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Proceedings of the Summit on Environmental Challenges to Reproductive Health and Fertility: Executive Summary

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Abstract

The 2007 Summit on "Environmental Challenges to Reproductive Health and Fertility" convened scientists, health care professionals, community groups, political representatives and the media to hear presentations on the impact of environmental contaminants on reproductive health and fertility and to discuss opportunities to improve health through research, education, communication and policy. Environmental reproductive health focuses on exposures to environmental contaminants, particularly during critical periods of development, and their potential effects on future reproductive health, including conception, fertility, pregnancy, adolescent development and adult health. Approximately 87,000 chemical substances are registered for use in commerce in the US, with ubiquitous human exposures to environmental contaminants in air, water, food and consumer products. Exposures during critical windows of susceptibility may result in adverse effects with lifelong and even intergenerational health impacts. Effects can include impaired development and function of the reproductive tract and permanently altered gene expression, leading to metabolic and hormonal disorders, reduced fertility and fecundity and illnesses such as testicular, prostate, uterine and cervical cancers later in life. This executive summary reviews effects of pre- and post-natal exposures on male and female reproductive health and provides a series of recommendations for advancing the field in the areas of research, policy, health care and community action.

Keywords

environmental contaminants; reproductive health; endocrine disrupting chemicals; fertility; fecundity; hormone disruption; sperm quality; reproductive tract development

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Background

On Jan 28–30, 2007, a Summit on "Environmental Challenges to Reproductive Health and Fertility" was convened at the Mission Bay Campus of the University of California San Francisco (UCSF). The Summit was the product of a collaboration between the UCSF Program on Reproductive Health and the Environment in the Department of Obstetrics, Gynecology and Reproductive Sciences, the UCSF National Center of Excellence in Women's Health and the Collaborative on Health and the Environment. This unique gathering coalesced the field of environmental reproductive health by bringing together over 400 scientists, researchers, health care professionals, trainees, health-affected groups, community and political representatives and the media to discuss what is currently known about the impacts of environmental contaminants on reproductive health and fertility. The compelling nature of the collective science, with observations in humans, animal models and wildlife, raised concern for the future health of individuals and families. The Summit also set the stage to improve health through research, education, communication and changes in public health policy. This executive summary presents the highlights from the accompanying *Supplement on Environmental Challenges to Reproductive Health and the Environment* (1), which summarizes the state of the science presented at the Summit, and outlines the key "next steps" Summit participants recommended for research, policy, health care, community action and safe work.

Defining the Field

Environmental reproductive health focuses on exposures to environmental contaminants (synthetic chemicals and metals), particularly during critical periods of development (such as prior to conception and during pregnancy), and their potential effects on all aspects of future reproductive health throughout the life course, including conception, fertility, pregnancy, child and adolescent development and adult health. (Figure 1).

Environmental Contaminants

Since World War II, there has been a dramatic increase in human exposures to both natural and synthetic chemicals. As of 2006, there are approximately 87,000 chemical substances registered for use in commerce in the U.S. (2). Common environmental pollutants include: pesticides and herbicides such as atrazine and chlorpyrifos; volatile organic compounds such as benzene, toluene and chloroform; heavy metals such as lead, mercury and arsenic; air contaminants such as carbon monoxide, ozone, particulate matter and environmental tobacco smoke; and persistent organic pollutants, such as the dioxins, polychlorinated biphenols (PCBs), the pesticide dichlorodiphenyltrichloroethane (DDT) and its breakdown product dichlorodiphenyldichloroethylene (DDE).

While many environmental contaminants can affect reproductive health (see Table 1), there is an important class of chemicals called endocrine disrupting chemicals (EDCs) that interfere with the production, release, transport, metabolism, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis and the regulation of developmental processes. Some of the common EDCs discussed at the Summit include bisphenol A (BPA), phthalates and certain pesticides (e.g., vinclozolin, dicofol, atrazine). Many of these compounds alter estrogen, androgen, and thyroid signaling, which are essential for normal embryonic development and reproductive activity in all vertebrates studied to date (3–5). They can also alter the synthesis, storage on plasma proteins and hepatic biotransformation and clearance of hormones (6) and disrupt neural and immune signaling pathways (7–9) and the regulation of gene expression (e.g., DNA methylation, RNA stability, protein degradation) (reviewed by (10)). In some cases, altered DNA methylation patterns have been shown to be heritable (11,12).

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Studying the effects of EDCs on the reproductive system is a natural area of inquiry, as EDCs can interact with the hormonal system, which regulates development and maintenance of the reproductive system. However, since EDCs also target the neuroendocrine system, which plays regulatory and homeostasis roles in the control of human physiology, exposure to EDCs has broader implications for health.

Exposure to Multiple Chemicals

Humans are exposed daily to a mixture of environmental contaminants in air, water and food. In a recent biomonitoring study of over 150 contaminants, the U.S. Centers for Disease Control and Prevention (CDC) reported that all 150 chemicals were detected in some portion of the U.S. population and that several of the chemicals, such environmental tobacco smoke, lead, mercury and phthalates, are detected in nearly all of the population (13). These and similar biomonitoring efforts improve our understanding of current body burdens of environmental contaminants. With this knowledge comes a need for better science on the health risks associated with current patterns of exposure, including increased risks resulting from exposures to multiple chemicals. For example, the majority of studies and regulatory focus has been on exposures to individual phthalates, which may underestimate the actual risks, as recent studies have found that simultaneous prenatal exposure to both di(*n*-butyl) phthalate (DBP) and di(2-ethylhexyl)phthalate (DEHP) produced reproductive malformations in the offspring in a cumulative, dose-additive manner (14). Finally, biomonitoring data indicate that more effort is needed toward approaches that identify and mitigate exposure to harmful chemicals prior to measuring harmful contaminants in people.

Susceptible Populations

Environmental chemicals can cause a broad spectrum of effects, which depend not only on route of exposure and dose, but on the susceptibility of the individual to the compound. Age, gender and genotype can influence susceptibility to disorders, anatomic abnormalities and diseases from exposures. For example, we know that children are not small adults; they have different behaviors, metabolism and responses to infectious and environmental challenges. The elderly may also be a population at special risk to environmental chemicals.

Critical and Sensitive Windows of Susceptibility

A *critical window of susceptibility* is a time-sensitive interval during development when exposures to environmental contaminants can disrupt or interfere with the physiology of a cell, tissue or organ (15,16). It is a period characterized by marked cellular proliferation and development and numerous changing metabolic capabilities in the developing organism (16, 17). Exposures to environmental contaminants during this window may result in adverse, permanent and irreversible effects that can have lifelong and even intergenerational impacts on health.

