

Chemical Exposures and Human Fertility

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Introduction: In recent years scientists have become increasingly aware that both naturally occurring and human-made chemicals can disrupt reproductive function in wildlife and experimental animals (Colborn, et al., 1993). With increased awareness there has been a parallel increased concern at all levels of society that exposure to environmental toxicants can have adverse effects on human fertility. Indeed, there is a perception that the prevalence of human infertility is increasing. The purpose of this article is to provide the reader with a critical assessment of the extensive literature pertaining to the association between exposure to chemicals such as dietary factors and environmental contaminants, and impaired human fertility. It is beyond the scope of this article to provide a detailed review of all of the chemicals that have been shown to have reproductive effects in animal or cell culture experiments. Therefore, we will provide the reader with examples of the evidence for potential adverse effects on reproductive function for some commonly encountered chemicals.

The endocrine system and reproductive endocrinology: A brief introduction to the endocrine system and reproductive endocrinology is essential to understand how chemicals can produce harmful effects in humans. Typically the endocrine system is composed of several brain regions (pineal and hypothalamus) and distinct glands (pituitary, thyroid, pancreas, adrenal, ovary, testis, and placenta) that produce both chemical messengers called *hormones* that are either proteins or steroids. Hormones produced by endocrine glands are secreted into the blood stream and direct the activity of cells in target tissues located elsewhere in the body. In general hormones of the endocrine system regulate metabolism, growth, development, stress responses, and reproductive function. Member glands of this system respond to changes in our physical (temperature and radiation) and chemical environment by making and releasing hormones that function to

maintain homeostasis (maintain body functions in balance) and coordinate the function of cells throughout the body. Protein and steroid hormones produced by glands of the endocrine system including the ovaries and testes are precisely regulated to deliver signals that govern everything from the development of sperm and eggs, the ovarian and menstrual cycles, development of the fetus to coordination of growth, metabolism, and temperature regulation in adults. While endocrine glands produce many hormones, cytokines and growth factors, the principle reproductive hormones are the protein hormones: luteinizing hormone (LH); follicle stimulating hormone (FSH); and the steroid hormones: estradiol (E₂); progesterone (P₄); testosterone (T); and dihydrotestosterone (DHT).

In recent years, animal experiments have demonstrated that chemicals that either compose the foods in our diet or contaminate them can: (1) act like the steroid hormones (Markey et al. 2001; Olea et al. 1996; Soto et al. 1995; 1994), (2) increase the production or metabolism of hormones (Chedrese and Feyles, 2001; Crellin et al. 2001; Andersen et al. 2002; Sanderson et al. 44-54; Sanderson et al. 2000; 2002), or (3) block the hormone signals at target tissues (Kelce et al. 1994; 1995; 1997). However applying results of animal experiments to humans is not as straightforward as it would seem. Although experimental animals like humans possess an endocrine system for signaling, the hormones and cellular functions they regulate are not exactly alike across species. For example, menopause in women is known to result when the number of eggs remaining in the ovaries falls below a threshold of approximately 1,000 and is associated with a decline in circulating estrogen (Lamberts et al. 1997; Stanford et al. 1987; O'Keane 1996). In contrast, in the Sprague Dawley rat, a species widely used in animal experiments, reproductive senescence or failure results from changes in the hypothalamus and is associated with an increase in circulating estrogens. Consequently, despite findings of adverse

reproductive effects in experimental animals and evidence of potential hazard to human reproductive health uncertainty still remains. Approaches used to reduce uncertainty include mechanistic studies in animals and tissue culture, epidemiological studies to determine if similar effects are found for people with occupational exposures, and quantification of exposure; measurement of chemicals in food, water, air, or body fluids (Chapin et al. 1998). While many animal studies have successfully documented potential hazards there are very few studies that have documented human exposure or explored the link between exposure and potential adverse health effects.

