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Exposure to endocrine disruptors during adulthood: Consequences for female fertility

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Abstract

Endocrine disrupting chemicals are ubiquitous chemicals that exhibit endocrine disrupting properties in both humans and animals. Female reproduction is an important process, which is regulated by hormones and is susceptible to the effects of exposure to endocrine disrupting chemicals. Disruptions in female reproductive functions by endocrine disrupting chemicals may result in subfertility, infertility, improper hormone production, estrous and menstrual cycle abnormalities, anovulation, and early reproductive senescence. This review summarizes the effects of a variety of synthetic endocrine disrupting chemicals during adult life. The chemicals covered in this review are pesticides (organochlorines, organophosphates, carbamates, pyrethroids, and triazines), heavy metals (arsenic, lead, and mercury), diethylstilbestrol, plasticizer alternatives (di-(2-ethylhexyl) phthalate and bisphenol A alternatives), 2,3,7,8-tetrachlorodibenzo-p-dioxin, nonylphenol, polychlorinated biphenyls, triclosan, and parabens. This review focuses on the hypothalamus, pituitary, ovary, and uterus because together they regulate normal female fertility and the onset of reproductive senescence. The literature shows that several endocrine disrupting chemicals have endocrine disrupting abilities in females during adult life, causing fertility abnormalities in both humans and animals.

Keywords

endocrine disrupting chemicals; adult; female; fertility

Introduction

EDCs are chemicals that disrupt endocrine properties in animals by either mimicking or blocking endocrine actions. Specifically, EDCs can interfere with receptor binding, steroidogenesis, and metabolism of hormones (Sanderson 2006; Sweeney 2002). EDCs have been shown to disrupt female fertility in a wide range of species including humans (Figure 1 and Figure 2) (Patel et al. 2015; Woodruff and Walker 2008).

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Declaration of Interest

The authors have no conflicts of interest that could be perceived as prejudicing the impartiality of the research reported.

Multiple recent reviews have previously summarized the effects of developmental exposure to EDCs (Katz et al. 2016; Walker and Gore 2016; Zama and Uzumcu 2010). Thus, this review focuses on adult exposure to synthetic EDCs such as pesticides (organochlorines, organophosphates, carbamates, pyrethroids, and triazines), heavy metals (arsenic, lead, and mercury), diethylstilbesterol, plasticizer alternatives (di-(2-ethylhexyl) phthalate and bisphenol A alternatives), 2,3,7,8-tetrachlorodibenzo-p-dioxin, nonylphenol, polychlorinated bisphenyls, triclosan, and parabens (Figures 1 and 2, Table 1). Further, this review focuses on the effects of the selected EDCs on the hypothalamus, pituitary, ovaries, and uterus in the adult female because normal function of these organs is required for normal fertility and onset of reproductive senescence.

Pesticides

Pesticides are a group of agents used as insecticides, fungicides, herbicides, and rodenticides. Based on chemical composition, the major classes of pesticides include: 1) organochlorines (e.g., dichlorodiphenyltrichloroethane (DDT)), lindane, endosulfan, aldrin, dieldrin, chlordane, and methoxychlor), 2) organophosphates (e.g., parathion, malathion, diaznon, and glyphosate), 3) carbamates (e.g., carbaryl, carbofuran, and aminocarb), 4) pyrethroids (e.g., permethrin, cypermethrin, deltamethrin), and 5) triazines (e.g., atrazine). These pesticides have been shown to impair female reproduction by targeting a variety of reproductive tissues and functions. The sections below summarize some of the impacts of pesticide exposure on the hypothalamus, pituitary, ovary, uterus, fertility, and reproductive senescence (Figure 1 and Figure 2).

Hypothalamus and Pituitary

Currently, limited information is available on the effects of pesticide exposure during adulthood on the hypothalamus/pituitary (Figure 1 and Figure 2). The organophosphate pesticide chlorpyrifos (0.01 – 100 μ M) and the organochlorine pesticide methoxychlor (0.01 – 100 μ M) significantly increased gonadotropin releasing hormone (GnRH) mRNA levels in GT1-7 cells (Gore 2001). The carbamate molinate (25 and 50 mg/kg) suppressed LH pulse frequency, leading to delayed ovulation in rats (Stoker et al. 2005). Atrazine (75 mg/kg) both activated the release of pituitary hormones (Fraits et al. 2009) and it (100 – 200 mg/kg) inhibited LH release from the pituitary in rats (Foradori et al. 2011; Goldman et al. 2013).

Ovary

Although limited information is available on the effects of pesticides on the human ovary (Figure 1), animal studies have indicated that organochlorine pesticides adversely affect the ovary by reducing ovarian weight, follicle growth, and oocyte viability and/or increasing atresia (Figure 2) (Borgeest et al. 2002; Tiemann 2008). For example, methoxychlor (32 – 200 mg/kg/day) decreased ovarian weight, increased the incidence of cystic ovaries, inhibited follicle growth, and induced atresia in rodents (Aoyama and Chapin 2014; Aoyama et al. 2012; Basavarajappa et al. 2012; Borgeest et al. 2004; Gupta et al. 2007; Gupta et al. 2009; Miller et al. 2005; Paulose et al. 2011; Paulose et al. 2012). Endosulfan (0.02 and 0.1 μ g/mL) decreased oocyte viability and competence in buffalo oocytes *in vitro* (Nandi et al. 2011). It (11 mg/kg) also decreased the number of healthy follicles and increased the

number of atretic follicles in rats (Koc et al. 2009). Malathion (1 and 10 nM) increased apoptosis in granulosa cells from goats (Bhardwaj and Saraf 2016). Similarly, pyrethroids (50 mg/kg) increased atresia in rats (Sangha et al. 2013) and a carbamate pesticide (2.5 and 1 mg/kg body weight) decreased the number of small follicles in mice (Shanthalatha et al. 2012).

Pesticide exposure also adversely affects the ability of the ovary to produce sex steroid hormones in women and animal models. For example, exposure to the organochlorine pesticide heptachlor was associated with a slower drop in the estradiol ratio and progesterone metabolites after ovulation in women (difference from estimated marginal mean of -2.00 was 0.263 with 95% CI: -0.001, -0.528) (Luderer et al. 2013). The organochlorine pesticides DDT and p,p'-dichlorodiphenyldichloroethylene (DDE) were associated with decreased progesterone levels and a shorter luteal phase in women (1.5 days at the highest quartile of DDT: 95% CI: -2.6, -3.0; or DDE: -2.6, -2.0) (Windham et al. 2005). The organochlorine pesticide methoxychlor (1 – 100 µg/mL) inhibited the production of estradiol, testosterone, androstenedione, and progesterone in isolated mouse antral follicles (Basavarajappa et al. 2011). The pyrethrin pesticide cypermethrin (50 mg/kg body weight) inhibited the activity of 3β-hydroxysteroid dehydrogenase (the enzyme that synthesizes progesterone production) in rats (Sangha et al. 2013) and it (10 – 100 ppm) inhibited progesterone secretion in the bovine corpus luteum (Gill et al. 2011). Atrazine (200 and 300 mg/kg) increased steroidogenic enzymes and sex steroid hormone levels *in vivo* (Quignot et al. 2012; Taketa et al. 2011). Further, atrazine (300 mg/kg) increased the estrogen-to-androgen ratio in rats (Quignot et al. 2012). It (10 µM) also increased progesterone and estradiol production and activity of aromatase (the enzyme that synthesizes estradiol from testosterone) in primary rat granulosa cells (Tinfo et al. 2011), and it (0.1 and 10 µM) disrupted steroidogenesis in swine granulosa cells (Basini et al. 2012).

Uterus

Several studies have indicated that pesticides can disrupt uterine structure and/or function in animal models (Figure 2) (Gore et al. 2015). For example, the organochlorine pesticide methoxychlor (500 and 1,500 ppm) increased uterine weight in rats (Aoyama et al. 2012; Yu et al. 2013), whereas carbendazim (500 mg and 1,000 mg/kg) decreased uterine weight in rats (Rama et al. 2014). Additionally, a mixture of organophosphate pesticides (dichlorovos, dimethoate, and malathion) (107.5 mg/kg) increased endometrial hyperplasia in rats (Aoyama et al. 2012; Yu et al. 2013). Expression profiling studies suggest that the organochlorine o,p-DDT (1 – 300 mg/kg) elicited estrogenic responses in uteri from immature ovariectomized mice and rats (Kwekel et al. 2013). However, pyrethroid metabolites (1 – 10 mg/kg) did not affect uterine weight in rats (Laffin et al. 2010).

