directly or indirectly in the care of patients. Examples of those at risk for exposure to hazardous drugs include pharmacists; pharmacy technicians; registered nurses, advanced practice registered nurses; licensed practical/vocational nurses; nurses' aides; physicians; physicians' assistants; home healthcare workers; and workers in environmental services (housekeeping, laundry, and waste disposal).

Mutagenicity: The ability of increasing the spontaneous mutation rate by causing changes in the DNA.

Personal protective equipment (PPE): Items such as gloves, gowns, respirators, goggles, face shields, and others that protect individual workers from hazardous physical or chemical exposures.

Reproductive hazard: An agent that interferes with the ability of a couple to achieve a successful birth.

Reproductive hazards affect fertility, conception, pregnancy, and/or delivery.

Reproductive risk: Reproductive risk refers to risks to the reproductive systems of adult men and women, and outcomes of pregnancies, including: measurements of fertility in men and women, menstrual function, miscarriage (spontaneous abortion), preterm birth, abnormal birth weight, and developmental and reproductive outcomes in offspring.

Reproductive toxicity: The ability to cause adverse effects on the male and/or female reproductive system.

Risk assessment: Characterization of potentially adverse health effects from human exposure to environmental or occupational hazards. Risk assessment can be divided into five major steps: hazard identification, dose–response assessment, exposure assessment, risk characterization, and risk communication.

Susceptible populations: Those individuals with medical history or personal fertility history (e.g., repeated miscarriages) or any other underlying medical conditions that may put them at exceptional risk of harm.

Temporary reassignment: An assignment to another position, at the same pay scale, for a specified period. At the end of the temporary reassignment, the employee returns to the original position or to a position of comparable status, tenure, and pay.

Teratogenicity: The capability of producing fetal malformations.

Reproductive Risks Associated with Hazardous Drug Exposures in Healthcare Workers and Recommendations to Reduce Exposures

Background

The acute and chronic toxicity of antineoplastic drugs is well recognized in treated patients including their reproductive and developmental toxicity. Healthcare workers who compound (prepare) or administer antineoplastic drugs, or who work in areas where these drugs are used can be exposed to these agents when they are present on contaminated work surfaces, drug vials and containers, contaminated clothing and medical equipment, and in patient excreta and secretions such as urine, feces, vomitus, and sweat (Appendix 1). The National Institute for Occupational Safety and Health (NIOSH) has developed an approach to minimizing exposure to antineoplastic and other hazardous drugs with the publication of the NIOSH Alert: Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings [NIOSH 2004] that includes a combination of industrial hygiene practices, starting with engineering controls. Engineering controls place a barrier between the worker and the hazard to reduce exposure. These engineering controls include biological safety cabinets (BSCs) or compounding aseptic containment isolators (CACIs), closed system transfer devices (CSTDs), robotic systems, and needleless systems. Additional controls should include vigilant adherence to safe work practices and administrative controls. The use of personal protective equipment (such as gowns, gloves, and eye and respiratory protection) is also essential for worker protection [NIOSH 2009].

Measurement of surface contamination is currently the best indication of the level of environmental contamination in areas where hazardous drugs are prepared, administered to patients, or otherwise handled (such as receiving areas, transit routes throughout the facility, and waste storage areas) [Hon et al. 2011]. In a follow-up study, Hon and coworkers [2014] reported that 20% of the workers sampled

had detectable amounts of cyclophosphamide on their hands. Studies that have attempted to do so have shown an association between surface contamination and worker exposure [Pethran et al. 2003; Connor et al. 2010; Villarini 2011], and surface contamination is the most commonly used metric for evaluating the workplace for hazardous drugs. Workplace contamination with hazardous drugs in the United States has not changed considerably over the past decade or more [Connor et al. 1999; 2010, Wick et al. 2003; Sessink et al 2011; 2013]. This finding indicates that worker exposure probably has remained constant over that time, despite efforts to reduce or eliminate environmental contamination.

The introduction of Class II BSCs for the preparation of hazardous drugs in the 1980s substantially reduced the potential for worker exposure [Anderson et al. 1982], but not as efficiently as first believed [Connor et al. 1999]. The more recent use of CACIs has not been widespread, and these have not been proven to offer more protection to workers than BSCs [Seger et al. 2012]. The use of robotic systems to prepare hazardous drugs may reduce environmental contamination and worker exposure to these drugs. However, their high cost makes them prohibitive for most facilities [Seger et al. 2012]. The addition of CSTDs for the preparation and administration of hazardous drugs has been shown to reduce surface contamination and possibly worker exposure, but they do not totally eliminate them [Connor et al. 2002; Wick et al. 2003; Harrison et al. 2006; Sessink et al. 2011, 2013]. Despite improvements in engineering controls and other attempts to reduce environmental contamination, hazardous drugs are still being released into the work environment and workers are being exposed to them. Therefore, for the foreseeable future, contamination of the workplace with hazardous drugs and/or worker exposure to them will be an issue with no suitable solution.

Recent research has shown that even when all of these controls are used in healthcare settings, the potential for exposure to antineoplastic drugs cannot be completely eliminated [Schierl et al. 2009; Connor et al. 2010; Siderov et al. 2010; Yoshida et al. 2010; Davis et al. 2011; Sessink et al. 2011; Turci

et al. 2011; Chu et al. 2012; Polovich and Martin 2011; Kopp et al. 2013]. Therefore, an additional level of protection might be required for those healthcare workers who are most vulnerable to the reproductive and developmental effects of hazardous drugs in the form of voluntary temporary alternative duty.[ASHP 1990, 2006; OSHA 1999; HSE 2003; Lawson et al. 2006; ACOEM 2011; ONS 2009; 2011].

Description of Exposure

In 2004, NIOSH published an alert on antineoplastic and other hazardous drugs that describes safe handling practices for all healthcare workers [NIOSH 2004]. The alert included a list of drugs that were considered hazardous to workers. That list of hazardous drugs was most recently updated in 2014 to include drugs newly approved by the U.S. Food and Drug Administration (FDA) and other drugs with new FDA safety warnings based on post-marketing information [NIOSH 2014]. This document also contains new guidance on the safe handling of hazardous drugs. Approximately half of the drugs listed as hazardous by NIOSH are classified as antineoplastic, and the remainder comprise hormonal agents, immunosuppressants, antiviral agents, and others. Although the current document pertains to published information on exposure to primarily antineoplastic drugs, the information and recommendations herein can be generalized to include other hazardous drugs.

Appendix 2 lists all drugs that NIOSH considers potentially hazardous to healthcare workers as of 2014 [NIOSH 2014]. Of the 184 drugs listed, 99 are FDA Pregnancy Category D and 43 are Pregnancy Category X; the remainder of the listed drugs is Category C or B. For Category D drugs, there is positive evidence of human fetal risk, based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks to the fetus (Appendix 3). Category X drugs are those for which the fetal risk clearly outweighs the benefits to patients [Timpe et al. 2004; Briggs et al. 2008; 21 CFR 201.57(c)(9)(i)]. Most of

the remaining 30 percent of the drugs are classified as Category C, in which animal reproduction studies have shown an adverse effect on the fetus; there have been no adequate, well-controlled studies in humans, but the potential benefits might warrant use of a Category C drug in pregnant patients despite the fetal risks. However, many drugs classified as Category C have reproductive warnings or properties similar to those of the drugs in Category D. Four of the drugs are classified as Category B, which differs from Category C in that animal reproduction studies have failed to demonstrate a risk to the fetus, but is similar in that there have not been adequate studies in humans and there is still potential for concern (Appendix 2). According to the FDA, the current pregnancy category labeling may be misleading [FDA, 2008]. Using A, B, C, D and X to describe the risk of fetal harm implies that risk increases from one category to the next. In fact, C- and D-category drugs may have risks similar to those in category X, but risk is weighed against benefit. When considered in the context of occupational exposure, there are no benefits associated with drug exposure; therefore, occupational exposure of pregnant workers cannot be assumed to be harmless especially since the workers may be exposed to multiple hazardous drugs daily over many years. Because exposure to drugs that have adverse reproductive effects is possible in many healthcare settings, additional precautions and safeguards might be required to better protect vulnerable populations such as fetuses and breastfed infants.

By definition, a reproductive hazard affects the reproductive function of women or men or the ability of couples to conceive or bear healthy children [HSE 2003]. Some chemicals, including many hazardous drugs, are considered reproductive hazards on the basis of laboratory studies in animals or epidemiological studies in humans that show they can affect fertility or pregnancy outcomes or cause birth defects. A substantial number of these drugs have been identified by NIOSH as hazardous and are also known or suspected human carcinogens [IARC 2014]. Many are teratogenic and/or have adverse reproductive effects. In addition, numerous highly hazardous but therapeutically useful drugs are known to be present in the breast milk of women who are being treated with them [Briggs et al. 2008]. Most

hazardous drugs are used to treat illnesses such as cancer, autoimmune disorders, or human immunodeficiency virus infection [NIOSH 2004; 2014]. However, healthcare workers who are unintentionally exposed to these drugs at work face several health risks, including reproductive risks (e.g., risks to the reproductive systems of adult men and women, and outcomes of pregnancies).

