



Human infertility: are endocrine disruptors to blame?

André Marques-Pinto¹ and Davide Carvalho^{1,2}

¹Serviço de Endocrinologia, Faculdade de Medicina da Universidade do Porto, Al. Prof. Hernâni Monteiro, 4200-319 Porto, Portugal

²Departamento de Endocrinologia, Diabetes e Metabolismo, Centro Hospitalar de São João, Porto, Portugal

Correspondence
should be addressed
to A Marques-Pinto
Email
andre.fmpinto@gmail.com

Abstract

Over recent decades, epidemiological studies have been reporting worrisome trends in the incidence of human infertility rates. Extensive detection of industrial chemicals in human serum, seminal plasma and follicular fluid has led the scientific community to hypothesise that these compounds may disrupt hormonal homeostasis, leading to a vast array of physiological impairments. Numerous synthetic and natural substances have endocrine-disruptive effects, acting through several mechanisms. The main route of exposure to these chemicals is the ingestion of contaminated food and water. They may disturb intrauterine development, resulting in irreversible effects and may also induce transgenerational effects. This review aims to summarise the major scientific developments on the topic of human infertility associated with exposure to endocrine disruptors (EDs), integrating epidemiological and experimental evidence. Current data suggest that environmental levels of EDs may affect the development and functioning of the reproductive system in both sexes, particularly in foetuses, causing developmental and reproductive disorders, including infertility. EDs may be blamed for the rising incidence of human reproductive disorders. This constitutes a serious public health issue that should not be overlooked. The exposure of pregnant women and infants to EDs is of great concern. Therefore, precautionary avoidance of exposure to EDs is a prudent attitude in order to protect humans and wildlife from permanent harmful effects on fertility.

Key Words

- ▶ endocrine disruptors
- ▶ reproduction
- ▶ infertility
- ▶ male
- ▶ female

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Introduction

Infertility, which is defined as the inability to conceive after 1 year of unprotected intercourse, has a global prevalence of 9% (1). Among infertile couples, it is estimated that the cause is predominantly feminine in 38% and primarily masculine in 20%, while 27% have both male and female abnormalities, and no evident cause is identified as for the remaining 15% (2).

Since the mid-20th century, numerous studies have reported an increasing incidence of human reproductive

diseases and a consequent decline in reproductive function worldwide (3). Given the short time frame, genetic changes cannot explain it. Thus, environmental substances may be accountable for the observed trends (4, 5). Indeed, both humans and wildlife are exposed to copious potentially hazardous chemicals that are released into the environment at an alarming rate (6).

One of the most significant landmarks in endocrinology over the past century was the recognition that



some of these chemicals are able to disrupt the closed feedback loops of the hormonal and homeostatic systems, thus being named endocrine disruptors (EDs) (7). The group of known ED is extremely heterogeneous. It embraces ubiquitous synthetic substances used as industrial lubricants and solvents, and their by-products: polychlorinated biphenyls (PCB) (8), polybrominated diphenyl ethers (PBDE) (9) and dioxins such as 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) (10); plastics: bisphenol A (BPA) (11) and bisphenol S (BPS) (12); plasticisers: phthalates (13); pesticides: atrazine (14), cypermethrin (15), dichlorodiphenyl-trichloroethane (DDT) (16), dieldrin (17), methoxychlor (MXC) (16) and vinclozolin (VCZ) (18); and drugs: diethylstilbestrol (DES) (19) and ethinyl oestradiol (EE) (20), as well as non-steroidal anti-inflammatory drugs (NSAID) and acetaminophen (21). Natural chemicals such as genistein, a phytoestrogen (22) and heavy metals (23) can also have endocrine-disruptive effects.

Consistent detection of ED residues in human serum, seminal plasma and follicular fluid has raised concern that environmental exposure to ED is affecting human fertility (24). Though ED are not considered major teratogens, reproductive function – from gamete production through to intrauterine development of the offspring – is believed to be particularly susceptible to endocrine disruption, triggering morphological and functional abnormalities (25, 26, 27).

The main purpose of this paper is to review and summarise the major scientific developments on the topic of human infertility associated with ED exposure, integrating evidence from epidemiological and experimental studies. Examples of well-known and hypothetical ED are selected to highlight the potential effects of ED on human fertility, identifying future research directions.