Fertility

Several studies show that pesticide exposure is associated with reduced fertility in women and animal models. For example, 2,2',4,4',5,5'-hexachlorobiphenyl (CB-153) and DDE exposure were associated with an increased risk of fetal loss in women (CB-153 odds ratio (OR): 2.4, 95% CI: 1.1, 5.5; DDE OR: 2.5, 95% CI: 0.9, 6.6) (Toft et al. 2010). Organochlorine pesticide exposure was associated with an increased time to pregnancy in

women (fecundability odds ratio (FOR): 0.46, 95% CI: 0.32, 0.66) (Chevrier et al. 2013). Furthermore, a mixture of organophosphate pesticides (43 and 107.5 mg/kg) (dichlorovos, dimethoate, and malathion) decreased pregnancy and live birth rates in Sprague-Dawley rats (Yu et al. 2013).

Reproductive Senescence

Limited data exist on the impact of pesticide exposure on reproductive senescence, but one cross-sectional showed that women with high levels of β -hexachlorocyclohexane and mirex had an earlier mean age at menopause compared to women with low levels of β -hexachlorocyclohexane and mirex (β -hexachlorocyclohexane average change in age of menopause β (SE) years: -0.07 (0.138); and mirex average change in age of menopause β (SE) year: -0.54 (0.084)) (Grindler et al. 2015). Another cross-sectional study showed that women with high serum levels of DDT, DDE, and β -hexachlorocyclohexane had an early age at menopause (5.7, 3.4, and 5.2 years earlier, respectively) (Akkina et al. 2004). Further, a case-control study showed that DDE exposure was borderline associated with an early age at natural menopause (OR: 1.4, 95% CI: 0.9, 2.1) (Cooper et al. 2002). Perinatal exposure to the organochlorine pesticide methoxychlor (20 μ g/kg and 100 mg/kg) advanced the onset of reproductive senescence in rats (Gore et al. 2011). In contrast, the Agricultural Health Study showed that women who use pesticides have a later age at menopause (about 5 months) than women who do not use pesticides (hazard ratio: 0.77, 95% CI: 0.65, 0.92) (Farr et al. 2006).

Overall, several studies show that pesticide exposure impairs female reproduction by targeting a variety of reproductive tissues and function. Although the majority of studies report adverse effects of pesticide exposure, some studies report conflicting results. The divergent results may be due to inherent differences between animal models and humans, genetic variability between humans and animal strains/species, chemical exposures, and doses. Additionally, the mechanism of action for pesticide exposure should be further investigated to aid in the understanding the impact of chemical exposure on human and animal health.

Heavy Metals

Humans are exposed to a variety of heavy metals through several different routes such as cigarettes, alcoholic drinks, dietary supplements, and contaminated food, air, and water (Mathur and D'Cruz 2011). Specifically, arsenic (As) can be found naturally in the environment. Humans are generally exposed to As through ingestion of contaminated food and water. Some geographical areas have naturally higher levels of As in soil and ground water than others, resulting in an increased level of exposure for residents in that area (Ferguson et al. 2013). Lead (Pb) exposure can occur through inhalation of fossil fuel combustion products, drinking water contaminated by Pb used in pipes, and ingestion or inhalation of flakes of Pb-based paints (Ferguson et al. 2013). Human exposure to Pb via contaminated air and food is roughly equal (Rzymiski et al. 2015). Mercury (Hg) is another heavy metal that can be found in air, soil, and fresh and salt waters. Human exposure to Hg can occur via inhalation as well as ingestion (Rzymiski et al. 2015); however, the most common exposure route is ingestion of contaminated fish (Ferguson et al. 2013). Recent

epidemiological and experimental studies focusing on the associations and the effects of heavy metal exposure on female reproduction are summarized in the sections below.

Hypothalamus and Pituitary

Information on heavy metal exposure and the effects on the hypothalamus and pituitary are scarce (Figure 1 and Figure 2). One study using data from 485 women who participated in the National Health and Nutrition Examination Survey (NHANES) reported an inverse association between inorganic Hg concentrations in the blood and LH levels (β coefficient: -0.0044 , 95% CI: -0.0071 , -0.0016 ; $p=0.003$) (Laks 2009). Similarly, exposure to Pb (0.05 mg/kg/day) decreased fluidity of the pituitary membrane in rats, a scenario that can impair secretion and receptor binding (Pillai et al. 2002). Further, sodium arsenite exposure (4 $\mu\text{g/mL}$ and 0.4 ppm) via drinking water lowered levels of serum LH and follicle stimulating hormone (FSH) in rats (Chatterjee and Chatterji 2010; Chattopadhyay and Ghosh 2010). In contrast, Pb (0.05 mg/kg/day) exposure did not change circulating levels of LH, FSH, or dopamine in rats (Pillai et al. 2003).

Ovary

Epidemiological studies on the associations between heavy metal exposures and ovarian follicle numbers and health primarily focus on assisted reproductive technology outcomes (Figure 1 and Figure 2). One study reported that women undergoing IVF treatments in Taranto, Italy, an area known for environmental heavy metal contamination via industrial processes, have a significant elevation of follicular fluid concentrations of several heavy metals, including Pb (women in Taranto: 2.00 ± 2.01 vs. women outside Taranto: 0.68 ± 0.22 ; $p=0.003$). This study also found that women from Taranto have a significantly lower number of mature oocytes retrieved when compared to a control group living outside of Taranto (women in Taranto 6.7 ± 3.8 vs. women outside Taranto 9.5 ± 3.5 ; $p=0.03$) (Cavallini et al. 2016). Further, studies indicate that Hg concentration in hair is negatively correlated with oocyte yield (β : 0.38; $p<0.05$) and follicle number (β : 0.19; $p=0.03$) after ovarian stimulation (Dickerson et al. 2011) and that women with hair Hg concentrations above the EPA reference level of 1 ppm have significantly lower oocyte yields than those with hair Hg concentrations below 1 ppm ($p=0.04$) (Wright et al. 2015).

Few experimental studies examined the effects of heavy metal exposure on follicle numbers and follicle health (Figure 2). One study reported that exposure to sodium arsenite (0.4 ppm) via drinking water decreased ovarian weight and healthy follicle numbers and increased atresia in rats (Chattopadhyay and Ghosh 2010). Another study showed that dermal exposure to creams that contain high Hg levels caused significant accumulation of Hg in mouse ovaries (87.79 ± 26.20 ng/g and $3,515.61 \pm 1,099.78$ ng/g), which could alter reproductive outcomes (Al-Saleh et al. 2009).

Uterus

Limited data exist on the associations between heavy metal exposure and uterine outcomes (Figure 1 and Figure 2). Urinary levels of Pb and blood levels of Hg were significantly associated with fibroids in a sample of 99 women with fibroids and 374 control women (adjusted odds ratio (AOR): 1.31, 95% CI: 1.02, 1.69) (Johnstone et al. 2014). Sodium

arsenite exposure via drinking water (4 µg/mL and 0.4 ppm) resulted in a decrease of uterine size, fewer invaginations of the uterine lumen, reduced height of luminal epithelial cells, fewer endometrial glands, and thinner myometrium in rats (Chatterjee and Chatterji 2010; Chattopadhyay and Ghosh 2010). Further, sodium arsenite exposure through drinking water (4 µg/mL) downregulated both mRNA expression and protein levels of ER α and reduced expression of vascular endothelial growth factor (VEGF), an estrogen responsive gene in the rat endometrium (Chatterjee and Chatterji 2010).