Chemical exposure and reproductive function: On a daily basis people are exposed to vast numbers of chemicals through food, air and water. While some chemical exposures are intentional others are inadvertent, unwanted, and potentially hazardous to human health. Wanted exposures include those chemicals that make up our food (proteins, minerals, and vitamins) and medications prescribed by a physician for a demonstrated health problem. For the most part these chemicals are regarded as safe and any documented risk is managed through restricted access such as prescription status for chemicals that are marketed as drugs. However, even with dietary components excessive exposure can be associated with negative health impacts. In recent years natural or complementary (alternative) medicines (black cohosh, Echinacea, evening primrose oil, and pregnancy tea) have emerged as major commercial health products, however, their efficacy in many cases has not been proven nor has their safety been examined experimentally. Moreover, the absence of quality control, lack of consistency in active product between different manufacturers, and reports of adulterated products naturally raise concern. While use of alternative medicines is generally thought to be safe and pose no threat to human

health, studies are starting to appear in the scientific and medical literature that are causing many scientists concern. For example, the isoflavones present in foods such as tofu, soybeans, and chickpeas have been shown to have estrogen-like activity (Soto et al. 1995) that is thought to have beneficial effects for older women entering menopause (Hale et al. 1999) and to provide protection against breast cancer (Lamartiniere et al. 1998; McMichael-Phillips et al. 1998; Peterson et al. 1996; Messina 1999; Messina and Loprinzi 2001). However, recent studies suggest that exposure to these chemicals at earlier life stages may have adverse health consequences for estrogen dependent diseases later in life such as breast cancer and endometriosis (Yang et al. 2000; Allred et al. 2001a; 2001b). Phytoestrogens have been shown to impair fertility in sheep and birds (Millam et al. 2001; Setchell et al. 1987). Hence, scientists are becoming aware that just because a chemical occurs naturally in the environment, it cannot be taken as an endorsement of its safety. Therefore, even with naturally occurring substances and health products, caution must be exercised and if uncertainty remains then consulting a physician, pharmacist or registered dietician may be helpful.

Exposure to tobacco smoke represents a unique set of circumstances since exposure can be both intentional (smoker) and unintentional (second hand smoke). Epidemiological studies have demonstrated that female smokers enter menopause approximately two years ahead of non-smokers (Harlow and Signorello 2000). In male smokers there is a greater risk of sexual dysfunction and decreased semen quality (Kunzle et al. 2003; Jensen et al. 1998; Vine et al. 1996; Chia et al. 1994; Saaranen et al. 1987). Tobacco smoke is composed of a vast number of chemicals and only a few have been studied for their effects on the reproductive system. Animal experiments have shown that some chemicals present in tobacco smoke are toxic to the development of sperm, eggs, and embryos (Zenzes 2000; Zenzes, Bielecki, and Reed 1999;

Zenzes et al. 1999; Zenzes, Puy, and Bielecki 1998; Zenzes and Reed 1998; Zenzes, Reed, and Casper 1997; Zenzes, Wang, and Casper 1995; Matikainen et al. 2001). There is also evidence that these chemicals adversely affect the transport of the egg along the fallopian tube (DiCarlantonio and Talbot 1999). Therefore, there is abundant evidence that direct exposure to tobacco smoke has a negative impact on human fertility and there is concern that this will extend to second hand smoke exposure as well.

Unwanted or inadvertent exposures describe exposure to chemicals that contaminate our food, our work environments or are present without our knowledge in our living environment. Scientists classify chemicals on the basis of their action or chemical characteristics of the compounds. For the purposes of our discussion we will refer to chemicals exposures that include solvents, polyhalogenated aromatic hydrocarbons (PHAHs, produced by combustion of fossil fuels, and charbroiling of food), pesticides, metals, and plasticizers (chemicals used to make plastics soft and pliable). Of the human-made chemicals recent concern has focused on those chemicals that possess estrogen like activity (Table I). However, it is now known, from animal experiments and tissue culture studies that chemicals can also: (1) increase the metabolism of estrogen and other reproductive hormones, (2) inhibit their activity, (3) increase the production of these hormones, and (4) affect reproductive and development through direct toxicity to cells. Chemicals that act in this manner are endocrine toxic and have been dubbed “endocrine disrupters”, “hormone mimics”, or “hormonally active chemicals”. While these compounds have been associated with adverse health effects in wildlife, fish, and experimental animals (Damstra et al. 2002), there is much less certainty about their effects in the general human population.