Methods

The PubMed database was used to search for articles published up to 31st May 2013, using the following MeSH keywords: endocrine disruptors, fertility and infertility. Only studies using the English language were considered. Altogether, 368 papers were retrieved. The abstract of every article was read. The leading review criterion was human epidemiological studies in which a link between ED exposure and infertility was evaluated. Moreover, as the interpretation of the scarce epidemiological data may be biased by many confounding factors, supporting experimental research in animal models was also considered. Although there has been an effort to list and rank all possible ED (28, 29), the number of evaluated chemicals

remains limited. The full texts of 225 selected articles were retrieved and read. Furthermore, the bibliographies from 41 selected review articles were analysed, and 153 further papers were read. Overall, 198 articles were deemed relevant and included in this review.

Endocrine disruptors

Mechanisms of action

Given the complexity of the endocrine system, the mechanisms of action of ED are difficult to unravel. So far, most EDs are known to act as imperfect ligands (either agonists or antagonists) to nuclear and membrane receptors (for both steroidal and non-steroidal hormones, and also for orphan receptors), thus interfering with hormone-regulated cell signalling pathways and gene expression (30). The relative importance of these types of receptors on the magnitude of the effects of ED remains unclear. Of note, while exogenous hormonally active agents are considered harmful in healthy individuals, they are the basis for hormonal therapy in some endocrinological diseases and hormone-dependent cancers (31). Thus, in those circumstances, they are not considered ED.

Most EDs are supposed to act through several mechanisms, which may have synergistic or antagonistic outcomes (32). Many are substances with oestrogenic/anti-androgenic activity that act by interfering with the oestrogen receptors (ER) or the androgen receptor (AR) (see Table 1).

Apart from ER and AR, the aryl hydrocarbon receptor (AhR) is the protein most studied regarding its interaction with ED. This orphan receptor acts as a transcription factor for detoxifying enzymes (43). Dioxins and some PCB exert their endocrine-disruptive effects through binding to AhR and impairing the usual gene transcription response (44). AhR ligands enhance the degradation of sex steroid receptors (45).

Some EDs are also capable of modifying hormone bioavailability by interfering with its secretion and transport or disrupting the enzymatic pathways involved in hormone synthesis and metabolism (46, 47). For instance, in either sex, androgens give rise to oestrogens, through aromatase, so together they play a vital role in homeostasis (48, 49). EDs that interfere with aromatase (BPA (50) and atrazine (51) stimulate its activity, while DDT and phthalates (47) inhibit it) disrupt the delicate androgen–oestrogen balance required for proper reproductive function. Recently, many anti-virilising EDs (e.g. phthalates and BPA) have been found to be



Table 1 Reported agonist and antagonist binding of several ED to ER and AR.

ED	ER agonism	ER antagonism	AR agonism	AR antagonism
PCB	(33)		(34)	(33)
PBDE	(35)	(35)		(35)
BPA	(36)			(37)
BPS	(38)			
Phthalates	(39)			
Cypermethrin	(40)			
DDT	(36, 40, 41)			(40, 41)
Dieldrin	(40, 41)			(40, 42)
MXC	(36, 40, 41)	(40, 41)		(40, 42)
VCZ	(41)			(40)
DES	(36)			
Phytoestrogens	(36)			

AR, androgen receptor; BPA, bisphenol A; BPS, bisphenol S; DDT, dichlorodiphenyltrichloroethane; DES, diethylstilbestrol; ED, endocrine disruptor; ER, oestrogen receptors; MXC, methoxychlor; PBDE, polybrominated diphenyl ethers; PCB, polychlorinated biphenyls; VCZ, vinclozolin.

powerful cyclooxygenase inhibitors, reducing prostaglandin synthesis, and this might be the foremost mechanism by which they exert their effects (52).

Dose–effect curves

The principle of endocrine disruption has always been controversial: it has been difficult to determine the lowest observed adverse effect level (LOAEL) and whether it is likely to be found *in vivo* (53). Current postulated LOAEL for most ED are outdated (54). As an example, BPA has been found to induce detrimental reproductive effects in levels several-fold below its conventional LOAEL – 50 mg/kg of body weight (BW) per day (55).