In the United States, an estimated 8 million healthcare workers [BLS 2011] are potentially exposed to hazardous drugs at their worksites. It is not known how many are exposed to hazardous drugs but many of these workers are women of reproductive age and should be aware of the potential [Hood 2008; Alex 2011]. Because the estimated number of U.S. workers potentially exposed to hazardous drugs is based on job classifications and work locations, not all of the workers in a particular job classification will be exposed. In addition, for males, the only reproductive risk is exposure during the period leading up to conception. Women who are not at risk for adverse reproductive outcomes are those who cannot conceive, are utilizing reliable means of contraception, or are post-menopausal. Therefore, the actual number of men and women who may be at reproductive risk while exposed to hazardous drugs is considerably less than 8 million. However, because of the nature of these drugs, workers may be at risk for other adverse health outcomes, such as acute and chronic effects of drug exposure.

These workers include pharmacists and pharmacy technicians, registered nurses, advanced practice registered nurses, licensed practical/vocational nurses, nurses' aides, physicians, physicians' assistants, operating room personnel, shipping and receiving personnel, waste handlers, maintenance workers, laundry workers, laboratory personnel, and workers in veterinary practices and potentially others working in healthcare settings who come into contact with drugs or drug waste [NIOSH 2004]. Healthcare workers are exposed to hazardous drugs when they compound, administer, or dispose of hazardous drugs, clean up spills or patient waste, or touch surfaces that are contaminated with these drugs. These activities can create aerosols or generate dust, thereby increasing exposure [OSHA 1999; NIOSH 2004; ASHP 2006; ONS 2011]. Skin absorption and inhalation are the most common ways a healthcare worker

may be exposed to hazardous drugs. However, ingestion (from hand-to-mouth contact), accidental injection through a needle stick, or other sharps injury is also possible [NIOSH 2014].

When is a Worker Particularly Vulnerable to Reproductive Hazards?

Antineoplastic drugs can affect reproductive function in both males and females exposed to the drug. For reproductive health hazards, there is a "window of risk" when men and women are particularly vulnerable. In women treated with antineoplastic drugs, adverse effects have been reported including damage to ovarian follicles, decreased ovarian volume, and ovarian fibrosis resulting in amenorrhea and menopausal and other symptoms [Knobf 2006]. For pregnant women, the window of risk begins approximately one month before conception and lasts through the pregnancy. However, specific drugs may remain in the body for an extended period of time, especially if exposure is continuous. In addition, some drugs are known to enter the breast milk of treated patients [NIOSH 1996, 1999; HSE 2003; Briggs et al. 2008]; therefore, the infants of healthcare workers could be exposed during breastfeeding.

In men, reported adverse effects include primary or secondary hormonal changes. In addition, a man can expose his female partner and/or her developing fetus via contaminants on his skin or clothing, or during sexual intercourse [Pichini et al. 1994]. Men produce sperm over approximately a 2-month cycle; therefore, a man's sperm is vulnerable to hazardous exposures from as early as 2 months before conception [Maltaris et al. 2006]. Consequently, both male and female workers who are handling hazardous drugs during any of these critical reproductive periods should be especially aware of risks to the health of their offspring.

Vulnerability of the Developing Fetus and Newborns

Although adults can be adversely affected by prolonged exposures to certain chemicals, developing fetuses and newborns up to the age of 6 months are usually more sensitive to chemical toxicity because of the incomplete development of systems for biotransformation/detoxification and elimination of toxicants. Unlike older children and adults, such pathways are underdeveloped and cannot efficiently detoxify or excrete drugs. Therefore, toxicants remain in higher concentrations in the blood for longer periods [Scheuplein et al. 2002]. Examples of toxic substances and carcinogens that affect infants more than adults include some pesticides, tobacco smoke, radiation, and a variety of chemicals. With many chemical exposures, it is known that the fetus is more susceptible than the mother to the toxic chemical [NRC 1993; Goldman 1995; Scheuplein et al. 2002; Brent et al. 2004; Perera 2011]. In addition, studies have shown that exposure to chemicals and radiation in utero and early in life can disproportionally increase the occurrence of childhood cancer compared with exposures that occur later in life [Perera 2011].

Reproductive effects might occur at lower exposure concentrations than exposure limits established by the Occupational Safety and Health Administration (OSHA) or recommended by NIOSH [2010] or the American Conference of Governmental Industrial Hygienists [ACGIH 2012]. This is because many of these limits are based on protecting adult workers from health effects other than reproductive endpoints (for example, neurotoxicity or cancer). In 1991, the General Accounting Office (GAO) reviewed regulations on environmental chemicals known to cause adverse reproductive and developmental outcomes. They reported that two-thirds of the major regulatory decisions for the 30 chemicals reviewed were based on cancer and acute toxicity, not reproductive or developmental effects [U.S. GAO 1991]. In addition, in most cases, exposure limits have not been established for hazardous drugs [NIOSH 2004].

Because the placenta is not an effective barrier to low-molecular-weight molecules, many of the antineoplastic and other hazardous drugs can reach the fetus in concentrations that could have deleterious effects [Arnon et al. 2001]. Drugs with a molecular weight of less than 600 Daltons usually

cross the placenta; those with molecular weights greater than 1000 Daltons typically do not. Since many antineoplastic drugs have a molecular weight within these parameters, they can readily cross the placenta [Pacifici and Nottoli 1995]. In addition, the placenta is also more permeable to lipophilic chemicals and drugs. Moreover, it has been hypothesized that many antineoplastic drugs actually target developing fetuses in the same way they target the rapidly proliferating cells and active DNA metabolism of cancer cells [Selig et al. 2012].

Experimental Studies

Animal Studies

Laboratory studies have demonstrated that many antineoplastic drugs are teratogenic, often in more than one animal species. Some classes of drugs are more hazardous than others [Shepard 1995; Schardein 2000]. As a group, the antineoplastic drugs have been shown in animal studies to be some of the most potent teratogenic agents known at doses typically used in cancer treatment. Alkylating agents, anthracycline antineoplastic antibiotics, and antimetabolites all have potent teratogenic activity in multiple animal species. Antimetabolites are associated with birth defects more frequently than other antineoplastic agents. Alkylating agents are generally less teratogenic than the antimetabolites. Vinca alkaloids are potent teratogens in animals but do not appear to have similar effects in humans [Meirow and Schiff 2005]. Many antineoplastic drugs, in addition to the alkylating agents and antimetabolites, are also teratogenic in laboratory animals. In addition to the antineoplastic drugs, numerous other drugs have been demonstrated to be teratogenic in one or more species [Schardein 2000]. Preclinical laboratory testing of drugs in general demonstrates various adverse effects on reproduction and fertility, often in the absence of maternal toxicity [NIOSH 2004; 2014]. Additional information on teratogenic, reproductive, and fertility effects of specific drugs can be found in the drug package inserts and in the Safety Data Sheets (SDSs).

Human Studies

Patients Treated with Antineoplastic Drugs

Infertility following treatment with antineoplastic drugs has been reported for both men and women because of the gonadal toxicity of the drugs [McInnes and Schilsky 1996; Maltaris et al. 2007]. A number of individual antineoplastic drugs and some combinations of antineoplastic drugs have been identified as causing gonadal dysfunction in male cancer patients [Meistrich et al. 1997; Wallace et al. 2005]. Individual drugs such as cyclophosphamide, melphalan, chlorambucil, procarbazine, and cisplatin and drug combinations such as MOPP (nitrogen mustard, oncovin, procarbazine, and prednisone) have produced prolonged azoospermia in males [Wallace et al. 2005]. The teratogenic effects on the fetuses of women treated with these drugs are well documented [Shepard 1995; Schardein 2000; Meirow and Schiff 2005; Shahab and Doll 2008; Azim et al. 2010a,b; NTP 2013]. The observed teratogenic effects depend on the drug, the dose, and the developmental stage of the fetus at exposure. Schardein [2000] lists several common antineoplastic drugs as human teratogens. Although information is available from human studies about individual drug exposures, most malignancies are treated with multi-drug regimens [Azim et al. 2010a,b]. Therefore, many of the known teratogenic effects of individual drugs have been derived from animal studies.