Fertility

Very few epidemiological studies have examined the associations between heavy metal exposure and fertility outcomes. Some studies reported associations between blood Pb levels and infertility (mean blood level of lead in women with unexplained infertility 130.0 ± 45.2 vs. mean blood level of lead in control women 78.3 ± 36.4 µ/L; $p < 0.001$) (Rahman et al. 2013). Further, studies reported reduced fertility among dental health care workers who performed procedures that exposed them to Hg (fecundability ratio (FR): 0.63, 95% CI: 0.42, 0.96) (Colquitt 1995). Additionally, a significantly negative association was observed between blood Hg levels and fecundity in first time pregnant mothers (FR: 0.22, 95% CI: 0.07, 0.72) (Cole et al. 2006). Consistent with epidemiological studies, experimental studies showed that sodium arsenite in the drinking water (4 µg/mL and 0.4 ppm) caused constant diestrus in rats (Chatterjee and Chatterji 2010; Chattopadhyay and Ghosh 2010). In contrast, some studies reported no associations between blood levels of As, Pb, or Hg with fecundity (Bloom et al. 2011; Buck Louis 2014), infertility (Tanrikut et al. 2014), and fertilization rates in women undergoing IVF (Wright et al. 2015).

Although limited information exists on heavy metal exposure and fertility, several epidemiological studies showed associations between heavy metal exposure and adverse pregnancy outcomes. Blood and serum Pb levels were significantly higher in women with pre-eclampsia than in women without pre-eclampsia (blood Pb levels in women with pre-eclampsia: 37.68 ± 9.17 µg/dL vs. blood Pb levels in women without pre-eclampsia: 14.5 ± 3.18 µg/dL; $p < 0.001$; and serum Pb levels in women with pre-eclampsia: 27.18 ± 2.13 µg/dL vs. serum Pb levels in women without pre-eclampsia: 18.23 ± 2.34 µg/dL; $p < 0.05$) (Jameil 2014; Motawei et al. 2013). Further, high levels of As in drinking water and blood Pb levels were significantly associated with increased odds of spontaneous abortion (As in drinking water OR: 1.98, 95% CI: 1.27, 3.10 and blood Pb levels OR: 1.8, 95% CI: 1.1, 3.1 for every 5 µg/dL increase in blood Pb) (Borja-Aburto et al. 1999; Quansah et al. 2015). In contrast, some epidemiological studies reported no associations between maternal urinary As levels (Rahman et al. 2010) or maternal blood Pb levels (Sengupta et al. 2015) and adverse pregnancy outcomes.

Further, environmental As exposure through drinking water, maternal blood As, maternal hair As, and urinary As levels have been associated with infants being classified as low birth weight, small for gestational age, or having a comparatively lower birthweight levels (maternal hair As levels β : -193.5 ± 90.0 ; $p = 0.04$ and urinary As levels (urinary monomethylarsonic acid (U-MMA) β : -24.4 ; 95% CI: $-46.8, -2.0$; $p = 0.03$) (Bloom et al. 2014; Huyck et al. 2007; Laine et al. 2015). Further, environmental exposure to Hg and

maternal blood Hg levels were significantly associated with reduced birth weight and low birth weight (0.29 – 0.62 ppm Hg in fish OR: 1.06, 95% CI: 1.02, 1.10; > 0.62 ppm Hg in fish OR: 1.04, 95% CI: 1.00, 1.09; total Hg blood levels 95% CI: –1.37, –0.13; inorganic mercury (iHg) 95% CI: –0.74, –0.08; and > 1.6 µg/L blood Hg level 95% CI: 1.04, 2.58) (Burch et al. 2014; Ou et al. 2015; Thomas et al. 2015). Similarly, high As levels in drinking water, urinary levels of As, (Laine et al. 2015) maternal blood Pb levels, placental Pb levels, maternal environmental Hg exposure, maternal hair Hg levels, and cord blood Hg levels were significantly associated with shortened gestation or preterm birth (As levels in drinking water p=0.018; urinary As levels –0.069 weeks gestation per unit increase in urinary inorganic arsenic (iAS), 95% CI: –0.13, –0.0043; p=0.03; maternal blood Pb levels OR: 5.51, 95% CI: 1.21, 25.15 for male infants only; > 0.17 – 0.29 ppm Hg in fish OR: 1.09, 95% CI: 1.06, 1.13; > 0.29–0.62 ppm Hg in fish OR: 1.09, 95% CI: 1.05, 1.13; maternal hair Hg levels AOR: 3.0, 95% CI: 1.3, 6.7; and cord blood Hg levels; p 0.05) (Ahmad et al. 2001; Bloom et al. 2014; Burch et al. 2014; Dallaire et al. 2013; Ferguson et al. 2013; Perkins et al. 2014; Xue et al. 2007). In contrast, one study conducted in Inner Mongolia, China reported that infants born in areas with the highest levels of As (> 100 µg/L) were heavier on average when compared to those born in the lowest levels of As (< 20 µg/L) (Myers et al. 2010). However, several studies reported no associations between maternal As exposure via drinking water (Bloom et al. 2014; Ferguson et al. 2013), maternal blood As levels (Bermudez et al. 2015; Thomas et al. 2015), cord blood As levels (Bermudez et al. 2015), maternal urinary levels of As or Hg (Bashore et al. 2014; Laine et al. 2015; Ou et al. 2015), maternal blood Hg levels (Al-Saleh et al. 2014), cord blood Hg levels (Al-Saleh et al. 2014; Bashore et al. 2014), maternal urinary Pb levels (Sun et al. 2014), maternal blood Pb levels (Al-Saleh et al. 2014; Sun et al. 2014; Thomas et al. 2015), or cord blood Pb levels (Al-Saleh et al. 2014; Torres-Sanchez et al. 1999) and infant birthweight or incidence of low birth weight or small for gestational age infants.

Overall, heavy metal exposure has been shown to interfere with female reproduction in both experimental and epidemiological studies. Although some epidemiological studies agree with each other, some show conflicting results. The contrasting results seen between epidemiological studies may be due to differing sample sizes, use of different tissue types to measure heavy metals, and/or genetic variation between populations that were sampled in each study. The animal studies report similar findings, but different heavy metal exposures often elicit different results.

Diethylstilbestrol

Diethylstilbestrol (DES) is a non-steroidal estrogen that was first synthesized in 1938. DES use was approved by the United States Food and Drug Administration and was prescribed to pregnant women until the 1970s to prevent spontaneous abortions (Giusti et al. 1995). The use of DES as an anti-abortive drug was based on the assumption that DES, which had biological properties similar to estrogen, would restore hormonal balance in the pregnant mother. In turn, this would theoretically result in reduced complications of pregnancies and prevent miscarriages (Smith and Smith 1949). Unfortunately, prenatal exposure to DES has been shown to impair female reproductive tract development and increase breast cancer risk

in offspring (Laitman 2002; Newbold et al. 2007; Tournaire et al. 2015). However, the effects of adult exposure to DES are less well studied, but are summarized below.

Hypothalamus and Pituitary

Currently, no information to our knowledge exists on the effects of adult exposure to DES on the hypothalamus and pituitary in women (Figure 1). However, daily exposure to DES (200 µg/kg body weight/day) suppressed serum LH and FSH levels in mice (Jaroenporn et al. 2007). Exposure to DES (5 mg/kg) also caused structural abnormalities in the pituitary gland such that the gland cavity size was decreased, but contained proliferated, tumor-like cells in rats (Zhao et al. 2010).

Ovary

Multiple studies demonstrated consistent effects of exposure to DES in adulthood on the ovary (Figure 1 and Figure 2). A common result seen from DES exposure (5 µg/g body weight and 50 – 2000 ppb) was a complete loss, degeneration, or a decrease in the number of corpora lutea in the adult ovary, suggesting that DES impaired ovulation (Hong et al. 2010; McAnulty and Skydsgaard 2005; Zhao et al. 2014). Additionally, DES exposure (200 µg/kg body weight/ day) decreased the numbers of primary, secondary, and pre-ovulatory follicles and increased atretic antral follicles in mice (Jaroenporn et al. 2007). DES (5 µg/g body weight and 250 – 2000 ppb) also caused atrophy of the ovary as well as the thickening and scarring of ovarian connective tissues in mice (Hong et al. 2010; McAnulty and Skydsgaard 2005). Further, DES (5 µg/g body weight) impaired reproductive activity in females by decreasing the maturation of ovarian follicles in mice (Hong et al. 2010).

