**Miller, Diane M. (CDC/NIOSH/EID)**

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**From:** Laura Beamer [labeamer@gmail.com]

**Sent:** Wednesday, September 30, 2009 10:55 PM

**To:** NIOSH Docket Office (CDC)

**Subject:** Pregnant Oncology Workers

**Attachments:** ACOEM_Reproductive_Hazard_Management_Guidelines..txt; 29cfr1604.10.pdf; TeratogenUpdate_PaternalExposures_60pg161.pdf; 20060926ACOGPositionStatementHB1215-2.pdf; RegGuide8-13_Prenatal_Radiation_Exposure.pdf; Declared Pregnancy Form_UMich.pdf

Attached you will find some items related to pregnant/trying to parent (male & female) oncology careproviders who administer therapeutic radiation treatments. Some of the concepts can be extrapolated to the administration of antineoplastics. Using a form to declare a pregnancy or plan to initiate a pregnancy is just one example.

Nurses are great at work-arounds. We do not assign pregnant (or lactating) nurses to administer antineoplastics. The pregnant nurse may monitor the patient receiving antineoplastics if transfer to another unit is not feasible or desired. Lactating/pregnant or trying nurses are not assigned to care for patients who have just received 131-iodine for thyroid cancer.

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These guidelines were drafted by M. Joseph Fedoruk, MD, Chairman of the American College of Occupational and Environmental Medicine's (ACOEM) Occupational and Clinical Toxicology Committee. The guidelines were reviewed, modified, and adopted by the Committee and approved by the ACOEM Board of Directors on April 18, 1994.

General Considerations

The purpose of the American College of Occupational and Environmental Medicine's (ACOEM) Reproductive Hazard Management Guidelines is to provide occupational medicine physicians, other health professionals, labor, and management with guidelines for managing potential occupational reproductive health hazards. Reproductive health hazards are defined as chemical, physical, or biological agents that can cause either reproductive impairment or adverse developmental effects. The ACOEM guidelines propose that persons responsible for workplace health and safety should assess their workplaces for potential reproductive hazards and implement appropriate responses for managing such hazards.

Reproductive toxicity can be defined as "the occurrence of adverse effects on the reproductive system that may result from exposure to environmental agents." Reproductive toxicity may be expressed as alterations to the reproductive organs and/or the related endocrine system. Developmental toxicity can be defined as "the occurrence of adverse effects on the developing organism that may result from exposure before conception (either parent), development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism."1,2 Developmental toxicity can include fetal death, structural abnormalities or birth defects, and functional deficiencies or altered growth.

The ACOEM Reproductive Guidelines are based upon the following principles:

1. 1. Reproductive health represents one of the major aspects of human life.

2. 2. The magnitude of occupational and environmental reproductive and developmental health risks in modern society is not well characterized.

3. 3. Scientific, epidemiological and toxicological data concerning the reproductive and developmental health risks of many chemicals, physical agents, and biological agents are limited and, in some instances, nonexistent.

4. 4. Industrial exposure limits for most chemical agents, which have been promulgated by the Occupational Safety and Health Act (OSHAct), ie, permissible exposure limits (PELs), or the American Conference of Governmental Industrial Hygienists (ACGIH), ie, threshold limit values (TLVs), have been established without consideration of protection from adverse reproductive or developmental health effects. Consequently, compliance with the Occupational Safety and Health Administration (OSHA) or ACGIH exposure limits for many compounds does not assure protection of reproductive health.

5. 5. Employees have a fundamental right to work in an environment that is free of significant reproductive health risks.

6. 6. Employees have a fundamental right to know about potential reproductive health risks encountered in the workplace.

7. 7. Reproductive policies must avoid sex discrimination and must consider potential adverse effects on males, females, and offspring. In some instances, previous reproductive policies have resulted in the exclusion of woman from jobs because of concern over fetal effects.

This report describes guidelines for occupational health professionals to manage reproductive and developmental risks and uncertainties. The guidelines have been established with the recognition that scientific data concerning the reproductive health effects of many occupational exposures is very limited, and consequently, there is considerable uncertainty about what action should be taken to adequately manage many potential workplace reproductive health hazards.

These guidelines describe measures to be used to assess the magnitude of potential reproductive risks in the workplace and options that can be taken to manage the uncertainty associated with these risks. The objective of the guidelines is to facilitate the protection of workers' reproductive health.

Reproductive and Developmental Toxicity

Reproductive and developmental toxic effects have unique characteristics from other patterns of organ-related toxicity that are limited to a single organ system. contains an overview of the reproductive process. The target of toxicity can include either parent or the offspring. Characteristics that distinguish reproductive and developmental toxicity from other toxic effects include: (1) adverse effects in the exposed person may only manifest in the other party. For example, an exposure to a reproductive toxicant in a male may produce an effect in the conceptus; (2) infertility may not become evident until children are desired, and may therefore go unnoticed for long periods; and (3) normal reproductive function is only expressed intermittently.

Disturbances of the reproductive process from occupational reproductive hazards can produce a broad range of potential toxic effects. Table 1 identifies some potential reproductive and developmental toxicity end points.

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TABLE 1. Reproductive End Points to Indicate Reproductive Dysfunction

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Reproductive toxicants 3 can be considered to act as direct or indirect toxicants, based upon their mechanisms of actions. Direct-acting toxicants do not require metabolic activation and can produce toxicity in two ways. Structural similarities between a direct-acting toxicant and an endogenous hormone may produce an adverse reproductive effect. For example, polychlorinated biphenyls (PCBs) and some organochlorine pesticides such as dichlorodiphenyl trichloroethane (DDT) act as estrogen agonists. Direct-acting toxicants can also produce toxicity because they are chemically reactive and affect cellular components of tissues involved in reproduction. For example, alkylating agents such as some antineoplastic drugs can be directly toxic to oocytes. Indirect-acting agents require metabolic activation after exerting toxicity. Indirect toxicants can become chemically reactive after metabolism or can modulate enzyme-controlled reproductive functions that are integral to intact hormonal homeostasis required for reproduction.

Magnitude of Workplace Reproductive Health Problems

There are no reliable estimates concerning the number of workers who are at significant risk of exposure to reproductive toxicants.4 Currently, only a few agents or conditions have been identified as being capable of producing structural abnormalities or birth defects and are classified as teratogens. Table 2 lists the agents that have been identified as known teratogens or possible human teratogens.

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TABLE 2. Known Human Teratogenic Agents

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A much broader range of agents is recognized as having an effect on or the potential to produce reproductive or developmental toxicity. Several agents, such as 1,2,-dibromochloropropane and lead, have been recognized to effect human spermatogenesis but are not proven teratogens. Lead is also a developmental toxicant and has been associated with neurobehavioral effects. There are several reasons for this lack of reliable present day information, perhaps the most important reason being limited epidemiologic and toxicologic data.

Limited Epidemiological Data

Epidemiological studies involving reproductive hazards are difficult to perform for several reasons:

1. 1. Reproductive and developmental toxicity end points are often difficult to measure. For example, spontaneous abortions commonly occur among the general population and some studies suggest that up to approximately 40% of fertilized eggs abort before the first missed menstrual period.5 Consequently, spontaneous abortions can occur without a woman's knowledge, making monitoring of this marker difficult.

2. 2. The frequency of some adverse reproductive health effects is rare, and large sample sizes are necessary for a study to have sufficient power. For example, congenital malformations are diagnosed in approximately 3% of all births, and large populations are required for an epidemiologic study to have sufficient power to detect a difference between exposed and nonexposed groups.6 Erroneous associations can be demonstrated between exposures and effect from studies with lower power.

3. 3. Reproductive studies can have confounding factors. Maternal age is associated with several birth abnormalities and diminished fertility, but is also likely to be associated with exposure to chemicals in the workplace. Persons with lengthy occupational histories will also be older. Other confounding factors, such as sexually-transmitted infections, sexual activity, and nutritional status may be difficult to control. Other factors that can affect fertility, such as smoking, alcohol and drug use, general health, and socioeconomic status, are more readily controllable.

4. 4. There can be uncertainty regarding the significance of the factor being measured. For example, there is scientific debate concerning which aspects of sperm, eg, number, motility, or morphology, are the most sensitive markers of certain reproductive effects.

Limited Toxicology Data

There is limited or no toxicological information for the majority of industrial chemicals used in industry. Animal developmental toxicity data are available for only 3000 of the 90,000 chemicals that are used in commerce in the United States.4 Furthermore, testing for some of these compounds has been limited and not included in assessment of the effects on males, females, and offspring.

There are several reasons for the limited information concerning the reproductive and developmental toxicity potential of the many industrial compounds. Tests for reproductive effects may not have been required in the past for many industrial chemicals. There is also uncertainty concerning the extrapolation of effects observed in animal toxicology studies to humans because of differences in species sensitivity and extrapolation of effects observed at high doses to low doses. Although information may be lacking for many chemicals, mutagenic agents should be considered to be potential reproductive toxicants since they are genotoxic and could produce adverse outcome from direct actions on germ cells.

Procedures for the Assessment of Reproductive and Developmental Health Risks

The assessment of occupational reproductive and developmental risks, like any risk from an occupational hazard, involves several distinct steps, including hazard identification, dose response assessment, exposure assessment, and risk characterization. For reproductive hazards, there is often very limited information concerning the effects of many chemical agents and there can be considerable uncertainties in determining reliable risk estimates.

This process often requires a multidisciplinary team of occupational health professionals from several disciplines, including occupational medical specialists, toxicologists, obstetricians, gynecologists, and exposure assessment specialists, such as industrial hygienists and other health professionals.

Hazard Identification

Hazard identification, the determination of whether an agent can cause a given effect, is the first step in assessing whether a workplace contains a significant reproductive hazard. This is a qualitative process involving several steps. The chemical, physical, and biological agents to which employees are potentially exposed in the workplace are identified. Available human and animal reproductive toxicity data for these agents are then reviewed to determine if there is any evidence that exposure to the agent could produce a reproductive health risk. Professional judgment is often required in hazard identification because information concerning the reproductive health hazards of many agents is limited and may be nonexistent. In addition, all chemicals can produce a toxic reproductive effect with sufficient exposure, especially if they produce maternal toxicity. Consultation with a reproductive toxicologist or other qualified health professional may be necessary to determine the significance of a reported reproductive health effect.

There are several sources of information concerning reproductive health risks. Reproductive and developmental toxicity information may be found in Material Safety Data Sheets (MSDSs), however, detailed information concerning the reproductive toxicity potential of many agents may not be included in an MSDS. Absence of reproductive information on an MSDS does not exonerate an agent. Other sources of information include text books, peer reviewed medical and toxicology journals, and toxicology data bases, including some that specialize in reproductive hazards (MEDLINE, TERIS, and the Toxicology Information Program). It is important to recognize that reproductive toxicology is a rapidly evolving field and information contained in textbooks may not be current or may not characterize the reproductive health risks of an agent. Table 3 includes a listing of information sources on occupational reproductive hazards.

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TABLE 3. Sources of Information Regarding Reproductive Hazards

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For agents for which there are recommended exposure limits, such as PELs, TLVs, or the National Institute for Occupational Safety and Health (NIOSH) recommended exposure limits (RELs), the basis for these exposure limits should be evaluated to determine if they were established with a consideration of protection against reproductive and developmental toxicity. Many exposure limits are based upon protection of some other toxicity end point, such as systemic toxicity, neurotoxicity, sensory irritation, or other health effects.

Exposure Assessment

Exposure assessment can be qualitative or quantitative in nature. Qualitative assessment can be used to enumerate exposures associated with the tasks of a particular job and to estimate on a relative scale (eg, none, negligible, low, medium, high) the magnitude of potential exposure for each listed agent and relevant route. This ranking can be based upon the volume of material present or used, the physical form of the material, volatility, frequency of contact, whether or not the material is contained within a closed system, and any engineering controls that might be in place.

Quantitative ambient air monitoring can then be directed toward those tasks that have the greatest potential for exposure. In some situations, analyses of surface samples and dust, soil, and water samples may be indicated to evaluate other potential exposure pathways. The assessment of potential reproductive and developmental risks associated with a particular job can be directed to those agents to which there is a likelihood of significant exposure.

Dose-Response Evaluation

The dose-response evaluation involves the determination of the relationship between an exposure and an effect. Estimation of the human reproductive health effects of many chemical agents is difficult because of the uncertainty in the extrapolation of animal reproductive toxicity data to humans. This process is often performed in conjunction with hazard assessment since many data sources contain both qualitative and quantitative information.

One approach to the dose-response evaluation entails identification of the relevant reproductive and developmental toxicology and epidemiology studies from the literature for the particular exposure agent. Once all technically acceptable studies are selected, no observed effect levels and the lowest observed effect levels can be determined for each class of reproductive or developmental adverse effect. Appropriate safety factors can then be applied to derive an estimated safe level of occupational exposure, based upon reproductive and developmental health considerations.

Risk Characterization

Risk characterization is the process of determining the potential health risks of an exposure based upon the site-specific exposure potential and the toxicity potential of the agent. The risk characterization process is based on information obtained in the hazard assessment, exposure assessment, and dose-response assessment, together with an estimate of the uncertainty of the risk estimate.

Reproductive Health Hazard Management Options

The ACOEM Reproductive Hazard Management Guidelines define several options that

should be considered in the management of reproductive risks and uncertainties. The consideration of which options should be implemented at a specific workplace should be based on an individualized assessment of the potential risks and characteristics of the population at risk. Before implementation of reproductive health hazard management measures, legal review should be considered to ensure compliance with all federal, state, and other regulations pertaining to discrimination and protection of employees' rights and disabilities. These options are listed in Table 4.