Three recent publications have reviewed the effects of cancer treatment on the developing fetus. The first reported the effects of antineoplastic drugs used to treat solid tumors, primarily breast and ovarian cancers [Azim et al. 2010a,b; Selig et al. 2012]. Although data are limited or not available for many drugs, the authors concluded that, in general, antineoplastic drugs have adverse effects on the fetus during the first trimester. Exposure during the first 2−3 weeks of pregnancy typically results in miscarriage, but not teratogenesis [Azim 2010a]. In patients treated with these drugs, brief exposures during early pregnancy to antineoplastic drugs (those for which there are data) had little effect on the

fetus. However, continued exposure resulted in congenital anomaly rates of approximately 20% which is in contrast to background rates that are normally 3-4 %. Most of the antineoplastic drugs they reviewed had little effect on the fetus in the second and third trimesters, with the exception of methotrexate. Since methotrexate causes malformations, the authors concluded this drug should be avoided altogether during pregnancy.

The second article reviewed antineoplastic drugs used in the treatment of hematological tumors [Azim et al. 2010b]. In contrast to the drugs used to treat solid tumors, those used to treat hematological tumors were significantly associated with both miscarriages and fetal malformations when administered during the first trimester. Patients treated with imatinib during the first trimester but not the second were at high risk of fetal malformations. Daunorubicin and idarubicin have been associated with a high incidence of fetal malformations even when administered after the first trimester, and therefore they should be avoided throughout pregnancy.

The third review article [Selig et al. 2012] evaluated the adverse reproductive effects of single-agent and combination therapy and reported outcomes similar to those of Azim [2010 a,b]. They reported that the antimetabolites and alkylating agents had the highest rates of adverse pregnancy outcomes in comparison with mitotic inhibitors and antibiotics. Findings about single-agent exposures were mixed, perhaps due to small sample sizes, but Selig et al. noted that exposure of the fetus during the first trimester was most critical. A recent report by the National Toxicology Program [NTP 2013] provides a comprehensive summary of the effects of some antineoplastic drugs on reproductive outcomes in patients. This report also briefly addresses occupational exposure to these drugs and possible adverse reproductive outcomes in healthcare workers. A large number of antineoplastic drugs are available for treatment of cancer and other diseases, and data are not available for all drugs regarding adverse reproductive effects. However, most of these drugs have an adverse effect—especially resulting in

miscarriages—when given during the first trimester, particularly during the first 2−3 weeks of pregnancy.

In summary, data from studies of patients being treated for cancer indicate that the first trimester is the most vulnerable time for exposure to result in adverse effects such as miscarriage and birth defects. This finding is supported by the recent study [Lawson et al. 2012] of occupational exposures among nursing personnel, which showed a stronger association of exposure to antineoplastic drugs with first-trimester miscarriages than with second-trimester miscarriages. However, as mentioned above, some drugs such as methotrexate, daunorubicin, and idarubicin might also have an effect on the fetus during the second and third trimesters. Post-marketing reports of adverse reproductive effects in patients and their offspring can often be found in the drug package inserts and the SDSs.

Patients Treated with Hazardous Drugs Other Than Antineoplastic Drugs

Although the occupational studies listed in Table 1 dealt with antineoplastic drugs used to treat cancer, NIOSH has identified hazardous drugs that are used to treat noncancerous conditions [NIOSH 2004; 2014]. Many of these drugs are reproductive hazards and are classified as FDA Pregnancy Category D or X (Appendix 2). Some examples of adverse reproductive effects in patients treated with hazardous drugs other than antineoplastic drugs include the following:

- Thalidomide, though now used as a cancer treatment, has caused severe birth defects or fetal death following treatment of pregnant women for morning sickness. It is now available only under a restricted distribution program in order to prevent fetal exposure [Shahab and Doll 2008].
- Diethylstilbestrol (DES), also commonly used in veterinary medicine, has been associated with

an increased risk of breast cancer in women who took this drug and is linked to breast, vaginal, and cervical cancers in the daughters of women who took it during their pregnancies [Hatch et al. 1998; Palmer et al. 2002]. Adverse effects, including increased rates of testicular cancer in male offspring of treated mothers, have also been reported [Strohsnitter and Noller 2001].

- The anti-seizure medication valproic acid and products containing valproic acid are associated with increased risk of major malformations, including neural tube defects, when taken during pregnancy. In addition, children of mothers who took one of these drugs during pregnancy have an increased risk of low cognitive test scores [Garry and Truran 2011].
- When Paxil, an antidepressant, is taken during the first trimester, there is evidence of increased risk of birth defects, particularly heart defects [GlaxoSmithKline 2011].
- Ribavirin, an antiviral drug administered via nebulizer, can cause harm or death to the fetus in women taking it when they become pregnant. Fetal harm or death may also occur if the father was taking it when his partner became pregnant. Thus, for both men and women taking ribavirin, there are warnings against pregnancy. Two forms of birth control are required for both men and women, along with monthly pregnancy tests for women taking ribavirin and for female partners of men during treatment. The pregnancy tests must continue for 6 months after treatment [Merck Sharp & Dohme 2003].
- Finasteride, a drug used to treat benign prostatic hypertrophy, can be absorbed through the skin. If the film coating of the tablet has been broken or the tablet crushed, it should not be handled by a woman who is pregnant or may potentially be pregnant due to the potential risk to the male fetus [Merck Sharp & Dohme 2014].

Healthcare Workers Exposed to Hazardous Drugs

Exposure to Antineoplastic Drugs

An extensive review of the literature linking occupational exposure to antineoplastic drugs and adverse reproductive effects was conducted through February 2014 using the databases as listed in Appendix 4.

Tables 1-3 include studies of healthcare workers occupationally exposed to antineoplastic drugs and the occurrence of adverse reproductive outcomes, including infertility, miscarriages, stillbirths, pregnancy outcomes, and congenital malformations. All relevant published studies from the open literature were included in this summary. These data were summarized by Connor et al. [2014].

Table 1 summarizes 8 studies of occupational exposure to antineoplastic drugs and congenital anomalies observed in offspring of workers. The primary limitation of these studies is the small sample sizes; five of the eight studies had 10 or fewer exposed cases, and all studies had fewer than 20 exposed cases. The small sample sizes resulted in several other important limitations. These included a limited ability to adjust for confounding; the need to group anomalies that had different etiologies; and wide confidence intervals, which reflect poor statistical power. However, of the studies that had more than five exposed cases, three showed significantly increased risks associated with exposure [Hemminki et al. 1985; McDonald et al. 1988; Peelen et al. 1999], and two showed increased risks that were not statistically significant [Skov et al. 1992; Ratner et al. 2010]. The odds ratios of adjusted models ranged from 1.36 (95% confidence interval, 0.59–3.14) [Skov et al. 1992] to 5.1 (95% confidence interval, 1.1–23.6) [Peelen et al. 1999]. A meta-analysis [Dranitsaris et al. 2005] of four studies with exposure periods ranging from 1966 to 1985 [Skov et al. 1992; Hemminki et al. 1985; Peelen et al. 1999; McAbee et al. 1993] reported a crude odds ratio of 1.64 (95% confidence interval, 0.91–2.94) for all congenital anomalies combined. Although the preceeding studies suggest an increased risk for congenital anomalies with maternal occupational exposure, the limitations and wide confidence intervals make the size of the adverse effect uncertain. In addition, studies that reflect current exposure levels are needed, because the studies published to date include data that were collected before the year 2000, the majority

of which were conducted prior to 1985.

Studies of maternal occupational exposure to antineoplastic drugs and miscarriage are shown in Table 2. We identified eight studies of miscarriage, an additional three studies that analyzed combined outcomes of miscarriage and stillbirth, four studies of stillbirths, and two studies of tubal pregnancies. The studies of miscarriage had mixed results, and three of these studies were limited by small sample sizes (fewer than 20 exposed cases). The three largest studies [Stücker et al. 1990; Valanis et al. 1999; Lawson et al. 2012] showed increased occurrence of miscarriages among women who reported handling antineoplastic drugs during the first trimester. Most exposures were among oncology nurses or pharmacists. Other studies that did not find statistically significant associations had odds ratios ranging from 0.7 to 2.8. A meta-analysis that pooled the results of five studies [Selevan et al. 1985; Stücker et al. 1990; Valanis et al. 1999; Skov et al. 1992; Peelen et al. 1999] found an overall adjusted increased risk of 46% among exposed workers (95% confidence interval, 11% to 92%) [Dranitsaris et al. 2005]. All studies published to date contain data collected before 2002.