Several studies have reported that there has been a dramatic decrease in semen quality. Numerous studies of semen quality have appeared in the literature in recent years, some showing

Table I. Chemicals from several different chemical classes that have been linked with reproductive effects demonstrated through animal experiments.

Chemical class	Chemical	Sources	Effects
Phytoestrogens	Genistein	Soybeans, tofu & chickpeas	Estrogenic effects & premature sexual development
Polyhalogenated aromatic hydrocarbons	Benzo[a]pyrene	Tobacco smoke, diesel exhaust	Oocyte demise & embryo destruction
	PCBs*	Oils, electric coolant	Loss of ovarian follicles & hormone dysregulation
	Dioxins and Polychlorinated dibenzofurans (PCDF)*	Incineration of plastics, forest fires, automobile exhaust, & pesticide manufacturing	Altered ovarian cycles and destruction of growing ovarian follicles.
	Brominated Diphenyl Ethers	Flame retardants	Thyroid toxic, ovarian toxic
Pesticides – Fungicide	Hexachlorobenzene*	Long range transport [#]	Spontaneous abortion [§] & luteal phase dysfunction
	Vinclozolin	Residues in food	Antiandrogen
- Insecticide	Mirex	Residues in food	Estrogenic effects
	Endosulfan	Residues in food	Estrogenic effects
	Dieldren	Residues in food	Estrogenic effects
	Dibromochloropropane		Decreased sperm counts & infertility [§]
	Carbaryl	Lawn spraying, skin & residues in food	No apparent effects alone, spontaneous abortion in mixtures?
- Herbicide	DDT/DDE*	Long range transport [#] , residues in food	Estrogenic, antiandrogen, decreased semen quality
	2,4-D	Lawn spraying	Spontaneous abortion, small for gestational age [§]
	Dicamba	Lawn spraying	No apparent effects alone, spontaneous abortion in mixtures?
	Mecoprop	Lawn spraying	No apparent effects alone, spontaneous abortion in mixtures?
Metals	Lead	Dust, cosmetics, game birds	Decreased semen quality and spontaneous abortion
	Cadmium	Tobacco smoke	Follicle loss
Solvents	Benzene	Tobacco smoke, gasoline	Follicle destruction
Plasticizers	Nonylphenol	Residues in food	Estrogenic effects & premature sexual development
	Di-butylphthalate	Residues in food	Estrogenic effects
	Alkylphenol ethoxylate	Residues in food	Estrogenic effects
	Bisphenol A	Residues in food	Estrogenic effects

* Chemical toxicants whose use has been banned in Canada

§ Effect documented in the human population

Long range transport = chemicals banned from use in NA but enter our environment through transport in the atmosphere following use or release elsewhere in the world.

a decline, no change or an increase (Reviewed in Damstra et al., 2002). While there is no conclusive evidence that semen quality has changed over time, it is possible that large population based studies may miss regional differences. Indeed, in Canada we have shown that there are some regions where semen quality is lower than for other centers (Younglai et al. 1998). However, the explanation for these differences is unclear, as no studies have been undertaken to explore potential causal relationships. In addition, there is very little information in the literature relating changes in semen quality with direct measurements of exposure to chemical contaminants and thus it is not possible to draw any conclusions about the potential role of environmental contaminants in changes in human semen quality.

There is a general perception that the prevalence of infertile couples has increased in recent years leading to speculation that environmental contaminants may be playing a role in this phenomenon. However, several studies conducted in the United States and Canada has been unable to show an increase in infertility rates. Regardless, a single study conducted in New York State has shown that the risk of infertility and endometriosis is greater for couples living in heavily contaminated regions compared to couples living in other regions of the State (Carpenter et al. 2003). Unfortunately, no measurements of chemical contaminants were performed in this study and thus there is no way to know what chemicals may or may not be involved. Therefore, although the literature does not support the conclusion that infertility rates are increasing, there is the potential for regional differences that may be related to exposure to environmental contaminants.