Uterus

DES exposure during adulthood impairs the uterus (Figure 1 and Figure 2). Specifically, DES exposure (5 µg/g body weight) increased *Sdd2* mRNA expression, which promoted programmed cell death, and increased *Psat1* mRNA expression, which inhibits uterine neoplasia (Hong et al. 2010). Further, adult exposure to DES (200 µg/kg body weight/ day) increased the thickening of the uterine endometrium, increased dilatation of uterine glands, and increased secretory proteins in mice (Jaroenporn et al. 2007). Additionally, DES exposure (250 – 2000 ppb) increased endometrial glandular hyperplasia and caused accumulation of hyaline cartilage in the endometrium of mice (McAnulty and Skydsgaard 2005). Finally, DES exposure (50 ppb) caused mouse uterine horns to become distended (Zhao et al. 2014).

Estrous Cyclicity and Fertility

DES exposure alters estrous cyclicity and fertility in animal models. Specifically, daily DES treatment (200 µg/kg body weight/ day) caused cornification of the vaginal epithelium (Jaroenporn et al. 2007) and it (250 – 2000 ppb) caused keratinization of the vagina (McAnulty and Skydsgaard 2005). Further, it (200 µg/kg body weight/day, 5µg/g body weight, and 50 ppb) decreased female fertility in mice by interfering with embryo transport, implantation, uterine receptivity, and preimplantation embryo development (Hong et al. 2010; Jaroenporn et al. 2007; Zhao et al. 2014).

Overall, DES exposure in adulthood has been shown to impair female reproductive outcomes in experimental studies. However, it has not been extensively studied in adult animals or women and the mechanism of action remains unclear. Thus, additional studies are needed to further elucidate the mechanism by which DES impairs female reproduction in adult animals and women.

Plasticizer Alternatives

Phthalates and bisphenol A (BPA) are plasticizers used to confer flexibility to plastic products. One of the most common phthalates, di-(2-ethylhexyl) phthalate (DEHP), leaches out of products and causes toxic effects. The use of DEHP has been challenged by European authorities because of its toxic properties (Bernard et al. 2014). Therefore, manufacturers began to replace DEHP with alternative plasticizers such as tri-2-ethylhexyl trimellitate (TETM), di-(2-ethylhexyl) terephthalate (DEHT), di-(isononyl)cyclohexanedicarboxylic acid (DINCH), di-isononyl phthalate (DINP), di-(2-ethylhexyl) adipate (DEHA), and acetyl tri-n-butyl citrate (ATBC). Another plasticizer, BPA, is a known reproductive toxicant and endocrine disrupting chemical (Peretz et al. 2014; Ziv-Gal and Flaws 2016). Within the last decade some restrictions have been placed on the use of BPA in children's products and thermal receipt paper (Usman and Ahmad 2016), leading to the development of alternative bisphenol plasticizers such as bisphenol S (BPS), bisphenol B (BPB), bisphenol F (BPF), and bisphenol AF (BPAF) (Liao and Kannan 2014). These alternative bisphenols are structurally similar to BPA and are thought to have equivalent toxicological effects (North and Halden 2013), but this has not been studied in detail. The section below highlights the effects of DEHP and BPA alternatives on the hypothalamus, pituitary, ovary, uterus, fertility, and reproductive senescence in mammalian models.

Hypothalamus and Pituitary

Limited information is available on the effects of plasticizer alternatives on the adult mammalian hypothalamus and pituitary (Figure 1 and Figure 2). One study showed that the BPA alternative, BPF (20 – 500 mg/kg/day), did not alter histopathology in the rat pituitary (Higashihara et al. 2007).

Ovary

Few published studies report the effects of plasticizer alternatives on the adult mammalian ovary (Figure 1 and Figure 2). DEHA (1,000 and 2,000 mg/kg/day), a phthalate alternative, increased atresia in preantral and antral follicles (Miyata et al. 2006; Wato et al. 2009). ATBC (5 and 10 mg/kg/day), a phthalate alternative, decreased the numbers of primordial, primary, and secondary follicles, but did not alter the numbers of corpora lutea or atretic follicles in mouse ovaries (Rasmussen et al. 2016). In contrast the BPA analogue, BPF (20 – 500 mg/kg/day), did not cause histopathological changes in the rat ovary (Higashihara et al. 2007).

Uterus

Few studies have investigated the effects of BPA alternatives on the uterus (Figure 1 and Figure 2), but one study reported that BPF exposure (100 – 1,000 mg/kg/day) induced

uterine growth in rats, indicating estrogenic activity (Rochester and Bolden 2015). Similarly, BPS (20 and 500 mg/kg/day) exhibited estrogenic activity by increasing the rate of uterine growth in rats, possibly through a mechanism involving estrogen receptors (Rochester and Bolden 2015). In contrast, a different study reported that BPF (20 – 500 mg/kg/day) did not cause histopathological changes in the rat uterus (Higashihara et al. 2007).

Fertility

Several studies show that plasticizer alternatives affect fertility in females. Exposure to ATBC (100 – 1,000 mg/kg/day), a phthalate alternative, decreased the number of implantation sites and litter size in rats (CPSC 2010), but it (5 – 10 mg/kg/day) did not affect implantation rates or litter size in mice (Rasmussen et al. 2016). Another phthalate alternative, DEHA (400 – 1080 mg/kg/day), caused prolonged pregnancies, smaller pups, and increased pup mortality rates in rats (CPSC 2010; Dalgaard et al. 2003). Additionally, DEHA (2,000 mg/kg/day) increased preimplantation loss rates in rats (Wato et al. 2009). In contrast, TETM (100 – 1,000 mg/kg/day), another phthalate alternative, did not affect the reproductive ability of maternal dams, viability or body weights of offspring (Van Vliet et al. 2011). Similarly, DINCH (1,000 mg/kg body weight/day), a phthalate alternative, did not cause maternal toxicity in rats (as reviewed in Van Vliet et al. 2011). DINP exposure (300 – 900 mg/kg BW/day) during pregnancy did not cause changes in maternal body weight gain during pregnancy, gestational length, postimplantation loss, litter size, sex ratio, or perinatal loss in rats (Boberg et al. 2011). BPF exposure (20 – 500 mg/kg/day) did not alter estrous cycles in rats (Higashihara et al. 2007). In contrast, DEHA (1,000 and 2,000 mg/kg/day) decreased average estrous cycle length in rats (Wato et al. 2009) and ATBC (5 mg/kg/day) decreased average estrous cycle length in mice (Rasmussen et al. 2016).

Overall, information regarding the effects of plasticizer alternatives for DEHP and BPA on female reproduction is scarce. From the limited information presented, there are conflicting results. The differing results are primarily due to the use of different chemicals, varying doses, and use of different animal models. There is a push to replace DEHP and BPA products with plasticizer alternatives, however, the lack of information on these plasticizer alternatives is concerning. Thus, there is a need for studies to examine the effects of plasticizer alternatives on female reproduction.

TCDD

2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) is perhaps the most potent polychlorinated dibenzodioxin and it has a long biological half-life of 2 – 5 years (Tavakoly Sany et al. 2015). TCDD is formed as a by-product during organic synthesis and burning, and it is a persistent environmental contaminant. Humans have been exposed to TCDD accidentally through contamination from Agent Orange during the Vietnam War and through an industrial explosion in Seveso, Italy. Both accidents resulted in high and long term TCDD exposure in humans. Recent studies indicate human and animal exposure to TCDD still occur (Tavakoly Sany et al. 2015). In this section, we briefly summarize recent research findings on the effects of adult exposure to TCDD on female reproduction.

Hypothalamus and Pituitary

Studies have shown that exposure to TCDD in adulthood can affect the hypothalamus and pituitary (Figure 2). In rats, exposure to TCDD (0.3 – 60 µg/kg/day) reduced preovulatory peak concentrations of FSH and LH, however, the mechanism is not clear (as reviewed in Petroff et al. 2001). In pig pituitary cell cultures, exposure to TCDD (100 nmol/L) altered the secretion of prolactin during both the follicular and luteal phases and induced LH secretion during the follicular phase (Jablonska et al. 2011).

Ovary

Studies have shown that TCDD can adversely affect adult ovaries (Figure 1 and Figure 2). Exposure to TCDD (5 – 200 ng/kg/week, 32 µg/kg/day) caused a reduction in ovarian weight, inhibition of estradiol production, and reduced follicular maturation and ovulation in rats (as reviewed in Bhattacharya and Keating 2012; Petroff et al. 2001). TCDD (20 – 125 ng/kg/day *in vivo*; 0.1 nM – 10 µM *in vitro*) also altered the expression of several enzymes and hormone receptors involved in the ovarian steroidogenesis pathway in both animal and human studies (Hutz et al. 2006; Karman et al. 2012a; Karman et al. 2012b; Patel et al. 2015; Petroff et al. 2001).