More research is needed to examine the effects of occupational exposure to antineoplastic drugs and stillbirth because this is an uncommon outcome and therefore difficult to study. All of the studies of stillbirths (or of fetal loss, which combines miscarriage and stillbirth) had insufficient numbers of exposed cases (n = 1 to 13), resulting in wide confidence intervals [McDonald 1988; McAbee et al. 1993; Rogers and Emmet 1987; Dranitsaris et al. 2005; Fransman et al. 2007; Peelen et al. 1999; Valanis et al. 1999; Ratner et al. 2010]. We found only two studies of tubal pregnancies, both with 10 or fewer exposed cases, and the results varied widely from OR=0.95 (95% CI 0.39-2.31) [Bouyer et al. 1998] to OR 11.4 (95% CI 2.7-17.6) [Saurel-Cubizolles et al. 1993].

We found only two studies of occupational exposure to antineoplastic drugs and fertility or time to pregnancy (Table 3), though the results suggest that exposure to antineoplastic drugs is associated with an increased risk of subfertility [Valanis et al. 1997; Fransman et al. 2007]. Only one study evaluated menstrual cycle; it showed a statistically significant three-fold increased risk of menstrual cycle irregularities from occupational exposure to antineoplastic drugs [Shortridge et al. 1995]. A study of Danish oncology nurses showed no statistically significant differences in birth weight, gestational age, or sex ratio among exposed mothers [Skov et al 1992], while a study of French oncology nurses found the mean birth weight of offspring to be lower than those of unexposed pregnancies [Stücker et al 1993].

In summary, although the results of occupational studies vary, they are generally indicative of an increased risk of adverse reproductive outcomes with occupational exposure [Connor et al. 2014]. The risks seem to be higher with first trimester exposure, though there may still be risks with exposure during the second and third trimesters, depending on the specific drug or drugs to which a worker may be exposed. While none of these studies were conducted after the release of the NIOSH Alert in 2004, more recent studies have documented that workplaces are still contaminated with these drugs [Schierl et al. 2009; Connor et al. 2010; Siderov et al. 2010; Yoshida et al. 2010; Davis et al. 2011; Sessink et al. 2011; Turci et al. 2011; Chu et al. 2012; Polovich and Martin 2011; Kopp et al. 2013] and exposures are most likely still occurring. When these data are considered in combination with the results of animal and patient studies, strong evidence shows a need for specific guidance for healthcare workers exposed to antineoplastic and other hazardous drugs in order to adequately protect the reproductive health of workers and their offspring.

Recommendations

Use of Industrial Hygiene Practices to Reduce Exposure to Hazardous Drugs

NIOSH recommends that a workplace be safe for all workers, regardless of their reproductive status, including workplaces where hazardous drugs are present. Recommendations to protect workers from occupational exposure to hazardous drugs have been developed by several organizations [OSHA 1999; NIOSH 2004; ASHP 2006; USP 2008; ONS 2011]. In general, they all adhere to the hierarchy of controls for standard industrial hygiene practices [Soule 1978]. These recommendations include the proper use of engineering controls, administrative controls, and personal protective equipment [NIOSH 2009]. In addition, training of personnel and other critical work practices are instrumental in protecting workers from exposure [NIOSH 2004, 2013]. However, NIOSH recognizes that current work practices do not completely eliminate hazardous drug contamination from the workplace, and therefore worker exposure to these drugs can occur. As noted above, several recent studies have added to the wealth of earlier information on workplace contamination with antineoplastic drugs. Therefore, employers should use and maintain the most up-to-date engineering controls and follow current recommendations in order to reduce as much as possible or eliminate worker exposure to hazardous drugs. These include recommendations from NIOSH, OSHA, ASHP, ONS, USP and other professional organizations. Additional information on adverse reproductive effects of these drugs can be found in the drug package inserts and in the SDS for the drugs. However, on the basis of recent studies of workplace contamination, current engineering controls and other precautions do not completely eliminate the potential for worker exposure and thus may not be enough to protect vulnerable offspring of male and female workers who handle these drugs.

Implementation of an Alternative Duty or Temporary Reassignment

Program

Given that a developing fetus and a newborn infant are uniquely vulnerable to certain hazardous drugs, especially antineoplastic drugs, because they are rapidly developing and their metabolic, detoxification and excretion processes are immature, and given the potentially devastating impact of such exposures, it is reasonable to take extra precautions to protect them [Gonzalez 2011]. One such additional precaution is to offer employees who are pregnant, breast-feeding, or actively trying to conceive the option of alternative duty. Alternative duty does not mean the worker is excused from work. It does suggest some reassignment of duties, often within the same job, to avoid handling hazardous drugs. For example, various nursing or pharmacy duties can be redistributed among a team of workers, or the organization of work can be altered to allow those needing reassignment to still work in many aspects of their jobs. In some instances, however, a true temporary position re-assignment might be necessary to avoid exposure to hazardous drugs.

It is estimated that 68% of working women will become pregnant at least once during their working life [Cleveland et al. 2000]. Two-thirds of women work during their first pregnancy, and more than half (55%) of all births are to working women [U.S. Census Bureau 2010]. Beyond the benefits to the health of workers and their offspring, providing accommodations to expectant and nursing workers may reduce turnover and increases morale and productivity.

NIOSH reviewed existing policies from several professional and government organizations that have recommendations for alternative duty or temporary reassignment for healthcare workers who may be at risk of exposure to hazardous drugs during critical times in reproduction (Appendix 5). Typically, these include times when couples (males and females) are actively trying to conceive and when women are pregnant and/or breastfeeding. However, conception can be a difficult issue to deal with because approximately 50% of all pregnancies are not planned [Finer and Zolna 2006]. Temporary reassignment

should also be considered when an individual's medical history or risk factors suggest a need for requesting reassignment from working with hazardous drugs based on personal fertility history and any other underlying medical conditions that may put a worker at exceptional risk of harm [ACOEM 2011]. The majority of these policies indicate that the employer should offer alternative duty and that the worker's decision to accept it should be voluntary. Since 1995, OSHA has recommended that healthcare facilities have a policy in place regarding reproductive risks associated with occupational exposure of workers to hazardous drugs and that such a policy should be followed [OSHA 1999]. Some recommendations state that an initial risk assessment should be performed in order to determine if there is potential reproductive harm to the fetus or offspring [HSE 2003; ACOEM 2011]. However, because there are no established permissible exposure limits (PELs) or other guidance values for these drugs [NIOSH 2004], a complete risk assessment is usually not possible. Nonetheless, workers potentially at risk may be identified by an exposure assessment. In some cases, workers (such as pharmacy personnel, nursing personnel, and housekeeping and waste disposal personnel) may be identified as at-risk on the basis of their job classification, indicating their duties may potentially expose them to hazardous drugs. An exposure assessment may also identify other workers with potential exposure, since studies have shown that wherever hazardous drugs are present in a healthcare facility, environmental contamination is common.

After carefully reviewing animal studies, human studies of patients and workers, and the properties of hazardous drugs that provide clues about the mechanistic plausibility of reproductive risk from exposure, NIOSH recommends that healthcare workplaces where antineoplastic and other hazardous drugs are present have a policy for alternative duty for exposed workers who are a reproductive risk [Figure 1]. An alternative-duty or temporary-reassignment program typically includes the following elements:

- Identifying drugs in the workplace with potential adverse reproductive effects.

- Identifying job functions or tasks that present a potential for exposure to reproductive hazards.

- Conduct an initial risk assessment for the drugs being used.
- Identifying job functions or tasks that can be safely performed by workers requesting alternative duty for reproductive issues.
- Developing new-employee and annual refresher training as part of the management's hazard communication program. Training should help healthcare workers identify their potential for exposure during their windows of risk. During training, workers should be informed that windows of vulnerability to developmental health typically begin before fertilization or before a pregnancy is recognized, thus necessitating the provision of alternative duty during or before actively trying to conceive.
- Developing mechanisms by which workers who are actively trying to conceive, who are pregnant, or who are breast-feeding can request alternative duty or reassignment.

Workers should be encouraged to notify their employer of their request for reassignment before their window of risk, or as soon as possible once risk is recognized, with the understanding that such information is confidential. The notification should be done through the employee health unit. If this is not feasible, then notification should be made through their immediate supervisor.

Medical, Legal and Ethical Issues

The development and implementation of policies for protection of reproductive health involve complex issues related to both science and law. Safety from reproductive hazards and freedom from discrimination on the basis of gender or pregnancy can appear to present conflict or appear intrusive into personal areas of an employee's reproductive and health status. When a worker requests alternative duty, confidential information and matters of the employee's privacy might become known in the workplace [Saiki et al. 1994]. Because of the legal implications of requests for special accommodations during pregnancy,

several states have adopted laws that require employers to provide at least some accommodations if requested.