Perhaps expectably, there is a sharp division between those who report detrimental effects of ED at environmental levels (micro- to picomolar range) – mostly academic experts – and those who appear unable to do so at any concentrations – industry corporations (56). Current data state that the most potent ED effects arise from minute environmental doses rather than from higher doses, which may induce receptor down-regulation and cytotoxicity (54).

Hormone-mimetic ED, similarly to endogenous hormones, may have non-monotonic tissue-specific effects due to: receptor selectivity, down-regulation/desensitisation, competition and negative feedback loops (57). EDs non-monotonic effects may also arise from the overlap of two or more monotonic responses through different pathways, resulting in biphasic or multiphasic curves (58).

Reliable evidence of both non-monotonic curves and low-dose detrimental effects has been gathered for BPA, many pesticides (54) and phthalates as well (59). Therefore, a threshold dose cannot be presumed, neither can low-dose effects be predicted from high-dose effects (30). However, assuming equivalent exposures, the incidence of detrimental reproductive effects of some ED may be significantly higher in vulnerable individuals, owing to several factors such as the genetic background, window of exposure and pre-existing disease. Nonetheless, these issues remain controversial (60).

Human exposure

Populations are exposed to ED in air, water, food and in a variety of industrial products, including personal care goods. The mixture of ED that leaches into the soil and waterbodies (e.g. pesticides, contraceptive pills and other chemicals from urban and agricultural waste) accumulates in the environment and in animals higher up on the food chain (6, 7). Indeed, some EDs that were banned decades ago, namely DDT and PCB, are still found in human serum (24). This is due to their lipophilicity and resistance to biodegradation (61).

Although there is chronic exposure to ED through inhalation and skin contact (62), the major route of human exposure is ingestion of food (e.g. meat, fish, dairy products and vegetables), as well as plain water and other beverages. ED-contaminated food and water may contain environmental pollutants such as pesticide residues (63) and heavy metals (23), in addition to processing aids and anabolic steroids used in food production. Most individuals have traceable amounts of these substances in their serum or urine (3, 64).

Recent studies have concluded that plastic packaging is an important source of ED in the average human diet (65). Repeated exposure of food-contact materials to u.v. light, heat and acidic/alkaline contents may cause polymers to breakdown into monomers as phthalates and BPA, which then leach into food and beverages (66). Thus, there is chronic intake of ED even from bottled water (67). Some of these EDs are being replaced by heat-stable analogues: many 'BPA-free' products contain BPS instead, which also exerts both genomic and non-genomic endocrine-disruptive effects at environmental concentrations as low as picomolar, leading to concerns regarding its safety (12, 38).

The average diet also contains natural ED such as phytoestrogens, which are compounds possessing strong oestrogen-like activity (22, 36). The eventual health



benefits of phytoestrogens on cardiovascular and menopause-related disorders (68) and the apparent absence of major long-term adverse effects have led to an increased consumption of these substances, mainly through soy-based food (69). However, effective but harmless doses have yet to be established. Studies have revealed that infants ingesting soy-based formulas may have a phytoestrogen serum concentration 13 000–22 000 times higher than endogenous oestrogen levels (70), leading to concerns about its possible adverse effects on brain and reproductive organ morphological and functional development and, ultimately, on fertility (71).

Windows of susceptibility

Human susceptibility to disruption during development has been proven (72, 73). Intrauterine exposure to ED may result in long-lasting changes. These may lead to immediate or deferred adverse outcomes on development and reproduction (74). The timing of exposure may explain this difference (75). If it occurs during critical windows, adverse effects may be very drastic and irreversible, including congenital abnormalities. On the contrary, if it happens during sensitive, non-critical windows, detrimental outcomes may still arise, such as mild functional deficits and adult-onset diseases.

Developmental programming ► The prenatal period has become a significant research topic regarding ED exposure because the placenta causes accumulation of ED in the foetus (76). BPA and other ED have low binding affinity to the sex hormone-binding globulin and α -fetoprotein, which prevent maternal sex hormones from crossing the placenta (77). Furthermore, detoxifying metabolic pathways only mature after birth (78). ED may therefore reach hormone-sensitive foetal tissues (e.g. the urogenital sinus and brain) and disrupt their proper development (see below). As programming of the hypothalamus–pituitary–gonadal (HPG) axis occurs during this period, ED exposure may determine fertility in the adulthood (79).