Uterus

Adult exposure to TCDD induces adverse effects on uterine tissues (Figure 2). Acute and chronic TCDD exposure (100 ng/kg/day) induced uterine tissue inflammation and increased the incidence of uterine lesions in rats (Yoshizawa et al. 2009). TCDD (30 µg/kg) also caused anti-uterotrophic effects in ovariectomized mice by inhibiting estrogen-mediated gene expression (Boverhof et al. 2008). Moreover, TCDD (30 µg/kg/day) inhibited estradiol-mediated uterine epithelial function via the aryl hydrocarbon receptor (Buchanan et al. 2000). During implantation, exposure to TCDD (1 and 10 µg/kg/day) decreased the number of successfully implanted embryos in mice (Kitajima et al. 2004).

Fertility

Adult TCDD exposure can reduce fertility. The comprehensive Seveso Women's Health Study (SWHS) was conducted to examine the association between TCDD exposure and female fertility after an explosion in Italy exposed residents to high levels of TCDD (Eskenazi et al. 2000). This study found that TCDD exposure was associated with a longer time to pregnancy and infertility (time to pregnancy adjusted fecundability odds ratio (AFOR): 0.75, 95% CI: 0.60, 0.95; and infertility AOR: 1.9, 95% CI: 1.1, 3.2) (Eskenazi et al. 2010). In addition, another SWHS study showed that within the first 8 years after TCDD exposure in Italy, maternal serum TCDD levels were associated with lower birth weight and smaller gestational age (birth weight adjusted β : -92, 95% CI: -204, 19; and gestational age AOR: 1.4, 95% CI: 0.6, 2.9) (Eskenazi et al. 2003). In animal studies, TCDD (2 µg/kg body weight/day and 10 µg/kg) interfered with fertility parameters in mammalian species, including estrous cyclicity, time to pregnancy, maintenance of pregnancy, fetal development, and birth outcomes (as reviewed in Bhattacharya and Keating 2012; Hutz et al. 2006).

Reproductive Diseases and Senescence

TCDD exposure during different exposure windows has been associated with the occurrence of endometriosis in rodents, monkeys, and humans (Foster 2008; Rier 2002). In a recent epidemiology study, adult TCDD exposure was associated with an increased incidence of endometriosis (OR: 2.44, 95% CI: 1.04, 5.70; $p=0.04$) (Simsa et al. 2010). Moreover, in the SWHS study, serum TCDD levels were associated with an increased risk of early menopause in some women (20.4–34.2 ppt adjusted hazard ratio (AHR): 1.1, 95% CI: 0.7 – 1.8; $p=0.77$; 34.3–54.1 ppt AHR: 1.4, 95% CI: 0.9 – 2.3; $p=0.14$; 54.2–118 ppt AHR: 1.6, 95% CI: 0.9 – 2.6; $p=0.10$; and > 118 ppt AHR: 1.1, 95% CI: 0.6 – 1.9; $p=0.82$) (Eskenazi et al. 2005).

Several recent studies show that humans and animals are still exposed to dioxin in various ways (Tavakoly Sany et al. 2015). Available studies have shown that dioxins are reproductive toxicants and can interfere with several reproductive organs in females. These studies consistently show adverse effects of dioxins in women and animal models. Studies, however, are still needed to examine the potential and mechanisms of dioxin to human and animal health.

Nonylphenol

Nonylphenols (NP) are organic compounds with a nine-carbon alkyl chain bound to a phenol ring. NP is commonly used in pesticides, lubricating oils, and laundry or dish washing detergents. The demand for NP in 2010 was 380 million pounds in the United States (Careghini et al. 2015). Because of the widespread use of NP, it is present in soil and sediments, groundwater and surface water, food, and bottled water (Careghini et al. 2015). NP is a mixture of more than 100 isomers, but 4-NP makes up over 90% of the NP (Lu and Gan 2014).

Hypothalamus and Pituitary

Limited information is available on the effects of NP on the hypothalamus and pituitary (Figure 1 and Figure 2). In a Taiwanese study, 162 singleton pregnant women were recruited for a study designed to examine the association of urinary NP levels and sex steroid hormone levels in pregnant women (Chang et al. 2014). The results showed that urinary NP levels were negatively associated with maternal plasma LH levels, suggesting compromised LH negative feedback in the hypothalamus-pituitary-ovary axis during pregnancy (generalized estimating equation model, β : -0.23 ; $p<0.01$) (Chang et al. 2014). In adult ovariectomized rats, NP (10 mg injection) increased progesterone receptor mRNA in anterior pituitary, decreased the amplitude of LH pulses and mean LH levels without affecting LH pulse frequency, and attenuated LH secretory responsiveness to GnRH stimulation at the anterior pituitary level (Furuta et al. 2006).

Ovary and Uterus

Very few studies have been conducted on the effects of NP exposure on female reproductive organs (Figure 2). In a study that focused on the progesterone production by ovarian granulosa cells of rats, exposure to NPs (13 and 43 μM and 100 $\mu\text{g}/\text{kg}/\text{day}$) significantly

increased progesterone production by increasing steroidogenic acute regulatory protein expression in both *in vitro* and *in vivo* experiments (Yu et al. 2011). In guinea pigs, NP administration (40 mg/kg/day) prevented uterine weight decline after castration and induced weak estrogenic effects on uterine tissue to maintain relatively normal histology in castrated animals (Danzo et al. 2002). Similarly, in adult ovariectomized rats, NP exposure (50 mg/kg) increased uterine weight during the 3-day uterotrophic assay (Laws et al. 2000). Further, one study showed that the uterotrophic action of NP is a direct result of interaction of NP (2.5 mg/kg) and uterine estrogen receptors in rats (Odum et al. 2001).

Fertility

Information on the effects of NP on female fertility is limited. Exposure to NPs has been associated with negative birth outcomes in humans, but the results are inconsistent. High maternal NP exposure during the second trimester has been associated with reduced gestational age, decreased birth body length and birth weight, and lower maternal weight gain (gestational age OR: 7.8; $p < 0.05$; body length β : -0.47 ; $p = 0.04$; birth weight OR: 1.18 for the 50th percentile, 2.12 for the 25th percentile, and 7.81 for the 10th percentile; and maternal weight gain: β : -1.55 ; $p = 0.02$) (Chang et al. 2013; Tsai et al. 2013). However, a Chinese population-based study did not find any associations between NP exposure and negative birth outcomes (Tang et al. 2013). In animal studies, NP exposure (100 mg/kg) for 25 days significantly disrupted estrous cyclicity in rats (Laws et al. 2000).

Although NPs have been shown to be estrogenic and to have endocrine disrupting characteristics (Lu and Gan 2014; Ponzo and Silvia 2013), the effects of adult exposure to NPs on female fertility are not well studied. Given the wide use of NPs and their frequent detection in the environment (Lu and Gan 2014), more information is needed to determine the toxicity of NPs on female reproduction, especially their mechanisms of action.

Polychlorinated Biphenyls

Polychlorinated biphenyls (PCBs) are organochlorine compounds that were once widely manufactured worldwide for industrial use (Fernandez-Gonzalez et al. 2015). Although their production in the United States was banned in the 1970s and their use today is highly controlled, PCBs persist in the environment and accumulate in the food web (Bell 2014; Fernandez-Gonzalez et al. 2015). Different PCB congeners have been associated with reproductive dysfunction in females. The following sections summarize the effects of adult exposure to PCBs on the mammalian hypothalamus, pituitary, ovary, uterus, as well as fertility and reproductive senescence.

Hypothalamus and Pituitary

Current information is very limited on the effects of adult exposure to PCBs on the hypothalamus and pituitary (Figure 2). *In vitro* data suggest that PCB congeners (0.01 – 100 μM) caused an increase and then a decrease in mRNA and peptide levels of GnRH in hypothalamic mouse cells, and increased apoptosis of hypothalamic GnRH containing cells in a non-monotonic manner in mice (Bell 2014).