The 1978 Pregnancy Discrimination Act amended Title VII of the Civil Rights Act to include the wording "because of or on the basis of pregnancy, childbirth, or related medical conditions" in reference to unlawful employment practices that "…in any way…would deprive or tend to deprive any individual of employment opportunities or otherwise adversely affect his [sic] status as an employee…" A woman or man cannot be denied employment or be removed from employment because of her or his reproductive status. If an employer provides alternative duty on the basis of reproductive status in order to limit workers' exposure to hazardous drugs, then the policy will not violate Title VII as long as employees retain the right to remain in their positions if they choose.

It is important that alternative duty or other workplace policies intended to protect workers and their offspring do so in a manner that does not discriminate against workers on the basis of gender or other protected characteristics. Forcing an employee to accept alternative duty on the basis of gender or pregnancy is unlawful; alternative duty policies should therefore be voluntary. Employers may offer voluntary alternative duty on the basis of reproductive status, even if alternative duty is not offered to other employees with temporary disabilities. Offering this type of accommodation should not be seen as an admission on the part of an employer of dangerous conditions in the workplace. Rather, offering the option for alternative duty should be seen as evidence of the employer's commitment to doing everything possible to assure the well-being of workers and their families. Reassigned workers should retain wages, seniority, and other benefits that might otherwise be lost by a job transfer and should not be discriminated against on the basis of their job status.

In preparing an alternative duty policy, it is important to consider both male and female reproduction issues equally. Alternative duty policies should protect the reproductive capacity and offspring of both

male and female workers, although the appropriate type and timing of accommodations may vary.

Summary

The primary limitation of the studies we evaluated is the era of the data collection; all studies published to date evaluate data collected prior to 2002, and most data were collected in the 1980's. Though there has been a lot of attention recently to raise awareness of controlling occupational exposure to antineoplastic and other hazardous drugs, studies continue to show that exposures are still occurring. Another important limitation of the literature is the small sample sizes, particularly the small numbers of exposed cases. Because of this limitation, studies were often unable to adjust for confounding factors and reported wide confidence intervals. However, most of the studies we reviewed that had larger relative sample sizes indicated an increased risk of adverse reproductive health outcomes. Though there are few studies of fertility, there appears to be an indication of a risk with exposure. Finally, most studies lacked enough statistical power or proper exposure assessment to evaluate dose.

Considering the biologic plausibility of the mechanisms of action of many hazardous antineoplastic drugs, and observations of adverse reproductive and developmental health outcomes observed in treated cancer patients, this review suggests, fairly consistently, that there are also elevated risks to reproductive health for exposed workers. Workplace contamination studies indicate that hazardous drug exposure is widespread, commonly occurring during any handling activity, despite use of current safety guidance. Therefore, additional precautions to prevent exposure during uniquely vulnerable windows of fetal and newborn development should be considered.

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Table 1. Studies of Congenital Anomalies Associated with Parental Occupational Exposure to Antineoplastic Drugs*

Reference	Exposure Period	Study Location	Population	Study Design	Overall Sample Size	Number of exposed cases	Results	Comments
Fransman et al. 2007	1990–1997	Netherlands	Oncology & other types of nurses	Survey	1,519	5 in highest exposure category	No significant associations; CIs were wide	Retrospective exposure assessment was based on frequency of tasks; estimated dermal exposure. No evidence of dose response.
Hemminki et al. 1985	<1985	Finland	Finnish hospital nurses	Case–control; survey	38 cases; 99 controls	19	Adj OR, 4.7 (1.2–18.1)	11 exposed cases handled less than 1/week; 8 expo cases handled once or more per week.
McAbee et al. 1993	1985	US	Nurses and university employees	Cross-sectional survey	633 women (1,133 pregnancies)	10	Oncology nurses reported more birth defects than the control group (p = 0.02 for crude analysis).	Response rate was 30%; analyzed first pregnancies separately from each additional pregnancy
McDonald et al. 1988	1982–1984	Montreal	Population based; doctors and nurses	Survey	152 exposed pregnancies	8	8/4 = observed / expected	Used medical records
Peelen et al. 1999	<1985	Netherlands	Oncology nurses	Survey	229 exposed + 956 unexposed	7	OR, 5.1 (1.1–23.6) among nurses who prepared hazardous drugs	Had to work in oncology for 2 months or more during pregnancy
Ratner et al. 2010	1974–2000	Canada	Registered nurses	Survey; registry	12,741	17	Adj OR, 1.42 (0.86–2.36)	Based on RNs who were ever or never employed in oncology
Skov et al. 1992	1985	Denmark	Oncology nurses	Retrospective cohort	266 exposed +770 unexposed	16	Adj OR, 1.36 (0.59–3.14) in highest exposure category	Prepared or administered hazardous drugs during pregnancy
Lorente et al. 2000	1989–1992	Europe	Population-based	Case–control	64 cleft lip / palate + 36 cleft palate + 751 controls	3	Cleft lip: OR, 3.35 (0.37–3.12); Cleft palate: OR, 11.25 (1.98–63.7)	CIs were wide.

*Previously published. Connor et al. 2014

Table 2. Studies of Miscarriage, Stillbirth, Tubal Pregnancy Associated with Occupational Exposure to Antineoplastic Drugs*

Reference	Exposure Period	Study Location	Population	Study Design	Overall Sample Size	Number of exposed cases	Results	Comments
Fransman et al. 2007	1990–1997	Netherlands	Oncology and other types of nurses	Survey	1,519	34, but divided into 3 categories	No significant associations; CIs were wide for miscarriage	Small numbers in catagories; sample sizes were not clearly reported. Retrospective exposure assessment among nurses
Hemminki et al. 1985	<1985	Finland	Finnish hospital nurses	Case-control	169 cases + 469 controls	12	Adj OR, 0.8 (0.3–1.7) for miscarriage	50% Response rate
Lawson et al. 2012	1993–2001	U.S.	U.S. registered nurses	Survey	775 cases + 6,707 live births	48	Adj OR, 1.94 (1.32–2.86) for miscarriage	
Peelen et al. 1999	<1985	Netherlands	Oncology nurses	Survey	249 exposed + 1,010 unexposed	Unclear	OR, 1.4 (0.8–2.6) for miscarriage	Small numbers, limitations in study design. See Fransman study that replaces this study.
Selevan et al. 1985	<1985	Finland	Nurses	Case–control	124 cases +321 controls	18	OR, 2.3 (1.21–4.39) for miscarriage	First-trimester exposure to hazardous drugs more than once per week
Skov et al. 1992	1985	Denmark	Oncology nurses	Retrospective cohort	281 exposed + 809 unexposed	18	Adj OR, 0.74 (0.40–1.38) for miscarriage	Prepared or administered hazardous drugs anytime during pregnancy
Stücker et al. 1990	1985	France	Hospital personnel	Survey	139 exposed +357 unexposed	36	Adj OR, 1.7 (1.03–2.80) for miscarriage	Prepared hazardous drugs
Valanis et al. 1999	1985	U.S.	Nurses and pharmacists	Survey	1,448 exposed + 5,297 unexposed	223	Adj OR, 1.50 (1.25–1.80) for miscarriage	Exposure to hazardous drugs during pregnancy
McDonald et al. 1988	1982–1984	Montreal	Population based	In-person survey	22,613	13	13 observed /13.4 expected miscarriages and stillbirths	Administered hazardous drugs during 1st trimester
McAbee et al. 1993	1985	U.S.	Nurses and university employees	Cross-sectional survey	663 women (1,133 pregnancies)	3	Adj OR of 0.67 for miscarriage and stillbirth	Low response rates (<30%)
Rogers and Emmett 1987	<1985	U.S.	Oncology and community health nurses	Survey	233	13	OR, 2.5 ($p < 0.04$) for miscarriage and stillbirth	OR didn't change with adjustment for age

Fransman et al. 2007	1990–1997	Netherlands	Oncology & other types of nurses	Survey	1,519	1 in the highest category	No significant associations; CIs were wide for stillbirth	Retrospective exposure assessment of frequency of tasks, dermal exposure
Peelen et al. 1999	1990–1997	Netherlands	Oncology nurses	Survey	249 exposed + 1,010 unexposed	2	OR, 1.2 (0.65–2.20) for stillbirth	Small numbers
Valanis et al. 1999	1985	U.S.	Nurses and pharmacists	Survey	7,094	12	Adj OR, 1.10 (0.55–2.20) for stillbirth	
Ratner et al. 2010	1974–2000	Canada	Registered nurses	Cohort	147/23,222	3	Adj OR, 0.67 (0.21–2.13) for stillbirth	
Bouyer et al. 1998	1993–1994	France	Hospital personnel	Case-–control	104 cases/ 279 controls	10	Adj OR, 0.95 (0.39–2.31) for tubal pregnancy	Studied only preconception exposures. Update of Saurel-Cubizolles 1993 article. Potentiallyover-adjusted; included previous SA in analysis. CIs were wide question.
Saurel-Cubizolles et al. 1993	1985	Paris	Hospital nurses	Self-administered survey	85 exposed and 599 unexposed	6	Adj OR, 11.4 (2.7–17.6) for tubal pregnancy	Exposure to hazardous drugs during 1st trimester. See Bouyer update from 1998.

