APPENDIX MM

INDEPENDENT CONSULTANT REPORT

BY

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(REPORT ON REPRODUCTIVE HAZARDS)

INTRODUCTION

The ambient environment encountered by deployed Desert Storm/Desert Shield personnel comprised a complex grouping of health hazards including virtually every known hazard class. Beyond the challenges of characterizing the chemical hazards of any wartime deployment, the added threat of chemical weapons use and proximity to chemical alarms, burning oil well fires and demolition of other chemical storage areas greatly enhanced the complexity of the exposure scenario. Add to this, the physical hazards of temperature extremes, physical exertion and noise, the biologic hazards of infectious diseases such as Leshmaniasis and Tuberculosis (TB) as well as the hazards of biological warfare agents and vaccines, and the social stresses of emergency situations and shift work. This constellation of hazards formed the environmental matrix in which deployed personnel served in the Gulf War conflict.

The complexity of this environment, the non-fixed nature of an individual's work location and the lack of record keeping for various potential exposures such as vaccines conspire to muddle associations between environmental exposures and health effects.

Among the array of symptomatic complaints and health effects reported by PGW veterans, problems of reproductive health have also been raised. The prominence of questions regarding environmental exposure during PGW deployment and reproductive health effects track the heightened awareness of society-at-large concerning possible reproductive health harm from environmental causes.

Complicating our understanding of reproductive health and environmental exposures, is the significant magnitude of " baseline" or "background" reproductive dysfunction in the U.S. For example, the proportion of infertile couples in the United States is estimated to range from 8% to 13% (Mosher, 1988; Pratt et al., 1984). The demand for physician consultation regarding infertility rose by 30% between 1968 and 1980 (Arab and Cates, 1983). Infertility is typically defined as the inability to conceive after one or more years of intercourse without contraception. The conception rate per menstrual cycle of normal couples of reproductive age having unprotected intercourse approaches 50%. However, the viable pregnancy rate, i.e., pregnancy resulting in the birth of a viable child, is about 25% (Soules, 1985). Estimates of total pregnancy loss, including very early pre-and post-implantation embryonic losses, are as high as 75% of

all conceptions (Arab and Cates, 1983; Kline and Stein, 1985). Major fetal malformations occur in about 3% of liveborn babies, and other impairments such as low birth weight occur in many more (Kalter and Warkany, 1983).

Attention has turned to the workplace to assist in unraveling potential associations between environmental exposures (present in the work environment) and reproductive health. This is because many environmental toxicants have their origin in a workplace and are present in work settings, often at much higher concentrations than they occur in the wider environment. However, the study of workplace reproductive hazards has in many cases been hampered for several reasons including its unique challenges. Unlike other physiologic functions for example, reproductive function is not continuously but rather intermittently expressed. (Mattison, 1981; Mattison and Nightengale, 1982). Therefore, assessment of toxicity after exposure may be dependent on the timing during which an exposure took place. If the exposure was during a vulnerable period, an adverse outcome may be seen. Otherwise, no apparent harm may be detected. Another complication of reproductive toxicology is differential species effects observed from toxic exposure. Also, reproductive health assessment requires evaluation of a two persons attempting pregnancy, as opposed to the functioning of other organ systems which can be assessed in the individual. These physiologic differences imply the need for alternative approaches in studying reproductive hazards and underscore the necessity of evaluating both male and female members of a couple in determining reproductive health harm.

However, until recently, the limited study of occupational reproductive hazards has focused primarily on female reproductive health. This focus has probably been stimulated by the entrance of women into traditional male sectors of the workforce. Although there are gender-mediated differences in chemically induced adverse reproductive outcomes, the majority of well-tested chemicals have demonstrated adverse reproductive outcomes in both males and females (Paul and Himmelstein, 1988). In fact, in recent studies, because of the accessibility of animal and human male gonads and gametes, more agents have been shown to be toxic to male reproductive processes than to female reproductive processes (Mattison, 1983).

MECHANISM OF REPRODUCTIVE TOXICITY

Adverse effects caused by reproductive toxicant exposure may be manifested at many sites in the complex pathway of reproductive function beginning with gametogeneses, and continuing through gamete interaction (fertilization), embryonic and fetal development and growth, parturition and sexual maturation of the offspring. Figure 1 displays the pathway of reproductive functions and the possible effects of toxic exposures.

Modulating the effects observed and the site of insult along this developmental continuum are both common toxicologic principles considered in any xenobiotic exposure and unique aspects of reproductive toxicity such as exposure timing during a vulnerable period of development.

Toxic effects of xenobiotic exposure are classically considered to be a function of an exposure - effect pathway including systemic absorption, distribution, metabolism and clearance (excretion) as some critical cellular or subcellular interaction takes place within the target organ to alter normal reproductive function. Anywhere along this exposure-effect continuum detoxification steps may also alter the toxicity ultimately observed. Additionally, subsequent to insult, repair may ensue, modifying or completely reversing an effect.

Reproductive toxicants may be broadly classified as direct or indirectly acting (Mattison and Thomford, 1989). The indirect acting agents may require metabolic activation before exerting toxicity, a notion reminiscent of the direct/indirect acting carcinogen classification. Alternatively, indirect acting reproductive toxicants may alter normal reproductive function via metabolism to a direct acting toxicant or by influencing an enzyme function such as induction or modulation of other enzymatically-controlled homeostatic mechanisms.

Direct acting agents may function in one of two ways, the first is via structural similarity to another biologically active molecule. The best examples here are the oral contraceptive drugs which act to limit pre-ovulatory gonadotropin excursions. Several occupational exposures to estrogenic compounds resulting in menstrual abnormalities have been reported in the literature (Pacynski, et al., 1971; Harrington et al., 1978).

A second mechanism of direct - acting toxicity is that of chemical reactivity. Some alkylating antineoplastic drugs are commonly cited examples of this type of reproductive toxicant. These genotoxic compounds, capable of covalently binding with cellular macromolecules, are mutagenic and many are human carcinogens or teratogenic. (IARC, 1982).

The special case of mutagens must be kept in mind in reproductive hazard identification. Although reproductive toxicologic data are often not available on specific toxicants, mutagenicity data often are. Certainly, a well-characterized mutagen should be considered a potential reproductive toxicant because of its genotoxic nature, even in the absence of reproductive toxicity data. In attempting to bridge the connection between mutagen exposure and reproductive outcome, one recent study showed a statistically significant difference between chromosomal aberrations in dysfertile persons with mutagen exposure compared to dysfertile persons with no mutagen exposure. (Kucerova

et al, 1992). Figure 2 displays types of mutagenic insult and potential adverse outcomes from mutagenic exposure in a germ cell.

Reproductive toxicants are generally detoxified as any xenobiotics, via classical phase I and phase II, metabolic enzyme systems. Non-polar compounds are usually metabolized by mono-oxygenases to more polar compounds before conjugation steps.

Highly reactive compounds like alkylating agents may be conjugated, sometimes through an epoxide intermediate. The presence of these detoxification enzyme systems has been documented in both ovary and testes. (Heinrichs and Juchan 1980; Mattison and Nightengale, 1982; Mattison et al, 1983).

Repair mechanisms may also be activated when detoxification systems are saturated or impaired. Simple repair mechanisms may include enhanced synthesis of biologically important macromolecules. Alternatively, the DNA repair mechanism's function in genotoxic insult and more commonly considered carcinogenic exposures will also be important for reproductive toxicants when the insult is genotoxically mediated. While not well characterized, limited evidence documents DNA repair capability in the ovulated oocyte (Perdersen and Manigia, 1978) and developing sperm (Dixon and Lee, 1980).

MALE-MEDIATED EFFECTS

The biologic plausibility of male-mediated reproductive effects has been increasingly considered and scientific evidence for such effects has grown rapidly. Wyrobek has recently reviewed the evidence for male-mediated effects manifested beyond fertilization and the multi-generational context in which reproductive health must be studied (Wyrobek, 1993).

The process of spermatogenesis, characterized by rapid cell development in the testes, is a likely target of mutagens which ordinarily interact with diving cells. Multiple outcomes could result from such interactions including male infertility and spontaneous abortion. Besides genotoxic mechanisms, other epigenetic and non-genetic mechanisms modulate male reproductive health at the level of the normal physiologic function and the control of erection and ejaculation. Neurotoxic agents such as lead (Lancranjan, 1975) and inorganic mercury (Wharton, 1983) may thus affect sexual function.

Other effectors of sperm production and male sexual performance include anatomic abnormalities such as cryptorchidsm, and varicocele, infectious agents such as the mumps virus, host factors such as autoimmunity and high fever. (Wharton, 1983)

Environmental agents purported to affect testicular function include alcohol consumption; and cigarette smoke has been reported to cause sperm abnormalities. (Wyrobek, 1993)

Extensively studied pharmacologic agents have also been evaluated for, or observed to cause, reproductive health effects. Detailed studies required in the drug-use approval process, as well as observational studies of therapeutically-treated patients combine to provide these data. Three classes of drugs have been shown to potentially cause some type of male reproductive health effects. These include hormones affecting secondary sex characteristics, sexual function and infertility, (estrogens, progesterones, testosterone, prednisone) alkylating anti-cancer drugs causing testicular toxicity and infertility (cyclophosphamide, chlorambucil) and anesthetic gases causing infertility and possibly increased spontaneous abortions (N_2O, halogenated agents). (McDiarmid, 1994)

Occupational studies have reliably demonstrated the often irreversible testicular toxicity of dibromo-chloropropane (DBCP), a herbicide. (Wharton, 1983) Other toxicants, especially heavy metals and neurotoxicants are also being investigated, with some positive evidence of lead causing sperm abnormalities at previously thought to be low concentrations (Lancrajan, 1975) and playing a role in paternally-mediated teratogenicity (structural abnormalities of the offspring).

A male contribution to spontaneous abortion can be hypothesized via a mutagenic insult to the sperm (Wyrobek, 1993), paraoccupational exposure resulting in home contamination and maternal exposure (McDiarmid and Weaver, 1993), concentration of the agent in semen (Stachel et al., 1989) and direct transmission of the agent on sperm (Yazigi et al., 1991).

REPRODUCTIVE OUTCOMES - BIOLOGIC PLAUSIBILITY

With the previous discussion of mechanisms of reproductive harm serving as a foundation upon which to build a comprehensive assessment of potential reproductive risk in the Gulf, a review of the published literature, as well as reports of the Presidential Advisory Committee (PAC) and the Institute of Medicine (IOM), and minutes of the PAC hearings on Reproductive Health of Gulf War Veterans and PAC staff consultations on reproductive health was performed. These sources reflect similar over-arching opinion on the biologic plausibility of reproductive health harm, methods to ascertain potential health effects, strengths and weaknesses of existing evidence, and recommendations for the future.

Adverse reproductive outcomes may be manifest anywhere along the pathway of reproductive function beginning with gametogenesis and extending into the post-natal development of the offspring. The two principal areas of concern resulting from the Gulf

War Conflict have centered on developmental abnormalities (malformations) and spontaneous abortion and infertility.

While the prevalence of malformations is variously reported at about 3-5% of newborns, increasing to 10% after the first two years of life, the general public's lack of knowledge of this baseline prevalence has helped to feed fears regarding clusters of birth defects. Epidemiologic studies to date have failed to show any excess of birth defects among deployed PGW veterans, although some studies are methodologically limited and others are ongoing. Various experts testified that chasing clusters is not a good use of the public health dollar when both statistical power and exposure assessment data are so lacking. As well, very few of the major birth defects have a recognized, discrete mechanism of causation making associations between outcomes and deployment exposure difficult.

The majority of the testimony was focused on male-mediated effects due to the disproportionate number of men deployed (about 700,000) versus women (35-50,000). The most consistent opinion among experts testifying regarding mechanisms of insult resulting in reproductive health harm focused on germ cell or other damage by a direct-acting mutagenic agent. The most commonly expected outcome from such an exposure would be a spontaneous abortion due to non-viability from chromosomal aberrations or other insult in the product of conception. Other opportunities for exposure to a toxic substance included a discussion of transport of a toxicant in seminal fluid and secondary paraoccupational exposure of the woman to contaminants tracked home by the man on the clothes and shoes. These mechanisms have been suggested in other occupational/environmental settings and enjoy more relative consensus than further issues to be discussed.

These same reports also discuss the biologic plausibility of a developmental abnormality (malformation) resulting from a male-mediated effect. There is less agreement on this point among the experts. Both genetic (mutagenic) and epigenetic mechanisms are discussed. There is theoretical evidence that such an outcome is possible, but the experience from atomic bomb offspring and cancer patients treated with alkylating (mutagenic) anti-cancer drugs do not consistently show increases in developmental abnormalities. This observation has been used to heavily weight the argument against the likelihood of male-mediated developmental toxicity. Some experts, however, believe there are methodologic reasons for these observations, including that the post-atomic bomb studies missed counting offspring in the first eighteen months after the bombing - the time when abnormalities would have been most likely to occur. (Olshan and Faustman, 1993).

Another argument against any excess in developmental toxicity is reflected in the opinion of Dr. Robert Brent who believes that the expected outcome from an exposure to a genetic toxicant is not a specific malformation, but an increase in diseases due to a genetic defect generally. Dr. Brent's opinion is that "If you're looking for genetic effects, then you

should want to find an increase in genetic diseases." (PAC Reproductive Hearing, p. 145). In further testimony he discusses loss of mutagenically exposed germ cells during the spermatic developmental cycle - the mutation is thus not seen because some of the affected sperm are not used (for fertilization), some are less efficient at fertilizing (or in the case of the egg - at being fertilized); early embryonic loss occurs during pre-implantation and early organogenesis (p. 151-154).

From p. 160 of his testimony, Dr. Brent states "There is no epidemiological information to support the suggestion that there is an increase in congenital malformations in the offspring of Desert Storm... The nature of the malformations, the types of exposures, prior studies involving human exposures to mutagenic agents and the concept of biologic plausibility make it very unlikely that there is an increase in the incidence of malformations in offspring." From p. 161, "We would not be in the present dilemma if we had a national program of congenital malformation surveillance involving every birth in the U.S."

Dr. Bernard Robaire testified regarding animal evidence for male-mediated developmental toxicity (p. 180) "that giving a drug to the male can affect - can have effects on pre-and-post implantation loss. We also know that these effects can be reversed, and there is a potential for them to be passed on to the next generation." (Refers to animal work), [p. 185], Recommendations of Dr. Robaire: "If we know that chemicals do not have effects, if they've been tested and they're not mutagenic, they're not teratogenic, they're not carcinogenic, then there's no point in worrying about male-mediated adverse progeny outcome."

