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Negative impact of endocrine-disrupting compounds on human reproductive health

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Abstract. There is increasing concern about chemical pollutants that are able to mimic hormones, the so-called endocrine-disrupting compounds (EDCs), because of their structural similarity to endogenous hormones, their ability to interact with hormone transport proteins or because of their potential to disrupt hormone metabolic pathways. Thus, the effects of endogenous hormones can be mimicked or, in some cases, completely blocked. A substantial number of environmental pollutants, such as polychlorinated biphenyls, dioxins, polycyclic aromatic hydrocarbons, phthalates, bisphenol A, pesticides, alkylphenols and heavy metals (arsenic, cadmium, lead, mercury), have been shown to disrupt endocrine function. These compounds can cause reproductive problems by decreasing sperm count and quality, increasing the number of testicular germ cells and causing male breast cancer, cryptorchidism, hypospadias, miscarriages, endometriosis, impaired fertility, irregularities of the menstrual cycle, and infertility. Although EDCs may be released into the environment in different ways, the main sources is industrial waste water. The present paper critically reviews the current knowledge of the impact of EDCs on reproductive disorders in humans.

Additional keywords: environment, reproductive problems, waste water.

Introduction

In recent decades, there has been increasing concern regarding disruption of the endocrine system in living organisms by synthetic organic chemicals because of the recognition that the environment is contaminated with numerous endocrine-disrupting compounds (EDCs) that exert hormonal activity (Metzler and Pfeiffer 2001). EDCs disrupt the normal actions of endogenous hormones. Many environmental pollutants, including polychlorinated biphenyls (PCBs), dioxins, polycyclic aromatic hydrocarbons (PAHs), phthalates, bisphenol A (BPA), pesticides, alkylphenols and heavy metals (arsenic, cadmium, lead, mercury), have been shown to significantly alter endocrine balance. Most EDCs are mutagenic and highly carcinogenic (Schantz and Widholm 2001; Rai and Pal 2002; Birkett 2003; Petrovic *et al.* 2004; Mocarelli *et al.* 2008). Human exposure to EDCs may result from the ingestion of contaminated food and water, inhalation of air and absorption of the EDCs through the skin. However, in most cases, human exposure to EDCs is through the ingestion of contaminated food.

Properties of EDCs

Many EDCs are organochlorine substances, which means that they contain chemically bound carbon and chlorine. This binding is strong and resistant to biochemical and physical degradation. The organochlorines have a long half-life and they accumulate in the environment as a persistent organic pollutant (Fisher 1999; Muir *et al.* 1999). Humans and most wildlife do not have biochemical pathways to detoxify or excrete these chemicals, so they tend to accumulate in the body. The log[octanol/water partition coefficient] (K_{ow}) values for most EDCs indicate a high degree of lipophilicity (see Table 1) (Birkett 2003).

The current knowledge of the way in which EDCs affect humans is patchy, although there is some evidence that these compounds have the potential to induce deleterious changes in the human reproductive system. In summary, there is evidence from many countries that exposure to EDCs can decrease sperm count and quality, increase in the number of testicular germ cells and the incidence of male breast cancer, cryptorchidism and hypospadias, disturb menstrual cycle and result in intrauterine growth restriction and polycystic ovarian syndrome (Toppari *et al.* 1996; Mylchreest *et al.* 1998, 1999; Sharara *et al.* 1998; Gray *et al.* 1999; Parks *et al.* 2000; McIntyre *et al.* 2001; Fisher *et al.* 2003). The evidence supporting the effect of EDCs on wildlife is stronger, although the validity of the results is widely disputed (Colburn and Clement 1992). In the present paper we

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Table 1. Endocrine-disrupting compounds: their lipophilic properties and impact on human health

Compounds	log K_{ow}	Impact on human health	References
PCBs	4.6–8.4	Infertility, certain types of cancer, shortened menstrual cycle and other non-specific reproductive effects	Li and Hansen (1997); Mendola *et al.* (1997); Kester *et al.* (2000); Birkett (2003)
Dioxins	6.15–7.28	Altered serum testosterone levels and decline in sperm concentrations	Sharpe and Skakkebaek (1993); Egeland *et al.* (1994); Carlsen *et al.* (1992); Auger *et al.* (1995); Menchini-Fabris *et al.* (1996); Toppari *et al.* (1996); Swan *et al.* (2000)
PAHs	≈6.0	Preterm birth and intrauterine growth restriction	Perera *et al.* (2002); Birkett (2003)
Phthalates	1.46–13.1	Reduced anogenital distance, nipple and areola retention, cleft phallus, hypospadias, cryptorchidism, reduction in fetal testosterone levels, abnormally located Leydig cells, abnormal seminiferous cord formation	Harris *et al.* (1997); Mylchreest *et al.* (1998, 1999); Gray *et al.* (1999); Parks *et al.* (2000); McIntyre *et al.* (2001); Fisher *et al.* (2003)
BPA	3.4	Decrease in the quantity and quality of sperm production, decreased fertility in males, hypospadias, cryptorchidism, endometrial hyperplasia, recurrent miscarriages, polycystic ovarian syndrome	Carlsen *et al.* (1992); Giwercman *et al.* (1993); Chitra *et al.* (2003); Muñoz de Toro *et al.* (2005)
Pesticides	0.2–7.0	Decrease in the quantity of sperm production, miscarriage, genital deformities, hypospadias	Singer (1949); Toppari *et al.* (1996); Walter *et al.* (1988); Finizio *et al.* (1997); Baskin *et al.* (2001); Nicolopoulou-Stamati and Pitsos (2001); Garry (2004); Carbone *et al.* (2006)
Alkylphenols	4.17–4.48	Decrease in the quantity and quality of sperm production, testicular cancer, hypospadias, cryptorchidism	Carlsen *et al.* (1992, 1995)
Arsenic	1.3	Decreased birthweight and miscarriage	Nordström *et al.* (1979)
Cadmium	3.5–4.2	Infertility and prostate cancer	Garcia-Sanchez *et al.* (1992); Kolonel (1996); Nampoothiri and Gupta (2006); Vinceti *et al.* (2007)
Lead	3.8–4.3	Infertility, miscarriage, low birthweight	Al-Saleh *et al.* (1995); Bellinger (2005); Nampoothiri and Gupta (2006)
Mercury	0.62	Infertility, miscarriage, disturbances in the menstrual cycle	Sharara *et al.* (1998); Schuurs (1999); Gardella and Hill (2000); Yoshida (2002)

focus on reproductive disorders caused by EDCs and, as such, we do not discuss the effects of EDCs on other hormones, such as thyroid hormones or glucocorticoids.

Oestrogenic properties

The three major endocrine systems that can be disrupted by EDCs are the oestrogen (i.e. EDCs mimic or block natural oestrogens), androgen (EDCs mimic or block natural testosterone) and thyroid (EDCs with direct and/or indirect effects on the thyroid) systems (Snyder *et al.* 2003). Natural oestrogens are involved in the development and adult function of organs in the female genital tract and mammary gland. At the cellular level, oestrogens promote cell proliferation and hypertrophy of female secondary sex organs. These effects are mediated through the oestrogen receptor (ER). The ERα is present in classical oestrogen target organs such as the uterus, ovary, testis and epididymis, while the ERβ is present in the ovary, uterus, prostate and testis (Kuiper *et al.* 1996, 1997).

Some of xeno-oestrogens have been identified among the alkylphenolic compounds, phthalates, PCBs, bisphenol A and some pesticides (Soto *et al.* 1994, 1995; Brotons *et al.* 1995).

One of the main questions regarding EDCs with oestrogenic properties or those that can prolong oestrogen activity is their impact on the occurrence of breast cancer (Davis *et al.* 1993). Over 500 weakly oestrogenic EDCs have been identified but, as yet, there is no definitive conclusion as to whether human exposure to these oestrogenic EDCs poses any risk to reproductive health (Brody and Rudel 2003; Sharpe and Irvine 2004).

The oestrogenic effects of compounds are mediated by binding to cytosolic oestrogen receptors in target cells, leading to dimerisation of the ligand–receptor complex. The homodimer binds to specific oestrogen-responsive elements of the DNA and promotes an oestrogen-specific gene expression pattern (Nimrod and Benson 1996). The liver is one of the major target organs for the female sex steroid 17β-oestradiol (E2). Oestrogenic effects are not restricted to a small group of therapeutic agents; several groups of compounds that are used daily in industry, agriculture or at home also exhibit oestrogenic effects. In the present article, we review the major groups of environmental chemicals, such as PCBs, dioxins, PAHs, phthalates, BPA, organochlorine pesticides, alkylphenols and some heavy metals, such as arsenic, cadmium, lead and mercury, which are currently known to have oestrogenic effects in vertebrates or in *in vitro* assays. At present, tens of thousands of man-made chemicals are being used, yet the direct effects of these chemicals on the human endocrine system have been estimated for only a few, mostly based on animal testing. The oestrogenic activity of most chemicals, such as phthalates, BPA and alkylphenols, has been detected accidentally. Only recently has the screening of chemicals that are used in large quantities been attempted. Hence, it is highly possible that many oestrogenic chemicals remain unidentified.

In general, EDCs modulate the hormonal function in the body and, in particular, affect the steroid hormone balance. There are many potential mechanisms of action of EDCs. At the cellular level, EDCs can induce endocrine disruption through several routes that involve steroid receptor binding, blockade of steroid receptor binding or disruption of the biosynthesis and/or metabolism of steroids (Sharpe and Irvine 2004). The classic view that steroids act only through the binding of the steroid to a high-affinity steroid receptor (Truss and Beato 1993) has also been challenged. There is an increasing body of literature regarding the rapid, non-genomic actions of steroid hormones (Simoncini and Genazzani 2003). The exact pathways for this form of steroid signalling are not yet fully elucidated and there is much debate and controversy in the literature. Changes in the effective concentrations of hormones can occur if an EDC binds to a specific hormone receptor. This compound may then either mimic the hormone or block the normal biological response by occupying the receptor site. Alternatively, EDCs may be able to react directly or indirectly with the hormone structure to alter its function, change the pattern of hormone synthesis or modulate the number of hormone receptors and their affinity for specific molecules (Simoncini and Genazzani 2003; Sharpe and Irvine 2004).

The EDCs are capable of causing and exacerbating disease in all forms of vertebrates, including humans. This is because the chemical structure of hormones varies little between species, and even classes, although the functions within different organisms may vary substantially (Kawauchi *et al.* 2002).

Most work has focused on the ER, but some evidence suggests that some abnormalities in male sexual development may be mediated at the level of the androgen receptor (AR; Kelce and Wilson 1997). The presence of a potent anti-androgen can create an oestrogenic environment, thus producing symptoms indicative of oestrogen exposure.

Diethylstilboestrol exposure

Considerable evidence for the potential effects of EDCs comes from diethylstilboestrol, a synthetic oestrogen. The results of the prescription of diethylstilboestrol are well known. Women who were exposed *in utero* to diethylstilboestrol are at risk of developing clear cell adenocarcinoma of the vagina (Giusti *et al.* 1995). In addition, diethylstilboestrol has been linked with irregularities of the menstrual cycle, altered uterine structure, infertility and breast cancer (Giusti *et al.* 1995). Several studies have shown that sons of mothers treated with diethylstilboestrol during pregnancy are at increased risk of hypospadias, cryptorchidism and a decreased sperm count (Stillman 1982). These observations led to the hypothesis that such disorders, in addition to their genetic component, may have a common exogenous origin related to prenatal exposure to EDCs (Skakkebæk *et al.* 2001; Sharpe 2003; Fisher 2004).

Many EDCs act in a similar way to diethylstilboestrol. However, the action of diethylstilboestrol is for a limited period of time only, whereas EDCs act throughout life since the duration of action of individual EDC is very much longer than that of diethylstilboestrol. Both the environmental concentration and type of EDC vary. Furthermore, EDCs do not necessarily remain where they are released into the environment and they may be transported in the water or air currents around the globe (Loganathan and Kannan 1994).