*Previously published. Connor et al. 2014

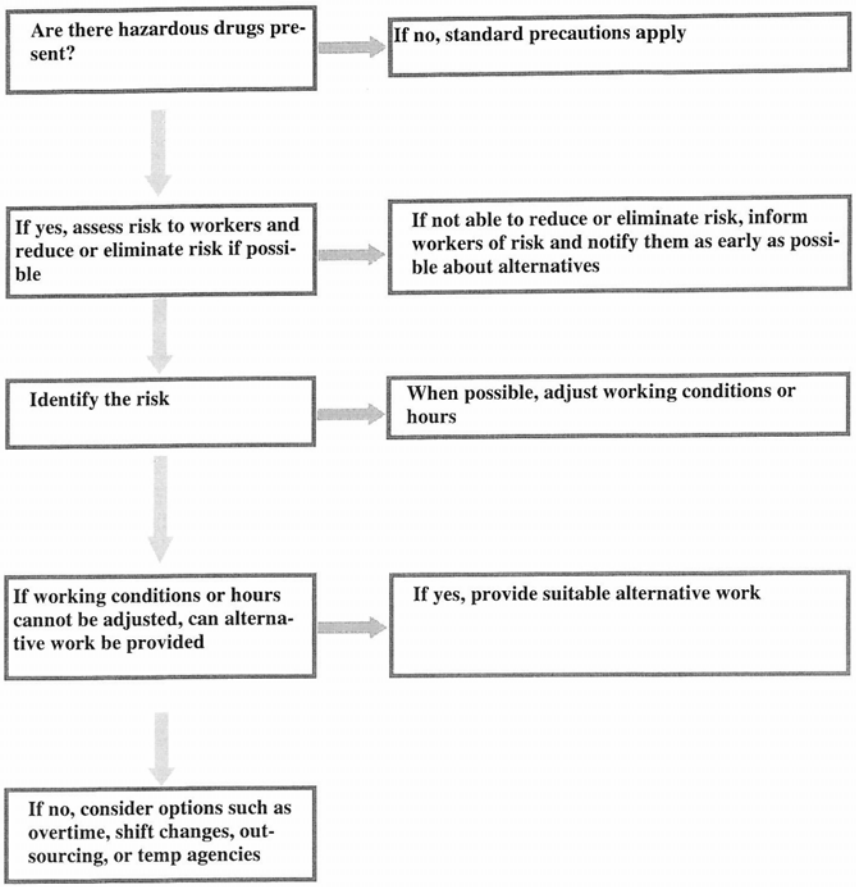
Table 3. Studies of Fertility, Time to Pregnancy, Menstrual Function, Birthweight, Gestational Age, and Sex Ratio. Associated with Occupational Exposure to Antineoplastic Drugs*

Reference	Exposure Period	Study Location	Population	Study Design	Overall Sample Size	Number of exposed cases	Results	Comments
Valanis et al. 1997	<1985	U.S.	Nurses and pharmacy personnel	Case- control	405 cases+ 1,215 controls	78	OR, 1.5 (1.1–2.0) for infertility	
Fransman et al. 2007	1990–1997	Netherlands	Oncology and other types of nurses	Survey	126	26 in highest category	Hazard ratio, 0.8 (0.6–-0.9) for time to pregnancy	Retrospective exposure assessment among nurses
Shortridge et al. 1995	1986	U.S.	ONS and ANA members	Survey	1,458	172	Adj OR, 3.4 (1.6–7.3) for menstrual dysfunction among nurses who administered chemotherapy	Menstrual dysfunction defined as one of the following: a) 3+ months of no periods, b) cycle length of <25 or >31 days, or c) flow duration of <2 or >7 days
Skov et al. 1992	1985	Denmark	Oncology nurses	Retrospective cohort	266 exposed / 770 unexposed	266	No statistically significant differences in adjusted analyses between exposed and unexposed for birthweight, gestational age, or sex ratio	
Stücker et al. 1993	1985–1986	France	Oncology nurses	Survey	420 Singleton live births	107 exposed pregnancies	In adjusted models, mean birthweight of exposed pregnancies was 56 g lower than unexposed (95% CI, minus 155.1 to 43.1)	No difference in gestational age between exposed and unexposed

*Previously published. Connor et al. 2014

Abbreviations used: OR-odds ratio; AdOR-adjusted odds ratio; CI-confidence interval

Figure 1. Initial Health and Safety Assessment for Couples Trying to Conceive and Women who are Pregnant or Breast feeding



Appendix 1. Hazardous Drug (HD) Handling Activities in Healthcare Workers that can Result in Exposure	
Workers Potentially Exposed	**Activity**
Pharmacists, pharmacy technicians	• Handling drug-contaminated vials • Reconstituting powdered or lyophilized drugs and further diluting either the reconstituted powder or concentrated liquid forms of hazardous drugs • Expelling air from syringes filled with hazardous drugs • Compounding HD powders into custom-dosage forms • Transferring drug solution to IV bag or bottle.
Pharmacists, pharmacy technicians, nursing personnel	• Counting out individual, uncoated oral doses from multidose bottles • Unit-dosing uncoated tablets in a unit-dose machine • Crushing tablets or opening capsules to make oral liquid dose • Opening ampoules • Preparing topical drugs
Nursing personnel	• Administering antineoplastic drugs by injection (intramuscular, subcutaneous or intravenous (IV)), by inhalation or by nasogastric tube • Spiking the IV set into an HD-containing IV bag (without a closed system)

	• Priming the IV set with a drug-containing solution at the administration location • Connecting and disconnecting the IV set to an IV pump or patient •
Nursing personnel, support staff, housekeeping personnel, laundry personnel	• Handling body fluids or body-fluid-contaminated clothing, dressings, linens, bedpans, urinals and other materials • Handling contaminated wastes generated at any step of the preparation or administration process
Pharmacists, pharmacy technicians, nursing personnel, housekeeping personnel, environmental services personnel	• Contacting hazardous drugs present on drug vial exteriors, work surfaces, floors, and final drug products (bottles, bags, cassettes, and syringes) • Handling unused antineoplastic drugs or antineoplastic drug-contaminated waste • Decontaminating and cleaning drug preparation or clinical areas • Cleaning hazardous drug spills
Physicians, nursing personnel, operating room personnel	• Performing certain specialized HD administration procedures such as intraperitoneal chemotherapy (in the operating room or other locations), bladder instillation, isolated limb perfusion
Support staff	• Transporting hazardous throughout the facility
Nursing personnel, housekeeping personnel, waste disposal personnel	• Transporting hazardous waste containers
Pharmacists, pharmacy technicians, nursing	• Removing and disposing of personal protective equipment after handling

personnel, housekeeping personnel	hazardous drugs or waste

Appendix 2. FDA Pregnancy Categories of Drugs Listed by NIOSH as Hazardous[1]		
Drugs that Should be Handled as Hazardous	**FDA Pregnancy Category[2]**	**AHFS Pharmacologic-Therapeutic Classification[2]**
Abacavir	C	8:18.08.20 Nucleoside and reverse transcriptase inhibitors
Abiraterone	X	10:00 Antineoplastic agents
Acitretin	X	88:04 Vitamin A
Ado-trastuzumab emtansine	D	10:00 Antineoplastic agents
Ambrisentan	X	24:12.92 Vasodilating agents, miscellaneous
Alefacept	B	84:92 Skin and mucous membrane agents, miscellaneous
Alitretinoin	D	84:92 Skin and mucous membrane agents, miscellaneous
Altretamine	D	10:00 Antineoplastic agents
Anastrozole	X	10:00 Antineoplastic agents
Apomorphine	C	28:36.20.08 Nonergot-derivative dopamine receptor agonists
Arsenic trioxide	D	10:00 Antineoplastic agents
Azacitidine	D	10:00 Antineoplastic agents
Azathioprine	D	92:44 Immunosuppressant agents
Bacillus Calmette-Guerin (BCG)	C	80:12 Vaccines
Bendamustine	D	10:00 Antineoplastic agents
Bexarotene	X	10:00 Antineoplastic agents
Bicalutamide	X	10:00 Antineoplastic agents
Bleomycin	D	10:00 Antineoplastic agents
Bortezomib	D	10:00 Antineoplastic agents
Bosentan	X	24:12.92 Vasodilating agents, miscellaneous
Brentuximab vedotin	D	10:00 Antineoplastic agents
Busulfan	D	10:00 Antineoplastic agents
Cabazitaxel	D	10:00 antineoplastic agents