Researchers have suggested the need to also define *sensitive windows of susceptibility*. Exposures during sensitive windows of susceptibility may still affect development or result in eventual adult disease, but with reduced magnitude compared to the effect of exposure during the critical window of susceptibility (16,18). For example, DES exposure reprograms the expression of estrogen responsive genes in Eker rats exposed on post-natal days 3–5 or 10–12 (critical window of susceptibility), leading to increased incidence of uterine leiomyoma. In contrast, rats exposed on post-natal days 17–19 (sensitive window of susceptibility) did not experience this developmental programming and had a rate of uterine leiomyoma that was elevated but not statistically different from control animals (19).

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Given that development continues after birth, critical and sensitive windows occur periconceptually (prior to, during and shortly after the fertilization of the egg) and during pregnancy; infancy, childhood and puberty (Figure 2).

Developmental Programming and Fetal Origins of Adult Disease

Studies from the 1990's found that adverse effects on the fetal environment, such as poor maternal nutrition, can result in an increased risk of adult onset of chronic conditions such as coronary heart disease (20–22). These findings led to the fetal origins of disease hypothesis (commonly known as the "Barker" hypothesis), which proposes that exposures to adverse insults during critical or sensitive windows of development can permanently reprogram normal physiological responses, and thus give rise to illnesses and metabolic and hormonal disorders later in life (23–28).

The DES Example—Prenatal exposure to diethylstilbestrol (DES), a synthetic estrogen and thus EDC, provides an unfortunate example of developmental programming. DES was given to U.S. pregnant women between 1938 and 1971 under the erroneous assumption that it would prevent pregnancy complications. In fact, *in utero* exposure to DES alters the normal programming of gene families, such as Hox and Wnt, that play important roles in reproductive tract differentiation (28–31). As a result, female offspring exposed to DES *in utero* are at increased risk of clear cell adenocarcinoma of the vagina and cervix, structural reproductive tract anomalies, infertility and poor pregnancy outcomes, while male offspring have an increased incidence of genital abnormalities and a possibly increased risk of prostate and testicular cancer (32). These observed human effects have been confirmed in numerous animal models which have also provided information on the toxic mechanisms of DES. Animal experiments have also predicted changes later found in DES-exposed humans, such as oviductal malformations (33), increased incidence of uterine fibroids (34–36) and second-generational effects (37,38) such as increased menstrual irregularities (39) and possibly ovarian cancer (40) in DES-granddaughters and increased hypospadias in DES-grandsons (41,42).

DES is but one example of how exposure to EDCs can disrupt developing organ systems and cause abnormalities, many of which only appear much later in life or in the subsequent generation (43), such as endometriosis, fibroids and breast, cervical and uterine cancer in women; poor sperm quality and increased incidence of cryptorchidism and hypospadias in men; and subfertility and infertility in men and women (28),

Signals from Wildlife

For over a century, wildlife and laboratory animals have been used to predict the human health effects of various environmental contaminants. Although each species has its unique attributes, a growing literature indicates that substantial conservation exists in the underlying molecular, cellular and physiological systems associated with vertebrate reproduction (44). For example, estrogen, androgen and thyroid signaling are essential for normal embryonic development and reproductive activity in all vertebrates studied to date (3–5). Furthermore, wildlife studies demonstrate the effects of levels and mixtures of exposures in our environment in genetically diverse populations (44). Therefore observations from wildlife are directly relevant to assessing potential environmental influences on human reproduction.

In the early 1990s, studies began to associate environmental contamination with altered reproductive performance in wild populations of fish, amphibians, reptiles and birds (45). For example, studies in fish demonstrate increased rates of feminized male phenotype and reduced fertility from environmental exposures to: ethynylestradiol, a synthetic estrogen found in birth control pills and increasingly in treated sewage effluent; tributyltin, an anti-fouling agent used on boats; BPA; tetrabromobisphenol A, a widely used flame retardant; and nitrate, a common

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fertilizer (44). Studies in alligators inhabiting pesticide-contaminated lakes report reduced fertility and increased occurrence of multioocyte follicles (ovarian follicles with multiple rather than the normal single oocyte) (46); alterations in folliculogenesis resulting in multioocyte follicles have been associated with infertility and early embryonic loss in DES-treated mice (47,48). Exposure of reptilian embryos to endogenous (estradiol-17β), pharmaceutical (e.g., ethynylestradiol, diethylstilbestrol) or industrial (e.g., DDT, DDE, BPA, trans-nonachlor) estrogens during a critical window of development induces sex reversal at male incubation temperatures, leading to increased female sex ratios (49–52). And, exposure to even lower concentrations of these contaminants alters steroidogenesis of the ovary or testis in neonates and juveniles (53). Fish and amphibians also experience effects following exposure to endocrine-active compounds, including aberrant gonadal morphology (e.g., the presence of oocytes in the testis, alterations in Leydig and Sertoli cell morphology or number) (54,55). This literature documents the endocrine-disruptive effects of a wide array of commercial chemicals and byproducts, including: pesticides; sewage contaminants, such as surfactants (e.g., octylphenol and nonylphenol) and pharmaceutical agents; plasticizers (e.g., phthalates); flame retardants (e.g., PCBs, polybrominated diphenol ethers, tetrabromobisphenol A) and industrial pollutants (e.g., heavy metals, dioxin, polycyclic aromatic hydrocarbons) (for reviews, see (3,6,56–58)). Furthermore, these effects were caused by exposure to levels of chemicals found in the environment.

Concerning Trends

There have been a number of concerning trends in human reproductive health. The incidence of testis cancer, primarily a disease of young men, has increased in Europe, with a lifetime risk approaching 1% (59). In addition, young men born today in Europe have remarkably low average sperm counts and a high prevalence (~1 in 6) of abnormally low sperm counts likely to cause fertility problems (60). New data in three cities (Boston, U.S., Copenhagen, Denmark and Turku, Finland) demonstrate a significant secular trend in serum testosterone (61–63). The details vary somewhat, but together these studies suggest that testosterone has declined about 1% per year for the past 40–50 years. This decline is consistent with the reduction in sperm concentration reported by Carlsen in 1992 (64) and these two trends taken together increase the plausibility of a significant decrease in male reproductive function. For girls in the U.S., there has been a reported decline in age of onset of breast development and menarche over the last 30 years (65). Rapid changes in health endpoints are of concern because they suggest environmental and lifestyle, and thus avoidable, causes..

Compelling New Science: Moving Beyond Genetic Determinants

Genetic mutations are known to alter gene expression and lead to disease. Environmental exposures have typically been thought of as influencing genetics and health by causing mutations. For example, it has long been known that radiation leads to genetic mutations and increased risk of disease, such as cancer.