Organic compounds

Polychlorinated biphenyls

The PCBs are a group of chemical compounds consisting of more than 200 possible congeners that differ in the number and position of the chlorine atoms on two basic benzene rings. Most PCB products have been used as dielectric fluids in capacitors; in addition, they have been used to a lesser extent as additives in paint (Jiang *et al.* 1997). The $\log K_{ow}$ values range from 4.6 to 8.4, so these chemicals are rapidly adsorbed in sediments and other particulate matter (Birkett 2003). Because of their physical and chemical properties, PCBs are highly stable and persistent in the environment and tend to accumulate progressively in the soil, plants and animals in the food chain in proportion to the trophic level (Agency for Toxic Substances and Disease Registry (ATSDR) 1997). The accumulation and amplification of PCBs through the food chain as a result of environmental contamination is a global issue because these compounds can cause endocrine disruption (Peterson *et al.* 1993; Johansson *et al.* 1998; Baccarelli *et al.* 2004). PCBs have been classified by the International Agency for Research on Cancer (IARC) as potentially carcinogenic to humans (IARC 1998) and may have non-carcinogenic health effects, particularly as endocrine disruptors (Integrated Risk Information System (IRIS) 2005). It has been suggested that chemicals such as PCBs in the environment can mimic natural hormones when internalised and that this endocrine disruption can lead to infertility, certain types of cancer, hermaphroditism, reduced testosterone levels, other hormone-related disorders, a shortened menstrual cycle and other non-specific effects on the female reproduction (Mendola *et al.* 1997). PCBs and their metabolites can exhibit agonistic and antagonistic behaviours in oestrogenic systems, although the exact mechanism by which hydroxylated PCBs produce their effects has not been established (Li and Hansen 1997; Kester *et al.* 2000). Conversely, some researchers deem reports that environmental oestrogen-mimicking compounds increase the incidence of male and female breast cancer or male reproductive problems as unproven and implausible (Ross 2004).

Dioxins

Dioxins are undesirable contaminants produced almost exclusively in industrial processes, including incineration, chlorine bleaching of paper and pulp and the manufacture of certain pesticides, herbicides and fungicides (Olie *et al.* 1977; Gilpin *et al.* 2003). The $\log K_{ow}$ values for this group of chemicals range from 6.15 to 7.28, indicating lipophilicity.

In humans and other vertebrates, dioxins have been shown to be risk factors for endocrine disruption, including reproductive abnormalities and altered serum testosterone levels (Egeland *et al.* 1994). In the past 50 years, a significant decline in human sperm concentrations of approximately 1% per year has been reported in the literature (Carlsen *et al.* 1992; Sharpe and Skakkebaek 1993; Auger *et al.* 1995; Menchini-Fabris *et al.* 1996; Toppari *et al.* 1996; Swan *et al.* 2000). Experimental animal data have shown adverse effects of exposure to

2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) on male reproductive function, including testicular function and reduced sperm count and motility (Faqi *et al.* 1998; Roman and Peterson 1998). The pre- and perinatal periods are particularly sensitive and, indeed, higher levels of exposure are required to produce similar effects in adult animals (Roman and Peterson 1998; Theobald *et al.* 2003). The results of Mocarelli *et al.* (2008) show a reduction in E2 and a permanent effect on semen quality in men as a result of the disruptive action of low concentrations of TCDD on the endocrine system. This effect was seen after exposure particularly in infancy and/or prepuberty to levels of TCDD that were, until recently, seen in the general male population of many industrialised countries and, to a lesser degree following exposure in puberty, but not following exposure in adulthood.

Polycyclic aromatic hydrocarbons

The PAHs are organic chemicals formed during the incomplete combustion of organic matter and, consequently, they have been found in cooked food, tobacco smoke and in gas and particle emissions from motor vehicles, domestic heating systems and power plants (Simko 2002; Li *et al.* 2003; Mabilia *et al.* 2004). The PAHs also have the potential to bioaccumulate and have $\log K_{ow}$ values in the region of 6, indicating a high degree of lipophilicity (Birkett 2003). PAHs have been found in the atmosphere, in terrestrial and aquatic ecosystems, in remote areas with no urban centres and in dietary products (Grova *et al.* 2002; Nadal *et al.* 2004; Tao *et al.* 2004; Cincinelli *et al.* 2005; Tsapakis and Stephanou 2005).

Several PAHs have endocrine-disrupting properties (IARC 1983; US Environmental Protection Agency (EPA) 1984). Damage to the human reproductive system (breast cancer and cancer on reproductive tract) by PAHs has been evaluated repeatedly by different authors (Santodonato 1997; Birkett 2003). Recent toxicological and epidemiological studies suggest that PAH exposure during the pre- and neonatal periods may have adverse reproductive or developmental effects (Perera *et al.* 2005). Airborne PAHs have been implicated in effects on human reproduction, such as preterm birth and intrauterine growth restriction (Perera *et al.* 2002). Determination of PAH levels in breast milk is of paramount importance to determining infant risk.

Phthalates

Phthalates are synthetic chemicals that are widely used in the production of plastics, as solvents in inks used in food packaging and in certain cosmetics (Thomas and Thomas 1984). The $\log K_{ow}$ values for this group of chemicals range from 1.46 to 13.1, indicating high lipophilicity (Harris *et al.* 1997).

When certain phthalate esters are administered during the period when the male reproductive tract is developing *in utero*, certain abnormalities can occur (e.g. reduced anogenital distance, nipple and areola retention, cleft phallus, hypospadias and undescended testes; Mylchreest *et al.* 1998, 1999; Gray *et al.* 1999; Parks *et al.* 2000; McIntyre *et al.* 2001; Fisher *et al.* 2003). The occurrence of these abnormalities suggests under virilisation of the Wolffian duct and urogenital sinus. The effects observed in rodents have been associated with a reduction in testosterone synthesis by the fetal testis (Mylchreest *et al.* 1998, 1999; Gray *et al.* 1999; Parks *et al.* 2000; McIntyre *et al.* 2001; Fisher *et al.* 2003). The wide spectrum of abnormalities that are induced following *in utero* exposure of rodents to certain phthalate esters is similar to the spectrum of reproductive disorders believed to occur within the human population. Testosterone production is essential for the normal masculinisation of the male reproductive tract, but dibutyl phthalate and diethylhexyl phthalate induce a 60–85% reduction in fetal testosterone levels during the critical period of development (Parks *et al.* 2000; Fisher *et al.* 2003).

Unlike other anti-androgens, phthalates do not interact with the androgen receptor (Mylchreest *et al.* 1999; Parks *et al.* 2000). Phthalate treatment interferes with the transcription of several key genes involved in cholesterol transport and the biosynthesis of testosterone (Shultz *et al.* 2001; Barlow *et al.* 2003; Thompson *et al.* 2004). Testicular cancer, cryptorchidism, hypospadias and poor sperm quality may all be manifestations of a single condition called testicular dysgenesis syndrome (Skakkebæk *et al.* 2001). Epidemiologically, testicular cancer and poor semen quality have been linked to birth cohort effects and, by definition, hypospadias and cryptorchidism are male congenital abnormalities suggesting that all these disorders have their root in fetal development.

The relative oestrogenic potencies of several phthalates are butyl benzyl phthalate > dibutyl phthalate > diisobutyl phthalate > diethyl phthalate > diisononyl phthalate (Harris *et al.* 1997). The potencies are approximately 1×10^6 to 5×10^7 less than that of E2 (Harris *et al.* 1997).

Bisphenol A

Bisphenol A (2,2-bis(4-hydroxyphenyl)propane) is an organic compound composed of two phenol rings connected by a methyl bridge, with two methyl functional groups attached to the bridge. The $\log K_{ow}$ value for BPA is 3.4, indicating its lipophilicity and tendency to bind to a solid phase in the aquatic environment. BPA is used as a source material for the production of phenol resins, polyacrylates and polyesters, but mainly for the production of epoxy resins and polycarbonate plastics. Epoxy resins are used as food contact surface lacquer coatings for cans, protective coatings and finishes, automobile parts, adhesives and as coatings for PVC pipes. Polycarbonate plastics are used in the manufacture of compact disks, automotive lenses, household appliances, food packaging and plastic bottles because they have high impact strength, hardness, toughness, transparency, resistance to temperatures between -40°C and $+145$°C and a resistance to many acids and oils (Staples *et al.* 1998). BPA is also used in resin-based dental sealants and bonding agents (Pulgar *et al.* 2000). As a result of an increase in the use of products based on epoxy resins and polycarbonate plastics, human exposure to BPA (both environmental and through food) has increased.

BPA is an endocrine disruptor with oestrogenic activity (Rubin and Soto 2009) and an oestrogenic potency that is approximately 1×10^4 less than that of E2 (Bergeron *et al.* 1999). Several studies have suggested adverse endocrine disruptive effects of low doses BPA on adults, such as decreased quantity and quality of sperm production, decreased fertility

in males, recurrent miscarriages, persistent alterations in peripubertal mammary gland development and polycystic ovarian syndrome (Carlsen *et al.* 1992, 1995; Chitra *et al.* 2003; Muñoz de Toro *et al.* 2005), as well as effects on the fetus, such as an increased incidence of hypospadias and cryptorchidism, stimulation of mammary gland development, endometrial hyperplasia and abnormal karyotypes (Carlsen *et al.* 1992; Giwercman *et al.* 1993; Markey *et al.* 2001; Chitra *et al.* 2003; Muñoz de Toro *et al.* 2005). Schönfelder *et al.* (2002) found that blood concentrations of BPA in humans were higher in male compared with female fetuses under normal environmental exposure.

Pesticides

Recently, the potential of certain pesticides to act as EDCs has been reported (see Table 2). Pesticide compounds include organometallic compounds, such as tributyl tin and many other organochlorine compounds that are toxic and persistent in the environment (Toppari *et al.* 1996; Vasseur and Cossu-Leguille 2006). Other pesticides, such as organophosphates, carbamates, triazines and pyrethrins, have been reported to be less persistent and less toxic than the organochlorines (Andersen *et al.* 2002).

Conventional toxicological testing of pesticides may miss the potential of a substance to disrupt the endocrine system, especially at the low concentrations likely to be found in the environment. EDCs in pesticides are active *in vivo* at extremely low doses (Hayes *et al.* 2002; Mankame *et al.* 2004; Weltje *et al.* 2005) and it has been suggested that the permitted levels in food may be too high (Hayes *et al.* 2003; Storrs and Kiesecker 2004; Weltje *et al.* 2005). There is also a concern that the values for acceptable levels have been set without taking into account the exposure of human fetuses, infants and children, who exhibit greater susceptibility to these compounds that adults (Goldman *et al.* 2004; Sharpe 2006).

Links between pesticide exposure and endocrine disruption were suggested as early as 1949, when low sperm counts were observed in men involved in the aerial application of dichlorodiphenyltrichloroethane (Singer 1949; Toppari *et al.* 1996). More recently, exposure to endocrine disrupting pesticides has been implicated in the aetiology of various cancers (Toppari *et al.* 1996; Mathur *et al.* 2002; Garry 2004), miscarriage and other reproductive disorders (Nicolopoulou-Stamati and Pitsos 2001; Garry 2004).