Cabergoline	B	28:36. 20.04 Ergot-derivative dopamine receptor agonists
Capecitabine	D	10:00 Antineoplastic agents
Carbamazepine	D	28:12.92 Anticonvulsants, miscellaneous
Carboplatin	D	10:00 Antineoplastic agents
Carmustine	D	10:00 Antineoplastic agents
Cetrorelix	X	92:40 Gonadotropin-releasing hormone antagonists
Chlorambucil	D	10:00 Antineoplastic agents
Chloramphenicol	C	8:12.08 Chloramphenicols
Choriogonadotropin alfa	X	68:18 Gonadotropins
Cidofovir	C	8:18.32 Nucleosides and nucleotides
Cisplatin	D	10:00 Antineoplastic agents
Cladribine	D	10:00 Antineoplastic agents

Drugs that Should be Handled as Hazardous (Continued)	**FDA Pregnancy Category**	**AHFS Pharmacologic-Therapeutic Classification**
Clofarabine	D	10:00 Antineoplastic agents
Clonazepam	D	28:12.08 Benzodiazepines
Colchicine	C	92:16 Antigout agents
Crizotinib	D	10:00 Antineoplastic agents
Cyclophosphamide	D	10:00 Antineoplastic agents
Cyclosporin	C	92:44 Immunosuppressive agents
Cytarabine	D	10:00 Antineoplastic agents
Dacarbazine	C	10:00 Antineoplastic agents
Dactinomycin	D	10:00 Antineoplastic agents
Dasatinib	D	10:00 Antineoplastic agents
Daunorubicin	D	10:00 Antineoplastic agents
Decitabine	D	10:00 Antineoplastic agents
Deferiprone	D	64:00 Heavy metal antagonists
Degarelix	X	10:00 Antineoplastic agents
Dexrazoxane	C	92:56 Protective agents
Diethylstilbestrol	X	Not in AHFS (nonsteroidal synthetic estrogen)

Dinoprostone	C	76:00 Oxytocics
Docetaxel	D	10:00 Antineoplastic agents
Doxorubicin	D	10:00 Antineoplastic agents
Dronedarone	X	20:04.04 Antiarrythmics
Dutasteride	X	92:08 5-alpha reductase inhibitors
Entecavir	C	8:18.32 Nucleosides and nucleotides
Epirubicin	D	10:00 Antineoplastic agents
Eribulin	D	10:00 Antineoplastic agents
Erlotinib	D	10:00 Antineoplastic agents
Ergonovine/ methylergonovine	C	76:00 Oxytocics
Estradiol	X	68:16.04 Estrogens
Estramustine	X	10:00 Antineoplastic agents
Estrogen-progestin combina-tions	X	68:12 Contraceptives
Estrogens, conjugated	X	68:16.04 Estrogens
Estrogens, esterified	X	68:16.04 Estrogens
Estropipate	X	68:16.04 Estrogens
Etoposide	D	10:00 Antineoplastic agents
Everolimus	X	10:00 Antineoplastic agents
Exemestane	D	10:00 Antineoplastic agents
Finasteride	X	92:08 5-alpha reductase inhibitors
Fingolimod	C	92:20 Biologic response modifiers

Drugs that Should be Handled as Hazardous (Continued)	**FDA Pregnancy Category**	**AHFS Pharmacologic-Therapeutic Classification**
Floxuridine	D	10:00 Antineoplastic agents
Fluconazole	C	8:18.08 Azoles
Fludarabine	D	10:00 Antineoplastic agents
Fluorouracil	D/X[3]	10:00 Antineoplastic agents
Fluoxymesterone	X	68:08 Androgens
Flutamide	D	10:00 Antineoplastic agents
Fosphenytoin	D	28:12.12 Hydantoins
Fulvestrant	D	10:00 Antineoplastic agents
Ganciclovir	C	8:18.32 Nucleosides and nucleotides
Ganirelix	X	92:40 Gonadotropin-releasing hormone antagonists
Gemcitabine	D	10:00 Antineoplastic agents
Gemtuzumab ozogamicin	D	10:00 Antineoplastic agents
Gonadotropin, chorionic	X	68:18 Gonadotropins
Goserelin	X	10:00 Antineoplastic agents
Hydroxyurea	D	10:00 Antineoplastic agents
Icatibant	C	92:32 Complement inhibitors
Idarubicin	D	10:00 Antineoplastic agents
Ifosfamide	D	10:00 Antineoplastic agents
Imatinib	D	10:00 Antineoplastic agents
Irinotecan	D	10:00 Antineoplastic agents
Ixabepilone	D	10:00 Antineoplastic agents
Leflunomide	X	92:36 Disease-modifying antirheumatic agents
Lenalidomide	X	92:20 Biologic response modifiers
Letrozole	X	10:00 Antineoplastic agents
Leuprolide	X	10:00 Antineoplastic agents
Liraglutide recombinant	C	68:20.06 Incretin mimetics
Lomustine	D	10:00 Antineoplastic agents
Mechlorethamine	D	10:00 Antineoplastic agents
Medroxyprogesterone	X	68:32 Progestins

acetate		
Megestrol	X	10:00 Antineoplastic agents
Melphalan	D	10:00 Antineoplastic agents
Menotropins	X	68:18 Gonadotropins
Mercaptopurine	D	10:00 Antineoplastic agents
Methotrexate	X	10:00 Antineoplastic agents
Methyltestosterone	X	68:08 Androgens
Mifepristone	X	76:00 Oxytocics

Drugs that Should be Handled as Hazardous (Continued)	FDA Pregnancy Category	AHFS Pharmacologic-Therapeutic Classification
Misoprostol	X	56:28.28 Prostaglandins
Mitomycin	D	10:00 Antineoplastic agents
Mitotane	D	10:00 Antineoplastic agents
Mitoxantrone	D	10:00 Antineoplastic agents
Mycophenolate mofetil	D	92:44 Immunosuppressive agents
Mycolphenolic acid	D	92.44 Immunosuppressive agents
Nafarelin	X	68:18 Gonadotropins
Nelarabine	D	10:00 Antineoplastic agents
Nevirapine	B	8:18.08.16 Nonnucleoside reverse transcriptase inhibitors
Nilotinib	D	10:00 Antineoplastic agents
Omacetaxin	D	10:00 Antineoplastic agents
Oxaliplatin	D	10:00 Antineoplastic agents
Oxcarbazepine	C	28:12.92 Anticonvulsants. Miscellaneous
Oxytocin	C	76:00 Oxytocics
Paclitaxel	D	10:00 Antineoplastic agents
Palifermin	C	84:16 Cell stimulants and proliferants
Paroxetine	D	28:16.04.20 Selective seretonin uptake inhibitors
Pazopanib	D	10:00 Antineoplastic agents
Pemetrexed	D	10:00 Antineoplastic agents
Pentetate calcium trisodium	C	Not in AHFS
Pentostatin	D	10:00 Antineoplastic agents
Phenoxybenzamine	C	12:16.04.04 Non-selective alpha-adrenergic blocking agents
Phenytoin	D	28:12.12 Hydantoins
Plerixafor	D	20:16 Hematopoietic agents
Pralatrexate	D	10:00 Antineoplastic agents
Procarbazine	D	10:00 Antineoplastic agents
Progesterone	B	68:32 Progestins

Progestins	X	68:12 Contraceptives
Propylthiouracil	D	68:36.08 Antithyroid agents
Raloxifene	X	68:16.12 Estrogen agonists-antagonists
Rasagiline	C	28:36 Antiparkinsonian agents
Ribavirin	X	8:18.32 Nucleosides and nucleotides
Risperidone	C	28:16.08.04 Atypical antipsychotics
Romidepsin	D	10:00 Antineoplastic agents
Sirolimus	C	92:44 Immunosuppressive agents
Sorafenib	D	10:00 Antineoplastic agents