Ovary

Although PCB congeners have been shown to be present in the ovarian follicular fluid of women (0.37 /g wet weight), limited information is available on their effects on the human ovary (Figure 1) (Craig et al. 2011). One study found that contamination of human follicular fluid with endocrine disrupting chemicals including PCBs was associated with a decreased rate of *in vitro* fertilization and oocyte development into high-quality embryos (Petro et al. 2012). Studies in different experimental models and animals show that PCBs are able to alter ovarian steroidogenesis and oocyte health. For example, PCBs (1–100 ng/mL) decreased LH-stimulated luteal phase secretion of progesterone in bovine luteal cells, and altered the secretion of progesterone, testosterone, and estradiol in porcine ovarian follicular cells *in vitro* (Craig et al. 2011). Exposure to PCBs (12.5 – 50 mg/kg) also inhibited maturation and parthenogenetic activation of mouse oocytes *in vivo*, and increased apoptosis of cumulus cells (Liu et al. 2014). Additionally, PCB exposure in free-living female polar bears in Norway has been linked to decreased plasma levels of androstenedione and pregnenolone (Gustavson et al. 2015). Specifically, several hydroxylated PCBs were negatively associated with androstenedione levels: 3'-OH-CB180 ($r_s = -0.626$, $p = 0.022$), 3'-OH-CB138 ($r_s = -0.791$, $p = 0.001$), 4-OH-CB187 ($r_s = -0.626$, $p = 0.022$) and 4'-OH-CB172 ($r_s = -0.665$, $p = 0.013$), PCB-128 ($r_s = -0.543$, $p = 0.037$). Additionally, 4-OH-CB146 ($r_s = -0.643$, $p = 0.018$) and 4'-OH-CB172 ($r_s = -0.582$, $p = 0.037$) were negatively associated with pregnenolone levels (Gustavson et al. 2015).

Uterus

Very limited information is available on the effects of PCBs on uterine structure and function (Figure 1 and Figure 2). Chronic oral exposure to PCB congeners (1,000 and 4,600 µg/kg) is associated with an increased incidence of uterine squamous cell carcinoma in adult female rats (NTP 2010; Yoshizawa et al. 2009). Chronic oral exposure to PCBs (300 ng/kg – 3,000 µg/kg) also induced chronic active inflammation in rat uteri (Yoshizawa et al. 2009). A study of bovine reproductive tissues found that PCB exposure (1 – 100 ng/mL) increased myometrial contractility *in vitro* (Kotwica et al. 2006).

Fertility

Studies indicate that PCB exposure is associated with subfertility in women and animals. For example, a moderate to high PCB exposure index in women consuming contaminated fish is associated with shortened menstrual cycles (–1.03 days; 95% CI –1.88, –0.19) (Mendola et al. 1997). Exposure to different categories and congeners of PCBs in women has been consistently associated with a shorter duration of gestation (Dallaire et al. 2013; Kezios et al. 2012). For example, exposure to mono-*ortho* substituted PCBs is associated with a 2.1 day decrease in gestational length, whereas exposure to di-*ortho* substituted PCBs is associated with a 1.4 day reduction in gestational length (mono-*ortho* substituted PCB 95% CI: –4.13, –0.11; and di-*ortho* substituted PCB 95% CI: –2.9, 0.1) (Kezios et al. 2012). Several studies show that PCB exposure is also associated with diminished couple fecundity as measured by time to pregnancy, with a fecundability odds ratio < 1.0 denoting significantly reduced fecundability (reviewed in Buck Louis 2014). Certain PCB congeners may be associated with endometriosis (reviewed in Leon-Olea et al. 2014). Mono-ortho PCBs are associated

with anovulation (OR: 2.36, 95% CI: 1.06, 5.28) (Gallo et al. 2016). Further, several PCB congeners are associated with uterine fibroids in women (Trabert et al. 2015). For instance, PCB 99, PCB 138, PCB 146, PCB 153, PCB 196, and PCB 206 have been significantly associated with uterine fibroids (PCB 99 OR: 1.64, 95% CI: 1.08, 2.49; PCB 138 OR: 1.64, 95% CI: 1.03, 2.59; PCB 146 OR: 1.54, 95% CI: 1.01, 2.37; PCB 153 OR: 1.88, 95% CI: 1.12, 3.13; PCB 196 OR: 1.60, 95% CI: 1.02, 2.51; and PCB 206 OR: 1.52, 95% CI: 1.01, 2.29) (Trabert et al. 2015). Similarly, PCBs may be associated with reproductive abnormalities in exposed marine mammal populations. A study from the United Kingdom shows that PCB exposure (6 – 18.5 mg/kg) may be associated with abortion, dystocia, still birth, and increased risk of reproductive disease in porpoises (Murphy et al. 2015).

Reproductive Senescence

Limited information is available on the effect of PCBs on reproductive senescence, but one study in rats found that prenatal exposure to a PCB mixture (1 mg/kg) increased estrous cycle lengths throughout the life-cycle, suggestive of an aging phenotype (Walker et al. 2013).

In conclusion, there is currently limited information available from experimental studies about the impact of PCBs on the female reproductive system. More studies are needed to fully understand the effects and mechanism of action of different PCB congeners on the hypothalamus, pituitary, ovary, and uterus. This is especially important because there are well-documented associations between PCBs and subfertility in women and other mammalian species (Buck Louis 2014; Gallo et al. 2016; Mendola et al. 1997; Murphy et al. 2015), although it is difficult to ascertain whether these associations are a direct cause-effect relationship. Further investigation is needed of these associations and should include efforts to relate PCB exposure in human and animal populations to effects observed in laboratory studies.

Triclosan

Triclosan (5-chloro-2-(2,4-dichlorophenoxy) phenol) is an anti-bacterial agent that has been used in the United States for over 40 years. It is found in many personal care products and consumer products including anti-bacterial soap, mouthwash, toothpaste, surgical scrubs, and sutures (Fang et al. 2010). As of 2002, over 1,500 tons of triclosan were produced annually around the world (Dann and Hontela 2011). Triclosan usually enters the body by ingestion or dermal contact, but it has also been shown to enter the body from inhalation of products including spray deodorants or air fresheners (Yang et al. 2015). The different sections below summarize the effects of triclosan on female reproduction.

Hypothalamus, Pituitary, Ovary and Uterus

No information to our knowledge is available on the effects of triclosan on the hypothalamus and pituitary (Figure 1 and Figure 2). Further, very little information is available on the effects of triclosan on the ovary and uterus (Figure 1 and Figure 2). Dermal triclosan exposure (125 mg/kg body weight/day) decreased ovary weights in adult mice (Fang et al. 2015), but aerosol inhalation of triclosan (0 – 0.40 mg/L) did not affect ovary weights in rats

(Yang et al. 2015). Subcutaneous injections of triclosan (18 and 27 mg/day) decreased the number of implantation sites in the uteri of adult rats (Crawford and Decatanzaro 2012). Further, triclosan exposure (600 mg/kg/day) decreased gravid uterine weights in rats (Feng et al. 2016). Triclosan exposure decreased sex steroid hormone levels in rats. Specifically, pregnant rats exposed to triclosan (30 – 600 mg/kg/day) through oral gavage decreased progesterone, estradiol, testosterone, and prolactin levels (Feng et al. 2016).

Fertility

Few studies are currently available on the effects of triclosan on human and animal fertility. Triclosan exposure has been associated with a reduction in fecundity, suggested by an increased time to pregnancy (FOR: 0.84, 95% CI: 0.72, 0.97) (Velez et al. 2015). Triclosan in drinking water (1 – 50 mg/kg/day) decreased live birth index and 6-day survival index in rats (Rodriguez and Sanchez 2010). Further, triclosan (10 and 100 mg/kg) increased fetal loss rate percentage, increased abortion rate, and decreased the number of live fetuses in mice (Wang et al. 2015).

Overall, very few studies have examined the effects of triclosan on adult female reproduction in humans and other mammals. Although some studies report similar effects of triclosan exposure, others show conflicting results. The differing results between studies may be due to the use of different animal models or exposure routes. Because triclosan can be found in consumer products and personal care products, more studies are needed to determine whether and how triclosan exposure affects female reproduction.