Dr. Brent clarifies on p. 187, "If you're talking about the induction of mutations ... you don't have a propensity to affect one gene or produce one type of chromosomal defect. So that what you would expect is an increase in the incidence of genetic disease." Dr. Robaire, [p. 191], "if he's home for three months before his wife becomes pregnant, it's unlikely that it would have been any chemical that he was exposed to during the Gulf with two qualifiers" - 1) the toxicant is not lipophilic and, 2) the effects of exposure are not to the stem cell.

SELF-REPORTED REPRODUCTIVE HEALTH PROBLEMS

There has been concern among PGW veterans regarding reproductive health and the questions of any adverse reproductive outcomes being deployment - related. Early versions of the CCEP and VA Gulf War Registry Examination questionnaires have been criticized for inadequate attention to these outcomes. The VA has since revised its questionnaire to include a more detailed reproductive health assessment. Dr. Susan Mather, Chief of DVA's directorate of Environmental Medicine and Public Health relates that 53,000 veterans were seen using the old questionnaire and all of these people were mailed the updated version in

the last year. She estimated that about 20,000 had been returned, but were still being analyzed. She also mentioned that phase II of the Gulf War Registry Health Examination program, although looking at a small subset of the total population, will include an evaluation of spouses and children. These approaches are appropriate given the time elapsed since expose and the attendant epidemiologic problems which arise from this.

EXPOSURE ASSESSMENT

Overview

The principal resource cited in the variety of reports reviewed regarding the exposure assessment performed for the presence of reproductive toxicants in the Gulf War theater is the U.S. General Accounting Office (GAO) report to the chairman, Committee on Veterans Affairs U.S. Senate. This August, 1994 document addressed a number of questions regarding reproductive health concerns in the Gulf, only one of which was a charge to characterize potential reproductive toxicants present. The report identified twenty-one agents distributed among three broad hazard types - pesticides, oil fires and soil samples, and decontaminating agents. The methodology used by GAO to assemble this list was only cursorily described to include interviews and document review. As well, the lack of any non-chemical hazards identified demonstrates a limited understanding of the array of reproductive toxicants with a potential role in health risk assessment.

The classical approach in performing an exposure assessment begins with assembling candidate toxicants present in the exposure cohort's environment. This process was partially completed by the GAO. Clearly, however, the non-chemical reproductive toxicants must also be cataloged. I will attempt to at least begin that process later in this report.

After identification of hazards, the next step in an exposure assessment is the determination of exposure dose. It is this critical step that is always challenging, but in this present scenario, all but impossible to achieve. As the GAO report states, "... we did not ascertain ... exposure rates for service men and service women for these toxicants... nor perform a risk assessment of these exposures and how they might relate to possible reproductive dysfunction...". In introducing the GAO findings in testimony before the Senate Committee, Capitol Issue Area Director, Kwai-Cheng Chan stated that (referring to the twenty-one toxicants cited above), "... the concentration levels of these compounds are unknown and so are the exposure rates for specific units".

Therefore, not only are quantitative assignments of exposure dose impossible to make for a given toxicant and a given service person, or even service unit, a qualitative assignment of exposure cannot even be reliably made.

Reinforcing this observation is Dr. Grace LeMaster's testimony to the Presidential Advisory Committee staff consultation on reproductive health of Gulf War veterans, page 34: "... exposures cannot be characterized very well. It is my understanding that even vaccination records were not kept... across all these pregnancies, you have no idea what the exposures are, it's almost like three strikes against uncovering anything in this particular situation."

While the absence of environmental sampling data for the twenty-one toxicants is understandable given the deployment scenario, as may be understood for who used how much pyridostigmine, the lack of performance type records, such as vaccination data, is less comprehensible.

Also disconcerting are the anecdotal reports cited in the GAO report. This from page two of that report (referring to the hazardous exposures in the Gulf) "such as the extensive use of diesel fuel as a sand suppressant in and around encampments, the burning of human waste with fuel oil, the presence of fuel in shower water, and the drying of sleeping bags with leaded vehicle exhaust...".

It appears that the most that is possible regarding exposure assessment will be very coarse assumptions made about certain deployed groups. Refinement as to individual toxicant exposure to an individual service person will be extremely difficult.

One potential approach to examining at least a "first cut" assessment might be that described in Dr. Linda Shortridge's testimony to the Presidential Advisory Committee (page 413). She is describing exposure assessment methodology that is being used at the University of Oregon and some of their epidemiologic studies. Regarding exposure assessment, she states, "We do, however, have an opportunity to compare and contrast groups of veterans who had separate sets of potential exposure, because they were deployed in the theater of operations for distinct identifiable periods." This might be a potentially useful and "transportable" approach to at least qualitatively refine different populations who, because of calendar time in the theater, were necessarily exposed (or not) to some different toxic substances.

EPIDEMIOLOGY OF SELF-REPORTED ENVIRONMENTAL EXPOSURES

The 1996 summary of the Department of Defense's (DOD) Comprehensive Clinical Evaluation Program (CCEP) for Persian Gulf War Veterans included data for more than 18,000 returned service members who requested a complete health evaluation. Part of the health evaluation involved questionnaire completion of a self-reported environmental history. The questions elicited information about food and water intake, and personal habits, such as smoking and exposure to passive smoke, as well as questions regarding the more uncommon chemical

environmental exposures. Obviously, the circumstances of exposure, and what determines the individual service member's positive response, are variable. Frequency of exposure is also not obtained by this method. Nonetheless, it gives a sketch of what individual soldiers reported.

A similar battery of questions were included in the Department of Veterans Affairs (DVA) Persian Gulf Registry questionnaire. Responses elicited are displayed in Table 1. Of interest is the close agreement between the two sources on frequency of environmental exposures. Passive cigarette smoke, diesel exposure, oil fire smoke and tent heater fumes were most commonly reported.

The detail of the questions in both the DOD's CCEP assessment, and the DVA's assessment are problematic. While a fairly complete "laundry list" of potential exposures is elicited, information regarding crucial aspects of the exposure are lost because of the way the question is worded. Most of the questions from both sources are worded like: "While in the Persian Gulf, do you believe you were exposed to any of the following?" It is not clear to the service member what constitutes a positive answer. For example, exposure to diesel fumes, the most common affirmative response reported (90% of veterans and 88% of active duty service members) could likely have been elicited by anyone riding in a vehicle. More discriminating information could have been elicited, such as attempting to determine more intense exposure, that is occupational diesel exposure arising from, say assignment to vehicle maintenance or transport. This is more informa
rider, which is what is suggested by an open ended question like "Have
This simple discrimination would lend some semi-quantitative information about exposure intensity. The DVA questionnaire gives a good example of a simple improvement in questioning, which refines the information elicited. When asking about diesel or petrochemical exposure, it asked about skin contact. While it is understood that only so much detail can be captured, some simple refinement of questions could enhance the value of the information obtained without increasing the number of questions. The overall summary questions could be tightened up from "were you ever" to "were you, as part of your job duties working with"; or "did you have skin exposure to..."; or "other than bystander exposure, did you work with or regularly (define time frequency appropriate to the substance in question) handle substance X ?"

There are some substances which we are more interested in chronic exposure, such as petrochemicals, diesel and particulates, and discriminating phrases could be added to those questions to enhance response value. For other substances, we are interested in only one time exposure, such as mustard agent, but even then, we are interested in whether there was skin contact or true breathing of fumes, such as in a fire or explosion.

To summarize, without adding to the number of questions either health assessment battery currently includes, more refinement of the language used in crafting questions, and some

guidance given to participants about what type of exposure constitutes a clinically important "yes" to the question, could greatly enhance the value of this information.

EXPOSURE ASSESSMENT IN REPRODUCTIVE HEALTH STUDIES

Most of the studies of reproductive health of Persian Gulf War veterans, whether they be those that have been completed, or those that are ongoing, suffer from extremely weak exposure assessment. A majority of the studies use exposure assessment definitions as simple as those deployed being exposed, and those non-deployed being unexposed for controls. This is clearly inadequate. The most seriously flawed in this regard are the birth defects studies which generally use birth defects registries as reporting data bases, and compare outcome with Persian Gulf deployed versus non-deployed members, and there is absolutely no discussion of exposure assessment. An exception to this, however, is the Iowa study of regular military and National Guard deployed versus non-Persian Gulf deployed regular and National Guard service members. Here, although the only reproductive outcome surveyed for was symptoms of sexual discomfort, there was a much greater emphasis on eliciting a fairly detailed environmental exposure history.

Of the studies that are ongoing, again the very large hospital based medical record studies, such as the Cowan and Calderon studies, as well as the Araneta studies 3, 4 and 7, referred to in Dr. Swan's report, all have this significant weakness of having no address of exposure assessment, except deployment status. Of other studies that are ongoing, several do, however, address environmental exposures. These include the National Health Survey performed by the Department of Veterans Affairs, which is going to include a detailed self report of a number of environmental exposures, as well as the University of Oregon's evaluation of infertility, menstrual abnormalities, fetal loss and genital tract symptoms, where they are
detailed environmental history of physical, biological and chemical agents. The planned study by the KLEMM group of 10,000 Persian Gulf War deployed women compared to non-deployed woman, looking at infertility, pre-term birth, still birth and birth defects, has a very detailed environmental exposure history proposed, and includes duration of exposure before, during and after deployment to the same environmental hazards. This is an added strength that is not seen in any of the other studies heretofore.

Also of interest, we should mention that the clinical study at the University of Cincinnati, looking at seminal plasma hypersensitivity reactions plans to address in a research format some of the environmental agents which may be active here by introducing some of these environmental substances in an in vitro system during the assessment of seminal plasma hypersensitivity. This type of inclusion of environmental effectors in a research protocol is something that we should like to see in future research studies. A summary of the exposure assessment component of completed and on-going studies is found in Tables 2 and 3.

CANDIDATE REPRODUCTIVE TOXICANTS

The Government Accounting Office (GAO) was asked by the Senate Veterans' Affairs Committee to specify reproductive toxicants to which deployed troops were potentially exposed. In their August 1994 report to the Senate Committee, the GAO identified three broad categories of reproductive toxicants present in the Persian Gulf area: Pesticides, oil fire contaminating and decontaminating agents. The GAO was unable to supply exposure dose data nor could they determine which specific units were exposed (if at all) to each of the agents. In addition to the agents the GAO listed, other reviews have also considered exposure to pyridostigmine bromide (PB), the prophylactic for nerve agent exposure, the various vaccine exposures, possible biologic agent exposure and mustard agent exposure. Reproductive and developmental toxicity data, as well as epidemiologic results, where available, are summarized in this section.

As a basic summary, the description of each of the 21 toxicants identified in the GAO report which appears in REPROTOX, the database of Reproductive Effects of Chemical, Physical and Biological Agents is provided here (Scialli et, al, 1995). Some toxicants deserve a more in depth treatment which follows. Other agents, not identified by the GAO will then be discussed.

Pesticides

Adverse reproductive outcomes from pesticide exposures have been studied by examining the reproductive outcomes of occupationally exposed farmers and farm workers. Summarizing data in this way does not allow association of a specific pesticide with any observed outcome, but does serve to evaluate a working cohort with exposures of the class of toxicants in question.

Frequently reported birth defects observed in the offspring of pesticide-exposed populations include neural tube defects, limb reduction defects and facial clefts. (White FM et. al., 1988; Field and Kerr 1979; Balarajan and McDowall, 1983; M. Paul, 1993). Facial clefts and neural tube defects have also been found in some studies of herbicide exposed agricultural workers and in one study of Vietnam Veterans exposed to the herbicide agent arrange. [Ref] clarity on this issue has been hampered by lack of exposure data and small sample sizes. Limb reduction defects have been associated with residence in farming areas and agricultural work (Schwartz DA, et. al., 1986; Schwartz and Longerfo, 1988).

Maternal pesticide exposure has been found to increase the risk of facial clefts (Brogan et. al., 1980; Gordon and Shy, 1981) and for all congenital abnormalities. There has also been some disagreement in the literature regarding increased risk for spina bifida with some reporting an increase and others not seeing one (White et. al., 1988; Golding and Sladden, 1983). Also of interest, in an interview study of crop duster pilots and their sibling

controls, there was no difference between groups in number of birth defects in offspring (Roan et. al, 1984).

The embryotoxicity and fetotoxicity of many pesticides is well documented. As well, a consistent association is seen with fetal death and pesticide exposure of both men and women (Paul, 1993). It is postulated that pesticides result in a less than expected impact on birth defects because fetal death results from exposure.

Increased risks of farm worker women for spontaneous abortion and stillbirth have been reported (Vaughn et. al., 1984; Hemminki et. al., 1980). A study of couples who were vineyard sprayers in India and lived in the vineyards found an excess of spontaneous abortions and stillbirth than in a comparison group (Rita et. al, 1987). The pesticides they were exposed to included DDT, lindane, Dithane M45, metasystox, parathion, copper sulfate, dichlorvos and dieldrin.

Generally these studies have examined people with an occupational exposure to pesticides, thus presuming a relatively longer duration of exposure opportunity and higher exposure intensity then would be the case of environmentally exposed persons (pesticide users). While adverse reproductive outcome cannot be ruled out in low level exposures to pesticides (OPS) for example, such adverse effects are much less likely in the environmentally (low dose) exposed service member population than in populations occupationally exposed, such as pesticide applicators and farm workers.

With this short summary as an overview, it is clear that there is epidemiologic evidence for pesticides as reproductive and developmental toxicants. However, their contribution to an adverse reproductive outcome on an individual basis is determined by the toxicity of the specific pesticides, the exposure intensity and circumstances as well as potential host factors, and other issues such as timing of exposure in a reproductive cycle, as discussed earlier. In the absence of exposure assessment data, hazard identification - that is, identifying specific agents as possessing the toxicologic capacity to act as a developmental or reproductive toxicant, is the only assessment activity which is possible. In that light, the reproductive toxicity of the six pesticides identified by GAO are summarized in Table 4 and reviewed in more detail in the appendix.

Oil Fires and Soil Samples

A number of toxic constituents characterize oil fire exposures, with much attention given to the polycyclic aromatic hydrocarbon benzo (a) pyrene.

Benzo (a) pyrene

Environmental characterization of Kuwait oil-well fires indicated the likely presence of numerous genotoxic contaminants. Mutagenic products of combustion including polycyclic aromatic hydrocarbons (PAH) such as benzo (a) pyrene (BAP) were a concern in performing a health risk assessment for troops deployed to Kuwait in June - September, 1991. As part of a larger health assessment of these troops, the U.S. Army Environment Hygiene Agency (USAEHA) assessed the potential for mutagenic exposure. The study employed a generic measure of mutagen exposure, sister chromatid exchange (SCE).