Indeed, much of the damage caused by EDCs appears to take place during gametogenesis and the early development of the fetus (Sultan *et al.* 2001; Skakkebæk 2002; Hardell *et al.* 2006; Sharpe 2006), although the effects may not be apparent until adulthood, making links between EDCs and human disease difficult to prove. Fetuses and babies also receive greater doses of EDCs because of the mobilisation of maternal fat reserves during gestation (Anderson and Wolff 2000; Waliszewski *et al.* 2000) and breast feeding (Anderson and Wolff 2000; Przyrembel *et al.* 2000), as well as because of the high consumption of food in relation to bodyweight in the case of infants and children (Tilson 1998). Recent studies suggest adverse endocrine-disrupting effects, such as hypospadias, cryptorchidism and other birth defects, on the fetus exposed to pesticides (Walter *et al.* 1988; Baskin *et al.* 2001; Schreinemachers 2003; Garry 2004; Mackenzie and Constanze 2005; Carbone *et al.* 2006).

Alkylphenols

Alkylphenols are the final products in the biodegradation of alkylphenol polyethoxylates, which are non-ionic surfactants widely used in detergents, paints, pesticides, cosmetics and other formulated products (Jobling *et al.* 1996). The log K_{ow} values for this group of chemicals range from 4.17 to 4.48, indicating lipophilicity and a tendency to partition to solid phases in the environment.

Based on a meta-analysis of 61 studies, it has been suggested that the human sperm count and quality have decreased in the past 50 years (Carlsen *et al.* 1992). There are also indications of an increased incidence of testicular cancer in human adults, as well as an increased occurrence of cryptorchidism and hypospadias in human fetuses (Carlsen *et al.* 1995). Soto *et al.* (1991) reported that nonylphenol released from plastic centrifuge tubes during cell culture procedures induced the proliferation of human breast tumour cells. Alkylphenols have the potential to interfere with the sexual development and reproduction of vertebrate organisms. Because a balance of steroid hormones

Table 2. Common endocrine-disrupting pesticide groups: their effects and modes of action

Pesticide group	Hormones affected	Mechanisms	References
Carbamates	Androgens, oestrogens, steroids	Androgen receptor dependent; oestrogen receptor interference with cellular microtubule formation in oestrogen-sensitive cells	Goad *et al.* (2004); Lu *et al.* (2004); Morinaga *et al.* (2004)
Organochlorines	Androgens, oestrogens, prolactin	Competitive inhibition of androgen receptor, inhibition at oestrogen-sensitive reporter, binding to androgen receptors, interference in induction of aromatase	Daxenberger (2002); Lemaire *et al.* (2004); Scippo (2004); Storrs and Kiesecker (2004)
Organophosphates	Oestrogens	Induction of oestrogen-related genomic activity	Kang *et al.* (2004); Gwinn *et al.* (2005); Jeong *et al.* (2006)
Pyrethrins	Oestrogens, progesterone	Antagonism or potentiation of oestrogen action by inhibition of progesterone action	Kim *et al.* (2004)
Triazines	Androgens	Competitive inhibition of androgen receptors, binding to androgen-binding proteins; induction or inhibition of aromatase	Meulenberg (2002); Ishihara *et al.* (2003)

is required to maintain normal gonadal differentiation and morphological development of male and female vertebrates, it is possible that exposure to EDCs may result in altered development of primary and secondary sexual characteristics (Jobling *et al.* 1996).

The relative oestrogenic potencies of alkylphenolic compounds are octylphenol > nonylphenol carboxylic acid > nonylphenol > nonylphenol ethoxylate, with potencies approximately 1×10^5 less than that of E2 (White *et al.* 1994).

Heavy metals (As, Cd, Pb, Hg)

The general population is exposed to metals at trace concentrations either voluntarily through supplementation or involuntarily through the intake of contaminated food and water or following contact with contaminated soil, dust or air. Some metals, such as cadmium (Cd), lead (Pb), arsenic (As) and mercury (Hg), are non-essential xenobiotics that are known to be harmful to human health. The accelerating industrialisation in developing countries with an enormous and increasing demand for heavy metals has resulted in the high anthropogenic emission of these pollutants into the biosphere. In the past century, there has been an increasing awareness throughout the world of the health and developmental risks associated environmental exposure to toxic metals, such as As, Cd, Pb and Hg. Exposure to toxic levels of any of these environmental contaminants may result in impaired health in adults, but the toxicological effects of these metals are often more devastating in the developing reproductive system of children.

Heavy metal pollution in water bodies is a serious environmental issue, threatening not only aquatic ecosystems, but also human health through the contamination of drinking water. Exposure to heavy metals (As, Cd, Pb, Hg) has been identified as a factor affecting human fertility (Sharara *et al.* 1998); these heavy metals may induce hormonal disorders, preventing ovulation and pregnancy, as well as abnormalities in sperm production (Sinawat 2000; Choi *et al.* 2004).

Arsenic

Exposure to excess As, principally from contaminated drinking water, is considered one of the top environmental health threats worldwide (Abernathy *et al.* 2003; Watanabe *et al.* 2003; Mukherjee *et al.* 2006). Most of this exposure is from natural geological sources of As that contaminate groundwater. The $\log K_{ow}$ value for As is 1.3, indicating lipophilicity.

Epidemiological studies have linked chronic exposure to As in drinking water with increased risks of developmental and reproductive problems (Smith *et al.* 1992; Abernathy *et al.* 2003; Watanabe *et al.* 2003; Tapio and Grosche 2006). Chronic exposure to As has been associated with increased numbers of spontaneous abortions in women working at or living in close proximity to smelters, as well as women whose partners worked at the smelters (Nordström *et al.* 1979). The rate of spontaneous abortion was even higher when both partners worked at the smelters.

Cadmium

Cadmium is highly toxic and one of the most important environmental pollutants in industrialised countries. For the general population, the main sources of Cd exposure are food, drinking water and tobacco smoke (Satarug and Moore 2004). The $\log K_{ow}$ value for Cd is 3.5–4.2, indicating its lipophilicity and tendency to bind to a solid phase in the aquatic environment.

Cadmium has pronounced toxic effects on most organisms and produces significant testicular injury in the fetus (Xu *et al.* 1996). This injury may include a progressive reduction of testis weight, accompanied by irreversible damage to the seminiferous tubules and decreased viability of testicular cells. Furthermore, Cd can cause a significant reduction in gonadotropin binding, which alters the steroidogenic enzyme activity of granulosa cells and thus a dysfunction in the production of hormones, leading to infertility (Nampoothiri and Gupta 2006). In experimental animals, Cd causes testicular cancer (Siu *et al.* 2009) and sarcomata (Haddow *et al.* 1964). Several studies on industrial workers have suggested links between Cd exposure and prostate cancer (Garcia-Sanchez *et al.* 1992; Kolonel 1996; Vinceti *et al.* 2007).

Lead

Lead is the most abundant of the heavy metals on earth (Tong and McMichael 1999). The main sources of lead exposure are paints, dust, soil, kitchen utensils and leaded gasoline (Järup 2003). Lead has the potential to bioaccumulate and has $\log K_{ow}$ values in the region of 3.8–4.3, indicating a high degree of lipophilicity.

Lead toxicity can result in a wide range of biological effects on various organ systems depending on the level and duration of exposure. Lead exposure is a more profound problem for infants or young children than for adults (Tang *et al.* 1999). Despite its toxicity, the physical and chemical characteristics of Pb mean that is has been used throughout history for a variety of purposes, resulting in increased human exposure to this heavy metal through a myriad of pathways, including air, food, soil, dust and water. Al-Saleh *et al.* (1995) reported that Pb can cross the placenta and have a negative effect on birth, inter alia low birth weight. Lead exposure during the early stages of human life poses a risk for the health and functional ability of vulnerable fetuses and infants. Lead can affect the developing fetus directly or indirectly through paternal or maternal physiology, both before and during the reproduction process (Silbergeld 1991). High levels of paternal Pb exposure appear to reduce the father's fertility and to increase the risk of miscarriage and reduced fetal growth (preterm delivery and low birthweight; Bellinger 2005). Exposure to Pb during fetal development and breast feeding depends on the maternal burden and factors that modulate Pb transfer through the placenta and the mammary gland. A recent study by Nampoothiri and Gupta (2006) has shown that Pb can cause a significant reduction in gonadotropin binding, which alters the steroidogenic enzyme activity of granulosa cells and thus interferes with the production of hormones, leading to infertility.

Mercury

Mercury is a naturally occurring metal that has several forms: (1) metallic or elemental Hg, which is commonly used in dental fillings and thermometers; (2) inorganic compounds that are

used in skin care and medicinal products; and (3) organic compounds that are used in fungicides and paints. Mercury has relatively good lipid solubility ($\log K_{ow} = 0.62$).

Mercury is one of the most toxic heavy metals commonly found in the global environment, including in the lithosphere, hydrosphere, atmosphere and biosphere. It persists in the environment and accumulates in the food chain. The general population is exposed to mercury primarily through the diet (contaminated fish) and dental amalgam (World Health Organization (WHO) 1991; Clarkson 2002).

Human exposure to Hg (usually in an inorganic form and at very low concentrations) commonly occurs as a result of inhalation, the consumption of water, fish and other foods and the ingestion of soil. After inhalation of Hg by humans, elemental mercury vapour diffuses rapidly through the alveolar membrane and is absorbed. McRill *et al.* (2000) have reported an association between women's use of skin-lightening creams and soaps and exposure to Hg.

Mercury and its compounds have a wide spectrum of toxicities, depending on the chemical form and mode of exposure (Satoh 2003). Mercury and its compounds are a significant threat to human health, particularly to pregnant women, women of child-bearing age, developing fetuses and breast-fed infants. Animal studies have demonstrated an adverse effect of Hg on spermatogenesis (Homma-Takeda *et al.* 2001). *In vitro* studies have shown that Hg is capable of inducing sperm abnormalities (Ernst and Lauritsen 1991; Choy *et al.* 2003). There have been numerous studies on the effects of Hg on the adult reproductive system (Zahir *et al.* 2005). According to published articles, Hg can cause spontaneous abortion, stillbirths, congenital malformations, infertility, disturbances in the menstrual cycle and inhibition of ovulation (Sharara *et al.* 1998; Schuurs 1999; Gardella and Hill 2000; Yoshida 2002). Shen *et al.* (2000) indicated that HgCl affected the meiotic maturation of mouse oocytes, obviously blocked IVF and injured or reduced the reproductive capacity of mice. Davis *et al.* (2001) reported that exposure to metallic Hg altered oestrous cyclicity, but had no significant effect on ovulation, implantation or maintenance of first pregnancy during short-duration exposure of female rats.

Removal of EDCs

The EDCs may be released into the environment in different ways and one of the most important sources is industrial waste water. Industrial effluent needs to be more strictly controlled to preserve the natural balance in the environment. According to the EU Water Framework Directive 2000/60/EC (The European Parliament and the Council of the European Union 2000), all industrial water pollution sources must be analysed regularly for the presence of numerous compounds that are toxic, bioaccumulative or function as endocrine disruptors (Hamm *et al.* 2005*a*, 2005*b*). According to Directive 2008/105/EC, the average annual values in surface waters must not exceed $0.3\ \mu g\ L^{-1}$ for nonylphenol and $1.3\ \mu g\ L^{-1}$ for di(2-ethylhexyl) phthalate (The European Parliament and the Council of the European Union 2008). Consequently, individual producers are obliged to reduce the concentration of EDCs in any discharge to fulfil the requirements of the directive. These steps will ensure better environmental management throughout Europe and will also help restore the already highly damaged equilibrium of natural surface and underground waters.

Conventional waste water treatment processes are not specifically designed to remove traces of dangerous organic contaminants, so these contaminants are consequently consumed by aquatic organisms and may then enter the human food chain. For this reason, it is essential that future research focuses on the investigation of appropriate water treatment methods to be integrated into waste water treatment facilities to prevent the release of EDCs into the natural waters. Research on ultrafiltration, nanofiltration and advanced oxidation processes (AOPs), such as the Fenton and photo-Fenton reactions, photocatalysis with TiO_2 reagents and ozonation (Chang *et al.* 2003; Snyder *et al.* 2003; Yoon *et al.* 2004, 2006; Esplugas *et al.* 2007; Gültekin and Ince 2007), in the past decade has resulted in promising techniques for the removal of EDCs from waste waters and/or surface waters.