Epigenetic modifications may have an important role in the observed ED effects in gametogenesis and foetal development (see below). The epigenome refers to changes made in gene expression by altering DNA structure through DNA methylation and microRNA, among other mechanisms, without changing the actual genomic sequence (80). BPA, phthalates and VCZ can alter the gene expression and imprinting patterns in mouse embryos (81). Very recently, intrauterine BPA exposure at

environmental doses was shown to impair steroidogenesis in sheep by down-regulating gonadal microRNA (82). These findings may partially explain the biological relevance of ED on gonadal differentiation.

Multi- and transgenerational effects ► EDs have been shown to disrupt the development of the human reproductive system, impairing fertility not only in directly exposed offspring but also in subsequent generations. A vast array of reproductive abnormalities has been reported in the offspring of women treated with DES during the mid-20th century, for miscarriage prevention (19, 83). Recently, a French epidemiologic study has shown that the grandchildren of DES-exposed women have a higher incidence of genital malformations, which may be explained by epigenetic changes of the AR gene transmitted through the female germ line (84).

Other ED have multigenerational effects: the offspring of TCDD-exposed mice show fertility disorders up to the third generation (85); the third generation of mice exposed *in utero* to environmental levels of PCB presented morphological reproductive abnormalities and impaired gamete quality (8).

Male germ cells are considered as the most vulnerable cells, as they have distinctive methylation patterns and epigenetic markers (80). Transient developmental exposure of male rats to VCZ and MXC during the epigenetic-reprogramming stage induces poor semen quality up to the fourth generation (86).

ED exposure in pregnant females can directly cause detrimental effects in the next two generations through the foetus and its germline, which is already formed. Only adverse effects in the third generation and beyond are considered truly transgenerational, as they are transmitted solely through the germline (87).

As current assisted reproduction techniques do not necessarily address the underlying infertility problem, their escalating use may accidentally convey serious genetic and epigenetic anomalies (27).

Susceptible population groups ► Millions of children are conceived by women while on contraceptive pills containing EE. Albeit most do not show conspicuous congenital abnormalities, long-term reproductive consequences may ensue in adulthood (88). Breastfeeding is another significant period of exposure to ED (89). As many ED accumulate in fat-rich tissues such as the breast, both mother and foetus are exposed to relatively high levels of these substances (90, 91). For these reasons, women of childbearing age, specifically those who are



pregnant/breastfeeding, constitute a population of utmost importance regarding ED exposure. Likewise, newborns and children deserve special consideration, as they have proportionally higher food and water intakes than adults, leading to a potentially higher body burden of such chemicals (92).

Effects of ED mixtures

ED may act synergistically to produce adverse effects at doses far below individual LOAEL, if there is enough overall exposure (93). Indeed, a combination of estrogenic ED at environmentally relevant doses was shown to lead to greater cellular disruption than single ED exposure (94). Furthermore, a study addressing the effects of developmental exposure of rats to a mixture of diverse-acting anti-androgenic ED has shown synergistic effects regarding the incidence of reproductive tract anomalies (95). In view of recent evidence, a number of brief intrauterine exposures to therapeutic doses of NSAID or acetaminophen (21, 96) adding to the potential long-lasting inhibition of prostaglandin synthesis by other ED could seriously impact human reproductive health by decreasing steroidogenesis.

Additionally, it is hypothesised that phytoestrogens, among other EDs, may be capable of altering cell responsiveness to endogenous hormones and other ED, thereby inducing wider negative effects when there is concomitant exposure (97). Two studies in rats have suggested that the effects of chronic ingestion of a low-dose genistein and VCZ mixture (at 1 mg/kg BW per day) diverge from those arising from exposure to each substance individually: genistein may potentiate the detrimental effects of VCZ when exposure occurs throughout adulthood (98) or ease them if exposure stops at birth (99). ED mixtures most likely produce very complex dose–response curves due to overlapping additive/synergistic effects, and may lead to more severe consequences than previously ascertained. Conversely, their effects may be antagonistic, and thus reciprocally annulled.