Drugs that Should be Handled as Hazardous (Continued)	FDA Pregnancy Category	AHFS Pharmacologic-Therapeutic Classification
Spironolactone	C	24:32.20 Mineralocorticoid receptor antagonists
Streptozocin	D	10:00 Antineoplastic agents
Sunitinib	D	10:00 Antineoplastic agents
Tacrolimus	C	92:44 Immunosuppressive agents
Tamoxifen	D	10:00 Antineoplastic agents
Televancin	C	8:12.28.16 Glycopeptides
Temozolomide	D	10:00 Antineoplastic agents
Temsirolimus	D	10:00 Antineoplastic agents
Teniposide	D	10:00 Antineoplastic agents
Testosterone	X	68:08 Androgens
Thalidomide	X	92:20 Biologic response modifiers
Thioguanine	D	10:00 Antineoplastic agents
Thiotepa	D	10:00 Antineoplastic agents
Topiramate	D	28:12.92 Anticonvulsants, miscellaneous
Topotecan	D	10:00 Antineoplastic agents
Toremifene	D	10:00 Antineoplastic agents
Tretinoin	C/D[3]	84:16 Cell stimulants and proliferants
Triptorelin	X	10:00 Antineoplastic agents
Ulipristal	X	68:12 Contraceptives
Uracil mustard	D	N/A
Valganciclovir	C	8:18.32 Nucleosides and nucleotides
Valproic acid/divalproex Na	D	28:12.92 Anticonvulsants. Miscellaneous
Valrubicin	C	10:00 Antineoplastic agents
Vandetanib	D	10:00 Antineoplastic agents
Vemurafenib	D	10:00 Antineoplastic agents
Vigabatrin	C	28:12.92 Antinconvulsants, miscellaneous
Vinblastine sulfate	D	10:00 Antineoplastic agents
Vincristine sulfate	D	10:00 Antineoplastic agents
Vinorelbine tartrate	D	10:00 Antineoplastic agents

Voriconazole	D	8:14.08 Azoles
Vorinostat	D	10:00 Antineoplastic agents
Warfarin	D	20:12.04.08 Coumarin derivatives
Zidovudine	C	8:18:08 Antiretroviral agents
Ziprasidone HCl	C	28:16.08.04 Atypical antipsychotics
Zoledronic acid	D	92:24 Bone resorption inhibitors
Zonisamide	C	28:12.92 Anticonvulsant, miscellaneous

[1]NIOSH 2014
[2]ASHP/AHFS 2012
[3]Varies with formulation

Appendix 3. FDA-Assigned Pregnancy Categories[1]	
FDA Pregnancy Category	**Description**
A	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.
C	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

[1]Briggs et al. 2008; 21 CFR 201.57(c)(9)(i)

Appendix 4.

Databases reviewed: Canadiana, CINAHL, CISILO, DTIC, Embase, Health & Safety Science Abstracts, HSELine, NIOSHTIC-2, NTIS, OSHLine, PubMed, Risk Abstracts, Toxicology Abstracts, Toxline, Web of Science, and WorldCat.

PubMed search terms: Antineoplastic agents/adverse effects, antineoplastic agents/prevention and control, Cytotoxins, Hazardous Substances/adverse effects, Hazardous Substances/toxicity, Pharmaceutical Preparations/adverse effects, antineoplastic, cytotoxic, cytostatic, chemotherap*, and Personnel, Hospital, Health Personnel, and Occupational Exposure, Occupational Diseases, Environmental Exposure, occupational, and Reproduction, Infertility, Fertility, Pregnancy Complications, pregnan*, infertility, reproducti*. In addition, the following terms were included in searching text: antineoplastic , chemotherapeutic, cytotoxic, cytostatic, pregnan*, infertility, reproducti*, and occupational.

Appendix 5. Reproductive Health Recommendations for Alternative Duty Practices	
Organization and Topic	**Reproductive Health Recommendations**
National Study Commission on Cytotoxic Exposure. Recommendations for Handling Cytotoxic Agents [1987].	There are substantial data regarding the mutagenic, teratogenic, and abortifacient properties of certain cytotoxic agents, both in animals and in 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.
European Agency for Safety and Health at Work [1992]. Directive 92/85/EEC: pregnant workers.	Pregnant and breastfeeding workers may under no circumstances be obliged to perform duties for which the assessment has revealed a risk of exposure to agents, which would jeopardize their safety or health. Those agents and working conditions are defined in Annex II of the Directive. Women must not be dismissed from work because of their pregnancy and maternity for the period from the beginning of their pregnancy to the end of the period of leave from work.
Occupational Safety and Health Administration (OSHA). OSHA Technical Manual, TED 1−0.15A, Sec VI Chapter 2: Categorization of drugs as hazardous.	The examining physician should consider the reproductive status of employees and inform them regarding relevant reproductive issues. The reproductive toxicity of hazardous drugs should be carefully explained to all workers who will be exposed to these chemicals, and [this action] is required for those chemicals covered by the HCS [hazard communication standard]. Unfortunately, no information is available regarding the reproductive risks of HD [hazardous drug] handling with the current use of BSCs [biological safety cabinets] and PPE [personal protective equipment]. However, as discussed earlier, both spontaneous abortion and congenital malformation excesses have been documented among workers handling some of these drugs without currently recommended engineering controls and precautions. The facility should have a policy regarding reproductive toxicity of HDs and worker exposure in male and female employees and should follow that policy.

Health and Safety Executive, United Kingdom (HSE) [2003]. New and expectant mothers at work; a guide to health professionals.	The law requires every employer to assess workplace risks for all their employees, and take practical action to control those risks. In addition, employers must take particular account of risks to new and expectant mothers. The definition of a new or expectant mother is someone who is pregnant, has given birth within the previous six months, or is breastfeeding. Employers must identify hazards in their workplace that could pose a health or safety risk to new and expectant mother and take appropriate action to remove or reduce the risk. They must also make this information known to all their female employees of childbearing age, not just those who have informed them they are pregnant. This is particularly important for expectant mothers, as it is possible for the first 4−6 weeks of pregnancy to go undetected. If risks are identified go beyond the level of risk found outside the workplace, but cannot be removed, employers should adjust the woman's working conditions or hours. If there is still a risk, she must be offered suitable alternative work or, if that is not possible, suspended on full pay for as long as is necessary to protect her and her child's health.
American Society of Health-System Pharmacists (ASHP) [1990]. ASHP guidelines on handling hazardous drugs.	Because reproductive risks have been associated with exposure to hazardous drugs, alternative duty should be offered to individuals who are pregnant, breast-feeding, or attempting to conceive or father a child. Employees' physicians should be involved in making these determinations.
BC Cancer Agency [2008]. Safe handling of hazardous drugs. In: BC cancer agency pharmacy practice standards for hazardous drugs.	It is the responsibility of the employee handling HDs [hazardous drugs] to discuss with their immediate supervisor any desired change in work assignment as a result of their pregnancy, breast-feeding, or attempt to reproduce. All attempts should be made by management to re-assign personnel who are pregnant, , or planning imminent parenthood to work in another area of the pharmacy in order to avoid working directly with hazardous drugs, if so requested.
Canadian Association of Pharmacy in Oncology (CAPhO) [2009]. Standards of Practice for Oncology Pharmacy in Canada. November (Version 2).	Employees who are pregnant, attempting to conceive or father a child, or are breast feeding may request to be transferred to alternate duties which do not involve handling hazardous drugs. A policy should exist to provide direction for personnel in these situations.
American College of Occupational and Environmental Medicine (ACOEM) [2011]. Reproductive and Developmental Hazard Management	…temporary reassignment should be recommended if the conclusion of the risk assessment is that there is exposure to a reproductive or developmental toxicant that cannot be adequately controlled through engineering or work practice controls alone. Assignment of women who are breast feeding to positions where there are exposures that would result in an infant receiving a chemical intake in excess of the acceptable daily intake for

Guidance.	that agent should be closely assessed.
Oncology Nursing Society (ONS) [2009]. Chemotherapy and Biotherapy Guidelines and Recommendations for Practice.	Employers should allow employees who are actively trying to conceive or are pregnant or breast feeding to refrain from activities that may expose them and their infant to reproductive health hazards such as chemical, physical, or biologic agents. Alternative duty that does not include HD [hazardous drug] preparation or administration must be made available upon request to both men and women in the aforementioned situations or who have other medical reasons for not being exposed to HDs.
American Nurses Association (ANA) [2012]. American Nurses Association's House of Delegates, Reproductive Rights of Registered Nurses Handling Hazardous Drugs.	Advocate that it is essential for all health care facilities to educate nurses who handle hazardous drugs about the risk of reproductive and developmental effects that have been associated with these drugs; and Actively advocate for the right of nurses to engage in alternative duty that does not require hazardous drug handling when trying to conceive, when pregnant, and when breastfeeding.
U.S. Department of the Army [2013]. Occupational Health and Industrial Hygiene Guidance for the Management, Use and Disposal of Hazardous Drugs.	…HCWs [healthcare workers] who are pregnant, breast-feeding, or are trying to conceive a child should be given the option of being transferred to other comparable duties that do not involve handling HDs.

NIOSH has published an alert describing measures to control worker exposure to hazardous drugs: www.cdc.gov/niosh/docs/2004-165.

Additional information about hazardous drugs is available on the NIOSH Web site at www.cdc.gov/niosh/topics/hazdrug/default.html.

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