Biological treatment, particularly by the activated sludge process, has been used widely to remove pollutants from waste waters (Thompson *et al.* 2001; Pokhrel and Viraraghavan 2004; Balabanič *et al.* 2009; Balabanič and Krivograd Klemenčič 2011). Biodegradation is the dominant mechanism of organic EDC degradation in water (Soares *et al.* 2008; Zhao *et al.* 2008). Many studies have reported on the biodegradation of phthalates, BPA and alkylphenols under aerobic or anaerobic conditions (Balabanič and Krivograd Klemenčič 2011). In particular, aerobic and combined aerobic–anaerobic biological waste water treatment plants have been effective in reducing the concentration of phthalates by 69–91% (Balabanič *et al.* 2009; Dargnat *et al.* 2009; Balabanič and Krivograd Klemenčič 2011), BPA by 74–92% (Vethaak *et al.* 2005; Balabanič and Krivograd Klemenčič 2011), nonylphenol by 33–94% (Drewes *et al.* 2005; Balabanič and Krivograd Klemenčič 2011) and heavy metals by >80% (Kulbat *et al.* 2003). The biodegradability of these compounds after biological treatment is strongly dependent on the characteristics of the waste water (Vidal and Diez 2005).

Some studies have shown that membrane bioreactors (MBRs) can remove more than 80% of EDCs from waste water (Wintgens *et al.* 2002). In addition, membrane filtration technologies, such as reverse osmosis (RO) and ultrafiltration (UF), have been shown to be a promising alternative for the removal of micropollutants (Yoon *et al.* 2004, 2006). RO results in the almost complete removal of micropollutants, but the higher implied energy consumption of this process is an important drawback that needs to be considered. Comparing membrane types, the rejection rate for EDCs is highest for RO, followed by nanofiltration (NF), UF and microfiltration (MF; Chang *et al.* 2003). Several studies have discovered that the rejection efficiency of EDCs by membranes strongly depends on the physicochemical properties of the EDCs, such as molecule weight, K_{ow}, water solubility, electrostatic properties, etc. (Liu *et al.* 2009).

The AOPs have proven to be powerful in destroying most EDCs in water (Chamarro *et al.* 2001; Fukushima and Tatsumi 2001; Malato *et al.* 2001, 2002; Katsumata *et al.* 2004; Will *et al.* 2004; Nogueira *et al.* 2005; Esplugas *et al.* 2007; Gültekin and Ince 2007; Mascolo *et al.* 2008; Xu *et al.* 2009), but the higher

energy consumption of the process must be taken into consideration.

Because some EDC present in waste water are harmful to the environment and organisms at very low concentrations, it will be necessary to prevent, or at least limit, their input in the production process or to treat any waste appropriately to ensure their removal (Gültekin and Ince 2007).

Conclusion

Of concern is the possibility that EDCs may adversely affect human health. Indeed, there is evidence now indicating that exposure to EDCs may be responsible for various reproductive problems. Endocrine disruption has been documented in a variety of vertebrates, in the laboratory and under field conditions. Numerous industrial chemicals, pesticides and commercial products that have been released into the environment are endocrine disrupters. Monitoring of animal tissues has shown that some of these chemicals biomagnify in the food chain, with significant concentrations reported in humans in some communities and regions of the world (Fisher 1999; Birkett 2003). Chemical substances acting as endocrine disrupters can exert oestrogenic or anti-oestrogenic effects, which interfere with the function of the sensitive human endocrine system. Limited results from epidemiological and laboratory studies on humans and more extensive results from experimental animals support the hypothesis that EDCs impair the functioning of the human endocrine system (Gray *et al.* 1999; Parks *et al.* 2000; Nicolopoulou-Stamati and Pitsos 2001; Hayes *et al.* 2003).

In most documented studies, animals were exposed to a few chemical substances for a certain period of time. However, humans are exposed to a great number of chemical substances simultaneously and throughout their lifetime, usually several decades. These various chemical substances may have synergistic or antagonistic effects on each other.

Conventional toxicological testing of pollutants may miss the potential of a substance to disrupt the endocrine system, especially at the low concentrations likely to be found in the environment.

Industry remains the largest source of EDCs and measures need to be taken to minimise the leakage of these substances into the environment. Preventing the discharge of EDCs is an important factor in the prevention of endocrine reproductive disorders in humans and animals. Filtration techniques and advanced oxidation processes are promising approaches for the removal of EDCs from waste water or surface water, thus reducing the load of these pollutants on human health.

The benefits of many EDCs in industry ensure that they will continue to be used, so they will continue to pose a threat, forcing individuals and populations to adapt in order to survive. To reduce the entry of EDCs into the human body, it would be necessary to develop and implement alternative manufacturing processes for certain human-use products and to use fewer chemicals for everyday purposes. Because many EDCs have *in utero* effects, it would good to be develop fetal programming for different chemicals with *in utero* endocrine-disrupting effects. In addition, education of medical and health care professionals regarding the sources of and the effects of exposure to environmental contaminants *in utero*, as well as throughout the lifespan, and sharing this information in an accessible way with patients and the general public are recommended. People should avoid EDCs sources, especially when they decide to have children. Our chemical policies and legislations at local and national levels, as well as globally, need to be formulated, financed and implemented to ensure the best public health.

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References

Abernathy, C. O., Thomas, D. J., and Calderon, R. L. (2003). Health effects and risk assessment of arsenic. *J. Nutr.* **133**, 1536–1538.

Agency for Toxic Substances and Disease Registry (ATSDR) (1997). 'Toxicological Profile for Selected Polychlorinated Biphenyls: Update.' (US Department of Health and Social Services, Public Health Service, Agency for Toxic Substances and Disease Registry: Atlanta, GA.)

Al-Saleh, I., Khalil, M., and Taylor, A. (1995). Lead, erythrocyte protoporphyrin and haematological parameters in normal maternal and umbilical cord blood from subjects of the Riyadh region. *Arch. Environ. Health* **50**, 66–73. doi:10.1080/00039896.1995.9955014

Andersen, H. R., Cook, S. J., and Waldbillig, D. (2002). Effects of currently used pesticides in assays for estrogenicity, androgenicity, and aromatase activity *in vitro*. *Toxicol. Appl. Pharmacol.* **179**, 1–12. doi:10.1006/TAAP.2001.9347

Anderson, H. A., and Wolff, M. S. (2000). Environmental contaminants in human milk. *J. Expo. Anal. Environ. Epidemiol.* **10**, 755–760. doi:10.1038/SJ.JEA.7500133

Auger, J., Kunstmann, J. M., Czyglik, F., and Jouannet, P. (1995). Decline in semen quality among fertile man in Paris during the past 20 years. *N. Engl. J. Med.* **332**, 281–285. doi:10.1056/NEJM199502023320501

Baccarelli, A., Pesatori, A. C., Masten, S. A., Patterson, D. G., Jr, Needham, L. L., Mocarelli, P., Caporaso, N. E., Consonni, D., Grassman, J. A., Bertazzi, P. A., and Landi, M. T. (2004). Aryl-hydrocarbon receptor-dependent pathway and toxic effects of TCDD in humans: a population-based study in Seveso, Italy. *Toxicol. Lett.* **149**, 287–293. doi:10.1016/J.TOXLET.2003.12.062

Balabanič, D., and Krivograd Klemenčič, A. (2011). Presence of phthalates, bisphenol A, and nonylphenol in paper mill wastewaters in Slovenia and efficiency of aerobic and combined aerobic-anaerobic biological wastewater treatment plants for their removal. *Fresen. Environ. Bull.* **20**, 86–92.

Balabanič, D., Zule, J., and Krivograd Klemenčič, A. (2009). Are biological waste water treatment plants efficient for removal of potential endocrine disrupters? *Papir* **37**, 25–28. [In Slovene]

Barlow, N. J., Phillips, S. L., Wallace, D. G., Sar, M., Gaido, K. W., and Foster, P. M. (2003). Quantitative changes in gene expression in fetal testis following exposure to di(n-butyl) phthalate. *Toxicol. Sci.* **73**, 431–441. doi:10.1093/TOXSCI/KFG087

Baskin, L. S., Himes, K., and Colborn, T. (2001). Hypospadias and endocrine disruption: is there a connection? *Environ. Health Perspect.* **109**, 1175–1183. doi:10.2307/3454866

Bellinger, D. C. (2005). Teratogen update: lead and pregnancy. *Birth Defects Res. A Clin. Mol. Teratol.* **73**, 409–420. doi:10.1002/BDRA.20127

Bergeron, R. M., Thompson, T. B., Leonard, L. S., Pluta, L., and Gaido, K. W. (1999). Estrogenicity of bisphenol A in a human endometrial

carcinoma cell line. *Mol. Cell. Endocrinol.* **150**, 179–187. doi:10.1016/S0303-7207(98)00202-0

Birkett, J. W. (2003). Scope of the problem. In 'Endocrine Disrupters in Wastewater and Sludge Treatment Processes'. (Eds J. W. Birkett and J. N. Lester.) pp. 1–34. (Lewis Publishers: London.)

Brody, J. G., and Rudel, R. A. (2003). Environmental pollutants and breast cancer. *Environ. Health Perspect.* **111**, 1007–1019.

Brotons, J. A., Olea-Serrano, M. F., Villalobos, M., and Olea, N. (1995). Xenoestrogens released from lacquer coating in food cans. *Environ. Health Perspect.* **103**, 608–612. doi:10.2307/3432439

Carbone, P., Giordano, F., Nori, F., Mantovani, A., Taruscio, D., Lauria, L., and Figà-Talamanca, I. (2006). Cryptorchidism and hypospadias in the Sicilian district of Ragusa and the use of pesticides. *Reprod. Toxicol.* **22**, 8–12. doi:10.1016/J.REPROTOX.2006.01.006

Carlsen, E., Giwercman, A., Keiding, N., and Skakkebaek, N. E. (1992). Evidence for decreasing quality of semen during the past 50 years. *BMJ* **305**, 609–613. doi:10.1136/BMJ.305.6854.609

Carlsen, E., Giwercman, A., Keiding, N., and Skakkebaek, N. E. (1995). Declining semen quality and increasing incidence of testicular cancer: is there a common cause? *Environ. Health Perspect.* **103**, 137–139. doi:10.2307/3432523

Chamarro, E., Marco, A., and Esplugas, S. (2001). Use of Fenton reagent to improve organic chemical biodegradability. *Water Res.* **35**, 1047–1051. doi:10.1016/S0043-1354(00)00342-0

Chang, S., Wait, D. T., Schafer, A. I., and Fane, A. G. (2003). Adsorption of the endocrine-active compound estrone on micro-filtration hollow fiber membranes. *Environ. Sci. Technol.* **37**, 3158–3163. doi:10.1021/ES0261574

Chitra, K. C., Latchoumycandane, C., and Mathur, P. P. (2003). Induction of oxidative stress by bisphenol A in the epididymal sperm of rats. *Toxicology* **185**, 119–127. doi:10.1016/S0300-483X(02)00597-8

Choy, C. M. Y., Lam, C. W. K., Cheung, L. T. F., Briton-Jones, C. M., Cheung, L. P., and Haines, C. J. (2003). Infertility, blood mercury concentrations and dietary seafood consumption: a case-control study. *Obstet. Gynecol. Surv.* **58**, 325–326. doi:10.1097/00006254-200305000-00020

Choi, S. M., Yoo, S. D., and Lee, B. M. (2004). Toxicological characteristics of endocrine-disrupting chemicals: developmental toxicity, carcinogenicity, and mutagenicity. *J. Toxicol. Environ. Health B Crit. Rev.* **7**, 1–24.