However, research during the past decade has revealed that many environmental exposures also act through modification of the epigenome (the collection of biochemical reactions that determine the gene expression) of cells, leading to either immediate or latent adverse effects on reproduction. For example, recent epigenetic research has revealed a possible mechanism by which *in utero* exposure to BPA heightens susceptibility to prostate cancer in adult rats: BPA altered the normal process of silencing, through hypermethylation, the phosphodiesterase type 4 variant 4 gene that occurs with aging, thus elevating gene expression (66). BPA also permanently alters expression of HOXA10, a gene necessary for uterine development (67). Epigenetic studies have also shown that DES causes alterations in uterine tissue architecture and morphology and heightens susceptibility to uterine adenocarcinoma by inducing

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permanent changes in several estrogen-responsive uterine genes (28) These are but a few examples of how the field of epigenetics has and will continue to contribute to our mechanistic understanding of the impact of environmental contaminants on reproductive health.

Environmental Contaminants and Effects in Males

Reproductive Effects of Early Life Exposures

Testicular Development and the Environment—Over the past 10–15 years, the central role that deficient androgen production and action during fetal testis development may play in the origin of disorders has been well documented and is reviewed in Sharpe and Skakkebaek (68).

There is a relatively high incidence of male reproductive disorders that manifest at birth (cryptorchidism, hypospadias) or in young adulthood (testicular germ cell cancer (TGCC) and infertility) (69,70). These four disorders are increasing in prevalence in the West (69). They are risk factors for each other and they share several, pregnancy-related risk factors (68–70). Skakkebaek hypothesizes that TGCC, cryptorchidism and some cases of hypospadias and low sperm count comprise a testicular dysgenesis syndrome (TDS) with a common origin in fetal life (69). The hypothesis proposes that "abnormal testis development (dysgenesis), which could have numerous primary causes, leads secondarily to hormonal or other malfunctions of the Leydig and Sertoli cells during male sexual differentiation, leading to increased risk of reproductive disorders of the testicular system" (Figure 3) (68–70).

This hypothesis has been supported by findings in an animal model of TDS involving fetal exposure to the phthalate DBP as well as by new clinical studies described in Sharpe and Skakkebaek (68). Exposure of rats *in utero* to DBP induces a TDS-like syndrome in the male offspring (71–73); this is manifest as dose-dependent induction of cryptorchidism, hypospadias and impaired spermatogenesis and infertility. Focal dysgenesis (73,74), subnormal fetal Leydig cell function (71–73) and subnormal Sertoli cell proliferation (75) and possibly function (73), consistent with changes predicted in the TDS hypothesis, are also demonstrated (69). Furthermore, the characteristics of the focal dysgenesis induced by fetal DBP exposure in rats (73,74) – malformed seminiferous cords, Sertoli cell-only tubules with immature-appearing Sertoli cells and the abnormal occurrence of intratubular Leydig cells – are all also reported in testes of men with TGCC (76–78).

A particularly important recent development is the observation that inhibition of androgen production or action in rodents, resulting from transgenesis (79), DBP exposure (75) or flutamide treatment (80), reduces Sertoli cell number substantially in the perinatal period and leads to downstream TDS disorders. Thus, androgens appear to play a determining role during the most important periods of Sertoli cell proliferation (fetal and early postnatal life) (68,81) (Figure 3). This finding is consistent with data in humans showing that Sertoli cell number increases during fetal life (when testosterone levels are high) and during the period of the neonatal testosterone rise (81,82). Since Sertoli cell number in adulthood is the primary determinant of sperm production and counts in men (81), it is hypothesized that reduction in testosterone levels in the fetal testis, as a secondary consequence of dysgenesis leading to reduced Sertoli cell numbers, could lead to low sperm counts in adulthood (Figure 3). This is an important finding because Sertoli cells in the fetal testis in all species so far examined do not express androgen receptors. Therefore, anti-androgens appear to exert toxic effects on male reproductive development through multiple pathways (75)

The TDS syndrome is further supported by studies that induce hypospadias in CD1 mice through exposure to EDCs during the critical period of urethral development. These chemicals include 17α estradiol, pesticides such as vinclozolin, pharmaceutical products such as the

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antihistamine loratadine and the flame retardant, benzophenone-2 (83). A recent human study by Swan et al. found *in utero* exposure to phthalates associated with shortened (and thus less masculine) male anogenital distance, which has been observed in animal studies (84).

Based on the increasing prevalence of TDS disorders and recent evidence for declining testosterone levels in men, endocrine disrupting chemicals in our environment are likely to become ever more important in shaping the reproductive health of young men in the present and next generation.

Prostate Development and the Environment—Similar to the testis, male accessory sex glands and organs are also vulnerable to environmental EDCs, with adverse effects in adulthood. The developing prostate gland is particularly sensitive to estrogens and high-dose exposures during a critical developmental window results in prostatic intraepithelial neoplasia (PIN) in adult rodent models (85). Early life exposure to estrogenic substances could sensitize the developing prostate to later risks from increasing estrogen levels that occurs in the aging male. A study of rats treated neonatally to BPA followed by hormones that mimic the aging male in adulthood showed a significantly higher PIN incidence and score compared to controls (rats exposed only to BPA neonatally or those given only the aging hormones in adulthood) (86). As discussed above, this heightened predisposition to prostate carcinogenesis results from permanent alterations to the prostate epigenome (66).

Reproductive Effects of Adult Exposures

Hauser and Sokol (87) review human and animal evidence on exposure to several classes of environmental contaminants during adulthood and adverse male reproductive outcomes. In the past two decades, numerous animal and clinical studies have provided evidence that a variety of chemicals can disrupt the hypothalamic-pituitary-testicular axis by acting as hormonal antagonists or agonists or by disrupting the biochemical processes regulating hormone secretion and sperm function (87).

Consistent with the effects of prenatal exposure discussed above, rodent models of pubertal and adult exposure to phthalate esters report testicular toxicity characterized by testicular atrophy, reduced sperm counts, altered Leydig cell structure and function, Sertoli cell toxicity and increased germ cell apoptosis (68). These studies indicate an age-dependent sensitivity to exposure, with prenatal exposure causing the most, and adult exposures the least, severe effects. Studies of phthalate exposure and male reproductive health in humans are limited and inconsistent. For example, certain phthalate metabolites (MBP and MBzP) were associated with decreased sperm quality among U.S. (88) but not among Swedish men (89). The differences across studies, such as the ages of the population (older in the U.S.) or the source of the men (general population in Sweden and infertile couples in the U.S.), may account for some of the differences in study results, but may also suggest that a subpopulation of men may have increased susceptibility to phthalate exposure (87).

PCBs are another industrial contaminant for which data on prenatal and adult exposures in humans are available. For example, epidemiologic studies of high-dose exposures from accidental food contamination report abnormal sperm morphology, higher oligozoospermia rates and reduced hamster oocyte penetration 20 years after exposure (90). Effects on sperm quality resulting from prenatal exposure were similar: abnormal morphology, decreased motility and reduced hamster oocyte penetration (91). Studies to date of lower-dose, environmental exposures to PCBs support an association with reduced semen quality, specifically reduced sperm motility (92).