Several studies have demonstrated that exposure to environmental toxicants from several different chemical classes are associated with adverse reproductive outcomes (Table I). Occupational exposure to pesticides has been linked with decreased semen quality, infertility,

and spontaneous abortion. The pesticide dibromochloropropane was convincingly linked to decreased semen quality and infertility in a population of workers exposed to this compound during manufacture (Slutsky et al. 1999; Goldsmith 1997; Potashnik and Porath 1995). To determine the effect of exposure to pesticides on reproductive health, agricultural workers have been studied in several studies from different countries. However, while there are published studies that report an association between pesticide exposure (Abell et al. 2000; Padungtod et al. 1998; Yousef et al. 1995), there are also studies that fail to demonstrate any relationship between exposure to pesticides and adverse outcomes (Juhler et al. 1999; Larsen et al. 1998; 1999). In a Canadian study, exposure to the phenoxy herbicide, 2,4-dichlorophenoxy acetic acid (2,4-D) was associated with spontaneous abortion (Arbuckle et al. 2001; Arbuckle et al. 1999) and small for gestation age (Savitz et al. 1997). However, other studies exploring the association between exposure to pesticides and reproductive function have failed to find a positive association (Axmon et al. 2000; Savitz et al. 1994; Willis et al. 1993). Hence, the effect of pesticides on human reproduction remains controversial. Reasons for failure to detect any relationship may be related to the small sample size of the studies as well as the low frequency of the adverse outcomes being studied. Studies examining occupational exposure to chemicals where the exposure is well defined have produced conclusive results whereas results of studies in which exposures are representative of the general population have failed to show any association between exposure and adverse outcomes on reproductive function.

To better understand the relationship between chemical contaminants and potential adverse reproductive outcomes, animal experiments have been conducted. Numerous studies have demonstrated that chemicals from almost every chemical class possess the potential to change reproductive function. However the dose levels used in these studies are several orders

of magnitude in excess of the concentrations to which people would be expected to be exposed. For example, animal experiments with chemicals such as metals, mirex, hexachlorobenzene, and PHAHs have been shown to affect circulating reproductive hormone levels, fertility, and reproductive behavior. Impaired development of reproductive tissues and reproductive function in adult animals has been demonstrated in experiments using human-made chemicals. Studies designed to test the ability of chemicals to bind with estrogen receptors and to stimulate estrogen dependent responses have been conducted in tissue culture. These studies have shown that many chemical contaminants can bind with estrogen receptors and stimulate estrogen-dependent gene responses. Results of these studies also suggest that human-made chemicals are much less potent than endogenous estrogens and estrogenic chemicals present in foods such as soybeans, chickpeas and tofu. Other chemicals such as vinclozolin and *p,p'*-DDE have been shown to block testosterone binding with the androgen receptor and are thus considered anti-androgens.

In summary there is a lack of evidence that there is an increase in the prevalence of infertility amongst the Canadian population. However, epidemiological studies have provided evidence that there may be regional differences in the reproductive capacity of Canadians. Laboratory animal experiments and cell culture studies have shown that chemicals from dietary sources and human-made compounds can interact with the reproductive endocrine system and possess the potential to affect human reproductive function. However, there is no evidence that exposures to human-made chemicals amongst the general population are sufficient to induce adverse effects.

Conclusions: Despite the prevailing popular opinion, there is no evidence that there has been any increase in the number of infertile couples in Canada. However, it is important to note that

regional changes in infertility or even greater rates of infertility in some regions compared to other areas may be missed by large population based studies. Occupational exposure to chemicals has been linked with adverse reproductive outcomes and infertility. However, there is no convincing evidence in the literature linking exposure in the general population to environmental contaminants and impaired fertility. By comparison, intentional exposure to toxicants present in tobacco smoke has been associated with decreased semen quality in humans, egg destruction and embryo loss in animal experiments. Animal studies reveal that chemicals from multiple chemical classes affect reproductive endocrine homeostasis and fertility. Hence, we conclude that chemical contaminants have the potential, when exposures exceed a threshold level, to affect human reproductive function. Continued investigation of the links between exposure to chemical contaminants and new chemicals, and reproductive function will be required to characterize hazards and define the human health risks associated with these exposures. A small group of Canadian scientists from government and university laboratories continue to study the reproductive effects of human-made and dietary chemicals. Regulatory bodies within Health Canada and Environment Canada review the published literature and where necessary take appropriate steps to restrict or eliminate the use of chemicals with the potential to adversely impact human health.