Cincinelli, A., Stortini, A. M., Checchini, L., Martellini, T., Del Bubba, M., and Lepri, L. (2005). Enrichment of organic pollutants in the sea surface microlayer (SML) at Terra Nova Bay, Antarctica: influence of SML on superficial snow composition. *J. Environ. Monit.* **7**, 1305–1312. doi:10.1039/B507321A

Clarkson, T. W. (2002). The three modern faces of mercury. *Environ. Health Perspect.* **110**, 11–23.

Colburn, T., and Clement, C. (1992). 'Chemically Induced Alterations in Sexual and Functional Development: The Wildlife/Human Connection. Advances in Modern Environmental Toxicology, vol. 12.' (Princeton Scientific Publishing: Princeton, NJ.)

Dargnat, C., Teil, M. J., Chevreuil, M., and Blanchard, M. (2009). Phthalate removal throughout wastewater treatment plant. Case study of Marne Aval station (France). *Sci. Total Environ.* **407**, 1235–1244. doi:10.1016/J.SCITOTENV.2008.10.027

Davis, D. L., Bradlow, H. L., Wolff, M., Woodruff, T., Howl, D. G., and Anton-Culver, H. (1993). Medical hypothesis: xenoestrogens as preventable causes of breast cancer. *Environ. Health Perspect.* **101**, 372–377. doi:10.2307/3431889

Davis, B. J., Price, H. C., O'Connor, R. W., Fernando, R., Rowland, A. S., and Morgan, D. L. (2001). Mercury vapor and female reproductive toxicity. *Toxicol. Sci.* **59**, 291–296. doi:10.1093/TOXSCI/59.2.291

Daxenberger, A. A. (2002). Pollutants with androgen-disrupting potency. *Eur. J. Lipid Sci. Technol.* **104**, 124–130. doi:10.1002/1438-9312(200202)104:2<124::AID-EJLT124>3.0.CO;2-T

Drewes, J. E., Hemming, J., Ladenburger, S. J., Schauer, J., and Sonzogni, W. (2005). An assessment of endocrine disrupting activity changes during wastewater treatment through the use of bioassays and chemical measurements. *Water Environ. Res.* **77**, 12–23. doi:10.2175/106143005X41573

Egeland, G. M., Sweeney, M. H., Fingerhut, M. A., Wille, K. K., Schnorr, T. M., and Halperin, W. E. (1994). Total serum testosterone and gonadotropins in workers exposed to dioxin. *Am. J. Epidemiol.* **139**, 272–281.

Ernst, E., and Lauritsen, J. G. (1991). Effect of organic and inorganic mercury on human sperm motility. *Pharmacol. Toxicol.* **68**, 440–444. doi:10.1111/J.1600-0773.1991.TB01267.X

Esplugas, S., Bila, D. M., Krause, L. G. T., and Dezotti, M. (2007). Ozonation and advanced oxidation technologies to remove endocrine disrupting chemicals (EDCs) and pharmaceuticals and personal care products (PPCPs) in water effluents. *J. Hazard. Mater.* **149**, 631–642. doi:10.1016/J.JHAZMAT.2007.07.073

Faqi, A. S., Dalsenter, P. R., Merker, H. J., and Chahoud, I. (1998). Reproductive toxicity and tissue concentrations of low doses of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in male offspring rats exposed throughout pregnancy and lactation. *Toxicol. Appl. Pharmacol.* **150**, 383–392. doi:10.1006/TAAP.1998.8433

Finizio, A., Vighi, M., and Sandroni, D. (1997). Determination of n-octanol/water partition coefficient (K_{ow}) of pesticide. *Chemosphere* **34**, 131–161. doi:10.1016/S0045-6535(96)00355-4

Fisher, B. E. (1999). Most unwanted. *Environ. Health Perspect.* **107**, 18–23.

Fisher, J. S. (2004). Environmental anti-androgens and male reproductive health: focus on phthalates and testicular dysgenesis syndrome. *Reproduction* **127**, 305–315. doi:10.1530/REP.1.00025

Fisher, J. S., Macpherson, S., Marchetti, N., and Sharpe, R. M. (2003). Human 'testicular dysgenesis syndrome': a possible model using *in utero* exposure of the rat to dibutyl phthalate. *Hum. Reprod.* **18**, 1383–1394. doi:10.1093/HUMREP/DEG273

Fukushima, M., and Tatsumi, K. (2001). Degradation of pentachlorophenol by photo-Fenton systems in the presence of iron(III), humic acid, and hydrogen peroxide. *Environ. Sci. Technol.* **35**, 1771–1778. doi:10.1021/ES001088J

Garcia-Sanchez, A., Antona, J. F., and Urrutia, M. (1992). Geochemical prospection of cadmium in a high incidence area of prostate cancer, Sierra de Gata, Salamanca, Spain. *Sci. Total Environ.* **116**, 243–251. doi:10.1016/0048-9697(92)90452-X

Gardella, J. R., and Hill, J. A., 3rd (2000). Environmental toxins associated with recurrent pregnancy loss. *Semin. Reprod. Med.* **18**, 407–424. doi:10.1055/S-2000-13731

Garry, V. F. (2004). Pesticides and children. *Toxicol. Appl. Pharmacol.* **198**, 152–163. doi:10.1016/J.TAAP.2003.11.027

Gilpin, R. K., Wagel, D. J., and Solch, J. G. (2003). Production, distribution, and fate of polychlorinated dibenzo-*p*-dioxins, dibenzofurans, and related organohalogens in the environment. In 'Dioxins and Health', 2nd edn. (Eds A. Schecter and T. A. Gasiewicz.) pp. 89–136. (Wiley: Hoboken, NJ.)

Giusti, R. M., Iwamoto, K., and Hatch, E. E. (1995). Diethylstilbestrol revisited: a review of the long-term health effects. *Ann. Intern. Med.* **122**, 778–788.

Giwercman, A., Carlsen, E., Keiding, N., and Skakkebaek, N. E. (1993). Evidence for increasing incidence of abnormalities of the human testis: a review. *Environ. Health Perspect.* **101**, 65–71. doi:10.2307/3431378

Goad, R. T., Goad, J. T., Atieh, B. H., and Gupta, R. C. (2004). Carbofuran-induced endocrine disruption in adult male rats. *Toxicol. Mech. Methods* **14**, 233–239. doi:10.1080/15376520490434476

Goldman, L., Falk, H., Landrigan, P. J., Balk, S. J., Reigart, R., and Etzel, R. A. (2004). Environmental pediatrics and its impact on government health policy. *Pediatrics* **113**, 1146–1157.

Gray, L. E., Jr, Wolf, C., Lambright, C., Mann, P., Price, M., Cooper, R. L., and Ostby, J. (1999). Administration of potentially antiandrogenic pesticides (procymidone, linuron, iprodione, chlozolinate, *p,p′*-DDE, and ketoconazole) and toxic substances (dibutyl- and diethylhexyl phthalate, PCB 169, and ethane dimethane sulphonate) during sexual differentiation produces diverse profiles of reproductive malformations in the male rat. *Toxicol. Ind. Health* **15**, 94–118. doi:10.1191/074823399678846664

Grova, N., Feidt, C., Crépineau, C., Laurent, C., Lafargue, P. E., Hachimi, A., and Rychen, G. (2002). Detection of polycyclic aromatic hydrocarbon levels in milk collected near potential contamination sources. *J. Agric. Food Chem.* **50**, 4640–4642. doi:10.1021/JF0201071

Gültekin, I., and Ince, N. H. (2007). Synthetic endocrine disruptors in the environment and water remediation by advanced oxidation processes. *J. Environ. Manage.* **85**, 816–832. doi:10.1016/J.JENVMAN.2007.07.020

Gwinn, M. R., Whipkey, D. L., Tennant, L. B., and Weston, A. (2005). Differential gene expression in normal human mammary epithelial cells treated with malathion monitored by DNA microarrays. *Environ. Health Perspect.* **113**, 1046–1051. doi:10.1289/EHP.7311

Haddow, A., Roe, F. J. C., Dukes, C. E., and Mitchley, B. C. V. (1964). Cadmium neoplasia: sarcomata at the site of injection of cadmium sulphate in rats and mice. *Br. J. Cancer* **18**, 667–673.

Hamm, U., Oller, H.-J., and Kuwan, K. (2005*a*). Endokrine Substanzen in Abwassern der Papierindustrie. *IPW* **1**, 45–48.

Hamm, U., Oller, H.-J., and Kuwan, K. (2005*b*). Endokrine Substanzen in Abwassern der Papierindustrie (II). *IPW* **2**, 47–49.

Hardell, L., Van Bavel, B., Lindström, G., Eriksson, M., and Carlberg, M. (2006). *In utero* exposure to persistent organic pollutants in relation to testicular cancer risk. *Int. J. Androl.* **29**, 228–234. doi:10.1111/J.1365-2605.2005.00622.X

Harris, C. A., Henttu, P., Parker, M. G., and Sumpter, J. P. (1997). The estrogenic activity of phthalate esters *in vitro*. *Environ. Health Perspect.* **105**, 802–811. doi:10.2307/3433697

Hayes, T. B., Collins, A., Lee, M., Mendoza, M., Noriega, N., Stuart, A., and Vonk, A. (2002). Hermaphroditic, demasculinized frogs after exposure to the herbicide atrazine at low ecologically relevant doses. *Proc. Natl Acad. Sci. USA* **99**, 5476–5480. doi:10.1073/PNAS.082121499

Hayes, T. B., Hoang, A., Haeffele, C., Haston, K., Tsui, M., and Vonk, A. (2003). Atrazine-induced hermaphroditism at 0.1 ppb in American leopard frogs (*Rana pipiens*): laboratory and field evidence. *Environ. Health Perspect.* **111**, 568–575. doi:10.1289/EHP.5932

Homma-Takeda, S., Kugenuma, Y., Iwamuro, T., Kumagai, Y., and Shimojo, N. (2001). Impairment of spermatogenesis in rats by methyl mercury: involvement of stage- and cell-specific germ cell apoptosis. *Toxicology* **169**, 25–35. doi:10.1016/S0300-483X(01)00487-5

Integrated Risk Information System (IRIS) (2005). 'Environmental Protection Agency. Polychlorinated Biphenyls (PCBs). Last Updated: 23rd January 2008.' Available at http://www.epa.gov/iris/subst/0294.htm [Verified 24 November 2010].

International Agency for Research on Cancer (IARC) (1983). Polynuclear aromatic compounds, Part 1, chemical, environmental and experimental data. In 'Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans', vol. 32. pp. 1–447. (IARC: Lyon.)

International Agency for Research on Cancer (IARC) (1998). 'Polychlorinated Biphenyls, vol. 18, 1978, p. 43. Last Updated: 27th March 1998.' Available at http://monographs.iarc.fr/ENG/Monographs/vol18/volume18.pdf [Verified 24 November 2010].

Ishihara, A., Nishiyama, N., Sugiyama, S., and Yamauchi, K. (2003). The effect of endocrine disrupting chemicals on thyroid hormone binding to Japanese quail transthyretin and thyroid hormone receptor. *Gen. Comp. Endocrinol.* **134**, 36–43. doi:10.1016/S0016-6480(03)00197-7

Järup, L. (2003). Hazards of heavy metal contamination. *Br. Med. Bull.* **68**, 167–182. doi:10.1093/BMB/LDG032

Jeong, S. H., Kim, B. Y., Kang, H. G., Ku, H. K., and Cho, J. H. (2006). Effect of chlorpyrifos-methyl on steroid and thyroid hormones in rat F0- and F1-generations. *Toxicology* **220**, 189–202. doi:10.1016/J.TOX.2006.01.005

Jiang, K., Li, L. J., Chen, Y. D., and Jin, J. (1997). Determination of PCDD/Fs and dioxin-like PCBs in Chinese commercial PCBs and emissions from a testing PCB incinerator. *Chemosphere* **34**, 941–950. doi:10.1016/S0045-6535(97)00397-4

Jobling, S., Sheahan, D., Osborne, J. A., Matthissen, P., and Sumpter, J. P. (1996). Inhibition of testicular growth in rainbow trout (*Oncorhynchus mykiss*) exposed to estrogenic alkylphenolic chemicals. *Environ. Toxicol. Chem.* **15**, 194–202.