ED and the male reproductive system

Trends in semen quality

Over the last decades, epidemiological studies have reported an ominous growth in the incidence of male infertility, accompanied by decreasing sperm quality, thus reflecting impaired spermatogenesis (100). A large review

of international studies showed that, over 50 years, the global average sperm count dropped by half (from 113 to 66 million/ml), reflecting an average yearly decrease of 1%, and sperm morphology/motility abnormalities significantly increased (101). A subsequent larger study confirmed the declining sperm concentration at a yearly rate of 1.5–3% (102). However, some consider those results are biased (103).

Studies comparing male reproductive disorders in the Nordic–Baltic countries have reported an East–West gradient showing higher reproductive tract abnormalities and infertility rates in Denmark compared with Finland (104, 105). ED may explain these differences because the Danish seem to have higher ED body burdens than the Finnish (90).

Actually, several epidemiological studies have found an association between inferior semen quality parameters and increased urinary and serum levels of phthalates (106), PCB (107), PBDE (108, 109) and BPA (110). ED may disrupt spermatogenesis by interfering with germ cells and spermatogenesis-supporting cells (111) (see Table 2). Interestingly, it has been shown that intrauterine exposure to BPA disrupts the blood–testis barrier, which may lead to infertility in adulthood through germ cell loss via immunological activity (79, 115).

The testicular dysgenesis syndrome

There is an epidemiological correspondence between lower semen quality and higher incidences of cryptorchidism, hypospadias and testicular cancer (116). These disorders have been regrouped as the testicular dysgenesis syndrome (TDS) (117), as they probably arise from intrauterine disruption of proper testicular development and function (118) under ED exposure (119). Impaired Leydig cells function is the main cellular trait of TDS (120, 121). In mild cases, men have low testosterone levels, slightly decreased penile/testicular volumes and poor semen quality, while in the more severe cases there is

Table 2 Cellular effects of ED on the testicle.

Cellular effect	ED
Germ cell apoptosis	Phthalates (112), DES and EE (113)
Reduced steroidogenesis in Leydig cells	PCB (114), phthalates (73), cypermethrin (15), dieldrin (14) and EE (20)

DES, diethylstilbestrol; ED, endocrine disruptor; EE, ethinyl oestradiol; PCB, polychlorinated biphenyls.



also hypospadias or cryptorchidism and an increased risk of testicular cancer (122). ED exposure has been suggested to have triggered the escalation of milder TDS cases, and it may explain a number of idiopathic infertility cases (123), which constitute half the men presenting at infertility clinics (124).

Epidemiological data suggest that human developmental exposure to environmental levels of ED (e.g. phthalates, PCB and pesticides) is indeed connected to an increased risk of TDS features such as hypospadias and cryptorchidism (91, 125, 126, 127).

Assuming the same circumstances of exposure, deleterious effects of ED may be more severe in individuals with genetic susceptibility. There are AR and ER- α genetic polymorphisms that cause mild functional impairments (128, 129). They can be expected to bring about manifest forms of TDS, when combined with ED exposure (119). Indeed, among men exposed to PCB and DDT, those having particular AR polymorphisms were found to have significantly inferior sperm quality (130). Furthermore, a correlation has been reported between cryptorchidism and ED-vulnerable ER- α polymorphisms (131).

Hypospadias ► Hypospadias, a condition in which the urethral meatus is on the ventral side of the penis, affects about 0.4% of males at birth and has been reported to have increased significantly over recent decades (132). EDs are regarded as a contributing factor, as VCZ (133) and phthalates (134) consistently induce hypospadias in the laboratory animals.

Cryptorchidism ► Cryptorchidism is defined as the failure of one or both testicles to descend into the scrotal sac and is the most common congenital abnormality in male children, affecting 2–4% of full-term males (104). Epidemiological studies suggest that the incidence of cryptorchidism is rising (135). It is currently the best characterised risk factor for infertility and testicular cancer in adulthood (97).