Reference List

- Abell, A., E. Ernst, and J. P. Bonde. "Semen quality and sexual hormones in greenhouse workers." Scand.J.Work Environ.Health 26.6 (2000): 492-500.
- Allred, C. D. et al. "Soy diets containing varying amounts of genistein stimulate growth of estrogen-dependent (MCF-7) tumors in a dose-dependent manner." Cancer Res. 61.13 (2001a): 5045-50.
- Allred, C. D. et al. "Dietary genistin stimulates growth of estrogen-dependent breast cancer tumors similar to that observed with genistein." Carcinogenesis 22.10 (2001b): 1667-73.
- Andersen, H. R. et al. "Effects of currently used pesticides in assays for estrogenicity, androgenicity, and aromatase activity *in vitro*." Toxicol.Appl.Pharmacol. 179 (2002): 1-12.
- Arbuckle, T. E., Z. Lin, and L. S. Mery. "An exploratory analysis of the effect of pesticide exposure on the risk of spontaneous abortion in an Ontario farm population." Environ.Health Perspect. 109.8 (2001): 851-57.
- Arbuckle, T. E. et al. "Exposure to phenoxy herbicides and the risk of spontaneous abortion." Epidemiology 10.6 (1999): 752-60.
- Axmon, A. et al. "Miscarriages and stillbirths in women with a high intake of fish contaminated with persistent organochlorine compounds." Int.Arch.Occup.Environ.Health 73.3 (2000): 204-08.
- Carpenter DO, et al., "Incidence of endocrine disease among residents of New York areas of concern." Environ Health Perspect 2001;109(Suppl 6):845-1.
- Chapin, R. E., R. A. Sloane, and J. K. Haseman. "Reproductive endpoints in general toxicity studies: Are they predictive?" Reproductive Toxicology 12 (1998): 489-94.
- Chedrese, P. J. and F. Feyles. "The diverse mechanism of action of dichlorodiphenyldichloroethylene (DDE) and methoxychlor in ovarian cells *in vitro*." Reprod.Toxicol. 15.6 (2001): 693-98.
- Chia, S. E., C. N. Ong, and F. M. Tsakok. "Effects of cigarette smoking on human semen quality." Arch.Androl 33.3 (1994): 163-68.
- Colborn, T., F. S. vom Saal, and A. M. Soto. "Developmental effects of endocrine-disrupting chemicals in wildlife and humans." environmental Health Perspectives 101 (1993): 378-84.
- Crellin, N. K. et al. "Inhibition of basal and stimulated progesterone synthesis by dichlorodiphenyldichloroethylene and methoxychlor in a stable pig granulosa cell line." Reproduction. 121.3 (2001): 485-92.

Damstra T, et al. 2002 Global assessment on the state-of-the-science of endocrine disruptors. WHO publication no. WHO/PCS/EDC/02.2 World Health Organization, Geneva, Switzerland.

DiCarlantonio, G. and P. Talbot. "Inhalation of mainstream and sidestream cigarette smoke retards embryo transport and slows muscle contraction in oviducts of hamsters (*Mesocricetus auratus*)." Biol.Reprod. 61.3 (1999): 651-56.

Foster, W. G. et al. "Mammary Gland Morphology in Sprague Dawley Rats Following Treatment with an Organochlorine Mixture in Utero and Neonatal Genistein." Toxicol.Sci. (2003).

Goldsmith, J. R. "Dibromochloropropane: epidemiological findings and current questions." Ann.N.Y.Acad.Sci. 837 (1997): 300-06.

Hale, G., M. Bievre, and C. Hughes. "Exploring the role of progestins and phytoestrogens in menopause." Integrative Medicine 2 (1999): 133-41.

Harlow, B. L. and L. B. Signorello. "Factors associated with early menopause." Maturitas 35.1 (2000): 3-9.

Jensen, T. K. et al. "Adult and prenatal exposures to tobacco smoke as risk indicators of fertility among 430 Danish couples." Am.J.Epidemiol. 148.10 (1998): 992-97.