Heavy metals such as lead were among the first recognized human reproductive toxicants (93). Animal, clinical and epidemiologic studies have demonstrated that exposure to lead

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disrupts all levels of the reproductive axis, with the central nervous system and testis appearing to be the most sensitive organs and puberty a critical window of susceptibility (94–96). Epidemiologic studies report a dose-related suppression of spermatogenesis, normal or decreased serum testosterone and inappropriately normal urinary gonadotropins in the face of low testosterone levels in men with higher blood lead levels (97). Recent findings suggest that lead may also induce chromosomal abnormalities and lead to infertility by interfering with the acrosome reaction in spermatozoa (98). Human studies evaluating other heavy metals suggest that cadmium, mercury and boron may also disrupt male reproduction (99).

Dibromochloropropane (DBCP) is the most characterized agricultural chemical with respect to male reproductive toxicity. Occupational exposure to DBCP produced: azoospermia and oligospermia, damaged germinal epithelium, genetic alterations in sperm (such as double Y-bodies), reduced male fertility, increased rates of spontaneous abortions in wives of exposed workers, hormonal imbalances and altered sex ratio in offspring (100). Reversibility of effects following cessation of exposure are variable (101,102). The reproductive toxicity of other agricultural chemicals such as organophosphate pesticides, vinclozolin and DDT is less well characterized in humans; nevertheless, animal and human studies demonstrate these chemicals to have adverse effects on semen quality as well as anti-androgen properties (100).

Additional classes of chemicals that are of particular interest due to widespread human exposure and animal evidence of reproductive toxicity, but for which human data are lacking or minimal, include those used in consumer products, such as BPA, parabens and phthalates, pyrethroid pesticides and air pollution (87).

Environmental Contaminants and Effects in Females

Reproductive Effects of Early Life Exposures

Prenatal exposure to environmental factors can modify normal cellular and tissue development and function through developmental programming, such that women may have a higher risk of reproductive pathologies and metabolic and hormonal disorders later in life (23–27). Woodruff and Walker (28) review new research on the effects of environmental estrogen exposure during key developmental windows on normal reproductive development of the ovaries and the uterus and the link to specific disease states in the adult.

Ovarian Follicular Development and the Environment—The ovarian follicle is the functional unit of the ovary and is comprised of an oocyte surrounded and supported by the somatic granulosa and theca cells (28). The health of the follicle can impact the health of the woman as well as the health of her offspring. For example, decreased numbers of follicles, multiple eggs per follicle and incomplete follicular development can all result in decreased fertility. The precise mechanisms involved in early ovarian follicle formation are not known, but are essential in organizing the fetal ovary and establishing the postnatal follicle number that will provide the female with sufficient oocytes for a lifetime of fertility (28).

Estrogen and activin are two known factors that play an important role in regulating oocyte and follicle development and function (103–112) and aberrant development and ovarian pathologies are observed in mice exposed to neonatal estrogen or activin. Neonatal exposure of rats to estradiol benzoate has been show to delay follicle and interstitial development (113). Neonatal exposure to DES or the natural estrogen estradiol (E_2) results in lack of corpora lutea in adult mice (114), suggesting that these effects persist beyond reproductive tract development and impact fertility in the adult. Neonatal exposure to DES, E_2, or the phytoestrogen genistein also induces formation of multi-oocytic follicles in mice (115–117) – an effect that is also reported in alligators exposed to environmental estrogenic contaminants (see above) (46). Additionally, activin administered during the critical, postnatal period of

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primordial follicle formation changes the number of postnatal follicles (28,118). Current mechanistic studies are exploring whether neonatal estrogen exposure alters activin signaling in the ovary; preliminary findings of decreased activin subunit gene expression and impacted activin signaling in the mouse ovary support this hypothesis (28)

Uterus Development and the Environment—Women exposed to DES in utero during critical periods of reproductive tract development developed several types of reproductive tract abnormalities, as well as an increased incidence of cervical-vaginal cancer later in life (118). Animal studies that simulate the human DES experience have since shown that exposure of the developing reproductive tract of CD-1 mice to DES imparts a permanent estrogen imprint that alters reproductive tract morphology, induces persistent expression of the lactoferrin and c-fos genes and induces a high incidence of uterine adenocarcinoma (119–121). Experiments in rats have shown exposure to DES during the critical window of uterine development leaves a hormonal imprint on the developing uterine myometrium in rats that were genetically predisposed to uterine leiomyoma (28), increasing the risk for adult uterine leiomyoma from 65% to greater than 90% and increasing tumor multiplicity and size (35). DES-induced developmental programming appears to require the estrogen receptor α (122), suggesting that signaling through this receptor is crucial for establishing developmental programming.

Studies have now been extended beyond DES to demonstrate that other environmental estrogens reprogram gene expression in the uterus (28): exposure to genistein and BPA during the period of maximum sensitivity to developmental programming induces the expression of the estrogen-responsive genes calbindin and progesterone receptor. Neonatal BPA exposure attenuated estrogen-responsive genes whereas genistein exposure induced an even higher level of estrogen responsiveness than DES exposure. In contrast to DES, exposure to these environmental estrogens does not disrupt ovarian function in adult females, which continue to cycle normally.

Reproductive Effects of Adult Exposures

Mendola et al. (123) review the growing body of epidemiologic and occupational studies demonstrating that environmental exposures can interfere with all developmental stages of reproductive function in adult females, including puberty, menstruation and ovulation, fertility and fecundity and menopause.

Puberty—Environmental contaminants can accelerate or delay pubertal development. Lead exposure delays puberty in girls, even at very low levels (<5 micrograms per deciliter) (124–126). Earlier age at puberty has been observed with phthalate exposure (127) and correlates with serum DDT (128), DDE (129) and PCBs (126).

Menstrual and Ovarian Function—Variations in menstrual and ovarian function have been observed following consumption of drinking water disinfection byproducts (DBPs) and fish contaminated with PCBs and other pollutants; similar associations were noted in studies using biological markers of 2,3,7,8 tetrachlorodibenzo-*p*-dioxin (TCDD), DDT, DDE and PCBs (123). These studies generally describe functional variations (e.g., long or short cycles, changes in luteal or follicular phase) that indicate an underlying perturbation of hormones rather than the development of clinical disorders, although long-term effects are not known.

Shorter cycles have been observed for occupational exposure to lead (130) and to chlordibromoethane in drinking water (131). Longer cycles have been observed in studies of EDCs such as TCDD (132), hormonally-active pesticides (133), serum PCBs (134) and multiple industrial chemicals (e.g., ethylene glycol ethers) used in the semi-conductor industry (135). Menstrual disorders such as missed periods and abnormal uterine bleeding were also

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observed (130,133,134). Other studies found menstrual abnormalities, such as abnormal menstrual bleeding with no change in cycle length, associated with PCBs or metal exposure (136,137). Follicle-stimulating hormone is decreased in women exposed to pentachlorophenol (138). Progesterone and estrogens are reduced in women exposed to DDT and DDE (139, 140).