Parabens

Parabens are a group of alkyl esters of p-hydroxybenzoic acid that are used as antimicrobial preservatives in personal care products and different foods. Besides being found in personal care products and food products, parabens are found in indoor dust. One study examined samples from the United States, China, Korea, and Japan discovered that the average paraben daily intake via ingestion of dust was 0.2 – 1.2 ng/kg/day (Wang et al. 2012). Estimated daily human exposure to parabens via personal care products was 5 – 50 µg/kg/day for adults and 15 – 230 µg/kg/day for infants and toddlers (Guo and Kannan 2013). The sections below discuss the known effects of parabens on female reproduction.

Hypothalamus, Pituitary, Ovary, and Uterus

To our knowledge, no information is available on exposure to parabens on the hypothalamus and pituitary and little information is available on the effects of paraben exposure during adulthood on the ovary and uterus (Figure 1 and Figure 2). In humans, increased levels of propylparaben (87.8 – 727 µg/L) were associated with a trend of lower antral follicle counts (estimated mean percent change in antral follicle count –16.3, 95% CI: –30.8, 1.3; p=0.07) (Smith et al. 2013). A study of Japanese university students showed that higher urinary estrogen-equivalent total paraben and butyl paraben concentrations were associated with shortened menstrual cycles (total paraben AOR: 0.73, 95% CI: 0.56, 0.96; p=0.027; and butyl paraben AOR: 0.83, 95% CI: 0.70, 0.99; p=0.037) (Nishihama et al. 2016). Further, subcutaneous exposure of multiple parabens (6 – 210 mg/kg) increased uterine weight in

ovariectomized mice (Lemini et al. 2003) and implants containing isobutylparaben (approximately 4.36 mg/L/day) increased dam uterine weights in rats (Kawaguchi et al. 2009).

Fertility

To date, few studies are available on the effects of parabens on animal and human fertility. In humans, maternal paraben exposure was positively associated with birth weight (β : 193, (-4 – 389)) (Philippat et al. 2014). A study examining a variety of parabens in pregnant mothers associated paraben concentrations with increased odds of preterm, decreased gestational age at birth, decreased birth weight, and decreased body length (butylparaben preterm birth OR: 60.77, 95% CI: 2.60, 1417.93; butylparaben gestational age β : -3.04, 95% CI: -5.09, -0.99; butylparaben birth weight β : -480.40, 95% CI: -976.68, 15.89; propylparaben body length β : -1.06, 95% CI: -2.06, -0.05) (Geer et al. 2017). In another study, increased amounts of butylparaben in urine were associated with decreased estradiol, along with a decreased ratio of estradiol/progesterone in women (butylparaben estradiol 95% CI: 16.92, 0.00; butylparaben estradiol/progesterone 95% CI: 18.31, 0.38) (Aker et al. 2016). Further, female urinary concentrations of methylparaben and ethylparaben were associated with decreased fecundity in women (methyl paraben FOR: 0.72, 95% CI: 0.51, 1.03 and AFOR 0.66, 95% CI: 0.45, 0.97; and ethylparaben FOR: 0.66, 95% CI: 0.47, 0.93 and AFOR: 0.66, 95% CI: 0.46, 0.95) (Smarr et al. 2016).

Oral exposure to methylparaben (0.1050 mg/kg/bw) increased litter size, however, it also increased pup mortality from postnatal day (PND) 7 and onwards in rats, possibly due to histological abnormalities in the mammary glands of the dams (Manservigi et al. 2015). Another study reported that butylparaben (100 – 200 mg/kg) exposure during pregnancy increased the proportion of live pups, and decreased the proportion of pups surviving until weaning in rats (Kang et al. 2002). Further, butylparaben exposure (160 – 1000 mg/kg/day) decreased the percent of males and caused a trend of reduced live birth rates in rats (Zhang et al. 2014).

To date, relatively little information is available on the impact of adult exposure of parabens on human and other mammal reproduction. Many studies have focused on birth outcomes, but given the limited information, additional studies are needed to determine whether paraben exposure affects reproductive outcomes.

Summary and Future Directions

Overall, the current literature shows that adult exposure to pesticides, heavy metals, diethylstilbestrol, DEHP and BPA alternatives, TCDD, nonylphenol, polychlorinated bisphenols, triclosan, and parabens may be associated with deleterious effects on adult female reproduction. Epidemiological data show that the selected EDCs are associated with adverse fertility outcomes such as reduced gestational age, weight, pregnancy gain, increased risk for miscarriage, and time to pregnancy in women, but some of these studies have limited sample sizes, exposure information, and/or outcome data. Experimental data show that EDC exposure during adulthood caused a range of effects such as estrous cyclicity abnormalities, decreased pregnancy rates, decreased pup survival, and increased onset of

reproductive senescence. However, limited information is available on the mechanisms by which these selected chemicals impair reproduction. An understanding of the mechanisms of action of EDCs effects on adult female fertility is important to better understand environmentally-induced reproductive disease. Some studies report that EDCs exert toxicity through estrogen receptors, aryl hydrocarbon receptors, and peroxisome proliferator-activated receptor activation mechanisms, but they have not examined other potential pathways (Hannon and Flaws 2015). The doses reported in various studies vary greatly and the complete dose-response relationships of several chemicals are unclear. It is important to include a wide range of doses in studies to better understand the impact and mechanism of action of EDCs on female reproductive outcomes. Further work should be done to examine the direct effects of EDCs on the hypothalamus, pituitary, ovary, and uterus using environmentally relevant doses of chemicals because these organs regulate female fertility and the onset of reproductive senescence. EDC effects on these organs could be involved in the underlying mechanisms by which EDCs cause reproductive abnormalities and diseases.

Collectively, the data presented in this review can be categorized by the strength of evidence presented.

Strong evidence exists that:

- Pesticide exposure during adulthood impaired ovarian follicular health in animal models, decreased ovarian sex steroid hormone production in animal models, reduced fertility in animal models, and was associated with reduced sex steroid hormone production, fertility, and a decreased mean age at menopause in women.
- Heavy metal exposure was negatively associated with ovarian follicular health, fecundity, and pregnancy outcomes in women.
- DES exposure during adulthood suppressed gonadotropin secretion and caused structural abnormalities in the pituitary, decreased ovarian follicular health, impaired uterus structure, and reduced fertility in animal models.
- DEHP and BPA alternative exposure during adulthood decreased fertility in several animal models.
- TCDD exposure during adulthood impaired ovarian sex steroid hormone production, reduced ovarian follicular maturation, and disrupted uterine functions in animal models. Adult human exposure to TCDD was associated with decreased fertility, time to pregnancy, and endometriosis in women.
- Nonylphenol exposure during adulthood disrupted ovarian sex steroid hormone production and induced estrogenic effects in the uterus in several animal models.
- PCB exposure during adulthood altered ovarian steroidogenesis and oocyte health, increased incidence of uterine squamous cell carcinoma, and increased uterine inflammation in animal models. Adult exposure to PCBs were associated with subfertility, endometriosis, and uterine fibroids in women.

- Triclosan exposure during adulthood decreased sex steroid hormone levels and the number of live fetuses in animal models.
- Paraben exposure was associated with decreased serum sex steroid hormone levels and decreased fecundity in women.

Limited evidence exists that:

- Pesticide exposure during adulthood affects the hypothalamus and pituitary in animal models and women. Pesticide exposure increased GnRH mRNA levels, suppressed LH pulse frequency, and inhibited LH release in animal models, however, human data are lacking.
- Heavy metal exposure during adulthood decreased serum LH levels in animal models, but no information is available on human exposure.
- DES exposure during adulthood impairs gonadotropin secretion in animal models, however, there is a lack of information on the effects of DES exposure in women during adulthood.
- TCDD exposure during adulthood reduced peak concentrations of FSH and LH in animal models, however, human data are lacking.
- PCB exposure altered the mRNA and peptide levels of GnRH in hypothalamic cells, but research on the effects of adult exposure to PCBs on the hypothalamus and pituitary are not available.

Insufficient evidence exists to make conclusions about the effects of DEHP and BPA alternatives on the hypothalamus and pituitary. Further, insufficient evidence exists to make conclusions about the effects of nonylphenols, triclosan, and paraben exposure on the reproductive organs in animal models and women.