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TABLE 4. Reproductive Hazard Management Options

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Hazard Elimination

Ideally, if a significant workplace reproductive health hazard is identified, the best option for elimination of the agent is through product substitution. However, the elimination of reproductive hazards is not feasible in all instances because of technological constraints, economic in-feasibility, or scientific uncertainty concerning the magnitude of the risk. Substitution should be carefully evaluated to assure that risk is eliminated and reduced rather than increased by procedural changes or by the toxic properties of the proposed substitute.

Exposure Controls

If a hazard cannot be eliminated, methods to reduce or limit exposure through the use of engineering controls should be implemented. When engineering controls cannot be implemented, personal protective equipment, including respirators, should be used in situations in which engineering controls are not feasible. Administrative workplace controls can also be considered as a method of limiting exposure, eg, alteration of the work schedule or work duties up to and including temporary reassignment.

Exposure-Control Monitoring

Exposure-control monitoring can be accomplished by environmental monitoring, which includes the measurement of chemical or other contaminants in the air and other environmental media such as work surfaces, soil, and water. Exposure-control monitoring is often a central component of a risk-management program because exposure potential can be quantified to determine whether there is an excessive exposure and whether exposure control measures are achieving goals in limiting air concentrations or dispersion of the chemical or other substance in the general environment. Personal monitoring of contaminants in the breathing zone (representative) workers is preferred over general environmental air monitoring because it provides far more accurate measures of worker exposure.

Biological monitoring that involves measurement of a chemical or its metabolites in blood, urine, or other media can be considered an extension of exposure-control monitoring. Biological monitoring has the potential for providing objective data concerning whether exposure control methods are effective because it provides a measure of chemical absorption by all routes, including inhalation, dermal exposure, and inadvertent ingestion. Biological monitoring should only be implemented after consideration of the many variables that can affect test results, including pharmacokinetic data, dose-response relationships, and laboratory quality-control procedures. When these are well known and adequately controlled, biological monitoring provides the best estimate of the dose

absorbed.

Risk Communication

Employees at risk of exposure to significant reproductive hazards must be informed of the potential health risks, to enable them to reach an informed decision concerning acceptance and continuation of employment in such a position. Employees may be planning to procreate and if the job could involve exposure to agents that could adversely affect their reproductive ability or produce developmental toxicity, then the employees involved should be informed of this risk. This is especially important for teratogens or developmental toxins because an employee could potentially experience toxic effects within the first few weeks of pregnancy without realizing that she is pregnant. Risk communication should be targeted to provide accurate and complete information based upon the best available scientific information.

Recommended or Required Notification of Pregnancy

If despite attempts at engineering or administrative controls, the job involves exposure to teratogens or developmental toxins, the employer may request that the employee provide notification of pregnancy. The purpose of employee notification is to provide an opportunity for counseling of the employee during pregnancy when issues concerning potential reproductive risk are most relevant to the employee. The employer may request information from the employee's personal physician concerning her ability to continue performing tasks associated with her job position. This option is not an adequate substitute for aggressive risk communication because notification may not be received until after the pregnancy is recognized and after the most critical period of fetal development. In addition, employees may choose not to identify themselves as being at risk. Employee notification of intended pregnancy, which is seemingly more intrusive, could offer the advantage of earlier intervention.

Temporary Reassignment

Employees may be temporarily reassigned from a job position when there is potential exposure to a reproductive or developmental toxin that cannot be adequately controlled through engineering or work-practice controls alone. Temporary reassignment should also be considered when an individual's medical history or risk factors suggest a need.

When personal protective equipment is required to control exposure, temporary reassignment should be considered in three specific circumstances:

1. 1. Pregnancy. An employee indicates that she is pregnant.

2. 2. Pre-Conception. A male or female employee indicates an intention to have a child.

3. 3. Infertility. A couple has sought medical consultation because of infertility and no cause has been discovered.

Medical Surveillance

Medical surveillance should be considered for populations at risk of exposure to a significant hazard. The components of any medical surveillance program should be based upon the type of hazard, the availability of appropriate tests to evaluate the adverse effects of the specific hazard, and the benefits of early detection. Medical surveillance of the reproductive system can be performed by using two types of screening methods. Reproductive history questionnaires can be administered to a population at risk for the purpose of determining whether there are any unusual patterns or clusters of reproductive health problems. Ideally, information from a control nonexposed population should be collected to serve as a comparison group. End points that can be considered include live

births, fetal loss, and birth defects. If potential problems are identified that could be related to occupational exposure, a reassessment of exposure potential and reproductive toxicity data may be required for a work site or a specific industrial process. Medical screening to assess the physiological status of the employee's reproductive system may also be indicated for assessment of unusual reproductive health problems if there is an available and appropriate test. Questionnaires also provide a database that could be used to facilitate a retrospective assessment of the effects of a workplace on reproductive function.

Consultation with an epidemiologist or biostatistician may be necessary to interpret the significance of population data from reproductive health questionnaires. If the population being monitored is small, it may be difficult to establish statistically significant findings large enough to enable a conclusion to be drawn. It is essential that reproductive health information be kept confidential. contains a sample reproductive health questionnaire that is recommended for use by OSHA workers covered by the cadmium standard (29 CFR 1910.1027).

Although several laboratory tests are available to assess reproductive function, their use is routine medical surveillance has not been established.7 In general, assessment of male fertility is simpler than female fertility since spermatozoa can be readily obtained by semen analysis and ova are difficult to harvest for analysis. However, collection of semen samples can be viewed as obtrusive. Sperm parameters that can be monitored include concentration and morphology, but any conclusions regarding the significance of a finding must consider variables that can affect one or more semen parameters, such as continence time, use of recreational or therapeutic medications, age, smoking, diet, radiation exposures, elevated scrotal temperature, and testicular trauma.8

Breast Feeding Policy

Employers who allow nursing mothers to work in environments in which they are exposed to substances that could be excreted in breast milk, such as selected organic solvents, metals, and pesticides, should assess whether exposure would be sufficient to produce significant concentrations in the breast milk of employees who are breastfeeding.

Human breast milk has been determined to contain a broad range of chemical contaminants.9 Table 5 identifies chemicals that have been found in breast milk. In general, there is no evidence that infants are being adversely impacted by the consumption of the many chemicals found in breast milk, although in some instances infants have received significant exposures. Chemicals found in human milk are generally fat soluble and poorly metabolized. Therefore they persist in body fat. In some instances, mothers with occupational exposures to certain chemicals can have concentrations of chemical contaminants that considerably exceed the levels that are permitted by the Food and Drug Administration in cow's milk.10

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TABLE 5. Chemicals in Breast Milk

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Employees should be notified of the potential for accumulation of chemical contaminants in breast milk. Assignment of women who are breast-feeding to positions in which there are exposures that would result in an infant receiving a chemical intake in excess of the recommended daily intake for that agent should be closely assessed.

Paraoccupational Disease Management

Employees should examine the possibility of bringing work contaminants that could affect the development of offspring into the home environment.11 Developmental processes are not limited to the embryonic period during which the basic pattern and formation of organs occurs. Development also occurs during the early postnatal period while organs are adjusting to an extrauterine environment and could be undergoing histological and cytological differentiation.12 The manifestation of such effects can potentially include decrements or aberrations of postnatal function rather than structural defects.

A number of approaches may be used to reduce or avoid contamination of the home environment and thereby protect a developing fetus or developing infant and child. These include improved housekeeping in the workplace, employer laundering of work clothes and protective garments, the construction and use of "clean" and "dirty" change rooms, and mandatory use of showers at the end of the workday.

Acknowledgments

Prepared by M. Joseph Fedoruk, David C. Logan. Melissa A. McDiarmid, Brian G. Forrester, William G. Hughson, Christopher Holland, Hi E. Newby, and James H. Saunders.

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## Appendix A: The Reproductive Process

The Reproductive Hazard Management Guidelines provide a brief overview of the reproductive process to illustrate the broad range of potential toxic end points or clinical manifestations by which a reproductive toxicant could exert an effect. Reproduction is a complex process requiring interactions among multiple physiological systems. In addition, the two individuals or couple who make up the reproductive unit must also be considered as a target in evaluating reproductive and developmental toxicity.

The reproductive process is not limited to reproductive organs that are governed largely by neuroendocrine influence, but also includes other organs that can indirectly affect reproductive ability.

### Male Reproductive Physiology

Male reproductive physiology requires the intact functioning of the neuroendocrine system, which involves several organs including the hypothalamus, anterior pituitary gland, and testes. The hypothalamus, a part of the central nervous system, releases gonadotropin-releasing hormone (GNRH), which acts upon the anterior pituitary gland. The anterior pituitary gland, in response to GNRH, secretes follicle-stimulating hormone (FSH) and luteinizing-hormone (LH). FSH and LH act on the testes. FSH plays a central role in initiating and maintaining spermatogenesis, the process that produces intact functioning sperm. Germ cells, the precursors of adult spermatozoa, are located in the testes and continue to be renewed throughout adult male life in response to FSH stimulation.

LH stimulates testicular Leydig's cells to produce testosterone. Testosterone regulates the release of GNRH. The growth, development, and function of male secondary sex glands, including the penis, prostate, and seminal vesicles, are affected by testosterone. In addition, testosterone probably has a role in the stimulation of sperm production.

The neuroendocrine process is complex and the role of other hormones such as prolactin, which is also secreted by the anterior pituitary gland, are currently being investigated.

### Female Reproductive Physiology

Female reproductive physiology is dependent on the intact functioning of the neuroendocrine system, which involves the hypothalamus, anterior pituitary gland and ovaries. The hypothalamus releases GNRH, which acts upon the anterior pituitary gland. In response to GNRH, the anterior pituitary gland secretes FSH and LH.

### Embryogenesis and Fetal Growth

After fertilization of the ovum, which occurs between 24 and 48 h after ovulation, cell division occurs over several days to produce a blastocyst. The blastocyst implants in the lining of the uterus within 6 to 7 days after ovulation. The extraembryonic membranes and the germ cell layers, including the endoderm, mesoderm, and ectoderm, are formed in the second to third wk. The period of embryonic development, a critical phase of development, occurs during the eighth to ninth weeks of pregnancy. During this phase, the organs are principally formed, including the brain, heart, eyes, and limbs. During the fetal period from the eighth or ninth wk of pregnancy to gestation, fetal growth is characterized by continued biochemical and physiological maturation.

## Appendix B: Sample Reproductive Health Questionnaire

The following questions pertain to reproductive history:

Have you or your partner had a problem conceiving a child?

[ ] yes

[ ] no

If yes, specify:

[ ] self [ ] present mate

[ ] previous mate

Have you or your partner consulted a physician for a fertility or other reproductive problem?

[ ] yes

[ ]no

If yes, specify who consulted the physician:

[ ] self [ ]spouse/partner

[ ] self and partner

If yes, specify diagnosis made:

Have you or your partner ever conceived a child resulting in a miscarriage, still birth or deformed offspring?

[ ] yes

[ ] no

If yes, specify:

[ ] miscarriage

[ ] still birth

[ ] deformed offspring

If outcome was a deformed offspring, please specify type:

Was this outcome a result of a pregnancy of:

[ ] yours with present partner

[ ] yours with a previous partner

Did the timing of any abnormal pregnancy outcome coincide with present employment?

[ ] yes

[ ] no

[ ] no List dates of occurrences:

What is the occupation of your spouse or partner?

For Women Only:

Do you have menstrual periods?

[ ] yes

[ ] no

Have you had menstrual irregularities?

[ ] yes

[ ] no

If yes, specify type:

If yes, what was the approximated date this problem began?

Approximate date problem stopped?

For Men Only:

Have you ever been diagnosed by a physician as having prostate gland problem(s)?

[ ] yes

[ ] no

If yes, please describe type of problem(s) and what was done to evaluate and treat the problem(s):

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or indirectly any limitation, specification, or discrimination as to sex shall be unlawful unless based upon a bona fide occupational qualification.

### § 1604.8 Relationship of title VII to the Equal Pay Act.

(a) The employee coverage of the prohibitions against discrimination based on sex contained in title VII is coextensive with that of the other prohibitions contained in title VII and is not limited by section 703(h) to those employees covered by the Fair Labor Standards Act.

(b) By virtue of section 703(h), a defense based on the Equal Pay Act may be raised in a proceeding under title VII.

(c) Where such a defense is raised the Commission will give appropriate consideration to the interpretations of the Administrator, Wage and Hour Division, Department of Labor, but will not be bound thereby.

### § 1604.9 Fringe benefits.

(a) "Fringe benefits," as used herein, includes medical, hospital, accident, life insurance and retirement benefits; profit-sharing and bonus plans; leave; and other terms, conditions, and privileges of employment.

(b) It shall be an unlawful employment practice for an employer to discriminate between men and women with regard to fringe benefits.

(c) Where an employer conditions benefits available to employees and their spouses and families on whether the employee is the "head of the household" or "principal wage earner" in the family unit, the benefits tend to be available only to male employees and their families. Due to the fact that such conditioning discriminatorily affects the rights of women employees, and that "head of household" or "principal wage earner" status bears no relationship to job performance, benefits which are so conditioned will be found a prima facie violation of the prohibitions against sex discrimination contained in the act.

(d) It shall be an unlawful employment practice for an employer to make available benefits for the wives and families of male employees where the same benefits are not made available for the husbands and families of female employees; or to make available benefits for the wives of male employees which are not made available for female employees; or to make available benefits to the husbands of female employees which are not made available for male employees. An example of such an unlawful employment practice is a situation in which wives of male employees receive maternity benefits while female employees receive no such benefits.

(e) It shall not be a defense under title VIII to a charge of sex discrimination in benefits that the cost of such benefits is greater with respect to one sex than the other.

(f) It shall be an unlawful employment practice for an employer to have a pension or retirement plan which establishes different optional or compulsory retirement ages based on sex, or which differentiates in benefits on the basis of sex. A statement of the General Counsel of September 13, 1968, providing for a phasing out of differentials with regard to optional retirement age for certain incumbent employees is hereby withdrawn.