Endometriosis has been widely studied in relation to environmental exposures. Most studies considering PCBs have found increased serum levels among endometriosis cases, compared with controls (123). Phthalate esters have also been associated with endometriosis among some women (141,142).

Fertility and Fecundity—Fertility and fecundity studies include time-to pregnancy and spontaneous abortion outcomes as well as studies of infecundity (lack of fecundity) and other measures of subfertility (123). Lead is consistently observed to be a reproductive toxicant, causing decreased fertility and increased pregnancy loss (130,143). Pregnancy loss has also been found to be associated with DDE in most studies (144–146).

Working with or applying pesticides, primarily in agricultural and horticultural settings, appears to consistently reduce fertility and fecundability (147–152). Preconception exposure, but not exposure during pregnancy (153), appears to elevate risk for spontaneous abortion (154). Pesticides are detrimental to both fecundity and fertility in the limited number of animal studies conducted to date (155,156).

Additional environmental exposures, including solvents, radiation and other compounds, are also associated with decrements in female fertility, but the literature is limited or inconclusive (123). In particular, studies on solvent exposure in a variety of settings (157–159) suggest decreases in fertility. One study in humans found an increase in recurrent miscarriage associated with BPA (160), a finding that is consistent with the disruption of oogenesis through meiotic disruption and aneuploidy in mice exposed to environmentally relevant levels of BPA (161,162).

Menopause—Menopause has not been extensively studied, but earlier age at menopause has been observed with exposure to serum dioxin (163), DDT, DDE and other pesticides (164–166). Animal studies report disruption of folliculogenesis in mice exposed to lead (167) as well as follicle destruction after exposures to mancozeb, dibromoacetic acid, polycyclic aromatic hydrocarbons, cyclophosphamide and 4-vinylcyclohexene diepoxide (168–173), suggesting possible mechanisms relevant to human disorders associated with these exposures.

Environmental Exposures During Pregnancy and Adverse Birth Outcomes

Windham and Fenster (174) review the epidemiologic literature on exposure to certain environmental contaminants during pregnancy and adverse birth outcomes, such as low birth weight, intrauterine growth retardation (IUGR), preterm delivery and stillbirth.

Exposure to ETS reduces mean birth weight (or slightly increasing the risk of IUGR), with suggestive evidence of an effect on preterm delivery as well (175,176). Studies of water disinfection byproducts (DBPs) support an association between DBP exposure and IUGR, with little consistent effect on preterm delivery (174,177–179). The weight of epidemiologic evidence also suggests that high levels of exposure to DDT or DDE is associated with adverse fetal growth outcomes and preterm delivery (174). Studies of organophosphate exposure and reproductive outcomes have suffered from lack of a standard validated measure of exposure. However, despite inconsistencies in study results, the weight of evidence and precautionary

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principle suggest that exposure to organophosphates should be avoided during pregnancy (174).

Moving Forward

At the Summit, participants from research, academic, health care, government, advocacy and community sectors identified the most important needs and directions for advancing reproductive environmental health through research, health care, policy community action and occupational health.

Research

Participants in the research breakout group focused on identifying the critical research directions and key needs for advancing the science database on environmental reproductive health. They identified priority actions in two main areas: communication and research priorities that will benefit from continued dialogue among government agencies, basic scientists, epidemiologists, clinicians and the general public, who all have critical voices in the discussion.

1. There is a need for better communication to foster collaborations—To enhance collaborations among researchers and between researchers and granting agencies, the group proposed the following:

- Fostering technologies that encourage collaboration, such as listservs and web-based databases of tissue banks.
- Working with government agencies and universities to promote collaboration among researchers, such as broadening the definition of a principal investigator to include project leaders in a program project or center grant.
- Developing opportunities for researchers to meet and discuss collaborations in
- environmental reproductive health research, such as at professional society meetings.

2. Critical research directions in environmental reproductive health—The following priorities were identified:

- Human and animal studies that are longitudinal and take into account the full life cycle, including prenatal exposures (e.g. The National Children's Health Study);
- Leveraging existing mechanisms of data collection to incorporate semen analysis into the CDC's NHANES study.
- Biological measurement collection and banking should be incorporated into
- epidemiological study designs for future research.
- Development of biomarkers of exposure and pre-clinical indicators of disease in animals and humans, and better biomarkers of human fertility.
- Regulatory obstacles need to be addressed, such as interpreting and working with the Health Insurance Portability and Accountability Act rules.
- Increased funding for emerging areas of research for individual chemicals and mixtures and their effects on epigenome; fetal programming and transgenerational effects; low-dose effects; non-traditional dose-response curves; and cross talk among endocrine systems and receptors.
- How do we identify new emerging contaminants?

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Health Professional Communication

Participants in this break out group, comprised primarily of health professionals and health-affected groups or patient advocates, discussed what clinicians need to educate and advocate for patients. Participants agreed that:

- Clinicians need to be well-informed about the sources and effects of environmental and workplace contaminant exposures, especially in relation to periconceptional, prenatal, early infancy and childhood windows of susceptibility.
- Due to the complexity of analyzing exposures and difficulty in predicting precise health effects in a given individual, the clinician must address uncertainty when communicating with patients on these issues.
- Health professionals need to take a precautionary stance and provide patients specific advice on avoiding exposures.
- Clinicians and scientists can help interpret complex scientific research for legislators and the public to support better regulation of contaminants, leading to reduced exposures.

Some important needs of health care professionals include:

- Clear, simple-to-use health information tools that list contaminants and sources of exposure and steps to take to reduce exposures and health effects of specific exposures. Tools need to be developed collaboratively by scientists, clinicians and advocacy and community groups in order to be relevant and appropriate to a diversity of populations.
- Education on reproductive environmental health should be included in health professional and public education
- Health care professionals should take a work history and inquire about patients' exposures, ideally *before* pregnancy. This is not the current standard of practice.

Examples of Health Information Tools available to Health Professionals—The Pediatric Environmental Health Tool Kit provides easy to use, anticipatory, age-appropriate guidance on how to minimize harmful pediatric environmental exposures (http://psr.igc.org/ped-env-hlth-toolkit-project.htm). The Hazard Evaluation System and Information Service is comprised of informational materials, training and a workplace hazard helpline for workers and health professionals for a number of workplace reproductive and developmental hazards (thttp://www.dhs.ca.gov/ohb/HESIS/hesispubs.htm.)

Policy

Participants from all sectors represented at the Summit identified four key policy needs:

1) Advance models for comprehensive chemicals evaluation at local, state and national levels and develop effective chemical regulation—Because there is such a lack of data on chemicals that are already on the market, comprehensive testing should be required for chemicals remaining on the market and pre-market testing should include reproductive environmental health outcomes. The testing should: evaluate effects on both the environment and human health; assess exposures at different stages of development; and identify cumulative and synergistic impacts. The review of the testing results needs to include mechanisms for reducing, limiting or removing chemicals that pose reproductive environmental health risks.