Elevations of baseline SCE frequencies have been employed as indicators of human genotoxic exposure to a number of environmental agents (Hansteen, 1982; Sorsa and Yager, 1987) including polycyclic aromatic hydrocarbons (PAHs) (Rudiger et al., 1976; Dosaka et al., 1987).

Frequencies of sister chromatid exchange (SCE), a measure of genotoxic exposure, were assessed in military troops deployed to Kuwait in 1991. Soldiers completed health questionnaires and had blood collected prior to, during and following deployment to Kuwait. Frequency of spontaneous SCE was determined on blood samples as a measure of mutagenic exposure and are displayed below in Table A. Compared to pre-deployment baseline SCE frequency means, levels obtained two months into the Kuwaiti deployment were significantly increased ($P < 0.001$) and persisted for at least one month after return to Germany. Outcome was unaffected by known personal SCE effect modifiers including smoking, age, and diet.

Table A. Comparisons of SCE frequencies for soldiers prior to, during and post deployment to Kuwait

n	Prior	During	Post
50[a]	4.33[b] $\pm$ 0.07[c]	5.12 $\pm$ 0.09	
35	4.38[c] $\pm$ 0.09		5.28 $\pm$ 0.12
26	4.41[c,d] $\pm$ 0.11[c,d]	5.11 $\pm$ 0.16	5.29 $\pm$ 0.15

[a]The number n varies due to differences in soldiers available for phlebotomy during each collection mission.
[b]$p < 0.0001$ comparing 'Prior' to 'During', paired t-test.
[c]$p < 0.0001$ comparing 'Prior' to 'Post', paired t-test.
[d]$p < 0.001$ comparing 'Prior' to "During' paired t-test.
[e]Mean $\pm$ SE of individual means of SCEs per cell.

This study reveals a highly significant increase in mean SCE for a population of soldiers serving in Kuwait while oil-well fires burned. This increase persisted for at least one month following return to their pre-deployment assignment in Germany.

Health concerns related to military service in Kuwait at the war's conclusion focused on consequences of exposure to constituents of smoke from burning oil well fires including potentially carcinogenic PAHs.

The genotoxicity of air particulates isolated during the Kuwait oil well fires was demonstrated by Kelsey et al. (1994) who reported a dose-response relationship for SCE induced in vitro with air particulate collected in Kuwait. However, a particulate sample collected in Washington, DC showed similar results, although not with the same intensity as the Kuwaiti sample. Kelsey also reported slight increases in the mutation frequency of the hprt locus induced by both particulate samples, with the Kuwaiti sample being more mutagenic. This study failed to demonstrate PAH-DNA adducts through ^{32}P-post-labelling experiments in a human lyphoblastoid cell line treated with the particulate samples. Darcey and colleagues also failed to show differences in levels of PAH-DNA adducts in lymphocytes of nine workers fighting oil fires in Kuwait (Darcey et al., 1992).
These observations suggest that other constituents of combustion products rather than PAHs may be responsible for the genotoxicity reported by Kelsey et al.

Environmental exposures not due to burning oil fires may have also caused the observed increases in SCE. There are several reports of increased SCE due to stress. One paper reported SCE elevations in bone marrow after rats were exposed to various stresses such as noise and foot shock (Fischman and Kelly, 1987). A human study on five volunteers showed a significant increase in SCE after sleep deprivation (Bamezai and Kumar, 1992). Stresses due to deployment must therefore be considered a potential SCE effector.

SCE frequency has been increased in three subjects recently vaccinated against measles (Knuutila et al., 1978). However, conflicting data have been observed from smallpox vaccine (Lambert et al., 1979; Kucerova et al., 1980). The study cohort received immunoglobulin prior to deployment, but no other uniform group of injections was given. However, individual soldiers may have received immunization to complete a required

schedule for deployment. The effect of immunoglobulin injections on SCE frequency is not reported in the literature.

Desert deployment also presents exposure to silica sand. The ability of alpha quartz and tridymite to induce SCE in lymphocyte culture with monocytes has been reported (Pairon et al., 1990).

While difficult to assess, soldiers may have had pesticide exposure as well. SCE increases have been widely reported in pesticide-exposed working populations such as florists and nursery workers (Doulout et al., 1985; Rupa et al., 1991; DeFerrari et al., 1991).

Principal activities of the troops in Kuwait evaluated in this study did not involve oil well fire suppression or combat, but included vehicle equipment operation, maintenance and repair, as well as patrolling and maneuver, and didactic training. It is assumed that technical job duties were similar in Germany and Kuwait, although slight differences in materials (such as degreasers) cannot be dismissed as an effector of SCE outcome.

The authors concluded that although a statistical increase in SCE frequency has been demonstrated in troops deployed to Kuwait, implying a genotoxic exposure, multiple candidates exist as the potential cause of this observation. At present, SCE elevations are thought to measure exposure to some genotoxic agent, but the long-term health consequences of this phenomenon have not been determined in this or other populations' exposure to genotoxicants. (McDiarmid, et al., 1995).

Another aspect of the Army's larger health risk assessment determined environmental PAH exposure which revealed low ambient levels of PAHs in the areas where soldiers were working in Kuwait. As well, measures of PAH interactions with human blood lymphocyte DNA (PAH-DNA adducts) and aromatic-DNA adducts were at their lowest levels in Kuwait compared to levels in Germany. (Poirier M. et al., in preparation). These results suggest that the SCE elevations observed by McDiarmid's group in this same cohort of soldiers are not due to environmental PAH exposure. It is important to realize however, that this group of soldiers was deployed in the June-September, 1991 time frame, and their duties did not involve oil well fire suppression, thus their proximity to the burning wells was not a likely risk factor, nor can these exposure circumstances be widely attributed to other deployed units. There is limited evidence, however, that environmental PAHs and BAP may not have played as significant a role as anticipated in potential health risks to soldiers during deployment.

The Reproductive and Developmental effects of selected oil fire and soil sample contaminants are summarized in Table 5 and reviewed in detail in the appendix.

Decontaminating Agents

A principal constituent of the decontaminating agent DS_2 is the compound ethylene glycolmonomethyl ether, 2-ME. DS_2 was produced by the U.S. Army Chemical Biological Defense Agency and used during the gulf war.

2-ME and a related compound, ethylene glycolmonoethyl ether (2-EE) are widely used in industry in paints, varnishes, and thinners, and as solvents in the textile and semi-conductor industries. Health effects data in animals and humans, together with estimates of large numbers of workers potentially exposed (850,000 U.S. workers, according to NIOSH) has prompted the OSHA to begin rule-making to limit worker exposure to 0.1 ppm for 2-ME and 0.5 PPM for 2-EE for an eight hour time weighted average (TWA) exposure. This is the first OSHA rule-making specifically driven by the adverse reproductive health effects of a workplace agent. From the proposed OSHA rule:

"Health effects data from experimental animal studies clearly and consistently show that 2-ME, 2-EE and their acetates produce dose related adverse hematologic, reproductive and developmental effects. These effects include testicular damage, reduced fertility, maternal toxicity, early embryonic death, external, skeletal and visceral malformations, delayed development, and adverse effects on the blood. Evidence also indicates that both inhalation and dermal exposures are significant routes of exposure for glycol ethers and the induction of adverse effects. In addition, persons occupationally exposed to 2-ME and 2-EE through inhalation and dermal exposures have exhibited adverse reproductive and hematologic effects. Although not as extensive, in major part due to methodological limitations, the human data are nevertheless highly consistent with and supportive of the strong body of data in experimental animals showing adverse hematologic, reproductive and developmental effects."
CFR Vol. 58, No. 54, Mar. 23, 1993.

Pyridostigmine Bromide

Pyridostigmine bromide (PB) is a cholinergic agonist used in the treatment of myasthenia gravis. PB has not been demonstrated to cause increased congenital defects in rats, when exposed throughout pregnancy (Levine, 1991). A number of myasthenic women treated with PB during pregnancy have not had adverse effects in offspring attributed to the drug (Pleuche, 1979). The American Academy of Pediatrics and the WHO working group on drugs and lactation have classified pyridostigmine as compatible with breastfeeding (AAP, 1994; WHO 1988).

Other Chemical Exposures

In examining the reproductive health of the Gulf War deployed population, information may be gained by examining data from working populations exposed to some of the same constituents thought to be present in the Gulf. A recent epidemiologic review of the experience of paternal exposure and spontaneous abortion experience (Savitz et al., 1994) may provide some insight into the present analysis The authors reviewed 39 studies performed in the previous 18 years examining the relation between paternal exposure and spontaneous abortion. They considered comments on study quality, including method of data collection and verification, power, response rates and other methodologic effectors of outcome. The reported outcomes were based on several groupings of hazard types, some of which are pertinent to gulf war exposure.

Several studies document elevated relative risk (RR) for spontaneous abortion in workers exposed to metals based on job title or employment sector such as a study of copper smelter workers (exposure to lead, arsenic, mercury and cadmium) with a RR=1.5 (95% C.I.=0.9-2.3) (Beckman and Norstrom, 1982). Others, more methodologically robust regarding exposure assessment, showed good evidence for a link between paternal exposure for heavy metals, particularly mercury (Alcser et al., 1989) and lead (Lindbohm et al., 1991b; Cordier et al., 1991). Negative studies in mercury exposed dentists (Brodsky et al., 1985) and in potentially lead exposed job titles (Lindbohm et al., 1991b) also must be mentioned.

Another category of toxicant exposure reviewed by Savitz for relation to spontaneous abortion was that of the group rubber, plastics and solvents. This group included agents such as vinyl chloride, toluene, benzene, trichloroethane and "petroleum refinery products". Many of these agents appear in the lists of toxicants potentially found in the gulf environment. Taskinen et al., 1989, performed a particularly careful exposure classification, and found a RR=2.3 for exposure to organic solvents in general and RR=1.5 for toluene exposure. An association with gasoline or benzene exposure in petroleum refineries reported a RR=2.2 and for trichorethane and methylene chloride exposure a RR=1.8 (Lindbohm et al., 1991a). A 1976 study of spouses of vinyl chloride exposed men found a RR=1.8, with an enhanced effect among younger fathers (RR=3.7). (Infante et al., 1976). Several studies failing to identify excesses in dry cleaning, or rubber workers (McDonald et al., 1989) and a number of other solvents [Lindbohn et al., 1991a] were stronger methodologically in Savitz's view (Savitz et al., 1994). He comments however, that the weaknesses of many of the negative studies do not exonerate the toxicants considered.

Savitz also reviewed exposures to hydrocarbons and exhausts and found generally null results with the exception of Lindbohm's finding of a RR=1.4 for chimney sweeps and 1.5 for refinery workers (Lindbohm et al., 1991a).

There are few data on the potential impact of particulate exposure on reproductive health. However, one in vitro study of human sperm motility exposed to diesel particle

extracts showed moderate but progressively stronger effects on motility with duration of exposure and increased dose (Fredricsson et al., 1993).

Non-Chemical Hazards

A number of non-chemical hazards have been identified which may impact the reproductive health of the Persian Gulf deployed. These hazards have been recently reviewed by Agnew et al., 1991 and are summarized in Table 6 (see end of document).

Heat

A hazard deserving specific discussion is heat. Heat causes well documented insult to the spermatogenic process (Henderson et al., 1986). Human sperm number decline and morphology is altered with an increase in ambient temperature (Mieusset et al., 1987a; Procope, 1965). This effect is apparently reversible, but time to normal sperm production is a function of degree and duration of hyperthermia experienced.

Biohazards

Exposure to various biological hazards including some uncommon and exotic organisms has been written about regarding PGW deployment, although not specifically regarding an adverse reproductive outcome. Biologic hazards, particularly viruses, are notorious reproductive and developmental toxicants and the more celebrated examples are outlined in Table 2.

SUMMARY

To sum up, various diverse and classical reproductive and developmental toxicants were apparently present in the gulf war theater of operation, allowing a partial hazard identification assessment to be made. As previously discussed, however, the absence of data regarding exposure concentration, duration and scenario details for personal and even troop unit exposure all but precludes our ability to perform a true risk assessment regarding abnormal reproductive and developmental outcomes. There are some lessons to be learned from this episode, however, and some recommendations to be made that may assist in preventing repetition of such a problem in future conflicts.

RECOMMENDATIONS FOR THE GULF WAR REPRODUCTIVE HAZARDS PROJECT

Prior to making my recommendations, I would first like to comment on the recommendations that the GAO made in their testimony from August 5, 1994 regarding reproductive hazards during Operation Desert Storm. They made four recommendations at that time. The first was to guide the Secretary of Veterans' Affairs to direct a revised and expanded questionnaire and to re-register veterans who had already completed the VA registry examination in order to include reproductive health endpoints in their surveillance. I understand that this is already being done.

Secondly, they recommend that the Environmental Protection Agency, Department of Health and Human Services and DOD make additional scientific inquiry into possible synergistic effects of multiple exposures to hazards found in the Persian Gulf War. This needs to be commented upon. This would be an extremely difficult task in that even some of the individual hazards have not adequately been reviewed for reproductive and developmental toxicity, and more importantly, the exposure assessments are so poor that it is hard to see the sense that this suggestion makes. It would not be a good use of the public health dollar to start here. Rather, there are some more fundamental issues that need to be addressed by DOD that include exposure assessments and basic hazard surveillance.

The GAO's third recommendation involved establishing baseline data on various reproductive outcomes, including birth outcomes, infertility and miscarriage rates among active duty military, reservists, presumably before future conflicts. While this is a laudatory notion, it is extremely complicated, though less daunting than their follow-up suggestion which is to ascertain exposures of reproductive toxicants and some type of a warning system when the concentrations of exposure rise to what they call "dangerous levels in future conflicts". It is unclear to me how this could be done and what is a realistic way of monitoring this separate from a more basic approach which is to use a classical industrial hygiene hierarchy of control technology which I will say more about in my recommendations.

The fourth GAO recommendation was that the DOD should develope procedures to better ensure that troops are informed of possible reproductive toxicants before future deployments and to monitor exposure levels to such hazards. Again, the hazard communication piece of this recommendation is appropriate and can certainly be built into existing training. The notion of monitoring exposure concentrations, however, is a little more naive. I think that it is more likely that exposures can be minimized by substitution and elimination of known reproductive toxicants where possible, which included the minimizing of inappropriate use of certain reproductive toxicants that have been reported by GAO and I am going to discuss further below.