Johansson, M., Nilsson, S., and Lund, B. O. (1998). Interactions between methylsulfonyl PCBs and the glucocorticoid receptor. *Environ. Health Perspect.* **106**, 769–772. doi:10.2307/3434119

Kang, H. G., Jeong, S. H., Cho, J. H., Kim, D. G., Park, J. M., and Cho, M. H. (2004). Chlropyrifos-methyl shows anti-androgenic activity without estrogenic activity in rats. *Toxicology* **199**, 219–230. doi:10.1016/J.TOX.2004.02.025

Katsumata, H., Kawabe, S., Kaneco, S., Suzuki, T., and Ohta, K. (2004). Degradation of bisphenol A in water by the photo-Fenton reaction. *J. Photochem. Photobiol. Chem.* **162**, 297–305. doi:10.1016/S1010-6030(03)00374-5

Kawauchi, H., Suzuki, K., Yamazaki, T., Moriyama, S., Nozaki, M., Yamaguchi, K., Takahashi, A., Youson, J., and Sower, S. A. (2002). Identification of growth hormone in the sea lamprey, an extant representative of a group of the most ancient vertebrates. *Endocrinology* **143**, 4916–4921. doi:10.1210/EN.2002-220810

Kelce, W. R., and Wilson, E. M. (1997). Environmental anti-androgens: developmental effects, molecular mechanisms and clinical implications. *J. Mol. Med.* **75**, 198–207. doi:10.1007/S001090050104

Kester, M. H. A., Bulduk, S., Tibboel, D., Meinl, W., Glatt, H., Falany, C. N., Coughtrie, M. W. H., Bergman, A., Safe, S. H., Kuiper, G., Schuur, A. G., Brouwer, A., and Visser, T. J. (2000). Potent inhibition of estrogen sulfotransferase by hydroxylated PCB metabolites: a novel pathway explaining the estrogenic activity of PCBs. *Endocrinology* **141**, 1897–1900. doi:10.1210/EN.141.5.1897

Kim, I. Y., Shin, J. H., Kim, H. S., Lee, S. J., Kang, I. H., Kim, T. S., Moon, H. J., Choi, K. S., Moon, A., and Han, S. Y. (2004). Assessing estrogenic activity of pyrethroid insecticides using *in vitro* combination assays. *J. Reprod. Dev.* **50**, 245–255. doi:10.1262/JRD.50.245

Kolonel, L. N. (1996). Nutrition and prostate cancer. *Cancer Causes Control* **7**, 83–94. doi:10.1007/BF00115640

Kuiper, G. G. J. M., Enmark, E., Pelto-Huikko, M., Nilsson, S., and Gustafsson, J. Å. (1996). Cloning of a novel estrogen receptor expressed in rat prostate and ovary. *Proc. Natl. Acad. Sci. USA* **93**, 5925–5930.

Kuiper, G. G. J. M., Carlsson, B., Grandien, K., Enmark, E., Häggblad, J., Nilsson, S., and Gustafsson, J. Å. (1997). Comparison of the ligand binding specificity and transcript tissue distribution of estrogen receptors α and β. *Endocrinology* **138**, 863–870.

Kulbat, E., Olańczuk-Neyman, K., Quant, B., Geneja, M., and Haustein, E. (2003). Heavy metals removal in the mechanical–biological wastewater treatment plant 'Wschód' in Gdańs. *Pol. J. Environ. Stud.* **12**, 635–641.

Lemaire, G., Terouanne, B., Mauvais, P., Michel, S., and Rahmani, R. (2004). Effect of organochlorine pesticides on human androgen receptor activation *in vitro*. *Toxicol. Appl. Pharmacol.* **196**, 235–246. doi:10.1016/J.TAAP.2003.12.011

Li, M. H., and Hansen, L. G. (1997). Consideration of enzyme and endocrine interactions in the risk assessment of PCBs. *Rev. Toxicol.* **1**, 71–156.

Li, C. T., Lin, Y. C., Lee, W. J., and Tsai, P. J. (2003). Emission of polycyclic aromatic hydrocarbons and their carcinogenic potencies from cooking sources to the urban atmosphere. *Environ. Health Perspect.* **111**, 483–487. doi:10.1289/EHP.5518

Liu, Z. H., Kanjo, Y., and Mizutani, S. (2009). Removal mechanisms for endocrine disrupting compounds (EDCs) in wastewater treatment: physical means, biodegradation, and chemical advanced oxidation: a review. *Sci. Total Environ.* **407**, 731–748. doi:10.1016/J.SCITOTENV.2008.08.039

Loganathan, B., and Kannan, K. (1994). Global organochlorine contamination trends: an overview. *Ambio* **23**, 187–189.

Lu, S. Y., Liao, J. W., Kuo, M. L., Wang, S. C., Hwang, J. S., and Ueng, T. H. (2004). Endocrine-disrupting activity in carbendazim-induced reproductive and developmental toxicity in rats. *J. Toxicol. Environ. Health A* **67**, 1501–1515. doi:10.1080/15287390490486833

Mabilia, R., Cecinato, A., Tomasi Scianò, M. C., Di Palo, V., and Possanzini, M. (2004). Characterization of polycyclic aromatic hydrocarbons and carbonyl compounds in diesel exhaust emissions. *Ann. Chim.* **94**, 733–740. doi:10.1002/ADIC.200490091

Mackenzie, C. A., and Constanze, A. (2005). Declining sex ratio in a first nation community. *Environ. Health Perspect.* **113**, 1295–1298. doi:10.1289/EHP.8479

Malato, S., Caceras, J., Aguera, A., Mezcua, M., Hernando, D., Vial, J., and Fernandez-Alba, A. R. (2001). Degradation of imidacloprid in water by photo-Fenton and TiO_2 photocatalysis at a solar pilot plant: a comparative study. *Environ. Sci. Technol.* **35**, 4359–4366. doi:10.1021/ES000289K

Malato, S., Blanco, J., Cáceres, J., Fernández-Alba, A. R., Agüera, A., and Rodŕýguez, A. (2002). Photocatalytic treatment of water-soluble pesticides by photo-Fenton and TiO_2 using solar energy. *Catal. Today* **76**, 209–220. doi:10.1016/S0920-5861(02)00220-1

Mankame, T., Hokanson, R., Chowdhary, R., and Busbee, D. (2004). Altered gene expression in human cells induced by the agricultural chemical Enable. *Toxicol. Ind. Health* **20**, 89–102. doi:10.1191/0748233704TH198OA

Markey, C. M., Luque, E. H., Munoz de Toro, M., Sonnenschein, C., and Soto, A. M. (2001). *In utero* exposure to bisphenol A alters the development and tissue organization of the mouse mammary gland. *Biol. Reprod.* **65**, 1215–1223.

Mascolo, G., Ciannarella, R., Balest, L., and Lopez, A. (2008). Effectiveness of UV-based advanced oxidation processes for the remediation of hydrocarbon pollution in the groundwater: a laboratory investigation. *J. Hazard. Mater.* **152**, 1138–1145. doi:10.1016/J.JHAZMAT.2007.07.120

Mathur, V., Bhatnagar, P., Sharma, R. G., Acharya, V., and Sexana, R. (2002). Breast cancer incidence and exposure to pesticides among women originating from Jaipur. *Environ. Int.* **28**, 331–336. doi:10.1016/S0160-4120(02)00031-4

McIntyre, B. S., Barlow, N. J., and Foster, P. M. D. (2001). Androgen-mediated development in the male rat offspring exposed to flutamide *in utero*: permanence and correlation of early postnatal changes in anogenital distance and nipple retention with malformations in androgen-dependent tissues. *Toxicol. Sci.* **62**, 236–249. doi:10.1093/TOXSCI/62.2.236

McRill, C., Boyer, L. V., Flood, T. J., and Ortega, L. (2000). Mercury toxicity due to use of a cosmetic cream. *J. Occup. Environ. Med.* **42**, 4–7. doi:10.1097/00043764-200001000-00004

Menchini-Fabris, F., Rossi, P., Palego, P., Simi, S., and Turchi, P. (1996). Declining sperm counts in Italy during the past 20 years. *Andrologia* **28**, 304. doi:10.1111/J.1439-0272.1996.TB02804.X

Mendola, P., Buck, G. M., Sever, L. E., Zielezny, M., and Vena, J. E. (1997). Consumption of PCB-contaminated freshwater fish and shortened menstrual cycle length. *Am. J. Epidemiol.* **146**, 955–960.

Metzler, M., and Pfeiffer, E. (2001). Chemistry of natural and antropogenic endocrine active compounds. In 'Endocrine Disruptors Part I'. (Ed. M. Metzler.) pp. 63–80. (Springer: Berlin.)

Meulenberg, E. E. (2002). A new test to identify endocrine disruptors using sex hormone-binding globulins from human serum. *Eur. J. Lipid Sci. Technol.* **104**, 131–136. doi:10.1002/1438-9312(200202)104:2<131::AID-EJLT131>3.0.CO;2-0

Mocarelli, P., Gerthoux, P. M., Patterson, D. G., Jr, Milani, S., Limonta, G., Bertona, M., Signorini, S., Tramacere, P., Colombo, L., Crespi, C., Brambilla, P., Sarto, C., Carreri, V., Sampson, E. J., Turner, W. E., and Needham, L. L. (2008). Dioxin exposure, from infancy through puberty, produces endocrine disruption and affects human semen quality. *Environ. Health Perspect.* **116**, 70–77. doi:10.1289/EHP.10399

Morinaga, H., Yanase, T., Nomura, M., Okabe, T., Goto, K., Harada, N., and Nawata, H. (2004). A benzimidazole fungicide, benomyl, and its metabolite, carbendazim, induce aromatase activity in a human ovarian granulose-like tumor cell line (KGN). *Endocrinology* **145**, 1860–1869. doi:10.1210/EN.2003-1182

Muir, D., Braune, B., DeMarch, B., Norstrom, R., Wagemann, R., Lockhart, L., Hargrave, B., Bright, D., Addison, R., Payne, J., and Reimer, K. (1999). Spatial and temporal trends and effects of contaminants in the Canadian Artic marine ecosystem: a review. *Sci. Total Environ.* **230**, 83–144. doi:10.1016/S0048-9697(99)00037-6

Mukherjee, A., Sengupta, M. K., Hossain, M. A., Ahamed, S., Das, B., Nayak, B., Lodh, D., Rahman, M. M., and Chakraborti, D. (2006). Arsenic contamination in groundwater: a global perspective with emphasis on the Asian scenario. *J. Health Popul. Nutr.* **24**, 142–163.

Muñoz de Toro, M., Markey, C. M., Wadia, P. R., Luque, E. H., Rubin, B. S., Sonnenschein, C., and Soto, A. M. (2005). Perinatal exposure to bisphenol A alters peripubertal mammary gland development in mice. *Endocrinology* **146**, 4138–4147. doi:10.1210/EN.2005-0340

Mylchreest, E., Cattley, R. C., and Foster, P. M. D. (1998). Male reproductive tract malformations in rats following gestational and lactational exposure to di(n-butyl) phthalate: an antiandrogenic mechanism? *Toxicol. Sci.* **43**, 47–60.