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2) Improve the science base: increase resources and improve methods to enhance research on reproductive environmental health—Key areas include improving research design to: better identify developmental effects that can occur from exposures during important reproductive windows: track impacts that can be passed on through multiple generations; assess low dose effects and effects from multiple exposures to chemicals; and develop improved and faster screening technologies to more quickly identify potentially harmful chemicals.

3) Improve the use of science in decision making—Participants noted that there are a number of steps between development of scientific findings and then using those findings to make decisions in a policy context. The process for doing this can be complicated and highly technical. Further efforts should focus on: acknowledging uncertainty in the science and allowing for action in the face of this uncertainty; increasing steps to limit undue influence or bias in the review process; and incorporating low dose effects and exposure to multiple chemicals into decision making and risk assessment.

4) Right to know: improve information given to consumers and workers on environmental contaminants in products—Participants identified the need to address the inadequacies of consumer product labeling and Material Safety Data Sheets, as well as the obstacles that trade secret protections place on accessing information on consumer product ingredients.

Community Action

Summit participants gathered to talk about the science in the context of environmental justice, occupational health and reproductive justice. Participants noted that learning about potentially hazardous chemicals in everyday products and in the workplace and their effects on babies *in utero* are powerful personal motivators toward further education and activism. However, placing the responsibility on women to avoid everyday toxins such as mercury in fish or hazardous chemicals in common household products is not an effective strategy for protecting reproductive health. Efforts by community members, scientists, epidemiologists, clinicians, activists, communications strategists and spokespeople will be more successful if they work towards a reformed and improved public health policy that adequately regulates chemicals and reduces exposures.

Safe Work

Participants in the Safe Work break out group discussed the implications of the science and key needs for improving worker health and safety. The group noted that more attention needs to be paid to workers' exposures within the area of environmental health. Their discussion also echoed themes from some of the groups, such as the need for better communication of the science, and improved methods for making decisions in the face of uncertainty that consider worker health. They also identified some unique needs of workers and proposed the following:

- Reduce permissible exposure levels to chemicals that harm reproduction and development so that they are more in line with environmental exposure limits. In addition, permissible exposure limits should reflect the toxicity of exposure to mixtures of chemicals used in the workplace, rather than exposure to chemicals individually.
- Exposure assessment and monitoring in occupational settings should be expanded.
- Expand occupational health researchers' access to workers so that health consequences can be identified and corrected.
- Develop alliances that can improve health across different sectors.

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For example, making the connections between worker safety and hospital patient safety (concerning phthalates) and fostering alliances between environmental health groups and labor and worker groups.

Conclusions

The Summit provided a view of critical scientific information that underscored the need for further efforts in areas to improve reproductive health. One common theme throughout the Summit was communication and collaboration. Scientists bring unique and important contributions to studying the impact of environmental contaminants on reproductive health. A goal of moving forward from the Summit is to bring together epidemiologists, basic scientists, clinicians and clinician researchers to approach the study of environmental contaminants on reproductive health in an integrated way. However, such research is most valuable and could be of highest benefit for human health if it is conducted in collaboration with health-affected and community based groups that can facilitate focusing research questions on the most pressing issues of the most affected constituencies.. Communication across scientific disciplines and among scientists, health care providers, health-affected groups and the public, as well as efforts in research, education and policy, are key to reducing the adverse impacts of environmental contaminants and enhancing the reproductive health of this and future generations.

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Abbreviations

AMH
anti-mullerian hormone

BPA
bisphenol A

CDC
US Centers for Disease Control and Prevention

CIS
carcinoma-in-situ

DBCP
dibromochloropropane

DBP
di(n-butyl phthalate

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DBPs
disinfection byproducts

DDE
dichlorodiphenyldi-chloroethylene

DDT
dichlorodiphenyl-trichloroethane

DEHP
di(2-ethylhexyl phthalate

DES
diethylstilbestrol

E2
estradiol

EDCs
endocrine disrupting chemicals

ETS
environmental tobacco smoke

HCB
hexachlorobenzene

Insl3
insulin-like factor 3

IUGR
intrauterine growth retardation

PCBs
polychlorinated biphenols

PIN
prostatic intraepithelial neoplasia

PTMC
peritubular myoid cell

SCO
Sertoli cell only

TCDD
2,3,7,8 tetrachlorodibenzo-p-dioxin

TDS
testicular dysgenesis syndrome

TGCC
testicular germ cell cancer

UCSF
University of California San Francisco

US
United States

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Environmental Reproductive Health: Interdisciplinary study of exposures to environmental contaminants, particularly during critical periods in development (such as prior to conception and during pregnancy), and their potential effects on all aspects of future reproductive health throughout the life course, including conception, fertility, pregnancy, child and adolescent development, and adult health.

Environmental Contaminants: synthetic chemicals and metals in our environment, including air, water, soil, food, consumer products, and the workplace.

Reproductive Health: Ability to conceive, to carry a pregnancy, pregnancy quality and outcomes, pubertal effects and adult reproductive health disorders.

Figure 1.
Key Definitions for Environmental Reproductive Health

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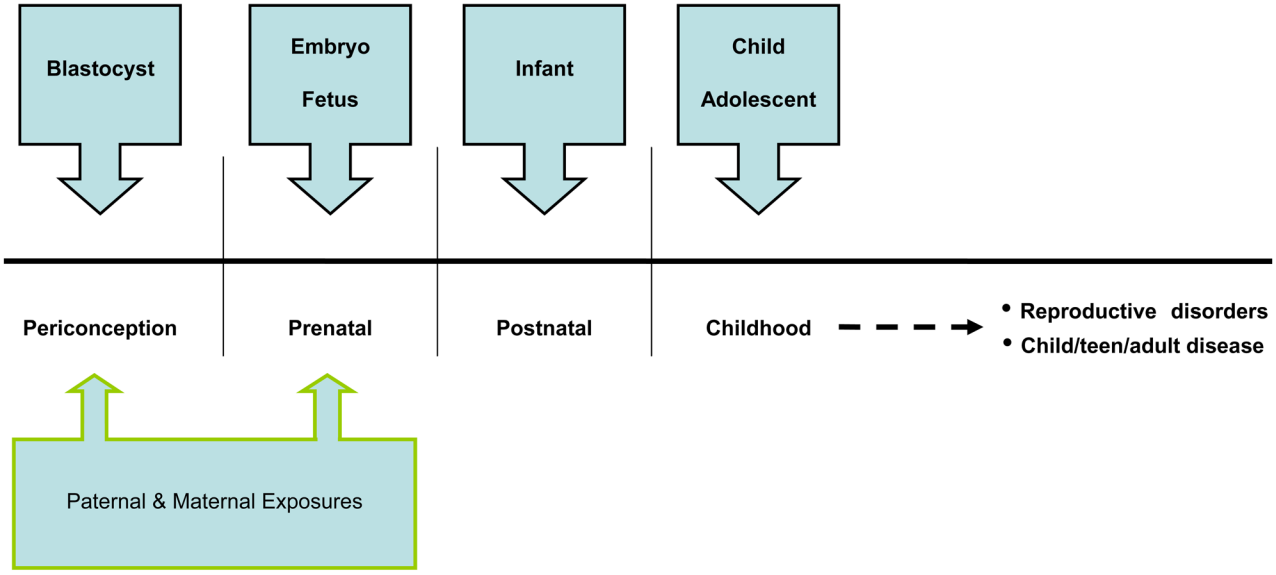

Figure 2. Windows of Susceptibility to Environmental Insults
Adapted from (253).