Recommendations

1. My first recommendation would be to "stop stupid stuff". This is language used in agency parlance to mean do not keep doing things that are not defensible. Examples here are those documented in various testimony, including the use of diesel fuel as a sand suppressant and using leaded gasoline exhaust for drying sleeping bags. These presented absolutely preventable and inappropriate overexposure to reproductive toxicants in the Gulf War theater. These types of examples of easily preventable scenarios are those that need to be included in some type of a hazard communication course or program for all deployed, especially for those that are going to be supervising ground troops.

2. There is a need to develop an environmental hazardous materials tiered training program. I would suggest here an approach similar to the National Institutes for Environmental Health Science (NIEHS) model for workers exposed to hazardous materials (hazmat). There are three or four tiers of training, the first being the most basic and the shortest, an awareness level of training, the second being more comprehensive perhaps for someone who will have some response capability, and finally a third and higher levels, perhaps a master or trainer level where there is much more detail pursued. This approach is based on a National Fire Protection Association (NFPA) standard on Professional Competence of Responders to Hazardous Materials Incidents (NFPA 472). The general purpose of the standard is to reduce the number of incidents, injuries and illnesses resulting from hazmat incidents. The scenarios reported of the inappropriate overexposure by using toxic substances in the wrong way, I think, are the best examples of case studies that could be used to promote the notion that there is a right way and a wrong way to handle a hazardous substance. In addition, the hazardous materials training can include some of the various health effects training and could be very similar to the hazard communication training that is required in various work places and also has been suggested by a number of experts who have testified in the various forums that were convened to examine this problem. This also would mirror recommendations for training that the GAO made as well.

3. Medical records for vaccinations and other types of health interventions must be kept. It is incomprehensible that these data were not kept during the Persian Gulf War conflict. Electronic dog tagging and other types of electronic code readers could be used and are used throughout the military to keep track of a number of less important issues and there really is no good explanation for failure to complete these types of records.

4. Documentation of pyridostigmine bromide directions given to troops needs to be made. In addition, because of the question about the potential toxicity of pyridostigmine bromide and the questionable evolution regarding safety available in the literature, it makes sense to be more careful regarding the hazard communication training that goes on for pyridostigmine bromide and to give consideration to how usage of pyridostigmine bromide could be tracked in conflict situations.

5. Serious consideration needs to be given to establishing a birth defects registry. GAO recommends looking at various outcomes in the military as a baseline, but other experts had also suggested that this really needs to be something established on a national basis. Precisely because of our inability to look at national norms, our current dilemma of trying to measure an excess of some type of untoward event in the deployed has been confounded. It is quite clear that much more of the public health dollar has been spent than would have been necessary had these types of registries been in place. The DOD

could go a long way as a significant partner to HHS in contributing funding to assist in setting up this very needed national resource, and it is clear that the DOD would be a significant recipient and beneficiary of this resource in future conflicts.

6. The recent down-sizing of occupational medicine capacity in the Army at the Center for Health Promotion and Preventive Medicine (USACHPPM), Aberdeen, Maryland and the apparent lack of recognition of the need for this expertise by the Army needs to be addressed. Many of the above cited "stupid" practices and under-recognition of toxic hazards would have been readily recognizable and easily prevented by occupational medicine personnel who possess training and expertise in toxicology and hazard prevention. The future likelihood of deployments involving ever-more complex toxic substances in weapons systems, CW counter measures, other medications and the chemical exposures of deployment itself suggest the strategic need for a substantial occupational medicine expertise.

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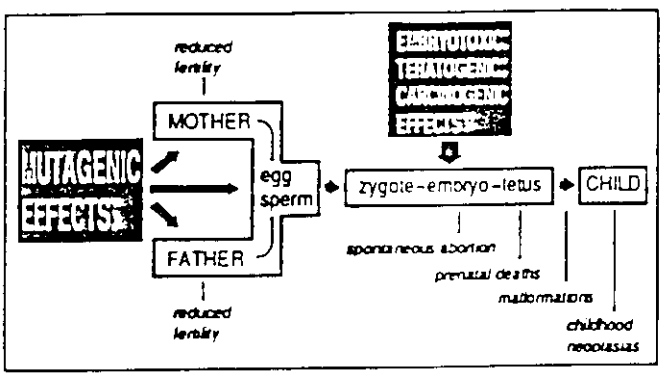

Figure 1 Effects of toxic exposure to the reproductive system

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TABLES

Table 1: Frequency of Self-Reported Environmental Exposures in Gulf War Veterans (GWV)[a] and Active Duty Service Member (ADS) [b]

EXPOSURE	POSITIVE RESPONSE	
	GWV[a] (%)	ADS[b] (%)
Passive Cigarette Smoke	88.5	88
Diesel/Other Fuels/Petrochemical Fumes	90.4	88
Oil Fire Smoke	72.6	71
Tank Heater Fumes	66.6	70
Pyridostigmine Bromide	64.2	74
Personal Pesticide Use	66.7	66
Burning Trash/Feces	73.9	N/A
Skin Exposure to Fuel	73.7	N/A
ATE Non-US Food	71.3	66
Chemical Agent Resistant Paint CARC)	34.5	47
Solvent /Paints	53.6	48
Anthrax Immunization	48.7	49
Ate Contaminated Food	33.2	21
Microwaves	34.2	N/A
Bathed in Contaminated Water	28.6	20
Bathed in Non-Military Water	30.5	N/A
Bathed in/Drank Non-US Water	N/A	32
Botulism Vaccine	26.8	26
Depleted Uranium	14.2	15
Nerve Gas	14.1	61
Took Oral Meds to Prevent Malaria	N/A	22
Mustard Gas/Blistering Agent	N/A	25
Chemical Alarm	N/A	65
Witnessed Casualty	N/A	56
Witnessed SCUD Attack	N/A	54
Witnessed Actual Combat	N/A	37
Wounded in Combat	N/A	2

a = From Office of Public Health & Environmental Hazard
s, DVA, "Review of DVA Revised Gulf War Registry & In-Patient Treatment Files (12/97) N = 10,075
b = Percent based on participants who answered Yes or No (excludes unknown) from DOD CCEP for PGW Veterans (4/96). N = 18,075

TABLE 2: COMPLETED EPIDEMIOLOGIC STUDIES OF REPRODUCTIVE HEALTH EXPOSURE ASSESSMENT CONSIDERATIONS

AUTHOR (YEAR)	DESCRIPTION	REPRODUCTIVE OUTCOME	EXPOSURE ASSESSMENT
Stretch (1995)	• Self-report questionnaire • Deployed-VS-non-deployed • Hawaii and Pennsylvania	• Menstrual difficulties	• Comment on Oil Fires
Penonmetal (1996)	• National Guard Units (282 veterans with 54 births post-deployment) • No internal controls • Mississippi	• Major/minor birth defects • Prematurity/low birth weight • Hyperbilirubinism • Stillbirths	• None
Iowa Persian Gulf Study Group (1997)	• PGW regular military and National Guard • Controls-non PGW regular military National Guard stratified sample	• Symptoms of sexual discomfort	• Fairly detailed • Vaccine/PB use • Environmental hazards • Psychological stresses • Physical trauma
Cowan et al (1997)	• Assessed births to PGW Veterans • Controls non-deployed military	• Major/minor birth defects • Live birth rate • Sex ratio	• None • During deployment
Araneta et al.	• Births to GW Veterans • Controls-non-deployed veterans	• Goldenhar syndrome	• None - deployment status only

TABLE 3: EPIDEMIOLOGIC STUDIES OF REPRODUCTIVE HEALTH (CURRENTLY ONGOING) EXPOSURE ASSESSMENT CONSIDERATIONS

AUTHORS	DESCRIPTION	REPRODUCTIVE OUTCOME	EXPOSURE ASSESSMENT
Study 3 (NHRC) (Cowan, Araneta)	• See Cowan (above)	• Reproductive outcomes • Birth defects • Prematurity • topic/molar pregnancies • mplications of Labor-Delivery	• None
Study 4 (9NHRC) (Calderon)	• Female PGW (deployed) - vs- non-deployed	• fertility/miscarriage	• No exposure information in phase I except field of operation • Phase II questionnaire not yet available
Study 77 (NHRC) (Araneta)	• PGW Veterans - vs - non-deployed	• rth defects	• No exposure assessment
Clinical Study in (Cinninnatia, Ohio) (Bernstein)	• PGW Veterans - (male) vs - non-deployed	• minal plasma hypersensitivity • ction	• In-vitro exposure to environmental agents
Feasibility Study CBDMP (Harris)	• PGW Veterans - vs - non-deployed	• ngenital anomolies animals (Feasibility study)	• ?
National Health Survey (Kang)	• Random sample 15,000 GWV - vs - 15, 000 Non-deployed	• Adverse reproductive outcomes in veterans/families	• Detailed self-reported environmental exposures
University of Oregon (McCauley)	• GWV deployed 8/90 - 8/91	• Infertility • Menstrual abnormalities • Fetal loss • Genital tract symptoms	• Detailed environmental history (chemical, biological, physical stressors)
Klemm Group	• 10,000 women PGW - vs - non-deployed	• Infertility • Preterm birth • Stillbirth • Birth defects	• Detailed environmental exposure history • Length of exposure to these endpoints - before, during and after PGW

TABLE 4: SUMMARY OF SELECTED REPRODUCTIVE/DEVELOPMENTAL EFFECTS OF PESTICIDES

AGENT	ANIMAL EFFECTS	HUMAN EFFECTS
Carbaryl (Sevin) (OP)	• Developmental/malformations	• Little data on developmental or reproductive risk
Dichlorvos (DDVP) (OP)	• Developmental and Reproductive abnormalities	• No references
Diazinon (OP)	• Teratogenic in birds • Stillbirths in dogs	• Insufficient data regarding human development
Ethanol		• Fetal alcohol syndrome (FAD) • Malformations/Mental retardation
Lindane (Hexachlorobenzene)	• + Genotoxicity in vitro • Testicular toxicant in animals	• Transplacental transfer • Excreted in breast milk • ? estrogenic properties • Little evidence of human toxicity reported
Warfarin		• Teratogenic (skeletal defects) • CNS defects

(See appendix for review of findings by agent and citations)

TABLE 5: REPRODUCTIVE/DEVELOPMENTAL EFFECTS OF SELECTED OIL FIRE AND SOIL SAMPLE TOXICANTS

AGENT	ANIMAL EFFECTS	HUMAN EFFECTS
Arsenic	• Teratogenic in animals	• Transplacental Transfer • One report of neonatal death
Benzene	• Genotoxic • Fetotoxic/Teratogenic	• Transplacental Transfer • Chromosomal aberrations CNS defects in organic solvent exposed women (Holinberg, 1979)
Benzo(a) Pyrene	• Transplacental transfer/adduct formation • Embryotoxicity/malformations • Sperm effects in rats	
Cadmium	• Teratogenic or embryolethal in several species • Testicular toxin/sperm effects	• Placental toxicity • Found in breast milk • ? relation to low birth weight
Hexachlorobenzene	• Transplacental transfer • Mammalian ovarian toxicity	• Transplacental transfer • Eliminated in breast milk; "pink sore" in poisoned children • Present in follicular fluid of women under - going IVF
Lead	• Transplacental transfer • Malformations in animals • "Behavioral Teratogen"	• Transplacental transfer • Stillbirths/miscarriage • Behavioral Teratogen • Sperm abnormalities
Mercury		• ?aborifacient • Teratogenic in organomercury form • Inorganic Hg in placenta of dental workers • ? of spontaneous abortions from exposed fathers • Present in breast milk
Nickel	• Congenital abnormalities/growth retardation • Genotoxicity/sperm head abnormalities in mice	• Transplacental transfer • One report of malformed infant death
Pentachlorophenol	• Transplacental transfer • Fetotoxic	• Present in semen of workers and associated with chromosomal abnormalities • No reports on human pregnancy
Toluene	• Chromosomal damage in bone marrow • Fetal abnormalities	• Transplacental transfer • Congenital abnormalities in occupationally exposed and toluene abusers
Xylene	• May be Fetotoxic	• Considered low-likelihood to cause reproductive harm

(See appendix for review of findings by agent and citations).

TABLE 6 Summary of Potential Reproductive Effects of Non-Chemical Exposures

	Animals		Human		
Agent	Male	Female	Male	Female	Reference
Hyperthermia	Decreased sperm number	Fetal malformations	Decreased sperm number	Birth defects, with maternal fever	Henderson et al., 1986 Edwards et al., 1986 Pleet et al., 1981 Clarren et al., 1979 Procope, 1965
			Abnormal sperm Delayed conception	Hearing loss in children of exposed mothers(?)*	Lalande et al, 1986 Rachootin and Olsen, 1983
Physical activity		Few effects noted on fetus	Trauma: testicular damage, hormonal change, impotence	Amenorrhea, strenuous job: prematurity and low birth weight	Lotgering et al., 1985 Steeno and Pangkahila, 1984 Armstrong, 1986 Warren, 1983 Naeye and Peters, 1982
				Heavy lifting or standing on job: miscarriages(?)*	Mamelle et al, 1984 Saurel-Cubizoles et al., 1987 Saurel-Cubizoles and Kaminski, 1987
				A 20+ weeks pregnant: problem with balance and agility	Taskinen et al., 1986 McDonald et al., 1988 AMA Council Sci Affairs, 1984
Noise		Increased litter resorption and fetal mortality, decreased fetal weight		Increased rates of birth defects and low birth weight(?)*	Kimmel et al., 1976 Nawrot et al., 1980 Cook et al., 1982 Edmonds et al., 1979 Jones and Tauscher, 1978
		Fetal malformations(?)*		Hormonal disturbances	Knipchild et al., 1981 Schell, 1981
				Idiopathic infertility	Rachootin and Olsen, 1983
Psychological stress	Decreased testosterone one level		Decreased testosterone levels	Amenorrhea	McGrady, 1984 U.S. Congress, OTA 1985 Fries et al., 1974
			Negative behavioral effects	Negative behavioral effects	

* ? indicates that strength of study design or results do not justify definite conclusions.

Adapted from Agnew J, McDiarmid MA, Lees PSJ, Duffy R: Reproductive hazards of fire fighting 1. Non-chemical hazards. Am J Ind Med 19:433–445, 1991.