### § 1604.10 Employment policies relating to pregnancy and childbirth.

(a) A written or unwritten employment policy or practice which excludes from employment applicants or employees because of pregnancy, childbirth or related medical conditions is in prima facie violation of title VII.

(b) Disabilities caused or contributed to by pregnancy, childbirth, or related medical conditions, for all job-related purposes, shall be treated the same as disabilities caused or contributed to by other medical conditions, under any health or disability insurance or sick leave plan available in connection with employment. Written or unwritten employment policies and practices involving matters such as the commencement and duration of leave, the availability of extensions, the accrual of seniority and other benefits and privileges, reinstatement, and payment under any health or disability insurance or sick leave plan, formal or informal, shall be applied to disability due to pregnancy, childbirth or related medical conditions on the same terms

and conditions as they are applied to other disabilities. Health insurance benefits for abortion, except where the life of the mother would be endangered if the fetus were carried to term or where medical complications have arisen from an abortion, are not required to be paid by an employer; nothing herein, however, precludes an employer from providing abortion benefits or otherwise affects bargaining agreements in regard to abortion.

(c) Where the termination of an employee who is temporarily disabled is caused by an employment policy under which insufficient or no leave is available, such a termination violates the Act if it has a disparate impact on employees of one sex and is not justified by business necessity.

(d)(1) Any fringe benefit program, or fund, or insurance program which is in effect on October 31, 1978, which does not treat women affected by pregnancy, childbirth, or related medical conditions the same as other persons not so affected but similar in their ability or inability to work, must be in compliance with the provisions of §1604.10(b) by April 29, 1979. In order to come into compliance with the provisions of 1604.10(b), there can be no reduction of benefits or compensation which were in effect on October 31, 1978, before October 31, 1979 or the expiration of a collective bargaining agreement in effect on October 31, 1978, whichever is later.

(2) Any fringe benefit program implemented after October 31, 1978, must comply with the provisions of §1604.10(b) upon implementation.

[44 FR 23805, Apr. 20, 1979]

### §1604.11 Sexual harassment.

(a) Harassment on the basis of sex is a violation of section 703 of title VII.[1] Unwelcome sexual advances, requests for sexual favors, and other verbal or physical conduct of a sexual nature constitute sexual harassment when (1) submission to such conduct is made either explicitly or implicitly a term or condition of an individual's employment, (2) submission to or rejection of such conduct by an individual is used as the basis for employment decisions affecting such individual, or (3) such conduct has the purpose or effect of unreasonably interfering with an individual's work performance or creating an intimidating, hostile, or offensive working environment.

(b) In determining whether alleged conduct constitutes sexual harassment, the Commission will look at the record as a whole and at the totality of the circumstances, such as the nature of the sexual advances and the context in which the alleged incidents occurred. The determination of the legality of a particular action will be made from the facts, on a case by case basis.

(c) [Reserved]

(d) With respect to conduct between fellow employees, an employer is responsible for acts of sexual harassment in the workplace where the employer (or its agents or supervisory employees) knows or should have known of the conduct, unless it can show that it took immediate and appropriate corrective action.

(e) An employer may also be responsible for the acts of non-employees, with respect to sexual harassment of employees in the workplace, where the employer (or its agents or supervisory employees) knows or should have known of the conduct and fails to take immediate and appropriate corrective action. In reviewing these cases the Commission will consider the extent of the employer's control and any other legal responsibility which the employer may have with respect to the conduct of such non-employees.

(f) Prevention is the best tool for the elimination of sexual harassment. An employer should take all steps necessary to prevent sexual harassment from occurring, such as affirmatively raising the subject, expressing strong disapproval, developing appropriate sanctions, informing employees of their right to raise and how to raise the issue of harassment under title VII, and developing methods to sensitize all concerned.

(g) Other related practices: Where employment opportunities or benefits are granted because of an individual's submission to the employer's sexual advances or requests for sexual favors,

[1] The principles involved here continue to apply to race, color, religion or national origin.

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# Teratogen Update: Paternal Exposures—Reproductive Risks

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The potential of many drugs and chemicals to cause prenatal harm is well-established. The types of effects seen vary and include spontaneous abortions, stillbirths, congenital malformations present at birth, and conditions detected only months to years after birth. Most studies designed to determine whether agents cause malformations have examined the effects of exposure of the embryo or fetus at various times during gestation. Thus the effects studied are *maternally-mediated*. Despite these drug studies and those on other causes of birth defects, such as chromosomal abnormalities, the cause of approximately 60% of congenital malformations is unknown. Fewer studies have examined the possibility that exposure of the male to a drug or chemical could lead to abnormalities in his offspring, i.e., be male- or *paternally-mediated*. Over the last 10–20 years, there has been more interest in addressing this question as increasing numbers of patients and workers are exposed to agents that alter fertility. A number of animal studies as well as more recent human epidemiological studies have demonstrated that exposure of males to various agents can result in abnormal reproductive, pregnancy, and/or progeny outcomes (Olshan and Mattison, '94).

## MECHANISMS OF MALE-MEDIATED EFFECTS

Drug treatment of the male prior to conception could affect the outcome of subsequent progeny due to a drug-induced defect in the spermatozoon itself, such as an effect on the DNA or chromosomal proteins, or due to an effect caused by the presence of the drug in the seminal fluid. There are three main mechanisms of male reproductive toxicity: nongenetic (e.g., due to the presence of a drug in seminal fluid), genetic (e.g., gene mutation or chromosomal abnormality), and epigenetic (e.g., an effect on gene expression, genomic imprinting, or DNA methylation). The male reproductive system has a number of unique properties that help us interpret some of the mechanisms underlying male-mediated drug effects. Germ cells in the testis show one of the highest mitotic activities of any tissue in the body, so that in the human adult about 100 million new cells are produced each day (Amann, '81). Spermatogenesis is highly regulated, starting with spermatogonial stem cells and ending with differentiated, motile spermatozoa. It is one of the few examples in the adult of a system where undifferentiated cells pass through a number of distinctly different developmental phases, i.e., mitosis (spermatogonia), meiosis (spermatocytes), differentiation (haploid-phase spermiogenesis), and maturation (in the epididymis). In man and other animals, the continued proliferation of germ cells throughout life, from puberty to death, is maintained by a process of stem-cell renewal and differentiation. Stem-cell spermatogonia are located at the base of the epithelium, where they give rise to new stem cells or to more differentiated spermatogonia (Hermo and Clermont, '95). Another population of stem cells rarely divides in adults and is tentatively classed as dormant reserve stem cells. In rodents, germ cells start to proliferate and proceed through spermatogenesis in the first month of life; in contrast, in humans there is a long juvenile period with spermatogenesis being initiated in the second decade, at puberty. Following proliferation, germ cells enter meiotic prophase (including leptotene, zygotene, and pachytene phases), and subsequently undergo two meiotic divisions to become haploid spermatids. During spermiogenesis, spermatids undergo a dramatic series of morphological changes, prior to being released into the epididymis. Within the epididymis spermatozoa pass through a final process of maturation whereby they become motile and able to fertilize the egg.

The kinetics of spermatogenesis have been worked out in detail for a number of species; it is well-established that the timing of each of the four phases mentioned above is constant for a given species. In man, it takes approximately 64 days (Heller and Clermont, '63) for germ cells to develop from spermatogonia to spermatozoa; a further 2–5 days (Rowley et al., '70) is required for spermatozoa to pass through the epididymis. The germ-cell stage(s) affected by a given drug can be determined by examining the time between drug exposure and conception (Table 1). For instance, an abnormal reproductive outcome occurring 5 days after treatment indicates a drug effect on maturation of

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**TABLE 1. Germ cell type affected in man at different times after exposure to a drug or chemical***

| Time of exposure (days) | Germ cell type affected | Activity affected |
|---|---|---|
| 1 | Drug in semen | Direct toxicity |
| 1–5 | Spermatozoa | Epididymal transit/storage |
| 6–29 | Spermatid | Differentiation |
| 30–53 | Spermatocyte | Meiosis |
| 54–69 | Spermatogonia | Mitosis |

*Adapted from Courot, '70.

sperm in the epididymis. A drug that causes DNA damage during synapsis of chromosomes during meiotic prophase would affect the progeny conceived approximately 40 days later.

Drug effects on any of the steps in the production of the mature spermatozoon could change any one of the components of this highly specialized cell. For example, both an alteration in the flagellum, which results in lower motility, or an effect of the drug on the plasma membrane could result in lower fertilization rates, whereas damage to the chromatin could lead to fetal death or heritable effects in the offspring. Epigenetic alterations, involving changes in gene expression without a change in nucleotide sequence, should also be considered. A number of human teratogens have been tentatively classed as having evidence of epigenetic activity (Bishop et al., '97). However, assays to determine whether a given paternal exposure has a direct epigenetic effect have not yet been developed. As for teratogens, it is often difficult to determine whether an alteration in gene expression is a direct effect or an indirect effect of a given chemical or drug on a different target. For the purposes of this review, no attempt has been made to separate genetic and epigenetic effects; however, exposures where epigenetic effects should be considered have been indicated. For paternal exposures, effects on imprinted genes may be particularly important. Imprinted genes are only expressed from either the maternal or paternal allele. For imprinted genes expressed from the paternal allele, inactivation of the paternal allele will result in loss of gene function, since the maternal allele is silent (Tycko et al., '97). Although genomic imprinting is not yet precisely defined at the molecular level, the process is initiated during gametogenesis and plays a role in regulating the growth of the conceptus during development. Alterations in imprinting can cause human genetic diseases and have been associated with the development of childhood tumors (Tycko et al., '97). A drug that alters the normal imprinting process during spermatogenesis could be expected to alter development of the resulting offspring. Additional epigenetic effects of paternal exposures on testis-specific gene expression might affect sperm number, morphology, and/or function.

At the DNA level, there are major differences among the various germ-cell types in their sensitivity and responses to mutagens (Witt and Bishop, '96). Slow-dividing, long-lived stem cells might be expected to face the greatest risk from chronic exposure to exogenous agents due to the potential accumulation of DNA damage, especially during the long human prepubertal period. Effects of a drug on the DNA of spermatogonial stem cells are of particular concern as they may persist throughout the reproductive life span of an individual, with the mutant stem cell serving as a long-lasting source of abnormal spermatozoa. To date, there are very few agents that have been shown to produce heritable damage in spermatogonial stem cells, perhaps due to efficient repair or selection mechanisms or the short prepubertal period in mice and rats (Shelby, '96). Differentiating spermatogonia are rapidly dividing cells and are most sensitive to killing by radiation and chemotherapy. The last round of DNA synthesis of spermatogenesis occurs in preleptotene spermatocytes. Preleptotene-leptotene and meiotically dividing spermatocytes are susceptible to killing by irradiation (Clermont and Harvey, '65; Henriksen et al., '96) and other agents. During spermiogenesis in postmeiotic germ cells, histones are replaced by protamines, nuclear condensation occurs, and DNA repair capability ceases. Damage to spermatids may pose a significant risk to the progeny because, despite DNA damage, these haploid cells can still develop into spermatozoa capable of fertilizing an egg (Meistrich, '93; Witt and Bishop, '96).

## EPIDEMIOLOGIC FINDINGS

Human exposures are often chronic in nature. If male-mediated effects are suspected, the physician needs first to rule out a direct effect of drug(s) present in semen as well as maternal exposure preconception. As outlined in this section, a number of epidemiologic studies over the last 10 years have started to identify exposures with suspected male-mediated effects.

### Occupational and environmental exposures

Most epidemiological studies have examined the effects of paternal occupational exposures on offspring. For most, paternal occupational/industrial exposure involves multiple agents, and it is difficult to identify the causative agent(s) (Olshan and Faustman, '93; Olshan and Schnitzer, '94). However, some suggestive associations have been reported and provide direction for future epidemiologic studies. An increased incidence of spontaneous abortion or miscarriage has been linked to paternal exposures to anesthetic gases, metals (mercury and lead), solvents, pesticides, and hydrocarbons (Savitz et al., '94). In the case of mercury, a dose-response relationship between urinary mercury concentrations and the rate of spontaneous abortions has been reported (Cordier et al., '91). An increased risk of stillbirth, preterm delivery, and small-for-gestational-age babies has been found for fathers employed in the art and textile industries (Savitz, '94). Fathers employed as janitors, woodworkers, firemen, electrical workers, printers, and painters have been reported to be at increased risk of having a child with a birth defect

(Olshan et al., '90, '91; Schnitzer et al., '95). Exposures related to these occupations include solvents, wood and wood products, metals, and pesticides (Olshan et al., '91); for most studies, quantitative exposure estimates have not been identified. Epidemiological studies have also suggested a link between childhood cancers and occupational exposures; however, the specific etiologic agents involved are not yet known (Savitz and Chen, '90; O'Leary et al., '91). Interestingly, some of the same exposures or occupations are associated with a number of outcomes, e.g., painters and welders with both birth defects and childhood cancer. Animal studies to explore mechanisms may be useful once repeat studies are done and information is available on specific agents or combinations that are associated with male-mediated effects on the progeny.

### Recreational exposure

Paternal exposures to most "recreational drugs" such as caffeine, cocaine, and methadone have not been studied in detail. However, among these agents, there is little consistent evidence that either paternal smoking or alcohol results in birth defects (Little and Vainio, '94). For example, although an initial positive association between paternal drinking and low birth weight was reported (Little and Sing, '85), a more recent large retrospective analysis, albeit with lower alcohol exposure than that in the study of Little and Sing ('85), found no adverse effect of paternal alcohol consumption on progeny outcome (Savitz et al., '92).