Mylchreest, E., Sar, M., Cattley, R. C., and Foster, P. M. D. (1999). Disruption of androgen-regulated male reproductive development by di(n-butyl) phthalate during late gestation in rats is different from flutamide. *Toxicol. Appl. Pharmacol.* **156**, 81–95. doi:10.1006/TAAP.1999.8643

Nadal, M., Schuhmacher, M., and Domingo, J. L. (2004). Levels of PAHs in soil and vegetation samples from Tarragona County, Spain. *Environ. Pollut.* **132**, 1–11. doi:10.1016/J.ENVPOL.2004.04.003

Nampoothiri, L. P., and Gupta, S. (2006). Simultaneous effect of lead and cadmium on granulosa cells: a cellular model for ovarian toxicity. *Reprod. Toxicol.* **21**, 179–185. doi:10.1016/J.REPROTOX.2005.07.010

Nicolopoulou-Stamati, P., and Pitsos, M. A. (2001). The impact of endocrine disrupters on the female reproductive system. *Hum. Reprod. Update* **7**, 323–330. doi:10.1093/HUMUPD/7.3.323

Nimrod, A. C., and Benson, W. H. (1996). Environmental estrogenic effects of alkylphenol ethoxylates. *Crit. Rev. Toxicol.* **26**, 335–364. doi:10.3109/10408449609012527

Nogueira, R. F. P., Silva, M. R. A., and Trovó, A. G. (2005). Influence of the iron source on the solar photo-Fenton degradation of different classes of organic compounds. *Sol. Energy* **79**, 384–392. doi:10.1016/J.SOLENER.2005.02.019

Nordström, S., Beckman, L., and Nordenson, I. (1979). Occupational and environmental risks in and around a smelter in northern Sweden. V. Spontaneous abortion among female employees and decreased birth weight in their offspring. *Hereditas* **90**, 291–296. doi:10.1111/J.1601-5223.1979.TB01316.X

Olie, K., Vermeulen, P. L., and Hutzinger, O. (1977). Chlorodibenzo-*p*-dioxins and chlorodibenzofurans are trace components of fly ash and flue gas of some municipal incinerators in the Netherlands. *Chemosphere* **6**, 455–459. doi:10.1016/0045-6535(77)90035-2

Parks, L. G., Ostby, J. S., Lambright, C. R., Abbott, B. D., Klinefelter, G. R., Barlow, N. J., and Earl Gray, L., Jr (2000). The plasticizer diethylhexyl phthalate induces malformations by decreasing fetal testosterone synthesis during sexual differentiation in the male rat. *Toxicol. Sci.* **58**, 339–349. doi:10.1093/TOXSCI/58.2.339

Perera, F., Hemminke, K., Jedrychowski, W., Whyatt, R., Campbell, U., Hsu, Y., Santella, R., Albertini, R., and O'Neill, J. P. (2002). *In utero* DNA damage from environmental pollution is associated with somatic gene mutation in newborns. *Cancer Epidemiol. Biomarkers Prev.* **11**, 1134–1137.

Perera, F. P., Tang, D., Rauh, V., Lester, K., Tsai, W. Y., Tu, Y. H., Weiss, L., Hoepner, L., King, J., Del Priore, G., and Lederman, S. A. (2005). Relationships among polycyclic aromatic hydrocarbons: DNA adducts, proximity to the World Trade Center, and effects on fetal growth. *Environ. Health Perspect.* **113**, 1062–1067. doi:10.1289/EHP.7908

Peterson, R. E., Theobald, H. M., and Kimmel, G. L. (1993). Developmental and reproductive toxicity of dioxins and related compounds: cross-species comparisons. *Crit. Rev. Toxicol.* **23**, 283–335. doi:10.3109/10408449309105013

Petrovic, M., Eljarrate, E., Lopez De Alda, M. J., and Barcelo, D. (2004). Endocrine disrupting compounds and other emerging contaminants in the environment: a survey on new monitoring strategies and occurrence data. *Anal. Bioanal. Chem.* **378**, 549–562. doi:10.1007/S00216-003-2184-7

Pokhrel, D., and Viraraghavan, T. (2004). Treatment of pulp and paper mill effluent: a review. *Sci. Total Environ.* **333**, 37–58. doi:10.1016/J.SCITOTENV.2004.05.017

Przyrembel, H., Heinrich-Hirsch, B., and Vieth, B. (2000). Exposition to and health effects of residues in human milk. *Adv. Exp. Med. Biol.* **478**, 307–325. doi:10.1007/0-306-46830-1_27

Pulgar, R., Olea-Serrano, M. F., Novillo-Fertrell, A., Rivas, A., Pazos, P., Pedraza, V., Navajas, J. M., and Olea, N. (2000). Determination of bisphenol A and related aromatic compounds released from bis-GMA-based composites and sealants by high performance liquid chromatography. *Environ. Health Perspect.* **108**, 21–27. doi:10.2307/3454291

Rai, U. N., and Pal, A. (2002). 'Health Hazards of Heavy Metals.' Available at http://isebindia.com/01_04/02-01-2.html [Verified 24 November 2010].

Roman, B. L., and Peterson, R. E. (1998). Developmental male reproductive toxicology of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and PCBs. In 'Reproductive and Developmental Toxicology'. (Ed. K. S. Korach.) pp. 593–624. (Marcel Dekker: New York.)

Ross, G. (2004). The public health implications of polychlorinated biphenyls (PCBs) in the environment. *Ecotoxicol. Environ. Saf.* **59**, 275–291. doi:10.1016/J.ECOENV.2004.06.003

Rubin, B. S., and Soto, A. M. (2009). Bisphenol A: perinatal exposure and body weight. *Mol. Cell. Endocrinol.* **304**, 55–62. doi:10.1016/J.MCE.2009.02.023

Santodonato, J. (1997). Review of the estrogenic and antiestrogenic activity of polycyclic aromatic hydrocarbons: relationship to carcinogenicity. *Chemosphere* **34**, 835–848. doi:10.1016/S0045-6535(97)00012-X

Satarug, S., and Moore, M. R. (2004). Adverse health effects of chronic exposure to low-level cadmium in foodstuffs and cigarette smoke. *Environ. Health Perspect.* **112**, 1099–1103. doi:10.1289/EHP.6751

Satoh, H. (2003). Behavioral teratology of mercury and its compounds. *Tohoku J. Exp. Med.* **201**, 1–9. doi:10.1620/TJEM.201.1

Schantz, S. L., and Widholm, J. J. (2001). Cognitive effects of endocrine-disrupting chemicals in animals. *Environ. Health Perspect.* **109**, 1197–1206. doi:10.2307/3454741

Schönfelder, G., Wittfoht, W., Hopp, H., Talsness, C. E., Paul, M., and Chahoud, I. (2002). Parent bisphenol A accumulation in the human maternal–fetal–placental unit. *Environ. Health Perspect.* **110**, A703–A707. doi:10.1289/EHP.021100703

Schreinemachers, D. M. (2003). Birth malformations and other adverse perinatal outcomes in four US wheat-producing states. *Environ. Health Perspect.* **111**, 1259–1264. doi:10.1289/EHP.5830

Schuurs, A. H. B. (1999). Reproductive toxicity of occupational mercury. A review of the literature. *J. Dent.* **27**, 249–256. doi:10.1016/S0300-5712(97)00039-0

Scippo, M.-L. (2004). Recombinant human estrogen, androgen and progesterone receptors for detection of potential endocrine disruptors. *Anal. Bioanal. Chem.* **378**, 664–669. doi:10.1007/S00216-003-2251-0

Sharara, F. I., Seifer, D. B., and Flaws, J. A. (1998). Environmental toxicants and female reproduction. *Fertil. Steril.* **70**, 613–622. doi:10.1016/S0015-0282(98)00253-2

Sharpe, R. M. (2003). 'The oestrogen hypothesis': where do we stand now? *Int. J. Androl.* **26**, 2–15. doi:10.1046/J.1365-2605.2003.00367.X

Sharpe, R. M. (2006). Pathways of endocrine disruption during male sexual differentiation and masculinisation. *Best Pract. Res. Clin. Endocrinol. Metab.* **20**, 91–110. doi:10.1016/J.BEEM.2005.09.005

Sharpe, R. M., and Irvine, D. S. (2004). How strong is the evidence of a link between environmental chemicals and adverse effects on human reproductive health? *BMJ* **328**, 447–451. doi:10.1136/BMJ.328.7437.447

Sharpe, R. M., and Skakkebaek, N. E. (1993). Are estrogens involved in falling sperm counts and disorders of the male reproductive tract? *Lancet* **341**, 1392–1396. doi:10.1016/0140-6736(93)90953-E

Shen, W., Chen, Y., Li, C., and Ji, Q. (2000). Effect of mercury chloride on the reproductive function and visceral organ of female mouse. *Wei Sheng Yan Jiu* **29**, 75–77. [In Chinese]

Shultz, V. D., Phillips, S., Sar, M., Foster, P. M., and Gaido, K. W. (2001). Altered gene profiles in fetal rat testes after *in utero* exposure to di(n-butyl) phthalate. *Toxicol. Sci.* **64**, 233–242. doi:10.1093/TOXSCI/64.2.233

Silbergeld, E. K. (1991). Lead in bone: implications for toxicology during pregnancy and lactation. *Environ. Health Perspect.* **91**, 63–70. doi:10.2307/3430984

Simko, P. (2002). Determination of polycyclic aromatic hydrocarbons in smoked meat products and smoke flavouring food additives. *J. Chromatogr. B Anal. Technol. Biomed. Life Sci.* **770**, 3–18. doi:10.1016/S0378-4347(01)00438-8

Simoncini, T., and Genazzani, A. R. (2003). Non-genomic actions of sex steroid hormones. *Eur. J. Endocrinol.* **148**, 281–292. doi:10.1530/EJE.0.1480281

Sinawat, S. (2000). The environmental impact on male fertility. *J. Med. Assoc. Thai.* **83**, 880–885.

Singer, P. L. (1949). Occupational oligospermia. *J. Am. Med. Assoc.* **140**, 1249.

Siu, E. R., Mruk, D. D., Porto, C. S., and Cheng, C. Y. (2009). Cadmium-induced testicular injury. *Toxicol. Appl. Pharmacol.* **238**, 240–249. doi:10.1016/J.TAAP.2009.01.028

Skakkebæk, N. E. (2002). Endocrine disrupters and testicular dysgenesis syndrome. *Horm. Res.* **57**, 43. doi:10.1159/000058100

Skakkebæk, N. E., Rajpert-De Meyts, E., and Main, K. M. (2001). Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects. *Hum. Reprod.* **16**, 972–978. doi:10.1093/HUMREP/16.5.972

Smith, A. H., Hopenhayn-Rich, C., Bates, M. N., Goeden, H. M., Hertz-Picciotto, I., Duggan, H. M., Wood, R., Kosnett, M. J., and Smith, M. T. (1992). Cancer risks from arsenic in drinking water. *Environ. Health Perspect.* **97**, 259–267. doi:10.2307/3431362

Snyder, S. A., Westerhoff, P., Yoon, Y., and Sedlak, D. L. (2003). Pharmaceuticals, personal care products, and endocrine disruptors in water: Implications for the water industry. *Environ. Eng. Sci.* **20**, 449–469.

Soares, A., Guieysse, B., Jefferson, B., Cartmell, E., and Lester, J.-N. (2008). Nonylphenol in the environment: a critical review on occurrence, fate,

toxicity and treatment in wastewaters. *Environ. Int.* **34**, 1033–1049. doi:10.1016/J.ENVINT.2008.01.004

Soto, A. M., Justicia, H., Wray, J. W., and Sonnenschein, C. (1991). *p*-Nonylphenol: an estrogenic xenobiotic released from 'modified' polystrene. *Environ. Health Perspect.* **92**, 167–173. doi:10.2307/3431154

Soto, A. M., Chung, K. L., and Sonnenschein, C. (1994). The pesticides endosulfan, toxaphene, and dieldrin have estrogenic effects on human estrogen sensitive cells. *Environ. Health Perspect.* **102**, 380–383. doi:10.2307/3431626

Soto, A. M., Sonnenschein, C., Chung, K. L., Fernandez, M. F., Olea, N., and Olea-Serrano, M. F. (1995). The E-SCREEN assay as a tool to identify estrogens: an update on estrogenic environmental pollutants. *Environ. Health Perspect.* **103**, 113–122. doi:10.2307/3432519

Staples, C. A., Dorn, P. B., Klečka, G. M., O'Block, S. T., and Harris, L. R. (1998). A review of the environmental fate, effects, and exposures of bisphenol A. *Chemosphere* **36**, 2149–2173. doi:10.1016/S0045-6535(97)10133-3

Stillman, R. J. (1982). *In utero* exposure to diethylstilbestrol: adverse effects on the reproductive tract and reproductive performance and male and female offspring. *Am. J. Obstet. Gynecol.* **142**, 905–921.