TABLE 7

Table . Viral Infections of Concern to the Pregnant Worker

	Transmission	*Effects*	*Intervention*
HIV	Sexual contact, parenteral exposure to infected blood or blood products. Seroconversion after needle stick exposure <0.5%.	Pregnancy may favor progression of disease. High neonatal morbidity/ mortality.	Universal precautions. No restrictions necessary.
CMV	Close contact with infected body fluids (usually sexual). >50% of women immune. Viral shedding in urine of children in day care centers common.	Congenital microcephaly, growth retardation, hearing loss, neurologic problems. 40% infection rate in infants born to mothers with primary infection during first half of pregnancy. About 1/5 of infected infants have serious sequalae.	Infectious precautions. Reassignment not necessary. No increased seroconversion rates in health care workers. Stress hygienic measures among day care and school teachers.
Hepatitis B	Contaminated needle sticks, blood exposures, sexual contact. Seroconversion after needle stick exposure from "e" antigen positive patient 20%.	Neonatal chronic HBV carrier state, with 25% developing cirrhosis or hepatocellular carcinoma.	Offer hepatitis B vaccine to employees in high risk occupations; infectious precautions. Neonatal HBIG and vaccine effective in preventing chronic carrier state.
Rubella (German Measles)	Respiratory route; close personal contact. Virus shed in pharyngeal secretions, open lesions, urine, stool.	Congenital cataracts, cardiac defects, deafness. Malformation rate up to 50% with first trimester infection.	Proof of immunity by titre or vaccination prior to employment in high-risk occupations. Vaccine not recommended during pregnancy. Non-immune employees should avoid contact with rubella-infected individuals.
Human parvovirus B19	Respiratory route; close contact; infected blood or blood products. Secondary attack rate 50% for susceptible household contacts, 20-30% for school staff.	Usually mild, self limited illness in children and adults. Fetal hydrops, fetal death. Risk of B19 associated fetal loss <10% in studies to date.	Infectious precautions. Serologic tests available for pregnant women to document recent infection or susceptibility. Reassignment of non-immune employees does not prevent risk of community acquired disease.
Varicella (chicken pox)	Respiratory route, Highly contagious. Most adults immune.	Pneumonia in pregnant women may be serious. Risk of congenital varicella after first trimester infection approx. 4%. If maternal infection in perinatal period, 50% of infants infected with 20% mortality.	Pregant women without proof of immunity should avoid contact with infected individuals. Offer VZIG within 96 hours of exposure to suspectible pregnant women and to neonates born to mothers with onset of chicken pox <4 days before delivery.

From Paul and Kurtz, 1990

APPENDIX

REPROTOX PROFILES FOR GAO IDENTIFIED TOXICANTS

PESTICIDES

2467 CARBARYL **CAS 63-25-2**

Carbaryl (Sevin) is one of the oldest and most widely used carbamate insecticides. Like the other carbamates, it is an anticholinesterase. Reproduction and teratology studies have been performed in a number of species. In pregnant mice, carbaryl administration at up to 30 mg/kg/day in the diet failed to increase adverse pregnancy outcome or abnormal development of the offspring (1). This study was criticized because the top dose failed to produce maternal toxicity. A study using up to 464 mg/kg by injection produced maternal toxicity at doses of 100 mg/kg or more. An increase in birth defects in one strain of these mice was seen at the maternally toxic doses (2). Another study gave more than 1 g/kg/day carbaryl in the diet of pregnant mice. Maternal toxicity was manifest as a decrease in weight gain but no increase in birth defects was seen in the offspring (3). As in the mouse studies, teratogenicity has not been found after the administration of carbaryl to pregnant rats in toxic doses (4-8). A study in which maternally toxic doses of carbaryl were administered to pregnant hamsters and guinea pigs, and similar high doses to pregnant rabbits, showed no significant increases in malformations except minor skeletal anomalies in the guinea pig fetuses (9). In another rabbit study, toxic doses of 200 mg/kg/day to the mother were associated with an increase in omphalocele in the offspring (3). In pregnant sheep, 250 ppm in the diet was associated with a very small and possibly insignificant incidence of ventricular septal defect in the offspring (10). In beagles, three studies have associated carbaryl administration during pregnancy with an increase in varied congenital anomalies in the offspring, one at 5 mg/kg or above and the other two at 6.25 mg/kg or above (11-13). Considerable maternal and fetal toxicity occurred at these doses and an increase in terata due to general maternal toxicity cannot be ruled out. Although only small numbers of animals were studied (14,15), carbaryl treatment of pregnant monkeys at up to 20 mg/kg/day was not associated with birth defects in the offspring.

Animal reproduction studies show an increase in resorptions and fetal deaths when maternally toxic doses of carbaryl are given. Studies in pigs demonstrate impaired fertility (13) and multiple generation studies in rats and gerbils (7,16) also show decreases in fertility and increases in perinatal mortality. Although human studies on reproductive effects of carbaryl have not been reported, the animal experience suggests that high doses, associated with significant maternal toxicity, may impair reproductive success, including fertility, embryonic development, and viability, but not necessarily through a specifically targeted mechanism. It is possible that reproductive impairment is a manifestation of generalized adult toxicity.

Experiments in cows show that 1% or less of radiolabelled carbaryl is recovered in milk, where most of it is converted to lactose (17,18).

An evaluation of men occupationally exposed to carbaryl showed no difference in sperm counts or reported ability to father a child when compared to nonexposed controls (19). There was, however, a report that sperm morphology was altered in these carbaryl-exposed individuals (20). It is not known whether carbaryl exposure might have adverse fertility effects in men.

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1272 BENZENE CAS 71-43-2

Benzene is the simplest aromatic hydrocarbon. It is commonly used as an industrial solvent and starting material in chemical syntheses. Benzene is also found in gasoline and some paints used in the home. Intact skin is an effective barrier to benzene absorption, but, because of its high volatility, inhalation is a common route of exposure. The general toxicology of benzene has been well studied. Acute intoxication is characterized by transient excitation and depression in the central nervous system; chronic intoxication induces bone marrow hypoplasia and aplastic anemia. There also appears to be an etiologic role for benzene in human leukemia (1-3). Inhibition of heme synthesis in bone marrow is a major effect of benzene, and there is ample evidence that benzene also causes chromosomal damage in marrow cells (4-6). The metabolites of benzene are under investigation as the suspected active agents in its genotoxic effects (7). The affinity of the compound for the central nervous system, and the abnormalities induced in chromosomes in dividing cells, have raised concerns that benzene may be toxic to the developing embryo.

Animal studies have demonstrated the fetotoxicity of benzene exposures, but have not indicated that it is highly teratogenic. One early teratogenicity study in mice reported that the subcutaneous injection of 3 mL benzene/kg during organogenesis induced cleft palate, agnathia, and micrognathia in exposed offspring (8). This study did not include groups of control animals, however, and the reported effects have not been reproduced in subsequent mouse studies (9-11). Inhalational exposures in rats decreased maternal and fetal weight gain, but caused only minor skeletal anomalies in the pups, which were probably associated with the maternal toxicity of benzene (12-15). Other investigators have reported that the induction of micronuclei formation by benzene was diminished in the adult mouse by pregnancy (16). The fetus was relatively insensitive to this effect of benzene, perhaps because the compound is not metabolized and activated in the fetal liver (17). A comprehensive teratology study in rabbits did not indicate significant developmental effects were caused by benzene when inhaled throughout pregnancy at concentrations up to 500 ppm (11). A recent study in mice reported that in utero exposure to relatively low concentrations of benezene (<20 ppm) produced enduring adverse effects on the erythroid colony forming cells of the offspring (17,18). The significance of this observation for human benzene exposures has not yet been investigated.

The placental transfer of benzene has been demonstrated in animal and human investigations (19,20). In case studies reported between 1934 and 1957, five pregnancies were identified in which exposure to benzene (and possibly other organic solvents) induced aplastic anemia (21) The outcomes of these pregnancies included four maternal deaths and only two surviving offspring. These results cannot, however, be exclusively attributed to the adverse effects of benzene intoxication.

Chromosomal aberrations in lymphocytes have been found in all patients with clinical signs of benzene intoxication, and in as many as 50% of those chronically exposed to benzene (22). There is a report on two women with benzene-induced hematopathy and chromosomal abnormalities who later gave birth to normal children without detectable chromosomal abnormalities in their cultured lymphocytes (5). It is difficult to reconstruct, however, the amount and timing of benzene exposure in relation to the reported pregnancies. A retrospective case-control study of children with central nervous system defects found a significant tendency for mothers to have been exposed to organic solvents. Of the 14 women so exposed, however, only one was exposed to benzene (23).

In male mice, exposures higher than 2.5 mL/kg were associated with an increase in abnormalities of sperm head shape (24), and other cytotoxic effects on germ cell histogenesis (25). At this time, these effects have only been investigated in rodents.

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1116 LEAD **CAS 7439-92-1**

Lead toxicity has been recognized for centuries, but the usefulness of various forms of lead has kept it widely available in many societies, including our own. In the recent past, the burning of lead alkyl additives in gasoline constituted the largest and most widespread exposure to lead. Now, federal guidelines are eliminating this use of lead, significantly lowering atmospheric exposures, but leaving residual soil contamination and a large variety of alternative sources. These include lead solders, pipes, storage batteries, construction materials (i.e., lead based paints), dyes, and wood preservatives. Although in the past, most lead exposure could be associated with atmospheric exposure, lead intake may now occur from variable and, at times, insidious sources. For example, growth retardation and neurologic deficits were found in a newborn whose lead exposure was identified and traced back to the chronic use of "moonshine" whiskey by the mother. The equipment used to distill the whiskey was found to contain lead solder, which contaminated the liquor (1).

Both animal and human studies indicate that lead can be readily transferred across the placenta to the fetus (2,3). Human data have identified this transfer as early as the 12th week of gestation (3). Generally, the alkyl lead salts (e.g., tetraethyl lead) have not been associated with teratogenic effects (4,5). Inorganic lead salts have been associated with malformations of the central nervous system and cleft palate in mice (6-8), tail defects in hamsters, as well as hydronephrosis and skeletal defects in rats (7). Administration of lead to pregnant mice on day 8 of gestation results in impaired fertility in female offspring, attributed to toxicity for primordial germ cells (34,35).

Behavioral studies in rats have given contradictory results with some studies showing alterations with perinatal lead treatment and other studies showing no effects (9,10,36,37). Sheep experiments indicated that maternal blood levels of 34 μg/dL induced learning defects in newborn lambs (11).

More than 100 years ago, the toxic effects of lead on human pregnancy were suspected in women who worked with lead salts (i.e., pottery glazes). Stillbirths and miscarriages were also recognized as common in this population (12). Lead salts were considered to be abortifacients (13,14). More recent data have further documented the association between occupational exposures to lead and miscarriage, premature rupture of amniotic membranes, and premature birth (15-17). Modern industrial hygiene has significantly limited occupational exposures to lead.

Whenever possible, however, women at risk of lead exposures in the workplace should be monitored for blood lead before becoming pregnant. If elevated blood lead is detected (>30 μg/dL), pregnancy should be postponed until chelation therapy and reduced exposures prove effective. There is growing concern regarding the possible elevation of maternal blood lead during pregnancy due to the mobilization of lead stored in bone (22-24). If a women was chronically exposed to elevated levels of lead, or she experienced significant lead intoxication at any time in her past, it would be appropriate to periodically monitor her blood lead levels during her pregnancy. There is no clear agreement on the management of elevated blood lead during pregnancy. Based on reports suggesting that the chelating agent, calcium edetate, may be teratogenic in animals (25), the use of chelation therapy during pregnancy is not recommended.

There is intense interest in identifying the possible behavioral and developmental toxicity of low levels of blood lead (<35 micrograms/dL). In one report, umbilical cord blood lead levels between 8.7 and 35.1 μg/dL were associated with a variety of minor anomalies, including hemangiomas, lymphangiomas, hydrocele, skin tags, papillae, and undescended testes (18). Because no pattern was evident in the anomalies detected, these findings can be alternatively interpreted as indicative of more serious malformations (18,19) or discounted as inadvertently associated with fetal lead. Another report suggests that measurable deficits in early cognitive development can be correlated with prenatal exposure as measured by more than 10 μg/dL in umbilical cord blood (20). It should be noted that the variations reported are small and only demonstrable when sophisticated behavioral and statistical analyses are applied to the available clinical data. This study was supported by the finding that decrements in the Bayley Mental Developmental Index correlated with increasing measures of intrauterine exposure to lead, even at maternal blood lead levels less than 30 μg/dL (21). These findings suggest that the current standards for blood lead levels in young children may not be adequate for fetuses and newborns. They do not establish that low level lead exposures, as might occur in a typical urban environment, pose a formidable health risk to newborns. The data of the Port Pirie Cohort Study did not find persistence into childhood of a relationship between IQ and antenatal or perinatal blood lead concentrations (45). While avoidance of fetal lead exposure is, of course, desirable, there are no data showing that elaborate alterations in the diet or health care of otherwise healthy pregnant women to minimize lead intake would significantly benefit fetal development.

Male reproductive toxicity from this metal is an issue of current concern. It is a frequently repeated anecdote that male lead workers early in the twentieth century had a higher than normal incidence of fathering pregnancies that ended in abortion. This is attributed, however, to these men's practice of wearing their contaminated work clothes home, no doubt to be laundered by their pregnant wives. In addition, many men working with lead had shops at home where direct intoxication of the pregnant wife could have occurred. It is a goal of modern-day industrial hygienists to have lead workplaces require changing of clothes at the end of the day, with attention to laundering the soiled work clothes in a safe manner.

This is not to say that lead is not a male reproductive toxicant. In rat experiments, lead exposure resulted in a dose-related suppression of serum testosterone levels and spermatogenesis (28). The proposed mechanism for this effect is a disruption of the hypothalamic-pituitary-testicular axis in which pituitary hormone secretion is decreased, impairing spermatogenesis (29). Azoospermia and oligospermia have been reported in lead-intoxicated workers (30-32), although these effects were not associated with endocrine dysfunction (32). In 1975, a landmark study was published by Dr. Lancranjan and her coworkers from eastern Europe. These investigators evaluated semen from men with different degrees of lead intoxication and found an association between elevated blood lead levels and sperm abnormalities, including abnormal sperm forms, decreased motility, and oligospermia (26). It should be recognized, however, that there are limitations to these data. First, single semen specimens were evaluated, rather than requiring three or more samples. In addition, semen abnormalities appeared at blood lead concentrations of 40 or 50 μg/dL, detracting from the relevance of this study for evaluating reproductive effects of low level lead exposure. Finally, the men with the highest lead levels and degree of sperm abnormality had higher incidence of self-reported infertility, suggesting that male reproductive effects of lead might produce abnormal sperm incapable of fertilization. There is, then, no evidence from this study that male exposure to lead gives rise to an increased risk of adverse fetal effects in a subsequently conceived pregnancy. There is a rat study, published in the same year as Dr. Lancranjan's report, showing that lead treatment of parents prior to mating impaired performance of the offspring in a swimming maze, whether the lead treatment was given to the mother or the father or both (27). Treatment of the male was continued until the time of mating, so transmission of lead to the female in semen could not be ruled out. In addition, the dose of lead used in this study was higher than would be expected from occupational exposures.