### Therapeutic drugs

With respect to male-mediated effects of most commonly used drugs, little work has been done. Among the therapeutic agents, there has been particular concern with the father's exposure to anticancer drugs. Cancer therapies have increased survival in young adults and children with cancers such as Hodgkin's disease, testicular cancers, and leukemia. Many of the drugs used in cancer treatment cause DNA damage, result in temporary or permanent infertility, and could theoretically alter the sperm genome. Drugs that are commonly used include doxorubicin, cyclophosphamide, vincristine, chlorambucil, melphalan, bleomycin, and 6-mercaptopurine, all of which are potent germ-cell mutagens and somatic cell clastogens in rodents (Shelby, '94; Witt and Bishop, '96). Unlike occupational exposures, exposures to anticancer drugs are relatively well-controlled and carried out in circumstances where dose-response relationships can be determined. To date, no increase in birth defects or in cancer or genetic disease in the offspring has been found (Hawkins, '91; Mulvihill, '94; Sankila et al., '98). However, relatively few children have been born to male cancer survivors, and it is estimated that many thousands of patients will be needed to rule out a relative risk for a germ-cell mutation in the range of 1.5. Further epidemiological studies of the offspring of males treated with anticancer drugs are ongoing. In North America, the Childhood Cancer Survivor Study, a large multicenter study of 25,000 long-term survivors of childhood and adolescent cancer, is currently underway and is looking for evidence of induced genetic disease in offspring as well as other health effects (Mulvihill, '94). Due to the risk of infertility, many cancer patients cryopreserve their sperm prior to treatment. For men who are infertile after therapy, cryopreservation of sperm gives them an opportunity to father children. For men in whom fertility returns, cryopreservation allows a comparison of pre- and posttreatment sperm samples for genetic damage.

### Large-scale exposures

One of the largest epidemiologic studies has been carried out on survivors of ionizing radiation from the atomic bombs at Hiroshima and Nagasaki. For the offspring of exposed men, no significant increase was found for a number of endpoints, including stillbirths, congenital abnormalities, low birth weight, cancer, and cytogenetic abnormalities (Neel and Schull, '91). Regarding paternal exposures, some limitations to this study (Neel and Schull, '91) have been reviewed, including inadequate statistical power to detect weak to moderate radiation effects, such as an increase in specific birth defects, incomplete ascertainment for fetal losses or severe congenital malformations due to the time lag between the bombing and the start of the study, and the fact that the spermatogenic cell type affected was spermatogonial stem cells, cells that are known from rodent studies to be more resistant to the induction of mutations by radiation than the later cell types (Olshan, '95). Taking into account these limitations, atomic bomb studies provide evidence that exposure of man to a single dose of ionizing radiation does not result in a detectable increase in genetic disease. The question of chronic radiation exposure was raised more recently when an excess risk of leukemia and non-Hodgkin's lymphoma was reported for children whose fathers were employed at the nuclear reprocessing plant near Sellafield, England (Gardner et al., '90; Gardner, '92). The Sellafield findings generated a lot of interest but remain controversial in the light of several factors, including alternative explanations for the data, the lack of an increase in genetic disease or congenital malformations in the area, and the lack of evidence from other studies for increased cancer risks in children of nuclear plant workers (Doll et al., '94; Olshan, '95). Nevertheless, continued studies of men working in nuclear facilities are useful, since exposure histories are well-documented and may help resolve questions raised by the Sellafield data.

More recently, Dubrova et al. ('96) reported an increased minisatellite mutation frequency in children born in contaminated areas of the Mogilev district of Belarus after the Chernobyl nuclear power station accident in 1986. The results suggest that the accidental release of radioactive material at Chernobyl may have resulted in induction of germline mutations. How-

ever, a similar study examining minisatellite mutations in the children of atomic bomb survivors did not find evidence of mutation induction (Kodaira et al., '95). Clearly, more work is needed to document effects of other chronic exposures, such as the Chernobyl accident, and to determine why effects of such chronic exposures apparently differ from acute exposures, like those following atomic bomb explosions.

Early attention to the area of male-mediated effects on offspring came from concerns that American veterans were exposed during military service in Vietnam to the herbicide Agent Orange, containing dioxin contaminants. It has been difficult to draw firm conclusions from the studies on reproductive outcomes among men who served in Vietnam due to difficulties in establishing exact levels of exposure (Erickson et al., '84; Aschengrau and Monson, '89; Centers for Disease Control, '88; Stellman et al., '88). There has been concern that men serving in the more recent Persian Gulf War were exposed to agents that affected their reproductive health and resulted in birth defects in their children. Although more studies are underway, an analysis by Cowan et al. ('97) found no evidence of an increase in birth defects among children of Gulf War veterans.

## EVIDENCE OF MUTATION INDUCTION IN HUMANS

In this section, several examples will be used to illustrate that paternal exposure can lead to sperm abnormalities, infertility, somatic chromosomal defects, and sperm chromosomal defects. In some cases, the effects may have an epigenetic origin. To date, there is no direct evidence for induced inherited genetic disorders in man (Robbins, '96). Only further study will help determine whether paternal exposures such as those mentioned above also lead to genetic abnormalities or abnormalities in offspring.

### Somatic chromosome abnormalities

A wide range of occupational exposures is associated with chromosomal mutations (Ashby and Richardson, '85). Evidence from occurrence of second treatment-related tumors in cancer survivors indicates that mutations in somatic cells are involved in the induction of cancer (Tucker et al., '88). Some common occupational exposures, such as 1,3-butadiene, have been linked to an increased risk of leukemia (Macaluso et al., '96), lymphosarcomas, and reticulosarcomas (Ward et al., '96). That many chemicals induce mutations in somatic cells suggests that mutations can also be induced in human germ cells. However, at present, there are no reliable, valid methods to link somatic and germinal mutations with the resultant phenotypes. At least one study has suggested that, following anticancer therapy, cytogenetic damage in somatic cells may not correlate with cytogenetic damage in sperm (Genesca et al., '90a).

### Infertility and sperm abnormalities

There are numerous well-known adverse reproductive effects of paternal treatment, including altered fertility and decreased sperm counts as well as abnormal sperm motility and morphology. Approximately 50 agents have been shown to affect the numbers, motility, or morphology of human sperm (Wyrobek et al., '83). Such effects indicate that germ-cell exposure has occurred and suggest the possibility of germ-cell mutations if the agent involved is mutagenic. One of the most well-known drug effects on sperm is the oligospermia and azoospermia seen in men following treatment with anticancer drugs, in particular, alkylating agents such as cyclophosphamide (Byrne et al., '87). In a well-publicized example, workers exposed to the pesticide dibromochloropropane (DBCP) reported infertility and were found to have decreased sperm counts (Whorton et al., '77). Lead exposure has been associated with abnormal sperm morphology and decreased fertility (Lancranjan et al., '75); both genetic and epigenetic mechanisms may be involved in the effects of lead on the male (Gandley and Silbergeld, '94).

### Chromosome aberrations in sperm

Two of the most widely used methods to detect cytogenetic damage in sperm are the human sperm/hamster egg technique pioneered by Rudak et al. ('78) and, more recently, fluorescence in situ hybridization (FISH). In the human sperm/hamster egg technique, capacitated human sperm are allowed to fuse with zona-free hamster oocytes, leading to decondensation and reconfiguration of the human sperm chromatin, permitting examination of human sperm metaphase chromosomes for structural and numerical abnormalities. The technique has been used by a number of investigators to study the effects of anticancer treatment on human sperm chromosomes. Martin et al. ('86) showed that sperm of men exposed to ionizing radiation contained a significant proportion of chromosomal aberrations up to 36 months after the termination of treatment, providing the first demonstration of induced chromosomal aberrations in functional human sperm, i.e., postfertilization survivability of radiation-induced mutations. For chemotherapy, although not all studies are positive, a number of different laboratories have reported elevated levels of structural aberrations and aneuploidy in the sperm of treated men (Brandriff et al., '94; Genesca et al., '90b; Jenderny et al., '92; Jenderny and Rohrborn, '87; Martin et al., '95). Interestingly, as with radiation, chromosome damage has been found a number of years after the cessation of treatment, suggesting effects on spermatogonial stem cells.

The human sperm/hamster egg procedure is difficult and labor-intensive. More recently, FISH has been used to assess disomy frequencies for specific chromosomes in individual human spermatozoa. FISH allows many thousands of sperm to be screened quickly for numerical chromosomal abnormalities; however, in the studies done to date, the assay used was unable to detect

structural aberrations. There are few large studies that have been carried out, and negative and positive results have been reported in studies on the effects of anticancer drugs on human sperm chromosomes (Robbins, '96; Martin et al., '97). A recent study in which pre-, during, and posttreatment sperm samples were available, found evidence of sperm aneuploidy in patients treated with chemotherapy for Hodgkin's disease; interestingly, damage decreased to pretreatment levels within 3–4 months after the end of therapy (Robbins et al., '97).

The cytogenetic studies mentioned above provide initial data on direct chromosomal damage in human sperm. Further studies are needed using both assays in homogeneous populations of cancer patients, on the same chemotherapy regimen, before, during, and after treatment. Whether the induced genetic damage is transmissible or not is unknown and will require studies in which sperm are examined and in which for the same patients, partners' pregnancies are monitored. It has been argued that we need to be concerned, since there appears to be no selection against chromosomally abnormal sperm in humans, and cytogenetically abnormal sperm can fertilize eggs (Martin, '89; Martin et al., '90).

## LIMITATIONS OF HUMAN STUDIES

Epidemiologic studies have identified a number of different types of paternal exposures, including environmental, occupational, and lifestyle exposures that result in a variety of abnormal pregnancy outcomes. Many findings await repeat studies for confirmation of the initial results. A number of questions arise for future human studies: What is the association of paternal exposures and postnatal abnormalities in children, e.g., behavioral deficits, increased cancer risk, or altered reproductive potential? Can alterations in spermatozoa be used to monitor human exposures or stem-cell damage? Are there ways to protect male germ cells from damage? Problems that have been encountered in human studies include limited sample size, incomplete documentation of exposure, high background rates (e.g., for birth defects, control rates in man are 3–7%), the inability to study subgroups such as spontaneous abortions and birth defects due to small sample size, the presence of unknown confounders, the lack of repeat studies with similar exposures by different investigators, and the endpoints studied, many of which (e.g., behavioral abnormalities) have complex etiologies, with the specific genetic components being varied or unknown.

## LESSONS FROM ANIMAL STUDIES

There are limitations to human epidemiologic and clinical studies, including the inability to identify the specific chemicals involved, as well as to control the timing of exposure and dosing. Studies performed in animals may avoid these problems, and give an indication of potential for risk in humans. Similarities between man and rodents in the process of spermatogenesis, as well as in response to injuries such as with radiation (Clifton and Bremner, '83), indicate that studies in animals can help us understand the mechanisms of male-mediated effects in man. In animal studies paternal exposure to numerous agents, including environmental chemicals, recreational substances, and therapeutic drugs, has been shown to cause adverse reproductive outcomes, including congenital malformations. Several examples will be used here to illustrate how well-controlled animal studies have contributed to a more mechanistic understanding of male-mediated developmental effects.

### Seminal fluid exposure

Drugs or environmental chemicals, present in the seminal fluid, could enter the female reproductive tract during intercourse and directly interfere with fetal development or may interfere with spermatozoa prior to fertilization. Many compounds have been shown to enter the semen, a fluid that is derived in large part from the secretions of the sex accessory glands and the epididymis (Pichini et al., '94). In animal experiments, methadone, morphine, thalidomide, and cyclophosphamide are examples of drugs that can cause increases in perinatal mortality and decreases in fetal weight through their presence in semen. In addition, in rabbit studies, the presence of thalidomide in semen has been linked with malformations in the offspring (Lutwak-Mann, '64), and in rat studies cyclophosphamide in semen resulted in increased preimplantation loss (Hales et al., '86). Since humans continue to have intercourse during pregnancy, there is the possibility that the conceptus may be exposed to drugs or chemicals in semen at various critical times during development. However, although many drugs will appear in semen, most will be present at such low levels that there would be little concern in humans. Drugs known to be teratogenic at low levels warrant further study. The 5-alpha reductase inhibitor, finasteride, is an example of such a drug, where the possibility of teratogenic effects of semen transmission was considered and tested experimentally in a primate model (Prahalada et al., '97). Pregnant female monkeys were administered, throughout pregnancy, daily doses of finasteride, within and above the range of semen levels of the drug, and effects on the offspring were assessed. No abnormalities were observed in the offspring, even at doses 60–750 times levels found in the semen of men treated with recommended doses of finasteride, suggesting a large safety margin for potential human exposures. Similar studies could be considered for other compounds where there is a concern that indirect exposure of the fetus to low levels of a drug through semen may occur.

### Hormonal effects

Alternatively, drugs could alter the male's hypothalamic-pituitary-testicular axis, leading to oligospermia. Do quantitative abnormalities, such as oligospermia,

affect fetal development? Studies to date indicate that quantitative decreases alone, with no qualitative abnormalities, induced by hormonal manipulations, do not adversely affect the progeny of rats (Robaire et al., '87). The issue of hormones and hormonal modulators in the environment and of potential effects on development and reproduction is currently very controversial, and beyond the scope of this review. Possible links between environmental estrogen exposure and testicular cancer are of particular concern. However, although hormonal exposure of developing male rodents has been linked to cryptorchidism, decreases in testis size, and other reproductive tract abnormalities (Gill et al., '79; Sharpe et al., '95), there are no data linking paternal exposure to hormones and birth defects in the fathers' offspring.