Testicular migration is a complex process involving a transabdominal stage and a transinguinal one. Developmental exposure to ED may act on Leydig cells thus disrupting both stages by i) reducing insulin-like factor 3 expression (136) and ii) impairing steroidogenesis (resulting in relative testosterone deficiency) respectively (119). Exposure to some ED, such as PBDE, through breastfeeding has been correlated with cryptorchidism in new borns (76). In a recent epidemiological study, NSAID or acetaminophen consumption during pregnancy has been shown to be directly related to a higher risk of

cryptorchidism in male infants, if intake had taken place for longer than one week or if there had been simultaneous ingestion of more than one of those drugs (21).

The differentiation of the male reproductive system

The differentiation of the male reproductive system is entirely dependent on foetal testicular androgen production (137). Thus, disruption of androgen activity by ED during the virilisation period (around 8–14 weeks into human foetal development) will perhaps cause TDS (138). Moreover, disproportionate oestrogenic exposure at this point may disturb the delicate androgen–oestrogen balance, leading to adverse consequences (139).

A recent study including a thousand new borns has found a linear correlation between maternal exposure to ED (e.g. pesticides and phytoestrogens) and lower testosterone levels, smaller penile length and higher incidences of reproductive anomalies including hypospadias (140).

In animal models, pregnant mice orally exposed to phthalates at doses as low as 1 μ g/kg BW per day consistently gave birth to male offspring presenting a syndrome of reproductive anomalies including cryptorchidism, testicular injury, reproductive tract malformations and shorter anogenital distance (AGD) (59, 134), reflecting ineffective perineal virilisation (141). This pattern of effects parallels TDS (142). Actually, developmental exposure to phthalates at environmental doses seems to cause reduced AGD in male infants (143).

Similarly to rodents, human male infants exhibit twice as long an AGD than females (144). Reduced male AGD may be considered a predictor of infertility as it correlates with poorer sperm quality parameters in otherwise normal men (145). Furthermore, hypospadias and cryptorchidism are also associated with shorter AGD (146).

Other anti-androgenic ED can induce TDS in animals: rats exposed to 150 mg/kg BW per day of acetaminophen during foetal development had AGD reductions comparable to those induced by phthalates (21). Additionally, intrauterine exposure to VCZ produces a wide spectrum of reproductive disorders (147). In a study, all male rats exposed *in utero* to 20–100 mg/kg BW per day of VCZ showed hypospadias and minute sperm counts (133).

Though average human ED exposure levels may be lower than those customarily used in animal studies, certain population clusters may be exposed to higher levels. Actually, occupational pesticide exposure has been connected to male infertility (125, 148, 149, 150).



ED and the female reproductive system

The ovarian dysgenesis syndrome

Data concerning ED effects on the female reproductive system and fertility are scant. Still, a correlation between developmental ED exposure and long-term effects is suggested (151). There is a significantly higher risk of infertility in women who have high serum concentration of BPA (152, 153), as well as in those whose mothers had high maternal serum concentrations of DDT during pregnancy (154). Moreover, occupational exposure to ED such as pesticides and plastics is a risk factor for female infertility (155).

The array of female reproductive disorders where ED have been implicated includes endometriosis, disorders of the uterus and disorders of the ovary, such as premature ovarian failure (POF) and polycystic ovary syndrome (PCOS) (26). The incidence of these conditions is growing (72). As they may arise from impaired ovarian development and function, the ovarian dysgenesis syndrome has recently been suggested as the female form of TDS (156).

Endometriosis ► Endometriosis affects up to 10% of women of childbearing age, causing infertility in about half those women (157). Recently, EDs have been proposed as a possible contributing factor for its development and exacerbation (158). Indeed, a significantly higher BPA (159) and phthalate (160) serum concentration has been found in women with this condition. Furthermore, women exposed to DES *in utero* may have an 80% higher risk of endometriosis than unexposed women (161).

Experimental studies support this hypothesis, as intra-uterine exposure of mice to BPA (162) or TCDD (85) produces an endometriosis-like adult uterine phenotype. A recent study has shown that women with endometriosis have significantly higher concentrations of TCDD and PCB in the peritoneal fluid (163), possibly leading to chronic inflammation, which may result in the stimulation of endometrial cells derived from retrograde menstruation (164).