Juhler, R. K. et al. "Human semen quality in relation to dietary pesticide exposure and organic diet." Arch.Environ.Contam Toxicol. 37.3 (1999): 415-23.

Kelce, W et al. "Persistent DDT metabolite p,p'-DDE is a potent androgen receptor antagonist." Nature 375 (1995): 581-85.

Kelce, W. "Environmental hormone disruptors: Evidence that Vinclozolin developmental toxicity is mediated by antiandrogenic metabolites." Toxicology and Applied Pharmacology 126 (1994): 276-85.

Kelce, W. R. et al. "Vinclozolin and p,p'-DDE alter androgen-dependent gene expression: in vivo confirmation of an androgen receptor-mediated mechanism." Toxicol.Appl.Pharmacol. 142.1 (1997): 192-200.

Kunzle, R. et al. "Semen quality of male smokers and nonsmokers in infertile couples." Fertil.Steril. 79.2 (2003): 287-91.

Lamartiniere, C. A., J. X. Zhang, and M. S. Cotroneo. "Genistein studies in rats: potential for breast cancer prevention and reproductive and developmental toxicity." Am.J.Clin.Nutr. 68.6 Suppl (1998): 1400S-5S.

Lamberts, S. W. J., A. W. van den Beld, and A-J. van der Lely. "The endocrinology of aging." Science 278 (1997): 419-24.

- Larsen, S. B. et al. "A longitudinal study of semen quality in pesticide spraying Danish farmers. The ASCLEPIOS Study Group." Reprod.Toxicol. 12.6 (1998): 581-89.
- Larsen, S. B. et al. "Semen quality and sex hormones among organic and traditional Danish farmers. ASCLEPIOS Study Group." Occup.Environ.Med. 56.2 (1999): 139-44.
- Markey, C. M. et al. "The mouse uterotrophic assay: A reevaluation of its validity in assessing the estrogenicity of bisphenol A." environmental Health Perspectives 109 (2001): 55-60.
- Matikainen, T. et al. "Aromatic hydrocarbon receptor-driven Bax gene expression is required for premature ovarian failure caused by biohazardous environmental chemicals." Nat.Genet. 28.4 (2001): 355-60.
- McMichael-Phillips, D. F. et al. "Effects of soy-protein supplementation on epithelial proliferation in the histologically normal human breast." Am.J.Clin.Nutr. 68.6 Suppl (1998): 1431S-5S.
- Messina, M. "Soy, soy phytoestrogens (isoflavones), and breast cancer." Am.J.Clin.Nutr. 70.4 (1999): 574-75.
- Messina, M. J. and C. L. Loprinzi. "Soy for breast cancer survivors: a critical review of the literature." J.Nutr. 131.11 Suppl (2001): 3095S-108S.
- Millam, J. R. et al. "Posthatch oral estrogen exposure impairs adult reproductive performance of zebra finch in a sex-specific manner." Horm.Behav. 40.4 (2001): 542-49.
- O'Keane, J. A. "Aging and reproduction: The biological clock-an alarming experience?" Journal of the Society of Obstetricians & Gynaecologists of Canada 18 (1996): 755-63.
- Olea, N. et al. "Estrogenicity of resin-based composites and sealants used in dentistry." environmental Health Perspectives 104 (1996): 298-305.
- Padungtod, C. et al. "Reproductive hormone profile among pesticide factory workers." J.Occup.Environ.Med. 40.12 (1998): 1038-47.
- Peterson, T. G. et al. "The role of metabolism in mammary epithelial cell growth inhibition by the isoflavones genistein and biochanin A." Carcinogenesis 17.9 (1996): 1861-69.
- Potashnik, G. and A. Porath. "Dibromochloropropane (DBCP): a 17-year reassessment of testicular function and reproductive performance." J.Occup.Environ.Med. 37.11 (1995): 1287-92.
- Saaranen, M. et al. "Cigarette smoking and semen quality in men of reproductive age." Andrologia 19.6 (1987): 670-76.
- Sanderson, J. T. et al. "Induction and inhibition of aromatase (CYP19) activity by various classes of pesticides in H295R human adrenocortical carcinoma cells." Toxicol.Appl.Pharmacol. 182.1 (2002): 44-54.