### Genetic and epigenetic effects

Qualitative defects in sperm may be expected to result in genetic defects or mutations that are transmitted to the offspring. In animal studies, the most frequently used assays for germ-cell mutagenicity are the dominant lethal, heritable translocation, and specific locus mutation assays (Shelby, '96). Dominant lethals allow fertilization but result in embryonic death and are thought to be a result of chromosomal abnormalities (structural or numerical) in germ cells of the treated male; the test does not assess heritable risks. The heritable translocation test measures chromosomal abnormalities (translocations) transmitted to the male offspring of treated males. Visible or biochemical specific locus mutation tests also estimate the frequency of heritable alterations: offspring of treated male mice are analyzed for alterations of visible morphological traits or biochemical parameters, indicative of specific gene mutations in male germ cells.

Numerous different chemicals and drugs produce positive results in these assays in animal studies (Olshan and Faustman, '93). From studies using these assays, a number of interesting points emerge, including the fact that different germ-cell types are sensitive to different chemicals. Most chemicals that are mutagenic induce mutations in postspermatogonial stages, and only a few chemicals to date have induced transmissible mutations in spermatogonial stem cells (Witt and Bishop, '96). For instance, only nine chemicals, of which three are anticancer drugs (mitomycin C, melphalan, and procarbazine), have been shown to induce specific locus mutations in spermatogonial stem cells (Witt and Bishop, '96; Shelby, '96). A large number of chemicals induce mutations in later germ-cell types (Witt and Bishop, '96). Alkylating agents, including the nitrogen mustards, platinum-based drugs, and nitrosoureas, are potent germ-cell mutagens and induce dominant lethals, heritable translocations, and specific locus mutations in poststem-cell stages of germ-cell development, clearly demonstrating that mutations in postspermatogonial germ-cell types can be transmitted. Interestingly, the mechanisms for induction of mutations in germ cells are stage-dependent, e.g., whereas melphalan induces large DNA sequence deletions and other rearrangements in postspermatogonial stages, it produces other types of mutations in spermatogonia (Russell et al., '92).

Germ cells, such as primordial germ cells and spermatozoa, that were traditionally thought not to be susceptible to drugs, are also at risk of transmitting damage. For example, in mouse studies, primordial germ cells were more sensitive than stem-cell spermatogonia to the effects of ethylnitrosourea (Shibuya et al., '93; Wada et al., '94). When ethylnitrosourea was administered to pregnant female mice, their male offspring had reduced fertility and produced offspring with phenotypic anomalies. These results suggest that the male germline may even be vulnerable in utero, e.g., in a woman undergoing chemotherapy during pregnancy. Dominant lethal mutations have been reported after exposure of spermatozoa in the epididymis to a number of agents, including cyclophosphamide (Qiu et al., '92) and acrylamide (Shelby et al., '86; Smith et al., '86), despite the fact that the chromatin is highly condensed in these cells.

Mutagenicity tests detect large chromosomal structural or numerical damage or gene mutations at selected loci. A positive response in a given mutagenicity assay indicates a true hazard; however, the absence of an effect does not mean that the chemical being studied holds no threat for future generations. More subtle effects, such as single or multiple nucleotide changes, errors in genomic imprinting, or altered regulation of gene expression, would not be detected. Much genetic disease in humans, including congenital malformations, results from mutations at poorly defined loci. In rodents, paternal exposures can induce various developmental defects or phenotypic anomalies, including decreased fetal size, increased stillbirth and neonatal death, birth defects, tumors, and behavioral or neurochemical abnormalities. Several diverse, nonspecific phenotypic anomalies, such as growth retardation, hydrocephaly, generalized edema, and micrognathia, have been reported after paternal exposure to known mutagens (Nomura, '82; Kirk and Lyon, '84; Trasler et al., '85; Nagao, '88; Jenkinson and Anderson, '90). Both acute and chronic exposures result in birth defects. For the commonly used anticancer drug cyclophosphamide, chronic low-dose exposure of male rats, using doses similar to those used in clinical regimens, did not affect various measures of male reproductive function but did result in increases in preimplantation and postimplantation loss and an increase in abnormal and growth-retarded fetuses when the males were mated with untreated females (Trasler et al., '85, '86). For individual agents, the type of reproductive outcome, such as preimplantation loss or birth defect, observed after paternal treatment, often depends on the germ-cell type exposed to the drug. For an endpoint such as birth defects, examination of thousands of offspring of paternally treated mice and rats showed 3–8-fold increases over control rates (Table 2). Similarly, large numbers of

**TABLE 2. Examples of paternal exposures in rodents that result in increased numbers of malformations in the offspring**

| Reference | Animal | Treatment | # of malformations | |
|---|---|---|---|---|
| | | | Control | Treated |
| Trasler et al., '85, '87 | Rat | Cyclophosphamide | 7/1,580 (.4%) | 23/2,096 (1.1%) |
| Kirk and Lyon, '84 | Mouse | X-ray | 17/2,020 (.8%) | 110/5,123 (2.1%) |
| Nomura, '78, '82, '88 | Mouse | X-ray | 26/4,867 (.5%) | 61/1,588 (3.8%) |
| | | Urethane | | 75/3,400 (2.2%) |
| | | 7,12-Dimethylbenz-(a)anthracene | | 19/1,321 (1.4%) |
| | | Ethylnitrosourea | | 29/1,175 (2.5%) |
| Nagao, '87 | Mouse | Methylnitrosurea | 28/5,086 (.6%) | 79/3,614 (2.2%) |

patients with well-defined paternal exposures are likely to be needed to show effects in human studies.

Some of the defects induced by paternal exposures to drugs may occur late in life. For instance, in mice, exposure of germ cells to carcinogens and mutagens leads to the occurrence of heritable tumors in the offspring (Tomatis et al., '92). Functional abnormalities in the progeny, such as behavior, may go undetected but may indicate a change in central nervous system (CNS) function. Male-mediated behavioral abnormalities have been reported in the offspring of males treated with various agents, including methadone (Joffe et al., '90), morphine (Friedler and Wheeling, '79; Cicero et al., '91), cyclophosphamide (Adams et al., '81; Auroux and Dulioust, '85), lead (Brady et al., '75; Gandley and Silbergeld, '94), and ethylene dibromide (Fanini et al., '84).

### Genomic imprinting

A subset of mammalian genes is subject to genomic imprinting, an epigenetic process that is thought to be initiated during spermatogenesis and oogenesis and then further modified during embryogenesis. For imprinted genes, the gene on either the maternal or the paternal allele is expressed. A drug-induced alteration in the male germline could lead to two theoretical outcomes in the offspring, i.e., expression from both alleles due to "relaxation" of the paternal imprint, or expression from neither allele due to failure to epigenetically mark the paternal allele for expression. The precise nature of the imprint and the timing during spermatogenesis when the process is complete are not known. Concern has been raised for men undergoing intracytoplasmic sperm injection (ICSI) as a treatment for infertility, where immature germ cells or sperm that may have abnormalities are used (Tycko et al., '97). Site-specific DNA methylation, catalyzed by DNA methyltransferase, has been implicated as an important biochemical modification of DNA underlying imprinting. In keeping with an important role for DNA methylation in imprinting, DNA methyltransferase-deficient mice show abnormal expression of imprinted genes (Li et al., '93). Few animal studies have investigated the possible link between paternal exposures and effects on genomic imprinting. Chronic treatment of male rats with 5-azacytidine, a drug that alters DNA methylation, resulted in abnormalities in male germ cells and early embryo development but no increase in the incidence of congenital malformations (Doerksen and Trasler, '96). This is an important area with potential consequences for the offspring of exposed males, and warrants further study.

### Heritability

An important question with clinical relevance is the heritability in future generations of the initial damage to male germ cells. In rodents, evidence of heritability (for malformations, postimplantation loss, and/or behavioral abnormalities) has been reported for a number of exposures, including radiation, urethane, and cyclophosphamide. Chronic paternal treatment with cyclophosphamide leads to decreases in litter sizes, but some pups survive without noticeable malformations. An increase in postimplantation loss and malformations among progeny resulted when these "normal" F1 animals whose fathers were treated with cyclophosphamide were mated with untreated females (Hales et al., '92). Similarly, another study with cyclophosphamide found behavioral abnormalities in the F2 and F3 generations, with disorders more severe in males than females (Auroux et al., '90). Heritable mutations were also found in mice whose fathers were treated with urethane and ionizing radiation (Nomura, '94), suggesting that drug-induced mutations in germ cells can be passed on to future generations. Tumors in the F1 and later generations have been reported following paternal treatment with ionizing radiation, ethylnitrosourea, and urethane (Nomura, '94; Tomatis et al., '81, '90).

### Other exposures

Epidemiological studies in humans have suggested that paternal occupational exposures may be linked to spontaneous abortions, miscarriages, and childhood cancers (McDonald et al., '89; Olshan and Faustman, '93). There are relatively few studies in animals regarding occupational-type exposures. Paternal treatment of mice with chromium chloride, a constituent in welding fumes, resulted in increased numbers of offspring with tumors; however, exposure to six other metal components resulted in no differences from controls (Anderson et al., '94). A comprehensive analysis of data from a

number of studies on the genetic effects of 1,3-butadiene and its metabolites was carried out in an effort to estimate the germ-cell genetic risk to exposed humans (Pacchierotti et al., '98). 1,3-Butadiene, a synthetic organic chemical used in the petroleum industry, tire plants, and polymer production, has been of particular interest as it is carcinogenic in mice at low-exposure concentrations and has been associated with an increased risk of leukemia and other cancers in exposed workers (Macaluso et al., '96; Ward et al., '96). Acknowledging that their conclusions on 1,3-butadiene were based on approximations, Pacchierotti et al. ('98) nevertheless concluded that a genetic hazard for the progeny of exposed workers exists at exposure concentrations still allowed in some countries. Paternal exposures to recreational drugs such as alcohol, opiates, and smoking have been examined in a number of studies. Common findings in offspring following paternal exposure to opiates such as morphine and methadone include low birth weight, and behavioral and endocrine abnormalities (Friedler, '96). In some rodent studies, paternal alcohol exposure was associated with increases in perinatal mortality, decreases in fetal size, and behavioral abnormalities in the progeny (Nelson et al., '96). Unlike drugs that are known mutagens and cause genetic damage, the mechanisms of paternal effects of alcohol and opiates are unclear and may involve epigenetic mechanisms.

### Germ-cell protection

Radiation and cancer chemotherapeutic agents can suppress spermatogenesis for prolonged periods of time in rodents and man and are known to be germ-cell mutagens in rodents (Witt and Bishop, '96). It would therefore be clinically useful to protect spermatogenesis from the damaging effects of chemotherapy and radiotherapy, and this has been attempted by several laboratories using animal models. Protection of spermatogenesis from cyclophosphamide was first shown in mice using pretreatment with daily injections of an analogue of gonadotropin-releasing hormone (GnRH) (Glode et al., '81). Pretreatment of rats with various regimens, all of which suppress intratesticular testosterone levels, including gonadal steroids, GnRH agonists, or antagonists, can protect the testis from cancer chemotherapy-induced damage (Meistrich et al., '98). Although the mechanisms are unclear, the hormonal treatments used to date in rodents are thought to protect the survival of spermatogonial stem cells and/or maintain an appropriate paracrine environment, to allow surviving stem spermatogonia to differentiate posttreatment. Hormonal protection of spermatogonial stem cells has been extended to some men undergoing cancer chemotherapy; however, mechanisms of protection and ideal dosing regimens still need to be established.

Another approach to decreasing gonadal injury associated with anticancer therapy is through the production of artificial cryptorchidism. The elevation of the testes into the inguinal canal results in reversible germ-cell loss; testicular injury following artificial cryptorchidism is thought to be due to increased gonadal temperature. In an experiment supporting the potential utility of this approach for male germ-cell protection, cryptorchid rats were protected from the irreversible effects of 2,5-hexanedione-induced germ-cell loss, possibly due to decreased exposure of germ cells in the cryptorchid testes to the compound (Boekelheide et al., '90).

Other potential avenues for future approaches to protecting germ cells include harnessing endogenous cellular protective mechanisms such as heat shock proteins and molecules that regulate apoptosis. Heat shock proteins, including spermatogenic cell-specific forms, are found in abundance in rodent and human germ cells (Miller et al., '92; Dix, '97); some heat shock proteins are induced in response to environmental stress and may play a role in protecting germ cells from various paternal exposures. Some heat shock proteins are essential for spermatogenesis. For instance, in mice homozygous for a targeted deletion in the *Hsp70-2* gene, pachytene spermatocytes fail to complete meiotic prophase and become apoptotic (Dix et al., '97). The *p53* tumor-suppressor gene prevents the propagation of DNA damage to daughter cells by causing cell-cycle arrest or by inducing apoptosis (Smith and Fornace, '96) and may also be involved actively in DNA repair (Smith et al., '95; Li et al., '96). In the mouse, p53 is expressed during meiotic prophase in pachytene spermatocytes (Schwartz et al., '93) and appears to be important for normal spermatogenesis, since the testes of mice with reduced levels of p53 are histologically abnormal, consistent with abnormalities in DNA repair and meiotic divisions (Rotter et al., '93). Interestingly, when homozygous p53-deficient male mice (*p53-/-*) were exposed to irradiation 4 weeks prior to mating, an increased level of exencephaly was found in the homozygous female p53-deficient progeny (Armstrong et al., '95). The results suggest the intriguing possibility that p53 may play a role in suppressing radiation-induced male-mediated teratogenesis.

## CONCLUSIONS

In man, there is as yet no documented transmission to the offspring of drug- or chemical-induced heritable changes; however, data are accumulating to suggest caution. Evidence from human studies includes documented decreases in the quality and quantity of sperm after paternal exposure to drugs and toxic chemicals, and needs to be considered in the light of the ability of cytogenetically abnormal sperm to fertilize oocytes. Clinically, a portion of chromosomal abnormalities occurring in embryos and newborns is known to be of paternal origin, and data from epidemiological studies suggest that men in certain occupations have increased risks of fathering children with birth defects or cancer (Savitz and Chen, '90; Olshan and Faustman, '93). In contrast, numerous observations from animal studies

indicate that paternal exposure to drugs and chemicals can result in adverse reproductive outcomes and the transmission of genetic damage. Low birth weight, congenital malformations, behavioral defects, delayed appearance of early postnatal landmarks, growth retardation, endocrine abnormalities, and cross-generational effects are some of the adverse outcomes resulting from paternal exposures in animal studies. Children are born with similar defects, and the available evidence does not allow us to rule out the possibility that some of these defects are caused by paternal environmental or therapeutic exposures.