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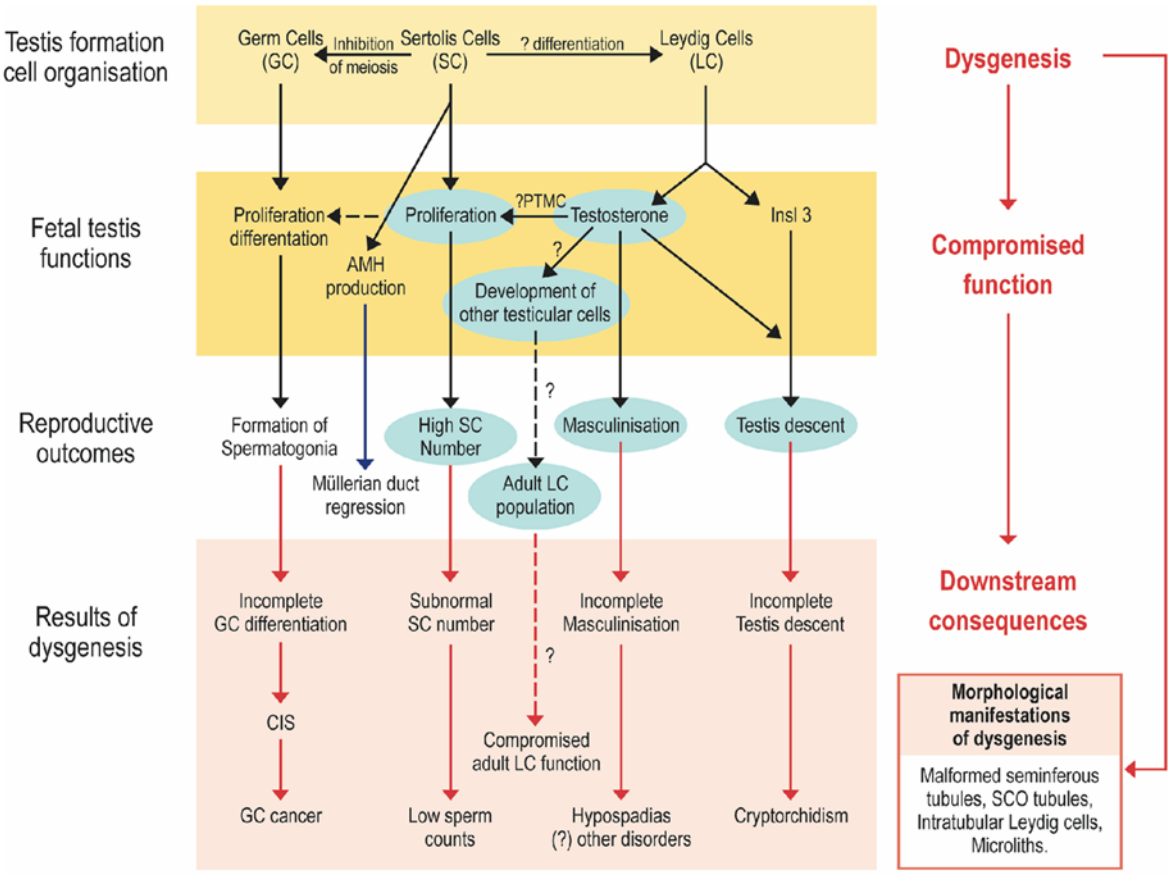

Figure 3.

Schematic diagram to illustrate how dysgenesis of the early fetal testis is thought to lead to abnormalities of somatic cell function, resulting in hormonal changes and the downstream disorders that comprise testicular dysgenesis syndrome (TDS). The central role of testosterone is highlighted by the blue boxes. Dashed lines show pathways that are hypothesized but unproven (68).

Abbreviations: PTMC=peritubular myoid cell; Insl3=insulin-like factor 3; AMH=anti-mullerian hormone; CIS=carcinoma-in-situ; SCO=Sertoli cell only.

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Table 1

Environmental Contaminants: Sources and Selected Health Effects from Developmental and Adult Exposures (Adapted from [254])

	Contaminant	Sources	Examples of health effects associated with exposure during adulthood (animal and/or human data)	Examples of health effects associated with exposure during development (animal and/or human data)
OTHER	Air Pollution	Common air pollutants include carbon monoxide, lead, ground-level ozone, particulate matter, nitrogen dioxide, and sulfur dioxide. Air pollution arises from a variety of sources, including motor vehicles, industrial production, energy (coal) production, wood burning, and small local sources such as dry cleaners.	fetal loss[d] (254)	low birth weight (254) preterm delivery (254)
	Bisphenol A (BPA)	Industrial chemical and building block for polycarbonate plastic and epoxy resins. Found in the lining of metal food and drink cans, plastic baby bottles, pacifiers and baby toys, dental sealants, computers, cell phones, hard plastic water bottles, paints, adhesives, enamels, varnishes, CDs and DVDs, and certain microwavable or reusable food and drink containers.	oocyte (egg) chromosome abnormalities (162) recurrent miscarriage (160) decreased semen quality (180,181)	altered puberty onset (182) obesity (182) altered prostate development (183,184) decreased semen quality (181, 185) hormonal changes (185)
	Disinfection by-products	Over 600 compounds formed by the reaction of chemical disinfectants (most often chlorine) with natural organic matter, primarily in surface waters. Most prevalent compounds are trihalomethanes.	menstrual irregularities (131,186)	fetal growth, IUGR (177–179)
	Ethylene oxide	Chemical sterilant used in dental and medical practices.	fetal loss[^] (187, 188) decreased semen quality[*] (188) miscarriage in female partner (188)	
	Glycol ethers	Used in paints, varnishes, thinners, printing inks, electronics, semi-conductor industry, leather, photographic film, varnish, enamels, cosmetics, perfumes, brake fluids, wood stains.	longer mentral cycles (135) decreased semen quality[*] (100, 189) reduced fertility[‡] (190, 191) fetal loss[^] (189,190)	
	Pesticides	Broad category that includes many classes of insecticides, fungicides, herbicides, rodenticides, and fumigants. Pesticides are used on food, in residential and industrial settings. Exposures can occur through food, drinking water, or from in home use.	menstrual irregularities (133,166) reduced fertility[‡] (147, 148, 188, 192) decreased semen quality[*] (189,193–195) miscarriage in female partner (151, 153,196,197) sperm chromosome abnormalities (198,199) hormonal changes (100,193,200)	altered sex ratio (100,201) altered puberty onset (202–204) malformations of reproductive tract[^] (205–207) reduced fertility (193,208) fetal growth, IUGR (209–211)
	Phthalates	Plasticizers added to soften plastics like PVC; also found in cosmetics, perfumes, toys, pharmaceuticals, medical devices, lubricans and wood finishers.	altered (earlier) menarche onset (127) estrous cycle, ovulatory irregularities (187) decreased semen quality[*] (212) reduced fertility[‡] (213) fetal loss[^] (187) endometriosis (141,142)	shortened anogenital distance (214) malformations of reproductive tract (215) hormonal changes (215) decreased semen quality[*] (215)
	Solvents	Benzene, toluene, xylene, styrene, 1-bromopropane, 2-bromopropane, perchloroethylene, trichloroethylene, and others. Solvents include some of the top production volume chemicals in the US Used in plastics, resins, and nylon, synthetic fibers,	hormonal changes (100,187,216) menstrual irregularities (187,188,193) decreased semen quality[*] (100, 188, 217, 218) reduced fertility[‡] (188, 218–222)	