Ovarian pathology ► There are growing concerns about the reproductive outcomes of ovarian exposure to ED during foetal development and after birth (165). Female germ cells are a fixed population, unlike male germ cells. Therefore, exposure of hormone-responsive, primordial and preantral follicles to ED may impair folliculogenesis, inducing meiotic aberrations (e.g. aneuploidy and multiple oocyte follicles) or even follicular atresia (see Table 3). Ultimately, ED may lead to depletion of follicular reserves, resulting in POF (176). This is a

syndrome consequent to impaired ovarian function before the age of 40 years, affecting about 1% of women (177).

Granulosa and theca cells, which are crucial for ovarian steroidogenesis and oocyte development, are also a target for ED (48). Chronic exposure to TCDD at environmental levels (lower than 1 ng/kg BW per day) induces ovarian insufficiency in rats by reducing steroidogenesis (10).

PCOS, consisting of hyperandrogenemia and chronic anovulation, affects 5–8% of women of childbearing age often leading to infertility (178). Higher serum BPA levels have been reported in women with PCOS compared with healthy women (153, 179).

The differentiation of the female reproductive system

Proper differentiation of the female reproductive system is regulated by oestrogens, but it proceeds even in their absence – it is the default developmental pathway (180). Nevertheless, oestrogenic overstimulation is known to result in irreversible abnormalities (19, 181).

The development of the female reproductive system is regulated by the differential expression of *HOX* genes in the Müllerian duct (182). Disruption of the precise chronological regulation of *HOXA10* by ED that either up-regulate (e.g. BPA) or down-regulate (e.g. DES and MXC) its expression has been shown to lead to uterine abnormalities and infertility (183). DES has also been found to contribute to uterine abnormalities by reducing the expression of other developmental genes such as the *WNT7* or *MSX2* genes (184).

Central actions of ED

Regulation of gonadotropin secretion

ED may modify steroidogenesis both locally and through the HPG axis (7). The human HPG axis is active *in utero* and

Table 3 Cellular effects of ED on the ovary.

Cellular effect	ED
Impaired folliculogenesis	PCB (8), phthalates (166), atrazine (167), MXC (168) and genistein (169)
Follicular atresia	BPA (170)
Meiosis disruption	BPA (170, 171), DES (172) and genistein (173)
Reduced steroidogenesis in granulosa/theca cells	TCDD (174), DDT and MXC (175)

BPA, bisphenol A; DDT, dichlorodiphenyltrichloroethane; DES, diethylstilbestrol; ED, endocrine disruptor; MXC, methoxychlor; PCB, polychlorinated biphenyls; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.



during the first year of life (185). Afterwards, gonadotropin secretion is reduced until puberty, when sequential endocrine changes set in motion the development of secondary sexual characteristics that will lead to sexual maturation (186).

Kisspeptin is broadly recognised as a fundamental activator of the HPG axis, at the onset of puberty (187). In rats, neonatal exposure to oestrogenic ED, such as BPA and genistein, suppresses kisspeptin synthesis (188, 189).

Some PCBs have been shown to alter gonadotropin-releasing hormone (GnRH) synthesis (190) and to decrease GnRH release (191). Conversely, DDT and BPA stimulate it (192). In rats, perinatal exposure to environmental BPA doses, below the current LOAEL, induced defective GnRH pulses up to adulthood, leading to infertility (193).

The biological ED effects through GnRH and kisspeptin neurons and the relative importance of disruption in each those cell clusters on the onset of puberty and fertility throughout life through remain unclear.

Disruption of the HPG axis leading to gonadal insufficiency by reducing steroidogenesis, following exposure to DES (113), PCB (190) and atrazine (14), was demonstrated in rats. Long-lasting reproductive disorders induced by developmental ED exposure may be more likely to arise from a dysfunctional HPG axis (194). Thus, the primary target of developmental ED exposure might be the hypothalamus and the pituitary gland rather than the gonads themselves (195).

Sexually dimorphic neural circuitry

Sex steroids have prominent roles in the differentiation of several sexually dimorphic neural circuits (195, 196). ED may cross the immature blood–brain barrier (11) and thereby reverse the neurochemical phenotype of these areas. Actually, developmental exposure to BPA, MXC and VCZ has been shown to produce gender-inadequate adult behaviours (197), possibly by disrupting specific neural pathways (e.g. nitrergic fibres) that influence complex functions and behaviours such as those related to reproduction (198).