A brief epidemiology study evaluated the odds ratios of paternal or maternal occupational lead exposure among parents of children with strabismus (33). The rationale for the investigation was that lead neurotoxicity might lead to disconjugate gaze disorders. The exposure assessment was performed by job description, and it is not possible to evaluate the accuracy of this method. No association was found between strabismus and maternal occupational lead exposure. The authors concluded that the study results "suggest the possibility of a weak association between paternal lead exposure and strabismus in the offspring"; however, the 95% confidence intervals for all odds ratios included 1.0. This statistical feature plus the lack of dose relationship in the findings suggest that the data in this study were not sufficient to demonstrate any association between lead exposure and gaze disorders.

Lead enters breast milk in rats and exposure by this route has been shown to influence play activity of juvenile animals (36) and to alter gonadotropin binding and steroid production of the ovary and testis when nursing rats grow older (38-40). Lactating monkeys given lead at a dose of 1 mg/kg/day showed blood lead concentrations of 116 μg/dL and milk concentrations of 222 μg/dL. Their offspring had blood lead concentrations of 30 μg/dL (41). It should be noted that these maternal blood lead concentrations are quite high compared to lead concentrations encountered in healthy women. In one survey, lactating women had mean blood lead concentrations of 12 μg/dL with corresponding

milk concentrations of 0.3 μg/dL (42). Another survey identified milk concentrations of about 1 ug/dL and calculated infant daily lead intake from this source to be 0.9 to 2.3 μg/kg/day (43). This was considered to be acceptable given a permissible daily intake of lead of 5 μg/kg/day. Lead concentrations in breast milk do not correlate well with maternal blood lead concentrations (44).

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2418 DICHLORVOS CAS 62-73-7

Dichlorvos (DDVP) is an organophosphorus insecticide that has also been used as an anthelminthic. This agent is a cholinesterase inhibitor. Dichlorvos is also formed from the pesticide, trichlorfon (see #2176). Dichlorvos has been found to be genotoxic in studies using bacteria and yeast (1,2). Mammalian genotoxicity studies have yielded conflicting reports with some positive (3-5) and some negative (all from the same laboratory) (6-9). Exposure of quail embryos to dichlorvos resulted in toxicity to the primordial germ cells with degeneration and a slowing of their migration to the gonads (10). In rats, exposure of pregnant animals to 15 mg/kg ip caused maternal toxicity and an increase in resorptions and birth defects in the offspring (11). Nonmaternally toxic doses had no adverse effects. Negative teratology studies have also been reported in rabbits (12) and pigs (13,14). Use of a dichlorvos-impregnated collar was not associated with adverse pregnancy outcome in goats (15). Exposure of breeding mice to dichlorvos vapors did not produce significant effects on the length of gestation or litter size (16). We have been unable to locate references on possible human reproductive effects of this agent.

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1143 DIAZINON **CAS 333-41-5**

Diazinon (diazide, dimpylate) is an organophosphate insecticide. It acts as a cholinesterase inhibitor. Diazinon and many other organophosphorus insecticides are teratogenic in birds (1-4). The mechanism of action of these avian teratogens may involve reduction in pyridine nucleotides in the embryo (5). When tested in rats and rabbits, diazinon did not increase the incidence of congenital anomalies (6). In dogs, administration of high doses to the pregnant animal resulted in stillbirth (7). It is possible that reproductive effects of diazinon poisoning may be attributable to maternal toxicity. Available data are not sufficient to determine whether this compound has adverse effects on human development. Insecticides are discussed in detail in the March, 1985, issue of "REPRODUCTIVE TOXICOLOGY, a medical letter", Vol. 4, No. 2.

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1290 ETHANOL CAS 64-17-5

Ethanol (ethyl alcohol) is a common component of many liquid non-prescription drugs and is widely consumed as a recreational drug. Although ethanol consumption in pregnancy has been associated with a variety of abnormalities in the newborn, a clearly defined syndrome of defects has been noted only for regular users of this drug. The fetal alcohol syndrome (FAS) is characterized by the presence of a spectrum of clinical features, including prenatal and postnatal growth deficiency, CNS dysfunction including mental retardation and behavioral abnormalities, a distinctive pattern of facial features (i.e. short palpebral fissures, hypoplastic philtrum, flattened maxilla), and major organ system malformations (1). FAS is likely to occur in the offspring of 30-45% of women who drink at least 5 ounces of absolute alcohol daily (2). As children with FAS age, the facial features become less distinctive, but short stature, microcephaly, behavioral abnormalities, and intellectual deficits persist (27).

It has proven more difficult to define the risk associated with binge drinking and moderate drinking during pregnancy; however, a study in neonatal rats published in abstract suggests that head growth is more impaired by binge-drinking patterns of exposure than by more continual ethanol treatment (3). Maternal self-report of alcohol use during pregnancy was used to identify a 7 point decrement in childhood IQ testing associated with 2 drinks/day (28). Binge drinking, defined as five or more drinks on one occasion, was associated in this study with a 1 to 3 month lag in reading and arithmetic levels at the end of the first year of schooling (28).

It has been suggested that beer drinkers are at greater risk than consumers of other alcoholic beverages for having children with fetal alcohol effects (7). Six beers is equivalent to about 3 ounces of absolute alcohol. Such a daily dose has been associated in some studies with birth weight reduction (4,5), and a significant increase in anatomic abnormalities (5,6). As would be expected from embryologic considerations, the critical period for exposure was in the early first trimester (5,6). In addition to possible unique forms of malnutrition that may be associated with beer drinking, the hypothetical mechanisms for this effect include the hyponatremia produced by the elevated fluid intake with beer consumption and the adverse effects of the subsequent hyponatremia on neural myelination (8).

Maternal alcohol abuse has also been associated with elevated fetal erythropoietin levels (9). It is not clear whether this is a direct effect of ethanol exposure or caused by the toxic effects of ethanol on the placenta, producing fetal hypoxemia (9). Some reports have also suggested that the risk of miscarriage is twice the normal rate in women who drink 1 oz of absolute ethanol two times per week (10). The difficulty of accurately monitoring dose and exposure of a widely available toxicant such as ethanol continues to undermine the strength of many observations regarding the adverse effects of moderate alcohol consumption during pregnancy. Recently composed guidelines for clinicians and public health professionals emphasize that heavy alcohol use during pregnancy (defined as more than two drinks per day) can be reasonably expected to compromise fetal health and development (11). For a more detailed discussion of the older references on this topic, please refer to the August, 1982, issue of "REPRODUCTIVE TOXICOLOGY, a medical letter", Vol. 1, No. 3.

[illegible] of paternal alcohol consumption on the offspring of laboratory animals include decreased litter size, altered birth weight, increased stillbirths and neonatal deaths, increased male:female ratio and behavioral abnormalities (12). Other studies also reported an increased incidence of soft-tissue malformations (13), and an increased susceptibility to Pseudomonas ocular infection (14). Many of these observations have been criticized because they were not based on data that had adequate controls for confounding variables, especially paternal nutrition. In one well-controlled series of mice experiments, paternal alcohol exposure did not have significant effects on offspring (15). Although some case reports have suggested that paternal alcoholism has been associated with poor pregnancy outcome (12), this observation has not been demonstrated in epidemiologic studies (16). One important aspect of the male reproductive toxicity of alcohol was well stated in a quote from Shakespeare: "Drink sir, . . . provokes the desire, but it takes away the performance." (Macbeth, Act II, scene III). Chronic alcoholism in men has long been associated with hypogonadism, impotence, and sperm abnormalities (10-12). Recent estimates suggest that as many as 80% of chronic alcoholic men may experience some degree of testicular atrophy, gynecomastia, infertility, and/or decreased libido (20).

Ethanol reaches levels in breast milk similar to those in maternal blood (21). At maternal blood levels of ethanol of 100 mg/dL (a common biochemical definition of "intoxication"), the nursling would receive 164 mg of ethanol per feeding (22). This dose is similar to 1% of the amount of ethanol in a mixed drink. On a mg/kg basis, this dose to the baby is comparable to ingesting one-quarter of a typical alcoholic beverage. One recent study found impaired motor development (but not mental development) in the one year old infants of mothers who consumed 4 or more drinks per day, and breastfed daily (23); however, this study has been criticized on methodologic grounds. There has been a case report of an illness like Cushing's syndrome associated with breast milk exposure to ethanol (24). In addition, women who drink heavily may experience an inhibited milk-ejection reflex (25). Finally, ethanol may change the taste of breast milk, a possibility suggested by a change in milk odor assessed by a panel of adults (26). A decrease in milk consumption associated with taste alterations was proposed by the authors of this study but evaluated only with a single acute feeding study. It is not known whether ingestion of moderate amounts of ethanol on a regular basis results in altered infant nutrition.

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1276 LINDANE **CAS 58-89-9**

Lindane is the gamma isomer of hexachlorobenzene, used topically in a 1% solution (Kwell) for the treatment of lice and scabies, and in higher concentrations as a component of insecticides. Animal studies in a variety of species, including mice, rats, hamsters, rabbits, cows, and pigs, have not associated this compound with teratogenic effects (1-6). A variety of in vitro tests have produced positive data on the genotoxicity of lindane (24). An increase in chromosomal aberrations and sister chromatid exchange in agricultural workers exposed to pesticides including lindane has also been reported, but human genotoxicity caused specifically by lindane has not been demonstrated.

Investigations regarding the possible effects of this compound on the developing immune system in rodents have been undertaken, but the absence of consistent effects at various dose levels limits the possible interpretation of the available data (22).

At least 10% of the topically applied dose of lindane is absorbed and can be recovered in the urine (7). Dermal absorption is increased by conditions that compromise the integrity of the skin (8) and in premature babies, in whom dermal tissues are not fully developed (9). Once absorbed, lindane is transferred across the placenta (10). Theoretical concerns regarding fetal exposure to lindane include the possibility that this compound may possess mild estrogenic properties (11) or alter fetal steroid metabolism by inducing hepatic microsomal enzymes (10,25). Despite the widespread use of this drug in the treatment of lice and scabies for more than 40 years, clinical reports supportive of these concerns were not located. Intoxications following the use of topical 1% lindane are associated with excessive use and overexposure to the product (12). Symptoms induced by overexposure include restlessness, muscle spasms, convulsions, and coma. Concern associated with these possible toxic effects and the relatively low level of effectiveness of lindane as a pediculicide (13) have led some observers to recommend the use of pyrethrins with piperonyl butoxide as the preferred treatments of lice during pregnancy (14,15,23).

Animal experiments indicate that lindane is a testicular toxicant in large doses. Male rats injected ip with lindane at 4 or 8 mg/kg for 10 days undergo a severe degeneration of testicular tissues (17). Similar adverse effects were reported in rats that were force-fed (21) or received testicular injections of lindane (18) and in mice fed a diet containing 500 ppm lindane (19). No reports of testicular toxicity in humans were located.

Lindane is concentrated in breast milk (20). The dose received by an infant through the milk has been estimated to be comparable in size to the amount that the infant might receive if the compound was applied topically to the infant's skin (15).

Such doses are not normally associated with adverse effects.

Lindane was discussed in the May, 1983, issue of "REPRODUCTIVE TOXICOLOGY, a medical letter", Vol. 2, No. 3.

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1069 COUMARIN DERIVATIVES **CAS NONE**

Coumarin derivatives (warfarin, dicumarol, phenindione, acenocoumarol, diphenadione, phenprocoumon, anisindione) are orally active anticoagulants. Warfarin (Coumadin) is by far the most widely used agent. The other members of this group are *generally more toxic and difficult to use safely. Phenindione*, although marketed, has been associated with such severe side effects that specific recommendations against its clinical use have been made (1).

The coumarin anticoagulants were at one time considered unique among agents that cause birth defects in humans because of the lack of an animal model (2,3). There has been the identi-

fication more recently of a rat model (4), which is discussed below. The major anomalies associated with first trimester human exposures to warfarin (the fetal warfarin syndrome) are skeletal defects, which include nasal hypoplasia and stippled epiphyses (5,6). The stippling of the epiphyses is a radiologic finding that apparently resolves as the epiphyses calcify; however, limb hypoplasia, primarily involving the distal digits, may be seen in up to one-third of children with the warfarin embryopathy (7). The nasal hypoplasia may be severe, and if associated with choanal atresia may require intubation for ventilatory support. Other abnormalities that have been associated with the warfarin embryopathy are central nervous system and ophthalmic anomalies, hearing loss, intrauterine growth retardation, and, in a small number of cases, congenital heart disease (7).

A proposed mechanism by which the coumarin anticoagulants induce bone and cartilage abnormalities involves the inhibition of vitamin K epoxide reductase by these agents (16). A rat model of maxillonasal hypoplasia and other skeletal anomalies induced by warfarin demonstrates that the anomalies are not prevented by co-administration of vitamin K (4). The authors suggest that the anomalies are most likely associated with extrahepatic vitamin K deficiency, which prevents the normal formation of bone matrix proteins. Additional case reports suggest that coumarin exposures during the first trimester may induce malformations of the central nervous system, eye, and jaw without causing the other stigmata of warfarin embryopathy (17,18). Two case reports associating 1st trimester warfarin exposure and fetal diaphragmatic hernia are now available (19,20). Another recent case report has suggested that kidney abnormalities and malformations of the urinary tract may be associated with maternal warfarin exposure (17).

Women with a history of thromboembolic disease or artificial heart valves often require long-term anticoagulant therapy. This patient population is likely to experience a high risk pregnancy no matter what class of anticoagulant is prescribed (8-10), although some reports suggest that obstetric risks may be less when heparin is used (9). In addition to increased pregnancy risks in women receiving anticoagulants, normal ovulation is more likely to induce a corpus luteum hemorrhage, and some clinicians recommend the suppression of ovulation to avoid this possibility (11). The frequency of adverse pregnancy outcome in this population includes 12-15% stillbirths, a prematurity rate as high as 20%, and an incidence of normal births of only 60 to 70%. Although there is general agreement that heparin, and perhaps dextran 70, are the anticoagulants of choice for pregnant women with thromboembolic disease (12,13), these agents may not be as effective in controlling thrombotic complications in patients with prosthetic heart valves (14). Thus, for such patients, the use of coumarin anticoagulants has been recommended by some authors, except during the 6th through 12th week of gestation, when warfarin teratogenicity is most likely (8,14,15). It should be recognized, however, that developmental toxicity associated with second and third trimester exposure has been described (see below).