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	Contaminant	Sources	Examples of health effects associated with exposure during adulthood (animal and/or human data)	Examples of health effects associated with exposure during development (animal and/or human data)
		rubbers, lubricants, dyes, detergents, drugs, pesticides, glues, paints, paint thinners, fingernail polish, lacquers, detergents, printing and leather tanning processes, insulation, fiberglass, food containers, carpet backing, cleaning products, and a component of cigarette smoke. Exposure is primarily through breathing contaminated air.	fetal loss^ (187,188,193,223) miscarriage in female partner (188)	
	Cigarette smoke	Includes active and/or passive smoking	hormonal changes (219,224) decreased semen quality* (219) reduced fertility‡ (188,219) miscarriage (219) early menopause (219)	IUGR (225) Low birth weight (225) Preterm delivery (225) decreased semen quality* (124, 226)
	Pharmaceuticals	Examples: DES, ethynylestradiol (birth control pill)		malformations of reproductive tract^ (227, 228) altered hormone response (228) menstrual irregularities (187, 227) reduced fertility‡ (187,227) uterine fibroids (227) miscarriage (187)
	Perfluorinated compounds (PFOS, PFOA)	Used to make fabrics and carpets stain-resistant and water-repellant; in coating of cooking pans, floor polish, insecticides, food wrap coatings. Accumulate in the environment and the food chain.		hormonal changes (229) reduced birth weight (230) fetal loss (230,231)
	Polybrominat ed Diphenyl Ethers (PBDEs)	Flame retardants found in furniture foam, mattresses, textiles, computers and electronics. Accumulate in the food chain.		decreased semen quality* (232)
	Octylphenol, Nonylphenol	Used to make surfactants (detergents), pesticides, paints, and other formulated products, and also as plasticizers and UV stabilizers in plastics. Primary exposure is through drinking water contaminated by sewage and wet-weather runoff.		hormonal changes (227) altered puberty onset (233) hormonal changes (185,234) decreased semen quality* (185, 235) decreased testes size (234,235)
CHLORINATED HYDROCARBONS	dioxins/furans	Byproducts of the manufacture and burning of products that contain chlorine.	menstrual irregularities (132,134,137, 140,166,187,236) hormonal changes (138–140,187,193, 236) reduced fertility‡ (187, 236) endometriosis (187, 237, 238) fetal loss^ (144, 236, 239) decreased semen quality* (236,239, 240) altered puberty onset (127,129,241) altered menarche onset (126,128,241, 242)	malformations of the reproductive tract^ (236, 243-245) altered estrous cycle (227) reduced fertility‡ (227) altered sex ratio (100, 186, 187, 236, 246) altered puberty onset (126, 241) decreased semen quality* (91, 243) delayed time to pregnancy (247)
	Polychlorinated biphenols PCBs	Industrial insulators and lubricants. Banned in the US in 1976. Persist for decades in the environment. Accumulate up the food chain.		
	Organochlorine pesticides	Class of pesticides used largely as insecticides. (ex: DDT, chlordane, HCB.) Largely banned in the US Persist for decades in the environment. Accumulate up the food chain.		
	pentachlorophenol	Wood preservative for utility poles, railroad ties, and wharf pilings. Formerly used as a pesticide.		
METALS	lead	Used in batteries, ammunition, metal products, X-ray shields. Reduced use in gasoline, paints, ceramic products, caulking, and pipe solder. Most common source of exposure in the US is lead-based paint in older homes, lead-	fetal loss^ (187, 217, 248) reduced fertility‡ (100,187,193,217, 249,250) hormonal changes (100,187,193,251) menstrual irregularities (130,187) abnormal sperm (94,100,252)	hormonal changes (227) altered puberty onset (84,126)

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	Contaminant	Sources	Examples of health effects associated with exposure during adulthood (animal and/or human data)	Examples of health effects associated with exposure during development (animal and/or human data)
		contaminated house dust and soil and vinyl products.	altered puberty onset (124–126)	
	mercury	Used in thermometers, dental fillings, batteries, vaccines and other industries. Air and water contaminated by industrial emissions and the combustion of coal and waste. Accumulates in food chain; most common source of exposure in US is contaminated seafood.		
	manganese	Used in the production of batteries, in dietary supplements, and as ingredients in some ceramics, pesticides, and fertilizers. Gasoline additive.		
	cadmium	Used in industry and consumer products, mainly batteries, pigments, metal coatings, plastics, and some metal alloys.		

[*] decreased semen quality could include low semen volume, abnormal sperm shapes or motility, decreased sperm counts.

[♯] - reduced fertility could include both infertility and increased time to pregnancy (reduced fecundity).

[Δ] menstrual irregularities could include short or long menstrual cycles, missed periods, abnormal bleeding, anovulation.

[^] malformations of the reproductive tract: In males, could include shortened ano-genital distance in animals or hypospadias (humans), undescended testicles (cryptorchidism), small testicles (hypoplasia), and structural abnormalities of the epididymis. In females, could include small ovaries, reduced number of follicles (eggs), and structural abnormalities of the oviducts, uterus, cervix, and/or vagina.

IUGR=intrauterine growth retardation; DDT=dichlorodiphenyltrichloroethane; DES=diethylstilbestrol; HCB=hexachlorobenzene.