Future studies need to:

- Use internal dose levels of EDCs that mimic human exposures.
- Elucidate a mechanism of action for the EDCs presented in this review.
- Include additional reproductive endpoints to further characterize the effects of adult exposure to EDCs on the hypothalamus, pituitary, ovary, uterus, fertility, and reproductive senescence.

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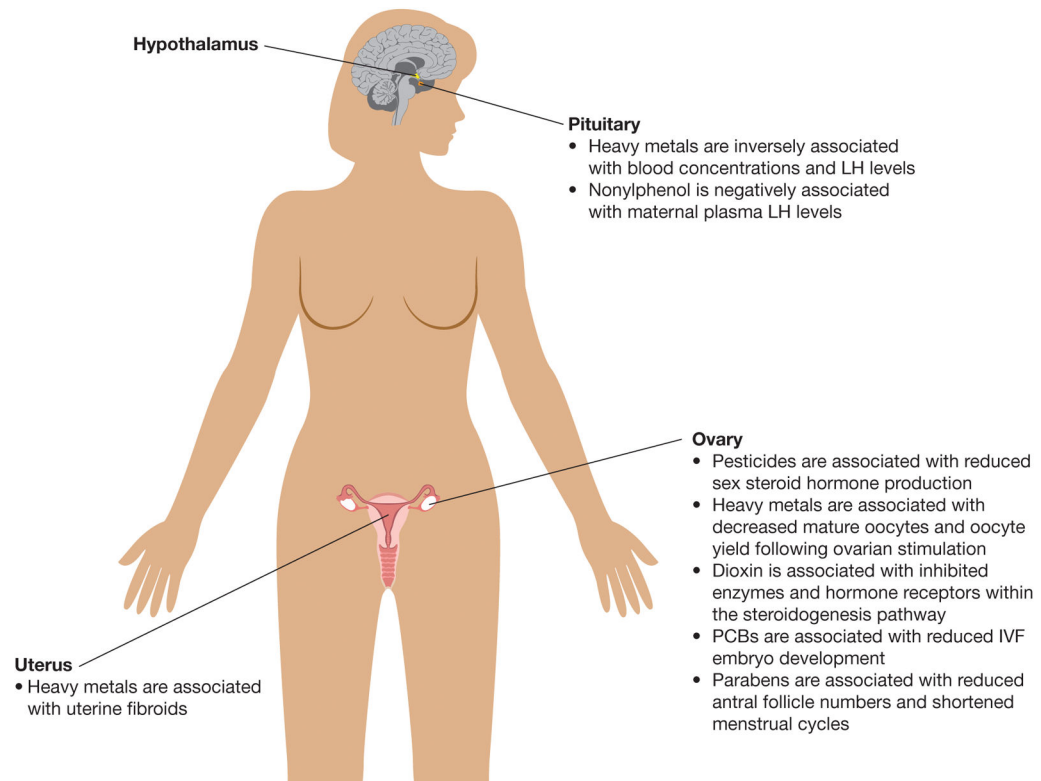


Figure 1. Overview of the associations between exposure to pesticides, heavy metals, 2,3,7,8-tetrachlorodibenzo-p-dioxin (dioxin), polychlorinated bisphenols, and parabens reproductive organs in adult women.

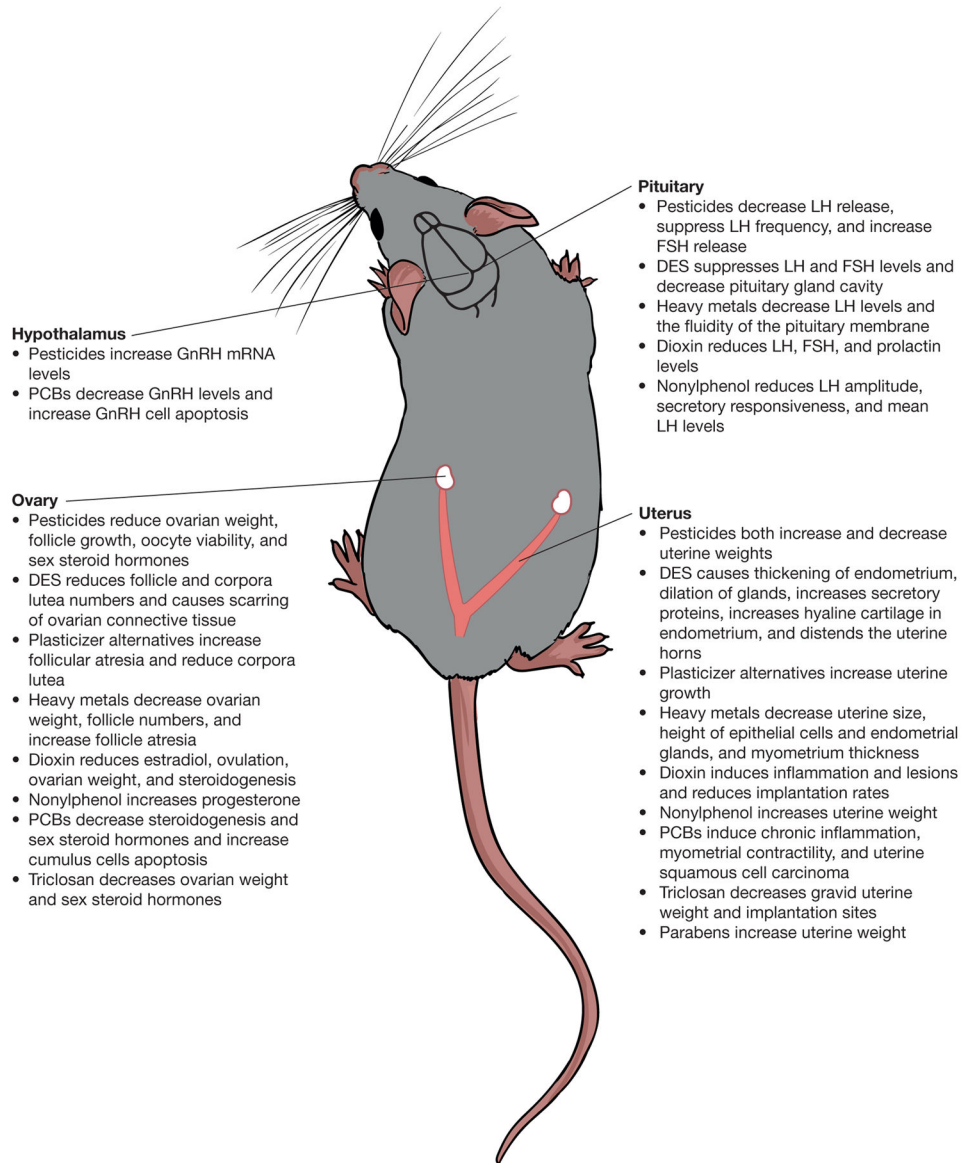


Figure 2. Overview of the effects of pesticides, heavy metals, diethylstilbestrol, plasticizer alternatives, 2,3,7,8-tetrachlorodibenzo-p-dioxin (dioxin), nonylphenol, polychlorinated bisphenols, triclosan, and parabens and their effects on the hypothalamus, pituitary, ovary, and uterus in adult female rodents.

Table 1

Overview of the chemical names and associated abbreviations discussed in the review.

Chemical Name	Chemical Abbreviation
dichlorodiphenyltrichloroethane	DDT
p,p'-dichlorodiphenyldichloroethylene	DDE
2,2',4,4',5,5'-hexachlorobiphenyl	CB-153
arsenic	As
lead	Pb
mercury	Hg
diethylstilbestrol	DES
bisphenol A	BPA
di(2-ethylhexyl) phthalate	DEHP
tri-2-ethylhexyl trimelliate	TETM
di-(2-ethylhexyl) terephthalate	DEHT
di-(isonyl)cyclohexanedicarboxylic acid	DINCH
di-isononyl phthalate	DINP
di-(2-ethylhexyl) adipate	DEHA
acetyl tri-n-butyl citrate	ATBC
bisphenol S	BPS
bisphenol B	BPB
bisphenol F	BPF
bisphenol AF	BPAF
2,3,7,8-Tetrachlorodibenzo-p-dioxin	TCDD
nonylphenols	NP
polychlorinated biphenyls	PCB
5-chloro-2-(2,4-dichlorophenoxy) phenol	Triclosan