Human epidemiologic data are very important due to the limitations in extrapolating from animal studies to human exposures. For the future, well-designed epidemiological studies, with large numbers of accurately identified cases, accurate exposure histories, and identification of confounders, are needed. For occupational exposures, parallel studies in animal models may help establish biological plausibility and discern underlying mechanisms. Coordination of international efforts will be important to respond quickly with well-designed studies to follow reproductive outcomes after environmental disasters. With the rapid advances that are occurring in the identification of genes involved in human disease and in the screening of genes for mutations, molecular and DNA-based approaches should be incorporated into these epidemiological studies to search for genetic changes in human germ cells and the resulting offspring.

## PRACTICAL CONSIDERATIONS AND COUNSELING

Physicians should be aware that there is increasing concern that both maternal and paternal exposures may be important to consider. Clearly, more basic and clinical research in this area is important (Olshan and Mattison, '94). Detailed histories of mothers' and fathers' exposures should be taken routinely. In man, the relationship between alterations in male fertility (including sperm abnormalities) and birth defects is unclear at present. The findings of increased chromosome aberrations in sperm of patients who have received radiotherapy and chemotherapy suggest that physicians should be cautious in predicting reproductive outcomes in these patients. Cancer patients interested in having children should receive genetic counseling informing them of the available data. Sperm samples for cryopreservation should be collected prior to but not during cancer therapy (Meistrich, '93). For those cancer patients who decide to conceive posttherapy, the data are still scarce; however, it appears that the general recommendation of delaying conception for at least 6 months after all therapy ceases is reasonable (Meistrich, '93; Robbins et al., '97). This timing will ensure that all spermatozoa that fertilize an egg derive from cells that were stem spermatogonia at the time of treatment and are thus expected to carry a lower genetic risk. High-resolution ultrasound and amniocentesis or chorionic villus sampling are the only other screening tools that can be offered to cancer patients at this time. Sperm banking in cancer patients may not only allow these men to have children in the future but may facilitate the comparison of pre- and posttreatment samples for genetic damage. Some of the approaches currently being used in cancer patients, such as delayed conception, sperm storage, and attempts to protect the seminiferous epithelium with hormones, may also be useful for certain occupational exposures in the future.

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**South Dakota Section of the**
**American College of Obstetricians and Gynecologists**

**September 26, 2006**

# Position Statement of the South Dakota Section of The American College of Obstetricians and Gynecologists Opposing H.B. 1215/ Referred Law 6

The South Dakota Section of The American College of Obstetricians and Gynecologists (ACOG) opposes H.B. 1215/Referred Law 6, a bill that not only bans abortion but also restricts basic reproductive health services in South Dakota.

We oppose this reproductive health ban that is not based on science, strips women of their legal rights, and criminalizes essential aspects of women's health care. The intervention of the legislature into medical decision-making is inappropriate, ill advised, and dangerous. We urge repeal of the ban, for the sake of women's health in South Dakota and for the protection of medical decision-making within our state.

ACOG is the leading professional association of physicians who specialize in the health care of women, with more than 51,000 members. The 69 ACOG board-certified obstetrician-gynecologists in our South Dakota Section provide care for many women in the state and manage most of the 11,000 births in South Dakota each year.

The position of the South Dakota Section of ACOG reflects ACOG's national policy on abortion, which recognizes that the issue of support for or opposition to abortion is a matter of profound moral conviction to its members. Like National ACOG, we respect the need and responsibility of our members in South Dakota to determine their individual positions on abortion based on personal values or beliefs. We note that, like other Americans in communities across the country, ob-gyns in South Dakota have diverse personal beliefs on abortion. As an organization, ACOG opposes unnecessary regulations that limit or delay women's access to needed medical care, including abortion, and that subject physicians to criminal charges for practicing according to accepted medical standards.

Our major objections to the ban are as follows:

**1. The reproductive health ban cruelly withdraws long-standing rights of South Dakota women.**

H.B. 1215/R.L. 6, by criminalizing almost all abortions, is the harshest abortion bill passed in the US in the last 33 years, taking away rights that have been available to women for over three decades.

The ban forbids a woman from having an abortion under any circumstance except when her life is in danger.

***Rape and Incest***

The ban includes no exception for rape victims, even though an estimated one in six US women has been the victim of attempted or completed rape. Approximately 340 forcible rape cases per year were reported in South Dakota in 2003 and 2004, according to state and federal statistics, or nearly one case a day. No doubt many other cases of rape occur but go unreported each year.

The ban includes no exception for victims of incest, often girls and young teens. Studies show that when young teens or girls are pregnant, the cause is often sexual abuse or incest.

Under this harsh ban, if any pregnant girl or woman comes to us for help in terminating a pregnancy forced upon her through incest or rape, we could not aid her, not even to refer her to a qualified physician in another state.

***Emergency Contraception and Rape/Incest***

Some supporters of this ban are claiming that the lack of a rape or incest exception is insignificant, because victims could take emergency contraception. Even if the ban is interpreted to allow the important option of emergency contraception (and, as discussed further below, that is not a certainty) no one should forget that access to emergency contraception can be difficult in South Dakota. The state was one of the first to have stiff rules allowing pharmacists to refuse to dispense emergency contraception. In this largely rural state, sometimes one pharmacy serves several towns. If the pharmacist in that area refuses to dispense emergency contraception, women for miles around will have no access to it.

In addition, emergency contraception will only work if taken within a short period after unprotected sex. Also called the morning-after pill, emergency contraception is a higher dosage of hormones found in ordinary birth control pills. (Methods of emergency contraception include progestin-only or combination estrogen-progestin oral contraceptives. The most common and effective form of hormonal emergency contraception contains levonorgestrel, a progestin. It is sold in the United States under the brand name Plan B.) Emergency contraception is highly effective in reducing a woman's chance of pregnancy after a contraceptive failure or unprotected sex. This can include rape. If taken within 72 hours of unprotected sex, EC prevents up to 89% of pregnancies; it is most effective if taken within 24 hours. However, incest or rape victims may be unable to find or take emergency contraception within that time frame.

In sum, access to emergency contraception -- claimed by some of the ban's supporters, yet questionable in our state, where pharmacists can outright refuse to fill prescriptions -- does not minimize or lessen this ban's impact on rape and incest victims.

***Lethal Birth Defects***

The ban includes no exception for lethal congenital birth defects. These are severe conditions in the fetus that, if they do not result in miscarriage, almost always lead to certain infant death -- usually upon or shortly after birth. Under this ban, South Dakota women will be forced to carry these doomed pregnancies for nine months, only to watch the predicted fatal outcome.

Examples of lethal congenital birth defects include: *Anencephaly* (where portions of the brain are missing or reduced to small matter attached to the base of the skull); *Iniencephaly* (severe abnormality of the spine and vertebrae, with the brain and much of the spinal cord occupying a single cavity); *Hydranencephaly* (complete or near complete absence of the hemispheres of the brain); *Infantile Polycystic Kidney Disease with anhydramnios* (a lack of amniotic fluid during development); and *Triploidy* (the presence of three full sets of chromosomes).

Other examples include congenital birth defects known as: *Pentalogy of Cantrell*; *Limb-Body Wall Complex*; *Bilateral Renal Agenesis*; *Sirenomelia*; *Achondrogenesis*; *Severe Amniotic Band Syndrome*; *Jeune's Thoracic Dystrophy—Asphyxiating Thoracic Dystrophy*; *Thanatophoric Dysplasia*; *Meckel-Gruber Syndrome*; and *Pena-Shokeir Phenotype*. And these are not the only severe life threatening and life altering anomalies.

Today, with advances in prenatal screening, many South Dakota women and couples understandably choose not to carry to term a pregnancy with lethal fetal birth defects. This ban takes that private decision away from them.

**2. <u>The reproductive health ban recklessly endangers the health of South Dakota women, by outlawing physicians' ability to make essential and timely medical decisions.</u>**

The ban includes no exception to protect a woman's health, permitting only an abortion "designed or intended to prevent the death of a pregnant mother."

Section 4 states that the physician "shall make reasonable medical efforts under the circumstances to preserve both the life of the mother and the life of her unborn child in a manner consistent with conventional medical practice."

This section creates impossibly conflicting mandates for physicians. Under "conventional medical practice," our obligation as physicians is to protect both the life *and* the health of the patient. Yet this ban requires us to make "reasonable efforts" to protect patient life only, but not patient health -- an impossible dictum.

Where a condition is not life-threatening but compromises or worsens a woman's health, physicians' hands are tied by this broad ban. For example, the ban could prohibit pregnancy termination for a woman who has cardiac problems or high blood pressure that has not yet reached life-threatening stages. It is unclear whether the ban's "life only"

exception applies to conditions that we doctors believe are likely to cause death, conditions that are possibly -- but not definitely -- fatal, or conditions that are certain to cause death, just not immediately.

By forbidding a woman's health exception, the ban also shows a dangerous misunderstanding of medical practice. We physicians cannot always predict what course medical complications will take in a given emergency situation or how quickly they may lead to mild health problems, severe injury, or even death. By requiring us to "wait and see" if a condition deteriorates into a clearly life-threatening situation before permitting us to provide medically indicated treatment, this ban indefensibly jeopardizes patients' health.

There are a number of medical conditions that, based on the physician's judgment in consultation with the patient, may require the termination of pregnancy to protect the pregnant woman's health or life. We note the following examples:

- **Diabetes with renal disease and retinopathy**: Pregnant women with these serious diabetic complications risk a worsening of their condition if they carry their pregnancy to term. They could face blindness or the need for dialysis. Yet, under the ban, these severe health conditions would be immaterial: a doctor's hands are tied unless death is the threatened outcome.

- **Preterm, premature rupture of membranes before fetal viability**: This condition is commonly seen in ob-gyn practice. At this stage, the fetus cannot survive outside the womb, yet under this ban a physician is forbidden to intervene until a woman is at risk of death -- such as when she is infected or hemorrhaging to death. By then, the intervention may be too late.

- **Cervical cancer first diagnosed in early pregnancy.** This malignancy is likely to be diagnosed in the first trimester, when pregnancy terminations are safer but the risk of maternal death from cancer is not yet high. The appropriate treatment may involve hysterectomy or radiation or both. Although the woman's life is not immediately threatened, if the cancer is not treated until after the nine-month pregnancy her life span could be shortened. Under this ban, any oncologist would be hesitant to treat the patient and yet could not refer her out of state.

Other medical conditions in the pregnant woman, which may require pregnancy termination depending on the physician's medical judgment in consultation with the patient, include:

- *Chorioamnionitis*: an inflammation of embryonic membranes
- *Unrelenting vaginal bleeding with anemia*
- *Cancer*
- *Severe preeclampsia before 24 weeks of pregnancy*: this involves high blood pressure, swelling, and excessive protein in the woman's urine

- *HELLP syndrome before 24 weeks*: a severe form of preeclampsia, with elevated liver enzymes and low platelet count
- *Severe pulmonary hypertension*: increased pressure within the lung's circulation system
- *A history of peripartum cardiomyopathy*: a disease of the heart muscle that occurred in prior pregnancies. The mortality rate for this disease is nearly 100% if a pregnancy is carried to term. The risk of getting this disease again, even if it has not appeared yet, could warrant pregnancy termination.
- *Eisenmenger's syndrome*: a pre-existing defect in blood flow, with pulmonary hypertension, which has a 50% mortality rate in pregnancy
- *Marfan's Syndrome with dilated aortic root greater than 40 mm*: a congenital disorder of connective tissue characterized by abnormally long extremities, heart abnormalities, and other deformities, with a 50% mortality rate in pregnancy
- *Prior myocardial infarction*: a history of a circulation obstruction in the heart
- *A high grade mitral valve stenosis*: an abnormal closing of a heart valve
- *Untreated cerebrovascular malformation or berry aneurysm*: obstructions or clots in the brain or blood vessels
- *Severe lupus flare*: a sudden worsening of a connective tissue disorder

All of the medical conditions mentioned here illustrate why physicians, not prosecutors, should be making the medical judgments necessary to protect not only the life, but also the health, of a patient.

**3. The reproductive health ban forces South Dakota physicians to violate our professional and ethical obligations to our patients.**

In scenarios such as those given above, we physicians are placed in the unconscionable position of either treating our patients in a medically appropriate fashion and being prosecuted as criminals under this ban, or not treating appropriately and not only facing claims of negligence but, worse, seeing our patients suffer.

The ban dangerously impedes the day-to-day medical decisions that we practicing physicians must make in caring for our patients. The ban requires us to compromise our medical judgment on what information or treatment is in the best interest of the patient. As stated in the Code of Professional Ethics of ACOG, "the welfare of the patient must form the basis of all medical judgments" and "the obstetrician-gynecologist should exercise all reasonable means to ensure that the most appropriate care is provided to the patient."

The ban deprives our patients of their fundamental right to optimal medical care without government interference. And by impeding day-to-day medical decisions, the reproductive health ban will undoubtedly reduce the number of new ob-gyns willing to practice in South Dakota, further jeopardizing women's health care in the state.

**4. The reproductive health ban could obstruct women's access to contraceptives in South Dakota.**

The vague and ambiguous language of the reproductive health ban raises a troubling question: Will South Dakota women, our patients, continue to have access to standard methods of birth control? There is a real possibility they won't.