Fetal coumarin exposure after the first trimester also increases the risk of central nervous system defects, probably caused by microhemorrhages in neuronal tissues (8,14,16,28). Two case reports have described massive intracranial hemorrhages that proved fatal to warfarin exposed fetuses (21). The authors of these case reports suggest that the fetus is uniquely susceptible to warfarin induced hemorrhage because of low stores of vitamin K and physiologically low levels of vitamin-K-dependent pro-coagulant factors (21). Because of possible developmental toxicity of coumarin anticoagulants during all stages of pregnancy, some clinicians consider the use of the coumarin anticoagulants contraindicated during pregnancy (12). There is, however, a single case report of "mini-dose" warfarin (1 mg/day) used from 32 weeks of pregnancy to term, in which fetal blood showed no evidence of an anticoagulant effect (22), and a series of 20 births in women exposed to 5 mg/day or less of warfarin in which none of the infants had signs of warfarin embryopathy (23).

Phenindione is the only member this group of anticoagulants known to be contraindicated in breastfeeding (24). There has also been a suspected problem with bleeding in babies exposed to ethyl biscoumacetate in breast milk (25). Phenindione and a metabolite of ethyl biscoumacetate are secreted in milk in an active form that can impair blood coagulation in the newborn (19,20). Warfarin levels in the milk of women on therapy are undetectable (26,27).

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2167 ETHYLENE GLYCOL MONOMETHYL ETHER
CAS 109-86-4

Ethylene glycol monomethyl ether (EGME, Methyl Cellosolve) is 2-methoxyethanol, a glycol ether solvent with a number of industrial applications. It is also a component of some nail polishes and polish removers. The glycol ethers were discussed in the July, 1985, issue of "REPRODUCTIVE TOXICOLOGY, a medical letter", Vol. 4, No. 4. Of these agents, EGME and the related ethylene glycol monoethyl ether (EGEE) appear to be the most toxic to reproductive processes.

An early evaluation of glycol ether reproductive toxicity used a short-term test in pregnant mice given doses intended to be minimally maternally lethal. EGME was viewed as requiring high priority for further testing because a dose of 1400 mg/kg prevented the birth of any viable litters in the face of a maternal mortality of only 14% (35). EGME is embryotoxic and teratogenic in mice and rats (1-11). Although multiple skeletal and visceral anomalies as well as reduced fetal weight and viability have been seen in mice (1), paw malformations, particularly involving the digits, appear characteristic of EGME embryotoxicity in this animal (2-5). There is evidence that such malformations are mediated by cell death in limb bud mesenchyme and, to a lesser extent, ectoderm (3). case reports and animal studies indicate that EGME is also toxic to the hematopoietic system, causing mild macrocytic anemia and leukopenia (37-39). Similar effects, impairing fetal immunity, have also been observed in mice (39).

It is believed that the teratogenic effects of EGME are mediated by its primary metabolite, methoxyacetic acid (MAA) (2,34), although it is possible that subsequent metabolites may also produce malformations (33). Rats exposed antenatally to EGME may be born with cardiac malformations and may show electrocardiographic evidence of abnormal conduction that does not correlate with the presence of gross anomalies (6,7). Polydactyly has also been associated with EGME exposure of rat embryos (10). Teratogenic effects of EGME in rats are seen at doses that do not cause overt maternal toxicity (8,9,11). As in mice, there is compelling evidence that MAA is the agent directly responsible for EGME teratogenicity in rats (10,12). EGME treatment of pregnant rats has been associated by one group of investigators with abnormalities of behavior and brain neurotransmitter levels in the offspring (13,14). The teratogenic effects of EGME in rats can also be produced by a single dermal dose (28). The embryotoxicity of EGME has also been demonstrated in cynomolgus monkeys (29).

EGME treatment of male rabbits, rats and mice has been associated with testicular toxicity (15-26,32,36). This is manifested by a reduction of testicular size due to degeneration of the tubules (20,32). The germinal epithelium appears particularly sensitive and delineation of the most sensitive cells in the spermatocyte series of the rat has been reported (17,22,23). Ultrastructural studies have shown that the Sertoli cell may also be subject to EGME-associated damage (16). EGME testicular toxicity in the rat is associated with infertility; however, some recovery of normal testicular histologic appearance and of fertilizing ability may occurs several weeks after exposure (21,26). As is the case for the embryotoxic effects of EGME, there is convincing evidence that testicular toxicity in the rat is mediated by MAA (18,19,24).

We have been unable to locate references on human reproductive effects of EGME. Although there are no data, it is reasonable to assume that a sufficiently high dose of EGME might have adverse reproductive effects in humans. In one case report, a woman who cleaned laboratory glassware and counter tops with ethylene glycol monomethyl ether acetate (which is readily metabolized to EGME) during two pregnancies gave birth to sons with hypospadias and bifid type scrotums (31). Other than solvent exposure, no other factors, such as family history, could be identified as possible cause of these anomalies. This single case does not, however, demonstrate a causal association between this solvent exposure and the reported congenital defects. In a paper reporting workplace air levels of this agent in semiconductor manufacturing plants, animal data and standard "safety factors" were used to estimate that employees would not be at risk for reproductive or developmental toxicity (27). One study did report finding no measurable amounts of EGME in the blood of exposed workers (30). This study has been criticized for failing to look for the longer lasting toxic metabolite, MAA (29).

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OIL FIRES

AND

SOIL SAMPLES

1401 ARSENIC **CAS 7440-38-2**

Arsenic is a toxic metal found as an environmental pollutant. At one time, the treatment of syphilis included organic arsenicals. Some commonly encountered inorganic arsenic salts include the trivalent sodium arsenite and the pentavalent sodium arsenate. Arsine (AsH3) is an arsenical that is used as a gas in manufacturing semiconductors (see Arsine #2799).

Both the inorganic arsenic salts and the organic arsenicals cross the human placenta and have been shown to accumulate in the placenta and the fetus in experimental animals (1-3). The inorganic arsenic salts are cytotoxic and genotoxic in a number of assays, with the trivalent arsenite displaying more toxic activity than the pentavalent arsenate. Arsenic and its salts are teratogenic in hamsters (4-7), mice (8,9), and rats (10,11). Many affected animals have neural tube defects. A small study of arsenic in pregnant sheep showed no adverse effect on the offspring (12); however, the use of only four animals in the study limits the conclusions permissible from this report. Gestational exposure to arsine gas at concentrations up to 2.5 ppm did not produce signs of developmental toxicity in mice or rats (15).

There have been five reported cases of human arsenic poisoning during pregnancy (13). None of the offspring showed evidence of adverse effects; however, none were apparently exposed prior to the second trimester. A case of neonatal death after arsenic poisoning of a pregnant woman has been reported (14). Although arsenic cannot be excluded with certainty as a cause of this adverse outcome, it appears likely in this instance that prematurity was responsible for the infant's death. There are no data on which to base an estimate of first trimester arsenic toxicity in humans; however, the general toxicity of this metal and the data from animals experiments amply support the recommendation that exposure of pregnant women to this material be minimized.

There is a continuing debate on whether the adverse effects of arsenic on reproduction are mediated by maternal illness rather than by direct toxicity of the metal to the embryo/fetus (16). If maternal illness does mediate the toxicity of arsenic on human development, low-dose or transient exposure of pregnant women to arsenic would not be expected to result in reproductive hazard.

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3075 BENZO(a)PYRENE **CAS 50-32-8**

Benzo(a)pyrene (BP) is a polycyclic aromatic hydrocarbon encountered as an environmental pollutant. It is mutagenic and carcinogenic. Exposure of chick embryos to BP results in retarded growth, edema, and limb abnormalities (1). A study in pregnant rats found 0.1% BP in the diet to cause resorptions and stillbirths but no apparent increase in malformations (2). BP is known to cross the placenta in rodents, producing evidence of adduct formation in fetal tissues after maternal treatment (3,4). Quantitative estimates of placental transfer differ; reports show both low (5) and high (6) amounts of BP or its metabolites in fetal mice. Placental transfer in guinea pigs has also been documented (7).

The embryotoxicity of BP appears due to biotransformation products rather than to the parent compound. In mice, a BP metabolite produces a high incidence of embryolethality with malformations in surviving fetuses (8). Abnormalities include exencephaly, ventral wall defects, and phocomelia. A BP metabolite is also responsible for toxicity to preimplantation mouse embryos resulting in impaired implantations (9). The ability to biotransform BP is genetically determined by the inducibility of aryl hydrocarbon hydrolase (AHH). Strains of mice with inducible AHH show more enzyme activity when exposed to PAHs (including BP) than do noninducible strains. This has been demonstrated to produce a difference in the genotoxicity seen in mouse embryos after maternal treatment with BP (10). The locus that determines AHH inducibility in mice is known as the Ah locus. Embryotoxicity from BP will be produced if the embryos bear Ah loci conferring inducibility. If the embryos do not have inducibility genes, BP toxicity may still occur if the mother is inducible. Under these conditions, the embryotoxicity of BP will be altered by the route of administration, because oral treatment permits greater access of the chemical to the mother's liver (11).

BP induction of tumors appears, at least under some experimental circumstances, to be due to heritable changes in genetic material. Treatment of pregnant mice with BP results in an increase in lung adenomas in four subsequent generations of animals (12).

Although direct embryotoxicity of BP or its metabolites is likely, resorptions and fetal wastage in the rat have also been hypothesized as due to toxic effects on the mother's genital tract. In a pseudopregnant model, BP treatment decreases uterine weight and cyclic nucleotide levels (13). Direct toxicity to the ovary has also been shown in mice (14,18) and the ovary itself appears capable of metabolizing BP to its toxic metabolites (15).

In male rats, BP minimally inhibits DNA synthesis in the seminiferous tubules and inhibits the progression of spermatocytes through meiosis (16,17).

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1373 CADMIUM **CAS 7440-43-9**

Cadmium is a metal found as an industrial and environmental contaminant in many parts of the world. In addition to the various amounts of cadmium that may be found in food, cigarette smoking has been shown to significantly elevate the amount of cadmium in the body (1,2). Smoking one pack of cigarettes results in the inhalation of 2 to 4 μg of cadmium (3). There is no known biologic function for this metal and it is toxic to many tissues.

Cadmium has been shown to be teratogenic or embryotoxic in several animal species (4-6). In some models (such as the rat), cadmium shows prominent toxicity for the placenta (7,8), and has been repeatedly associated with fetal growth retardation (9,10). Human developmental toxicity of cadmium has not been established; however, a number of in vitro studies suggest that this metal is likely to be toxic to the human placenta (11,12). The increase in placental cadmium levels found in women who smoke (13,14) and the experimental association of cadmium with decreased placental function have raised the possibility that cadmium is one of the factors involved in the relationship between low birthweight and maternal smoking (15,16). Some investigators are pursuing the possibility that zinc supplements may be useful in reducing the decreased birth weight associated with smoking (15). This approach assumes that elevated levels of placental cadmium displace placental zinc, creating a relative deficiency of zinc, and thereby impairing placental function (see also: Zinc, #1314).

Cadmium occurs in low levels in breast milk (17,18) and these levels may be significantly elevated if the mother or father smokes (19,20). The subject of cadmium developmental toxicity is reviewed in the May, 1986, issue of "REPRODUCTIVE TOXICOLOGY, a medical letter", Vol. 5, No. 3.

A number of animal experiments have investigated the toxicity of cadmium on male reproductive function (21,22). In high doses and after chronic administration cadmium produces vascular changes and ischemic necrosis in the testes (21). Recently, single low dose studies have indicated that cadmium can have selective effects on sperm formation, impairing the release of sperm from the seminiferous epithelium in the rat (23). Also, at low doses that do not interfere with testicular function, cadmium exposure in rats has been associated with an increased incidence of prostate tumors (27). At present, reports on testicular and endocrine function in men occupationally exposed to cadmium are quite limited, and no clearly identified testicular toxicity has been demonstrated in these workers (24-26).

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PI-N-BUTYL PHTHALATE

(not found)

2356 HEXACHLOROBENZENE CAS 118-74-1

Hexachlorobenzene is a fungicide present in many communities as an environmental pollutant. In spite of concerns about the toxicity of polyhalogenated aromatic compounds, this agent has not been shown to be genotoxic (1). Hexachlorobenzene has been shown to cross the placenta in a number of species (2-8) including humans (9). Treatment of pregnant rats and mice with hexachlorobenzene produced an increased incidence of enlarged kidneys in the offspring (10). Increased perinatal mortality and abnormal immune system development have also been reported in mice pups after treatment of the pregnant dam (11,12,22). Negative teratology studies have been reported as well in mice (13) and rats (14). In these reports, abnormalities in the offspring were not seen in the absence of maternal toxicity. Human teratogenicity studies with hexachlorobenzene have not been reported. An Italian group reported the observation that women with miscarriages did not have higher blood levels of this agent compared to women with successful reproductive histories (15). This observation offers little insight because hexachlorobenzene was not expected to be a predominant cause of human miscarriage, and the absence of this compound in the blood stream of most women who miscarry would be expected.

One area of developmental toxicity of particular concern is that associated with hexachlorobenzene excretion in breast milk. Hexachlorobenzene is highly lipid soluble and appears in breast milk in a number of tested species, including humans (2,4,9,16). Milk excretion has been shown to be a quantitatively important route for elimination of hexachlorobenzene from treated rodent and ferret dams (2,17). This exposes the suckling animal to large amounts of hexachlorobenzene, even when maternal exposure occurred prior to birth. The hexachlorobenzene burden of mice pups, in fact, is greater after lactational exposure than after transplacental exposure (4) and may be responsible for the increased perinatal mortality seen in this species after treatment of the pregnant animal (7,18). In one human study, milk levels of hexachlorobenzene from environmental contamination were measured at 0.08 to 0.2 ppm, although one sample in this group of 100 women was as high as 0.7 ppm (19). In another study, milk levels were as high as 0.23 ppm (20). Levels in the adipose tissue of breastfed children correlated with the amount of mother's milk consumed. The most dramatic exposure of humans to hexachlorobenzene occurred in Turkey during the late 1950s when the fungicide was added to wheat seedlings. More than 3000 individuals developed hexachlorobenzene-induced porphyria and a dermatologic abnormality called kara yara ("black sore"). Breastfed children of the era often developed a fatal condition called pembe yara ("pink sore"). A follow-up study performed 20 to 30 years after exposure found milk from exposed women still to contain hexachlorobenzene at a mean level of 0.29 ppm with a level as high as 2.8 ppm in one subject (21,23). Levels of hexachlorobenzene in cows milk at the same time were 140 times less.