Storrs, S. I., and Kiesecker, J. M. (2004). Survivorship patterns of larval amphibians exposed to low concentrations of atrazine. *Environ. Health Perspect.* **112**, 1054–1057. doi:10.1289/EHP.6821

Sultan, C., Balaguer, P., Terouanne, B., Georget, V., Paris, F., Jeandel, C., Lumbroso, S., and Nicolas, J. C. (2001). Environmental xenoestrogens, antiandrogens and disorders of male sexual differentiation. *Mol. Cell. Endocrinol.* **178**, 99–105. doi:10.1016/S0303-7207(01)00430-0

Swan, S. H., Elkin, E. P., and Fenster, L. (2000). The question of declining sperm density revisited: an analysis of 101 studies published 1934–1996. *Environ. Health Perspect.* **108**, 961–966. doi:10.2307/3435055

Tang, H. W., Huel, G., Campagna, D., Hellier, G., Boissinot, C., and Blot, P. (1999). Neurodevelopmental evaluation of 9-month-old infants exposed to low levels of lead *in utero*: involvement of monoamine neurotransmitters. *J. Appl. Toxicol.* **19**, 167–172. doi:10.1002/(SICI)1099-1263(199905/06)19:3<167::AID-JAT560>3.0.CO;2-8

Tao, S., Cui, Y. H., Xu, F. L., Li, B. G., Cao, J., Liu, W. X., Schmitt, G., Wang, X. J., Shen, W. R., Qing, B. P., and Sun, R. (2004). Polycyclic aromatic hydrocarbons (PAHs) in agricultural soil and vegetables from Tianjin. *Sci. Total Environ.* **320**, 11–24. doi:10.1016/S0048-9697(03)00453-4

Tapio, S., and Grosche, B. (2006). Arsenic in the aetiology of cancer. *Mutat. Res.* **612**, 215–246. doi:10.1016/J.MRREV.2006.02.001

The European Parliament and the Council of the European Union (2000). Directive 2000/60/EC of the European Parliament and of the Council of 23 October 2000 establishing a framework for community action in the field of water policy. *Off. J. Eur. Communities* **327**, 1–73. Available at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2000:327: 0001:0072:EN:PDF

The European Parliament and the Council of the European Union (2008). Directive 2008/105/EC of the European Parliament and of the Council of 16 December 2008, on environmental quality standards in the field of water policy, amending and subsequently repealing Council Directives 82/176/EEC, 83/513/EEC, 84/156/EEC, 84/491/EEC, 86/280/EEC and amending Directive 2000/60/EC of the European Parliament and of the Council. Off. J. Eur. Communities 384, 84–97. Available at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:348:0084:0097:EN:PDF

Theobald, H. M., Kimmel, G. L., and Peterson, R. E. (2003). Developmental and reproductive toxicity of dioxins and related compounds. In 'Dioxins and Health', 2nd edn. (Eds A. Schecter and T. A. Gasiewicz.) pp. 329–431. (John Wiley and Sons: Hoboken, NJ.)

Thomas, J. A., and Thomas, M. J. (1984). Biological effects of di-(2-ethylhexyl) phthalate and other phthalic acid esters. *Crit. Rev. Toxicol.* **13**, 283–317. doi:10.3109/10408448409023761

Thompson, C. J., Ross, S. M., and Gaido, K. W. (2004). Di(n-butyl) phthalate impairs cholesterol transport and steroidogenesis in the fetal rat testis through a rapid and reversible mechanism. *Endocrinology* **145**, 1227–1237. doi:10.1210/EN.2003-1475

Thompson, G., Swain, J., Kay, M., and Forster, C. F. (2001). The treatment of pulp and paper mill effluent: a review. *Bioresour. Technol.* **77**, 275–286. doi:10.1016/S0960-8524(00)00060-2

Tilson, H. A. (1998). Developmental neurotoxicology of endocrine disruptors and pesticides: identification of information gaps and research needs. *Environ. Health Perspect.* **106**, 807–811. doi:10.2307/3434193

Tong, S., and McMichael, A. J. (1999). The magnitude, persistence and public health significance of cognitive effects of environmental lead exposure in childhood. *J. Environ. Med.* **1**, 103–110. doi:10.1002/(SICI)1099-1301(199904/06)1:2<103::AID-JEM15>3.0.CO;2-S

Toppari, J., Larsen, J. C., Christiansen, P., Giwercman, A., Grandjean, P., Guillette, L. J., Jr, Jégou, B., Jensen, T. K., Jouannet, P., Keiding, N., Leffers, H., McLachlan, J. A., Meyer, O., Müller, J., Rajpert-de Meyts, E., Scheike, T., Sharpe, R., Sumpter, J., and Skakkebaek, N. E. (1996). Male reproductive health and environmental xenoestrogens. *Environ. Health Perspect.* **104**, 741–803. doi:10.2307/3432709

Truss, M., and Beato, M. (1993). Steroid hormone receptors: interaction with deoxyribonucleic acid and transcription factors. *Endocr. Rev.* **14**, 459–479.

Tsapakis, M., and Stephanou, E. G. (2005). Occurrence of gaseous and particulate polycyclic aromatic hydrocarbons in the urban atmosphere: study of sources and ambient temperature effect on the gas/particle concentration and distribution. *Environ. Pollut.* **133**, 147–156. doi:10.1016/J.ENVPOL.2004.05.012

US Environmental Protection Agency (1984). 'Health Effect Assessment for Polycyclic Aromatic Hydrocarbon (PAH). EPA 540/1–86–013.' (Environmental Criteria and Assessment Office: Cincinnati, OH.)

Vasseur, P., and Cossu-Leguille, C. (2006). Linking molecular interactions to consequent effects of persistent organic pollutants (POPs) upon populations. *Chemosphere* **62**, 1033–1042. doi:10.1016/J.CHEMOSPHERE.2005.05.043

Vethaak, A. D., Lahr, J., Schrap, S. M., Belfroid, A. C., Rijs, G. B. J., Gerritsen, A., de Boer, J., Bulder, A. S., Grinwis, G. C., Kuiper, R. V., Legler, J., Murk, T. A., Peijnenburg, W., Verhaar, H. J., and de Voogt, P. (2005). An integrated assessment of estrogenic contamination and biological effects in the aquatic environment of The Netherlands. *Chemosphere* **59**, 511–524. doi:10.1016/J.CHEMOSPHERE.2004.12.053

Vidal, G., and Diez, M. C. (2005). Methanogenic toxicity of wood processing effluents. *J. Environ. Manage.* **74**, 317–325. doi:10.1016/J.JENVMAN.2004.09.008

Vinceti, M., Venturelli, M., Sighinolfi, C., Trerotoli, P., Bonvicini, F., Ferrari, A., Bianchi, G., Serio, G., Bergomi, M., and Vivoli, G. (2007). Case-control study of toenail cadmium and prostate cancer risk in Italy. *Sci. Total Environ.* **373**, 77–81. doi:10.1016/J.SCITOTENV.2006.11.005

Waliszewski, S. M., Aguirre, A. A., Infanzón, R. M., and Siliceo, J. (2000). Carry-over of persistent organochlorine pesticides through placenta to fetus. *Salud Publica Mex.* **42**, 384–390. doi:10.1590/S0036-36342000000500003

Walter, B. A., Agha, B. J., and Digenis, G. A. (1988). Disposition of [^{14}C]nonoxynol-9 after intravenous or vaginal administration to female Sprague-Dawley rats. *Toxicol. Appl. Pharmacol.* **96**, 258–268. doi:10.1016/0041-008X(88)90085-3

Watanabe, C., Inaoka, T., Matsui, T., Ishigaki, K., Murayama, N., and Ohtsuka, R. (2003). Effects of arsenic on younger generations. *J. Environ. Sci. Health A Tox. Hazard. Subst. Environ. Eng.* **38**, 129–139. doi:10.1081/ESE-120016885

Weltje, L., vom Saal, F. S., and Oehlmann, J. (2005). Reproductive stimulation by low doses of xenoestrogens contrasts with the view of

hormesis as an adaptive response. *Hum. Exp. Toxicol.* **24**, 431–437. doi:10.1191/0960327105HT551OA

White, R., Jobling, S., Hoare, S. A., Sumpter, J. P., and Parker, M. G. (1994). Environmentally persistent alkylphenolic compounds are estrogenic. *Endocrinology* **135**, 175–182. doi:10.1210/EN.135.1.175

Will, I. B. S., Moraes, J. E. F., Teixeira, A. C. S. C., Guardani, R., and Nascimento, C. A. O. (2004). Photo-Fenton degradation of wastewater containing organic compounds in solar reactor. *Separ. Purif. Tech.* **34**, 51–57. doi:10.1016/S1383-5866(03)00174-6

Wintgens, T., Gallenkemper, M., and Melin, T. (2002). Endocrine disrupter removal from wastewater using membrane bioreactor and nanofiltration technology. *Desalination* **146**, 387–391. doi:10.1016/S0011-9164(02)00519-2

World Health Organization (WHO) (1991). 'Environmental Health Criteria 118: Inorganic Mercury.' (WHO: Geneva.)

Xu, C., Johnson, J. E., Singh, P. K., Jones, M. M., Yan, H., and Carter, C. E. (1996). *In vivo* studies of cadmium-induced apoptosis in testicular tissue of the rat and its modulation by a chelating agent. *Toxicology* **107**, 1–8. doi:10.1016/0300-483X(95)03195-L

Xu, X. R., Li, S. X., Li, X. Y., Gu, J. D., Chen, F., Li, X. Z., and Li, H. B. (2009). Degradation of n-butyl benzyl phthalate using TiO_2/UV. *J. Hazard. Mater.* **164**, 527–532. doi:10.1016/J.JHAZMAT.2008.08.027

Yoon, Y., Westerhoff, P., Yoon, J., and Snyder, S. A. (2004). Removal of 17β estradiol and fluoranthene by nanofiltration and ultrafiltration. *J. Environ. Eng.* **130**, 1460–1467. doi:10.1061/(ASCE)0733-9372(2004)130:12(1460)

Yoon, Y., Westerhoff, P., Snyder, S. A., and Wert, E. C. (2006). Nanofiltration and ultrafiltration of endocrine disrupting compounds, pharmaceuticals and personal care products. *J. Membr. Sci.* **270**, 88–100. doi:10.1016/J.MEMSCI.2005.06.045

Yoshida, M. (2002). Placental to fetal transfer of mercury and fetotoxicity. *Tohoku J. Exp. Med.* **196**, 79–88. doi:10.1620/TJEM.196.79

Zahir, F., Rizwi, S. J., Haq, S. K., and Khan, R. H. (2005). Low dose mercury toxicity and human health. *Environ. Toxicol. Pharmacol.* **20**, 351–360. doi:10.1016/J.ETAP.2005.03.007

Zhao, J., Li, Y., Zhang, C., Zeng, Q., and Zhou, Q. (2008). Sorption and degradation of bisphenol A by aerobic activated sludge. *J. Hazard. Mater.* **155**, 305–311. doi:10.1016/J.JHAZMAT.2007.11.075

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