Although the ban appears to exempt the dispensing of contraception from prosecution under abortion laws, the ban could be interpreted by a zealous prosecutor as prohibiting certain types of hormonal contraceptives such as IUDs or emergency oral contraceptives. And, even if the ban did permit one type of emergency oral contraception, it could disallow others.

This ambiguity is illustrated by the contradictions in how the ban treats pregnancy testing versus how it defines pregnancy itself (and thus contraception).

For example, Section 3 of the bill would allow

> [the] sale, use, prescription, or administration of a ***contraceptive*** measure, drug or chemical, if it is administered prior to the time ***when a pregnancy could be determined through conventional medical testing*** and if the ***contraceptive measure*** is sold, used, prescribed, or administered ***in accordance with manufacturer instructions.*** (Emphasis added.)

***Conventional Medical Testing***
The ban permits contraception administered "prior to the time when a pregnancy can be determined through conventional medical testing." According to both conventional medical pregnancy tests and conventional medical definitions of pregnancy, this would mean contraception administered before a fertilized egg has implanted in a woman's uterus (the definition of pregnancy). Hormonal forms of contraception such as emergency oral contraception and IUDs -- which can work by preventing ovulation, fertilization or implantation -- would appear to be exempt from the ban.

***Medical Definitions of Pregnancy and Contraception***
Contrary to established medical definitions, the ban also defines pregnancy in Section 5 as beginning at fertilization [union of sperm and egg], and it defines an "unborn child" as existing upon fertilization. In some cases, hormonal contraception such as emergency oral contraception and IUDs prevent pregnancy by working after fertilization but before implantation. Under this ban, both emergency oral contraception and IUDs could be considered -- incorrectly -- abortifacients, and therefore not "contraceptive measures" exempt under the ban's medical testing clause of Section 3.

Even if the ban is interpreted or enforced to permit emergency oral contraception, it may permit only one type. Section 3 refers to contraceptive measures "sold, used, prescribed, or administered ***in accordance with manufacturer instructions***." (Emphasis added.) A product like Plan B, specifically designated by the manufacturer for use as an emergency

contraceptive, might be permissible under this clause. But if Plan B is not available, there is another long-standing way physicians can provide emergency oral contraception to women after incidents of unprotected intercourse, such as rape -- by combining different types of ordinary birth control pills. Under this ban, however, this method of dispensing emergency contraception might be considered inconsistent with "manufacturer instructions" and thus a prosecutable offense.

The ban's ambiguous language and the threat of prosecution could inhibit many doctors from prescribing birth control for their patients, further restricting women's access to contraception in South Dakota.

***Summary***

In conclusion, as physicians who provide reproductive health care in South Dakota, we urge repeal of this ban that harms the women of South Dakota, jeopardizes health care within our state, and strips South Dakota residents of their fundamental right to appropriate and safe medical care without harmful government interference. We urge the citizens of South Dakota to overturn this ban.

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U.S. Nuclear Regulatory Commission

# REGULATORY GUIDE

Office of Nuclear Regulatory Research

**REGULATORY GUIDE 8.13**
(Draft was issued as DG-8014)

## INSTRUCTION CONCERNING PRENATAL RADIATION EXPOSURE

### A. INTRODUCTION

The Code of Federal Regulations in 10 CFR Part 19, "Notices, Instructions and Reports to Workers: Inspection and Investigations," in Section 19.12, "Instructions to Workers," requires instruction in "the health protection problems associated with exposure to radiation and/or radioactive material, in precautions or procedures to minimize exposure, and in the purposes and functions of protective devices employed." The instructions must be "commensurate with potential radiological health protection problems present in the work place."

The Nuclear Regulatory Commission's (NRC's) regulations on radiation protection are specified in 10 CFR Part 20, "Standards for Protection Against Radiation"; and 10 CFR 20.1208, "Dose to an Embryo/Fetus," requires licensees to "ensure that the dose to an embryo/fetus during the entire pregnancy, due to occupational exposure of a declared pregnant woman, does not exceed 0.5 rem (5 mSv)." Section 20.1208 also requires licensees to "make efforts to avoid substantial variation above a uniform monthly exposure rate to a declared pregnant woman." A declared pregnant woman is defined in 10 CFR 20.1003 as a woman who has voluntarily informed her employer, in writing, of her pregnancy and the estimated date of conception.

This regulatory guide is intended to provide information to pregnant women, and other personnel, to help them make decisions regarding radiation exposure during pregnancy. This Regulatory Guide 8.13 supplements Regulatory Guide 8.29, "Instruction Concerning Risks from Occupational Radiation Exposure" (Ref. 1), which contains a broad discussion of the risks from exposure to ionizing radiation.

Other sections of the NRC's regulations also specify requirements for monitoring external and internal occupational dose to a declared pregnant woman. In 10 CFR 20.1502, "Conditions Requiring Individual Monitoring of External and Internal Occupational Dose," licensees are required to monitor the occupational dose to a declared pregnant woman, using an individual monitoring device, if it is likely that the declared pregnant woman will receive, from external sources, a deep dose equivalent in excess of 0.1 rem (1 mSv). According to Paragraph (e) of 10 CFR 20.2106, "Records of Individual Monitoring Results," the licensee must maintain

records of dose to an embryo/fetus if monitoring was required, and the records of dose to the embryo/fetus must be kept with the records of dose to the declared pregnant woman. The declaration of pregnancy must be kept on file, but may be maintained separately from the dose records. The licensee must retain the required form or record until the Commission terminates each pertinent license requiring the record.

The information collections in this regulatory guide are covered by the requirements of 10 CFR Parts 19 or 20, which were approved by the Office of Management and Budget, approval numbers 3150-0044 and 3150-0014, respectively. The NRC may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

## B. DISCUSSION

As discussed in Regulatory Guide 8.29 (Ref. 1), exposure to any level of radiation is assumed to carry with it a certain amount of risk. In the absence of scientific certainty regarding the relationship between low dose exposure and health effects, and as a conservative assumption for radiation protection purposes, the scientific community generally assumes that any exposure to ionizing radiation may cause undesirable biological effects and that the likelihood of these effects increases as the dose increases. At the occupational dose limit for the whole body of 5 rem (50 mSv) per year, the risk is believed to be very low.

The magnitude of risk of childhood cancer following in utero exposure is uncertain in that both negative and positive studies have been reported. The data from these studies "are consistent with a lifetime cancer risk resulting from exposure during gestation which is two to three times that for the adult" (NCRP Report No. 116, Ref. 2). The NRC has reviewed the available scientific literature and has concluded that the 0.5 rem (5 mSv) limit specified in 10 CFR 20.1208 provides an adequate margin of protection for the embryo/fetus. This dose limit reflects the desire to limit the total lifetime risk of leukemia and other cancers associated with radiation exposure during pregnancy.

In order for a pregnant worker to take advantage of the lower exposure limit and dose monitoring provisions specified in 10 CFR Part 20, the woman must declare her pregnancy in writing to the licensee. A form letter for declaring pregnancy is provided in this guide or the licensee may use its own form letter for declaring pregnancy. A separate written declaration should be submitted for each pregnancy.

## C. REGULATORY POSITION

### 1. Who Should Receive Instruction

Female workers who require training under 10 CFR 19.12 should be provided with the information contained in this guide. In addition to the information contained in Regulatory Guide 8.29 (Ref. 1), this information may be included as part of the training required under 10 CFR 19.12.

### 2. Providing Instruction

The occupational worker may be given a copy of this guide with its Appendix, an explanation of the

contents of the guide, and an opportunity to ask questions and request additional information. The information in this guide and Appendix should also be provided to any worker or supervisor who may be affected by a declaration of pregnancy or who may have to take some action in response to such a declaration.

Classroom instruction may supplement the written information. If the licensee provides classroom instruction, the instructor should have some knowledge of the biological effects of radiation to be able to answer questions that may go beyond the information provided in this guide. Videotaped presentations may be used for classroom instruction. Regardless of whether the licensee provides classroom training, the licensee should give workers the opportunity to ask questions about information contained in this Regulatory Guide 8.13. The licensee may take credit for instruction that the worker has received within the past year at other licensed facilities or in other courses or training.

**3. Licensee's Policy on Declared Pregnant Women**

The instruction provided should describe the licensee's specific policy on declared pregnant women, including how those policies may affect a woman's work situation. In particular, the instruction should include a description of the licensee's policies, if any, that may affect the declared pregnant woman's work situation after she has filed a written declaration of pregnancy consistent with 10 CFR 20.1208.

The instruction should also identify who to contact for additional information as well as identify who should receive the written declaration of pregnancy. The recipient of the woman's declaration may be identified by name (e.g., John Smith), position (e.g., immediate supervisor, the radiation safety officer), or department (e.g., the personnel department).

**4. Duration of Lower Dose Limits for the Embryo/Fetus**

The lower dose limit for the embryo/fetus should remain in effect until the woman withdraws the declaration in writing or the woman is no longer pregnant. If a declaration of pregnancy is withdrawn, the dose limit for the embryo/fetus would apply only to the time from the estimated date of conception until the time the declaration is withdrawn. If the declaration is not withdrawn, the written declaration may be considered expired one year after submission.

**5. Substantial Variations Above a Uniform Monthly Dose Rate**

According to 10 CFR 20.1208(b), "The licensee shall make efforts to avoid substantial variation above a uniform monthly exposure rate to a declared pregnant woman so as to satisfy the limit in paragraph (a) of this section," that is, 0.5 rem (5 mSv) to the embryo/fetus. The National Council on Radiation Protection and Measurements (NCRP) recommends a monthly equivalent dose limit of 0.05 rem (0.5 mSv) to the embryo/fetus once the pregnancy is known (Ref. 2). In view of the NCRP recommendation, any monthly dose of less than 0.1 rem (1 mSv) may be considered as not a substantial variation above a uniform monthly dose rate and as such will not require licensee justification. However, a monthly dose greater than 0.1 rem (1 mSv) should be justified by the licensee.

## D. IMPLEMENTATION

The purpose of this section is to provide information to licensees and applicants regarding the NRC staff's plans for using this regulatory guide.

Unless a licensee or an applicant proposes an acceptable alternative method for complying with the specified portions of the NRC's regulations, the methods described in this guide will be used by the NRC staff in the evaluation of instructions to workers on the radiation exposure of pregnant women.

## REFERENCES


1. USNRC, "Instruction Concerning Risks from Occupational Radiation Exposure," Regulatory Guide 8.29, Revision 1, February 1996.

2. National Council on Radiation Protection and Measurements, *Limitation of Exposure to Ionizing Radiation*, NCRP Report No. 116, Bethesda, MD, 1993.

## APPENDIX

## QUESTIONS AND ANSWERS CONCERNING PRENATAL RADIATION EXPOSURE

**1. Why am I receiving this information?**

The NRC's regulations (in 10 CFR 19.12, "Instructions to Workers") require that licensees instruct individuals working with licensed radioactive materials in radiation protection as appropriate for the situation. The instruction below describes information that occupational workers and their supervisors should know about the radiation exposure of the embryo/fetus of pregnant women.

The regulations allow a pregnant woman to decide whether she wants to formally declare her pregnancy to take advantage of lower dose limits for the embryo/fetus. This instruction provides information to help women make an informed decision whether to declare a pregnancy.

**2. If I become pregnant, am I required to declare my pregnancy?**

No. The choice whether to declare your pregnancy is completely voluntary. If you choose to declare your pregnancy, you must do so in writing and a lower radiation dose limit will apply to your embryo/fetus. If you choose not to declare your pregnancy, you and your embryo/fetus will continue to be subject to the same radiation dose limits that apply to other occupational workers.

**3. If I declare my pregnancy in writing, what happens?**

If you choose to declare your pregnancy in writing, the licensee must take measures to limit the dose to your embryo/fetus to 0.5 rem (5 millisievert) during the entire pregnancy. This is one-tenth of the dose that an occupational worker may receive in a year. If you have already received a dose exceeding 0.5 rem (5 mSv) in the period between conception and the declaration of your pregnancy, an additional dose of 0.05 rem (0.5 mSv) is allowed during the remainder of the pregnancy. In addition, 10 CFR 20.1208, "Dose to an Embryo/Fetus," requires licensees to make efforts to avoid substantial variation above a uniform monthly dose rate so that all the 0.5 rem (5 mSv) allowed dose does not occur in a short period during the pregnancy.

This may mean that, if you declare your pregnancy, the licensee may not permit you to do some of your normal job functions if those functions would have allowed you to receive more than 0.5 rem, and you may not be able to have some emergency response responsibilities.

**4. Why do the regulations have a lower dose limit for the embryo/fetus of a declared pregnant woman than for a pregnant worker who has not declared?**

A lower dose limit for the embryo/fetus of a declared pregnant woman is based on a consideration of greater sensitivity to radiation of the embryo/fetus and the involuntary nature of the exposure. Several scientific advisory groups have recommended (References 1 and 2) that the dose to the embryo/fetus be limited to a fraction of the occupational dose limit.

**5. What are the potentially harmful effects of radiation exposure to my embryo/fetus?**

The occurrence and severity of health effects caused by ionizing radiation are dependent upon the type and total dose of radiation received, as well as the time period over which the exposure was received. See Regulatory Guide 8.29, "Instruction Concerning Risks from Occupational Exposure" (Ref. 3), for more information. The main concern is embryo/fetal susceptibility to the harmful effects of radiation such as cancer.

**6. Are there any risks of genetic defects?**

Although radiation injury has been induced experimentally in rodents and insects, and in the experiments was transmitted and became manifest as hereditary disorders in their offspring, radiation has not been identified as a cause of such effect in humans. Therefore, the risk of genetic effects attributable to radiation exposure is speculative. For example, no genetic effects have been documented in any of the Japanese atomic bomb survivors, their children, or their grandchildren.