Effects of hexachlorobenzene on fertility have been less extensively investigated. In a chronic feeding study in rats, up to 40 ppm in the diet did not adversely influence reproductive parameters (22). There is more recent concern, however, that the primate ovary may be sensitive to hexachlorobenzene toxicity. Female moneys fed up to 10 mg/kg/day for 13 weeks showed increased variability in menstrual cycle length with a decrease in luteal phase progesterone (24). Electron microscope evidence of ovarian epithelial damage was also evident at these doses (25,26). Hexachlorobenzene toxicity to the monkey primordial oocyte occurs independent of other toxicity of this compound for the animal, and is likely to be a specific gonadotoxic effect (27). The implications of these data for reproductive function in women have not been established as yet; however, hexachlorobenzene has been identified in the follicular fluid of women undergoing IVF (28).

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3844 HEXACHLOROCYCLOPENTADIENE CAS 77-47-4

Hexachlorocyclopentadiene is an intermediate in the synthesis of certain pesticides and flame retardants. Administration to pregnant mice and rabbits at up to 75 mg/kg/day did not produce an increase in adverse outcome in the offspring (1). Maternal toxicity was noted in the rabbits but not the mice at the top dose. In a short term (Chernoff-Kavlock) test in pregnant mice, 45 mg/kg did not cause a reduction in fetal weight or viability (2). Observation of the offspring into adult life did not reveal any reduction in growth or viability or problems with reproducing an F1 generation (3).

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2829 HEXACHLOROETHANE CAS 67-72-1

Hexachloroethane is also called carbon hexachloride, perchloroethane, and ethylene hexachloride. It is a pesticide that has appeared under the names Avlothane, Distropan, Falkitol, Fasciolin, Mottenhex, and Phenohep. This agent is capable of binding cellular macromolecules (1) and has produced genotoxic effects in yeast (2). Such data are used primarily to assess possible oncogenicity. We have been unable to locate references on possible reproductive effects of this agent.

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1123 MERCURY CAS 7439-97-6

Mercury has not had a long history as a reproductive toxicant. At the turn of the century, the use of mercurial salts to treat syphilitic mothers was frequently associated with abortion, but it was not clearly established whether the mercurials or the syphilis played a primary role in the miscarriages (1). In the mid-1960s, mercury toxicity became highly publicized after an outbreak of cerebral palsy and microcephaly in newborns of the fishing village of Minimata Bay, Japan (2,3). These abnormalities were caused by methyl mercury contamination of the fish in the bay. Since that incident, fetal intoxication with organic mercurials has been termed Minimata Disease. Similar intoxications also occurred in Iraq after seed grain contaminated with methyl mercury was mistakenly used to make bread (4,5). In this population infants exposed in utero also demonstrated psychomotor retardation and cerebral palsy. Similar congenital neurologic

disease has been reported in other instances of methyl mercury food contamination (6,7). Experimental animal models of organic mercury embryotoxicity have associated prenatal exposures with a variety of different birth defects, many not seen in human case reports, but the neurologic effects are generally consistent with the human experience (7-14).

The marked potential for reproductive toxicity of organic mercurials such as methylmercury does not appear to apply to inorganic mercury. Inorganic mercury is lipophilic, so mercury vapor is more readily distributed to brain tissue than mercuric salts (15). Inorganic mercury does not cross the placenta readily, however (16). Dental personnel working with mercury-containing amalgams may be chronically exposed to considerable amounts of mercury vapor. In spite of poor placental passage, one study found levels of mercury in the placentae and fetal membranes of exposed pregnancies in dental assistants to be about twice those of nonexposed controls (17). Available reports have not indicated a mercury-associated increase in birth defects or neurologic sequelae in the offspring of dentists or their assistants (18). One study in Denmark (19) also failed to show an increase in spontaneous abortions among dental assistants compared to a control population. Another study in female dental assistants sought to identify a reduction in fertility associated with mercury exposure but was unable to do so (20).

There have also been investigations into the possible effects of paternal exposure to mercury and risk of spontaneous abortion (21,22). Although both of these reports included suggestive data of increased risk of miscarriage among the pregnancies fathered by exposed men, neither study was able to control adequately for possible direct effects of maternal mercury exposure or other high risk occupational exposures (23), leaving this question unsettled.

Inorganic mercurial ointments, such as red or yellow mercuric oxide, may also be associated with the topical absorption of significant amounts of mercury (24). We have not identified any reports on possible adverse human reproductive effects from mercury absorbed in this manner. Although the release of mercury from amalgam ("silver") dental fillings has been demonstrated repeatedly in the past (25,26), a more recent study in sheep utilized radiolabelled mercury to monitor the release of this element from dental amalgam fillings and transfer to the fetus (27). The highest fetal concentrations of mercury from the amalgam fillings were found in the liver and pituitary gland. The transfer of amalgam mercury from the fillings to the fetus by way of breast milk was also demonstrated. Neither maternal nor fetal toxic effects were associated with mercury released from the large quantities of dental amalgam that were used in these studies, but the authors of this report suggest that the use of mercury containing amalgams for tooth restorations be avoided during pregnancy and childhood to limit what may be an unnecessary exposure to mercury during early development of the central nervous system (27). Although this report was cited in the literature reviewed by a Public Health Service committee that reviewed the safety of dental amalgam, this group concluded: "available data do not support such a restrictive policy (32)." Since the late 1980s, both the German and Swedish public health agencies have recommended that procedures involving amalgam restorations not be done during pregnancy (32).

Pregnant rodents exposed to very high concentrations of mercury vapor or fed inorganic mercurials show an increase in stillbirths, congenital anomalies, and neonatal mortality in their offspring (28,29). Teratogenic effects are generally minor and may be attributable to general maternal or fetal toxicity rather than to a specific defect in organogenesis. A preliminary report on the daily exposure of pregnant squirrel monkeys to mercury vapor has described a variety of adverse effects, including abortion and neonatal mortality, reduced brain weights, and structural abnormalities (16). Details on the maternal toxicity of the mercury exposure were not described, however, and it is not possible to interpret the offspring data without more information on maternal effects. There are two case reports of women exposed chronically to high levels of inorganic mercury during pregnancy (30,31). In both instances, the offspring appeared to be normal.

Safe levels of mercury during pregnancy have not been established although suggested guidelines are that environments have a mercury vapor concentration less than 0.01 mg/m3. Organic mercurials should be avoided entirely and some authorities have suggested limiting the intake of fish to no more than 350 g/week due to concerns about environmental contamination with organic mercurials (7).

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1153 NICKEL CAS 7440-02-0

Nickel is an element commonly used in its metallic form to manufacture alloys, including stainless steels. Nickel salts are also widely used in industry as chemical catalysts as well as pigments in inks and paints. Nickel is also found in coal fly ash, the particulate environmental pollutant generated during combustion of coal (1).

The use of radionuclides of nickel has demonstrated that this metal can cross the placenta and accumulate in the fetus in late gestation (2). The nickel content of human fetal tissues suggests that comparable nickel transfer also occurs during human development (2). In animal experiments, gestational exposures to a variety of nickel salts have been associated with congenital abnormalities and growth retardation. In mice, nickel chloride administration during gestation can increase the incidence of anencephalia, exencephaly, cerebral hernia, open eyelid, cleft palate, micromelia, and skeletal anomalies (3). High concentrations of nickel chloride in the drinking water of rats increased stunting but did not produce other congenital defects (4,5). The intraperitoneal injection of nickel chloride on gestational days 8 or 12 was associated with an increased incidence of fetal hydrocephalus, hydronephrosis and poor ossification (6). Nickel acetate administration was associated with multiple malformations in hamsters (7). This nickel salt was also teratogenic when given to mice during the preimplantation period (8). Nickel carbonyl, the most toxic nickel salt, is a well-studied carcinogen (2). This nickel compound can selectively induce ocular abnormalities in fetal rats (9). In all of the preceding animal experiments the exposure to nickel salts was generally high and maternal illness (although not specifically reported) was a possible contributor to some of the adverse fetal effects. Caution must be used in applying these results to estimates of the reproductive risks associated with human nickel exposures. Unfortunately, only fragmentary and incomplete data are available on the pregnancy status and follow-up for women who were occupationally exposed to nickelous compounds (10). Thus, there is little basis for estimating the human pregnancy risks that may be associated with exposures to nickel and its salts. In some industrial settings, the exposure of fertile females to nickel carbonyl has been stringently avoided because of the demonstrated toxicity of the therapeutic agents used for treating carbonyl poisoning (10). One report that has been cited to suggest a possible association between human nickel exposure and adverse fetal outcome is a case report of a single malformed infant who died shortly after birth and was found to have unusually high nickel levels in bone and kidney (11).

The normal nickel content of human milk has been estimated as 1.2 μg/liter (12). At high levels, nickel can inhibit prolactin secretion and alter the quality of rat milk (13). Although a theoretical possibility, there are no clinical reports indicating that maternal nickel toxicity has interfered with lactation or infant growth.

Nickel salts, including the chloride, nitrate, and sulfate, have shown genotoxity in mammalian test systems (14). These included the induction of sperm head abnormalities in mice. Nickel salts are believed to be genotoxic through the production of DNA crosslinks and single strand breaks produced by divalent nickel ion (15). Whether this mechanism is relevant in human reproduction is not known.

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1420 PENTACHLOROPHENOL CAS 87-86-5

Pentachlorophenol is used as an herbicide, insecticide, and wood preservative. Because of its chemical stability, pentachlorophenol is a widespread environmental pollutant. One observer has estimated that 85% of all humans excrete pentachlorophenol in their urine (1). The placental transfer of pentachlorophenol has been demonstrated in rats (2). When administered to pregnant rats, pentachlorophenol was associated with decreased fetal body weight and crown-rump length (3-5) but it did not produce teratogenic effects in mice and hamsters (6,7). Pentachlorophenol has been found in the semen of male workers and has been associated with chromosomal abnormalities in the lymphocytes of such workers; however, male-mediated reproductive effects have not been described (8). We have been unable to locate any studies on possible adverse effects of this agent on human pregnancy.

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1273 TOLUENE CAS 108-88-3

Toluene (methylbenzene) is a volatile, aromatic hydrocarbon, commonly used in industry, and found in the home in some spray paints, glues, and lacquers. For safe use in occupational settings, toluene in air should not exceed 100 ppm (1). Toluene is sometimes intentionally inhaled to produce an acute intoxication characterized by light-headedness, dizziness, and temporary loss of consciousness. Typically, this form of toluene abuse is performed using a sock or rag which is coated with spray paint (usually clear or gold) and placed over the nose and mouth for inhalation. Chronic toluene abuse (consumption of one to four 16-oz cans of spray paint per day) has been associated with a constellation of toxic symptoms, including muscle weakness, gastrointestinal complaints, neuropsychiatric abnormalities with peripheral neuropathy (3), and severe renal tubular acidosis (4).

In adults, toluene is metabolized to hippuric acid, but as much as 50% of inhaled toluene may be excreted unchanged in the urine. Toluene crosses the placenta, but is not converted to hippuric acid by the fetus or neonate (4). High doses of toluene cause chromosomal damage in rat bone marrow cells, but no consistent marrow effects in humans have been seen with this compound (2).

Animal reproduction experiments show impaired growth of mother and fetus and fetal skeletal anomalies after exposure to large doses of toluene (5,6). Behavioral effects of toluene in mice exposed pre- and postnatally have been described (7). Two children with multiple malformations were born to mothers who worked as shoemakers and were chronically exposed to toluene and trichloroethylene, used in a soling solution (8). There are a growing number of case reports on congenital defects in children born to mothers who had intentionally inhaled toluene in high doses throughout pregnancy. In one study, five women in the third trimester developed severe renal tubular acidosis from paint sniffing and subsequently gave birth to five infants, three of whom were growth-retarded at birth; two showed craniofacial anomalies, and neonatal hyperchloremic acidosis (4). Microcephaly, CNS dysfunction, growth deficiency and craniofacial anomalies, similar to those seen in fetal alcohol syndrome, were also described in five children born of women who had sniffed toluene during their pregnancies (9,11). Cerebellar dysfunction has also been reported in the child of a woman who chronically abused toluene (3). Another report included 30 pregnancies in 10 women who sniffed glue or paint (12). There were 3 miscarriages, 3 voluntary abortions, and 3 normal pregnancies that antedated toluene abuse. In the remaining 21 pregnancies, preterm labor was a common complication (86%), and preterm delivery occurred in more than half. Maternal renal tubular acidosis and associated electrolyte abnormalities were noted and, among infants, intrauterine growth retardation, dysmorphic facies, and increased tone were common. Developmental delay occurred in two-thirds and microcephaly in one-third of the children available for follow-up.

Only one case report involving possible effects of toluene on male reproduction was located. Dizziness, headache, tinnitus, insomnia and weight loss developed in two male workers after repeated exposures to mixtures of solvents that included concentrations of toluene greater than 1000 ppm; one worker also complained of impotence (10).

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1220 XYLENE **CAS 1330-20-7**

Xylene (dimethylbenzene, xylol) is the name given to three isomeric compounds. These are commonly encountered solvents used in paints, lacquers, and adhesives. Inhalation of xylene vapor is the most common route of exposure. Some absorption of the liquid through the skin can occur. Xylenes have been shown to cross the placenta in mice (1), rats (2), and a small number of human subjects (3). Xylenes may be genotoxic (1) and mutagenic effects have been described experimentally with xylenes as well as with similar solvents (4).

A number of original reports and reviews of xylene teratogenicity studies in rodents (chiefly rats) conclude that these compounds may be fetotoxic but this may be due to maternal toxicity from the chemicals. Although minor skeletal anomalies have been described in the offspring of xylene-exposed rats, no significant increase in birth defects has been attributed to xylenes (5-11). The same conclusion is predicted by the hydra assay, which examines the relationship between doses of agents toxic to developing organisms compared to doses toxic to adult organisms. In this assay, xylenes do not appear to be developmental hazards (12).

There are reports of adverse human pregnancy effects associated with exposure to organic solvents, including xylenes (7). Among these is a well-known collection of 5 cases of sacral agenesis in which antepartum exposure to solvents had occurred (13). One of these cases included xylene exposure. No conclusion is possible from this report, the results of which have since been modified by the original author (7). Based on animal experiments and available human experience, low level exposure to xylenes is considered unlikely to cause harm to human reproduction (7,14).

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