- Sanderson, JT et al. "2-chloro-s-triazine herbicides induce aromatase (CYP19) activity in H295R human adrenocortical carcinoma cells: a novel mechanism for estrogenicity?" Tox.Sci. 54 (2000): 121-27.
- Savitz, D. A. et al. "Male pesticide exposure and pregnancy outcome." Am.J.Epidemiol. 146 (1997): 1025-36.
- Savitz, D. A., N. L. Sonnenfeld, and A. F. Olshan. "Review of epidemiologic studies of paternal occupational exposure and spontaneous abortion." Am.J.Ind.Med. 25.3 (1994): 361-83.
- Setchell, K. D. et al. "Dietary estrogens--a probable cause of infertility and liver disease in captive cheetahs." Gastroenterology 93.2 (1987): 225-33.
- Slutsky, M., J. L. Levin, and B. S. Levy. "Azoospermia and oligospermia among a large cohort of DBCP applicators in 12 countries." Int.J.Occup.Environ.Health 5.2 (1999): 116-22.
- Soto, A. M., K. L. Chung, and C. Sonnenschein. "The pesticides endosulfan, toxaphene, and dieldrin have estrogenic effects on human estrogen-sensitive cells." Environ.Health Perspect. 102 (1994): 380-83.
- Soto, A. M. et al. "The E-Screen assay as a tool to identify estrogens: An update on estrogenic environmental pollutants." environmental Health Perspectives 103(Suppl. 7) (1995): 113-22.
- Stanford, J et al. "Factors influencing the age at natural menopause." J.Chron.Dis. 40 (1987): 995-1002.
- Vine, M. F. et al. "Cigarette smoking and semen quality." Fertil.Steril. 65.4 (1996): 835-42.
- Willis, W. O. et al. "Pregnancy outcome among women exposed to pesticides through work or residence in an agricultural area." J.Occup.Med. 35.9 (1993): 943-49.
- Yang JZ, Agarwal SK, Foster WG. Subchronic exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin modulates the pathophysiology of endometriosis in the Cynomolgus monkey. Tox. Sci. 56 (2000):374-381.
- Younglai, E. V., J. A. Collins, and W. G. Foster. "Canadian semen quality: an analysis of sperm density among eleven academic fertility centers." Fertil.Steril. 70.1 (1998): 76-80.
- Yousef, M. I. et al. "Toxic effects of carbofuran and glyphosate on semen characteristics in rabbits." J.Environ.Sci.Health B 30.4 (1995): 513-34.
- Zenzes, M. T. "Smoking and reproduction: gene damage to human gametes and embryos." Hum.Reprod.Update. 6.2 (2000): 122-31.
- Zenzes, M. T., R. Bielecki, and T. E. Reed. "Detection of benzo(a)pyrene diol epoxide-DNA adducts in sperm of men exposed to cigarette smoke." Fertil.Steril. 72.2 (1999): 330-35.

Zenzes, M. T., L. A. Puy, and R. Bielecki. "Immunodetection of benzo[a]pyrene adducts in ovarian cells of women exposed to cigarette smoke." Mol.Hum.Reprod. 4.2 (1998): 159-65.

Zenzes, M. T. et al. "Detection of benzo[a]pyrene diol epoxide-DNA adducts in embryos from smoking couples: evidence for transmission by spermatozoa." Mol.Hum.Reprod. 5.2 (1999): 125-31.

Zenzes, M. T. and T. E. Reed. "Interovarian differences in levels of cotinine, a major metabolite of nicotine, in women undergoing IVF who are exposed to cigarette smoke." J.Assist.Reprod.Genet. 15.2 (1998): 99-103.

Zenzes, M. T., T. E. Reed, and R. F. Casper. "Effects of cigarette smoking and age on the maturation of human oocytes." Hum.Reprod. 12.8 (1997): 1736-41.

Zenzes, M. T., P. Wang, and R. F. Casper. "Cigarette smoking may affect meiotic maturation of human oocytes." Hum.Reprod. 10.12 (1995): 3213-17.