**7. What if I decide that I do not want any radiation exposure at all during my pregnancy?**

You may ask your employer for a job that does not involve any exposure at all to occupational radiation dose, but your employer is not obligated to provide you with a job involving no radiation exposure. Even if you receive no occupational exposure at all, your embryo/fetus will receive some radiation dose (on average 75 mrem (0.75 mSv)) during your pregnancy from natural background radiation.

The NRC has reviewed the available scientific literature and concluded that the 0.5 rem (5 mSv) limit provides an adequate margin of protection for the embryo/fetus. This dose limit reflects the desire to limit the total lifetime risk of leukemia and other cancers. If this dose limit is exceeded, the total lifetime risk of cancer to the embryo/fetus may increase incrementally. However, the decision on what level of risk to accept is yours. More detailed information on potential risk to the embryo/fetus from radiation exposure can be found in References 2-10.

**8. What effect will formally declaring my pregnancy have on my job status?**

Only the licensee can tell you what effect a written declaration of pregnancy will have on your job status. As part of your radiation safety training, the licensee should tell you the company's policies with respect to the job status of declared pregnant women. In addition, before you declare your pregnancy, you may want to talk to your supervisor or your radiation safety officer and ask what a declaration of pregnancy would mean specifically for you and your job status.

In many cases you can continue in your present job with no change and still meet the dose limit for the embryo/fetus. For example, most commercial power reactor workers (approximately 93%) receive, in 12 months, occupational radiation doses that are less than 0.5 rem (5 mSv) (Ref. 11). The licensee may also consider the likelihood of increased radiation exposures from accidents and abnormal events before making a decision to allow you to continue in your present job.

If your current work might cause the dose to your embryo/fetus to exceed 0.5 rem (5 mSv), the licensee has various options. It is possible that the licensee can and will make a reasonable accommodation that will allow you to continue performing your current job, for example, by having another qualified employee do a small part of the job that accounts for some of your radiation exposure.

**9. What information must I provide in my written declaration of pregnancy?**

You should provide, in writing, your name, a declaration that you are pregnant, the estimated date of conception (only the month and year need be given), and the date that you give the letter to the licensee. A form letter that you can use is included at the end of these questions and answers. You may use that letter, use a form letter the licensee has provided to you, or write your own letter.

**10. To declare my pregnancy, do I have to have documented medical proof that I am pregnant?**

NRC regulations do not require that you provide medical proof of your pregnancy. However, NRC regulations do not preclude the licensee from requesting medical documentation of your pregnancy, especially if a change in your duties is necessary in order to comply with the 0.5 rem (5 mSv) dose limit.

**11. Can I tell the licensee orally rather than in writing that I am pregnant?**

No. The regulations require that the declaration must be in writing.

**12. If I have not declared my pregnancy in writing, but the licensee suspects that I am pregnant, do the lower dose limits apply?**

No. The lower dose limits for pregnant women apply only if you have declared your pregnancy in writing. The United States Supreme Court has ruled (in *United Automobile Workers International Union v. Johnson Controls, Inc.*, 1991) that "Decisions about the welfare of future children must be left to the parents who conceive, bear, support, and raise them rather than to the employers who hire those parents" (Reference 7). The Supreme Court also ruled that your employer may not restrict you from a specific job "because of concerns about the next generation." Thus, the lower limits apply only if you choose to declare your pregnancy in writing.

**13. If I am planning to become pregnant but am not yet pregnant and I inform the licensee of that in writing, do the lower dose limits apply?**

No. The requirement for lower limits applies only if you declare in writing that you are already pregnant.

**14. What if I have a miscarriage or find out that I am not pregnant?**

If you have declared your pregnancy in writing, you should promptly inform the licensee in writing that you are no longer pregnant. However, if you have not formally declared your pregnancy in writing, you need not inform the licensee of your nonpregnant status.

**15. How long is the lower dose limit in effect?**

The dose to the embryo/fetus must be limited until you withdraw your declaration in writing or you

inform the licensee in writing that you are no longer pregnant. If the declaration is not withdrawn, the written declaration may be considered expired one year after submission.

**16. If I have declared my pregnancy in writing, can I revoke my declaration of pregnancy even if I am still pregnant?**

Yes, you may. The choice is entirely yours. If you revoke your declaration of pregnancy, the lower dose limit for the embryo/fetus no longer applies.

**17. What if I work under contract at a licensed facility?**

The regulations state that you should formally declare your pregnancy to the licensee in writing. The licensee has the responsibility to limit the dose to the embryo/fetus.

**18. Where can I get additional information?**

The references to this Appendix contain helpful information, especially Reference 3, NRC's Regulatory Guide 8.29, "Instruction Concerning Risks from Occupational Radiation Exposure," for general information on radiation risks. The licensee should be able to give this document to you.

For information on legal aspects, see Reference 7, "The Rock and the Hard Place: Employer Liability to Fertile or Pregnant Employees and Their Unborn Children—What Can the Employer Do?" which is an article in the journal *Radiation Protection Management*.

You may telephone the NRC Headquarters at (301) 415-7000. Legal questions should be directed to the Office of the General Counsel, and technical questions should be directed to the Division of Industrial and Medical Nuclear Safety.

You may also telephone the NRC Regional Offices at the following numbers: Region I, (610) 337-5000; Region II, (404) 562-4400; Region III, (630) 829-9500; and Region IV, (817) 860-8100. Legal questions should be directed to the Regional Counsel, and technical questions should be directed to the Division of Nuclear Materials Safety.

## REFERENCES FOR APPENDIX


1. National Council on Radiation Protection and Measurements, *Limitation of Exposure to Ionizing Radiation*, NCRP Report No. 116, Bethesda, MD, 1993.

2. International Commission on Radiological Protection, *1990 Recommendations of the International Commission on Radiological Protection*, ICRP Publication 60, Ann. ICRP 21: No. 1-3, Pergamon Press, Oxford, UK, 1991.

3. USNRC, "Instruction Concerning Risks from Occupational Radiation Exposure," Regulatory Guide 8.29, Revision 1, February 1996.[11] (Electronically available at www.nrc.gov/NRC/RG/index.html)

4. Committee on the Biological Effects of Ionizing Radiations, National Research Council, *Health Effects of Exposure to Low Levels of Ionizing Radiation* (BEIR V), National Academy Press, Washington, DC, 1990.

5. United Nations Scientific Committee on the Effects of Atomic Radiation, *Sources and Effects of Ionizing Radiation*, United Nations, New York, 1993.

6. R. Doll and R. Wakeford, "Risk of Childhood Cancer from Fetal Irradiation," *The British Journal of Radiology*, 70, 130-139, 1997.

7. David Wiedis, Donald E. Jose, and Timm O. Phoebe, "The Rock and the Hard Place: Employer Liability to Fertile or Pregnant Employees and Their Unborn Children—What Can the Employer Do?" *Radiation Protection Management*, *11,* 41-49, January/February 1994.

8. National Council on Radiation Protection and Measurements, *Considerations Regarding the Unintended Radiation Exposure of the Embryo, Fetus, or Nursing Child*, NCRP Commentary No. 9, Bethesda, MD, 1994.

9. National Council on Radiation Protection and Measurements, *Risk Estimates for Radiation Protection*, NCRP Report No. 115, Bethesda, MD, 1993.


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[1]Single copies of regulatory guides, both active and draft, and draft NUREG documents may be obtained free of charge by writing the Reproduction and Distribution Services Section, OCIO, USNRC, Washington, DC 20555-0001, or by fax to (301)415-2289, or by email to <DISTRIBUTION@NRC.GOV>. Active guides may also be purchased from the National Technical Information Service on a standing order basis. Details on this service may be obtained by writing NTIS, 5285 Port Royal Road, Springfield, VA 22161. Copies of active and draft guides are available for inspection or copying for a fee from the NRC Public Document Room at 2120 L Street NW., Washington, DC; the PDR's mailing address is Mail Stop LL-6, Washington, DC 20555; telephone (202)634-3273; fax (202)634-3343.

10. National Radiological Protection Board, *Advice on Exposure to Ionising Radiation During Pregnancy*, National Radiological Protection Board, Chilton, Didcot, UK, 1998.

11. M.L. Thomas and D. Hagemeyer, "Occupational Radiation Exposure at Commercial Nuclear Power Reactors and Other Facilities, 1996," Twenty-Ninth Annual Report, NUREG-0713, Vol. 18, USNRC, 1998.[22]

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[2]Copies are available at current rates from the U.S. Government Printing Office, P.O. Box 37082, Washington, DC 20402-9328 (telephone (202)512-1800); or from the National Technical Information Service by writing NTIS at 5285 Port Royal Road, Springfield, VA 22161. Copies are available for inspection or copying for a fee from the NRC Public Document Room at 2120 L Street NW., Washington, DC; the PDR's mailing address is Mail Stop LL-6, Washington, DC 20555; telephone (202)634-3273; fax (202)634-3343.

## FORM LETTER FOR DECLARING PREGNANCY

This form letter is provided for your convenience. To make your written declaration of pregnancy, you may fill in the blanks in this form letter, you may use a form letter the licensee has provided to you, or you may write your own letter.

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DECLARATION OF PREGNANCY

To:_____

In accordance with the NRC's regulations at 10 CFR 20.1208, "Dose to an Embryo/Fetus," I am declaring that I am pregnant. I believe I became pregnant in_____ (only the month and year need be provided).

I understand the radiation dose to my embryo/fetus during my entire pregnancy will not be allowed to exceed 0.5 rem (5 millisievert) (unless that dose has already been exceeded between the time of conception and submitting this letter). I also understand that meeting the lower dose limit may require a change in job or job responsibilities during my pregnancy.

_____

(Your signature)

_____

(Your name printed)

_____

(Date)

## REGULATORY ANALYSIS

A separate regulatory analysis was not prepared for this regulatory guide. A regulatory analysis prepared for 10 CFR Part 20, "Standards for Protection Against Radiation" (56 FR 23360), provides the regulatory basis for this guide and examines the costs and benefits of the rule as implemented by the guide. A copy of the "Regulatory Analysis for the Revision of 10 CFR Part 20" (PNL-6712, November 1988) is available for inspection and copying for a fee at the NRC Public Document Room, 2120 L Street NW, Washington, DC, as an enclosure to Part 20 (56 FR 23360).

## Declaration of Pregnancy Form RSS-105A

The Declaration of Pregnancy Form RSS-105A provides the formal means by which a pregnant occupational radiation worker voluntarily notifies Radiation Safety Service (RSS) of her choice to authorize the application of federal and/or state radiation dose limits to an embryo/fetus as a condition of her radiation related work at the University of Michigan. A declaration of pregnancy to the Department of Occupational Safety & Environmental Health - Radiation Safety Service can only be made by use of this form. **Complete and submit this form only if you knowingly and voluntarily intend to declare your pregnancy to RSS.**

The choice of whether to declare one's pregnancy is a personal one and is to be an informed one. A pregnant occupational radiation worker needs to be cognizant of information supplied by the NRC, the University of Michigan-Radiation Policy Committee (RPC) and RSS as to the potential health effects from radiation to herself and to an embryo/fetus. RSS supplies written instructional material discussing such potential effects and will assist the pregnant worker in understanding the material contained therein so as to allow her to make an informed choice.

### Revocation, Expiration and Lapse of Declarations of Pregnancy

Revocation: A declared pregnant worker may voluntarily revoke her declaration of pregnancy at any time and for any reason without explanation. This can be done whether or not pregnancy has concluded. However, revocations can only be made through the submission to RSS of a signed and dated Revocation of Declaration of Pregnancy Form (RSS- 105B) to RSS. Revocation forms are available from RSS.

Expiration: A declaration of pregnancy automatically expires when the associated condition of pregnancy actually ceases or upon termination of employment as an occupational radiation worker with the University of Michigan. A declared pregnant worker should provide RSS with a signed and dated written notice of the expiration of the declaration of pregnancy. This can be done by completing and submitting a Pregnancy Declaration Expiration Form (RSS-105C).

Lapse: RSS reserves the option to deem that a declaration of pregnancy has lapsed and no longer is in effect on the earlier of either: 1) 60 days after the estimated date of delivery designated by the declarant on the form of declaration; or 2) one year after the date of receipt of the declaration form at RSS offices.

### Limitations

The Declaration of Pregnancy Form (RSS-105A), the Revocation of Declaration of Pregnancy Form (RSS-105B) and the Pregnancy Declaration Expiration Form (RSS-105C) serve the sole purpose of providing the means of election and choice in compliance with NRC dose limit rules and regulations. It does not serve as actual or

implied notice to any other department or unit within the University of Michigan regarding the declarant's physical status or condition.

## Privacy

The information contained in the Declaration of Pregnancy Form (RSS-105A), the Revocation of Declaration of Pregnancy Form (RSS-105B) and the Pregnancy Declaration Expiration Form (RSS-105C) constitutes a record subject to the confidentiality provisions of applicable federal and/or state privacy laws and becomes part of the declarant's confidential record with RSS.

## Issuance of Dosimeter

If you declare your pregnancy, you will be issued dosimeters and receive reports of results periodically to help monitor the dose to the fetus during the course of your pregnancy. In most instances, those dosimeters will be in addition to dosimeters you may already be receiving. A fetal monitor dosimeter usually will have a monthly wear period and, upon completion of each wear period, it will be exchanged with a replacement. You may elect to either: 1) arrange to personally collect fetal monitor dosimeters and corresponding reports at RSS offices at the start of each wear period; 2) have the fetal monitor dosimeters and reports delivered directly to you at your work address by campus mail; or 3) have the fetal monitor dosimeters and reports delivered in the usual manner to the contact person designated for the dosimeter series assigned to the authorized user or facility where you work. You will continue to receive other dosimeters that you get routinely to monitor your own dose, if any, in the usual manner through your dosimetry series contact person.