Conclusion

This paper has reviewed the existing evidence regarding ED and the rising rates of human infertility. Although the number of ED mentioned is not comprehensive, an adequate amount of data has accumulated demonstrating that EDs may have deleterious effects on human reproduction via numerous mechanisms. ED may be blamed for the

rising incidence of human reproductive disorders, and may also explain some idiopathic infertility cases, both in men and women.

Endocrine disruption is a serious public health problem that must not be ignored. Authorities should endorse preventive measures regarding exposure to EDs, such as limiting their production in industry worldwide, as the removal of these substances from the environment is neither simple nor cheap.

Meanwhile, the general population might reduce ED exposure by following some simple yet important advice such as i) choose glass over plastics, ii) avoid using plastic containers repeatedly or plastic wrapping to microwave food, iii) reduce consumption of fatty animal products, iv) prefer pesticide-free vegetables and fruits and v) avoid excessive utilisation of cosmetics and other personal care items, particularly during pregnancy. As ED exposure at any dose may impair human development and reproduction, precautionary avoidance of exposure to well-known and putative ED is a prudent attitude.

Further research is needed to improve current knowledge about known ED, and to identify potential endocrine disruptive activity by other chemicals, especially those replacing current ED before they are widely distributed. Dose–effect curves should be thoroughly studied, even at minute concentrations, as all EDs are likely to show non-monotonic responses and low-dose effects, resembling those elicited by endogenous hormones. Also, the impact of exposure to low doses of complex mixtures of ED and the prospective transgenerational effects should be evaluated, specifically concerning genetic polymorphisms, especially during gametogenesis and foetal development. It would be important to examine adult fertility and hormonal parameters of infants inadvertently exposed to contraceptive hormones during pregnancy and of infants fed cow milk/soy-based formula using baby bottles made of different substances, as opposed to breastfed infants. Clinical and laboratorial research on ED is essential, in order to protect wildlife and humans, particularly developing foetuses and children, from permanent effects on fertility.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review reported.

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References

- Boivin J, Bunting L, Collins JA & Nygren KG. International estimates of infertility prevalence and treatment-seeking: potential need and demand for infertility medical care. *Human Reproduction* 2007 **22** 1506–1512. (doi:10.1093/humrep/dem046)
- Bretveld R, Brouwers M, Ebisch I & Roeleveld N. Influence of pesticides on male fertility. *Scandinavian Journal of Work, Environment & Health* 2007 **33** 13–28. (doi:10.5271/sjweh.1060)
- Woodruff TJ. Bridging epidemiology and model organisms to increase understanding of endocrine disrupting chemicals and human health effects. *Journal of Steroid Biochemistry and Molecular Biology* 2011 **127** 108–117. (doi:10.1016/j.jsbmb.2010.11.007)
- Balabanic D, Rupnik M & Klemencic AK. Negative impact of endocrine-disrupting compounds on human reproductive health. *Reproduction, Fertility, and Development* 2011 **23** 403–416. (doi:10.1071/rd09300)
- Woodruff TJ, Carlson A, Schwartz JM & Giudice LC. Proceedings of the summit on environmental challenges to reproductive health and fertility: executive summary. *Fertility and Sterility* 2008 **89** 281–300. (doi:10.1016/j.fertnstert.2007.10.002)
- Letcher RJ, Bustnes JO, Dietz R, Jenssen BM, Jørgensen EH, Sonne C, Verreault J, Vijayan MM & Gabrielsen GW. Exposure and effects assessment of persistent organohalogen contaminants in arctic wildlife and fish. *Science of the Total Environment* 2010 **408** 2995–3043. (doi:10.1016/j.scitotenv.2009.10.038)
- Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, Hauser R, Prins GS, Soto AM, Zoeller RT & Gore AC. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. *Endocrine Reviews* 2009 **30** 293–342. (doi:10.1210/er.2009-0002)
- Pocar P, Fiandanese N, Secchi C, Berrini A, Fischer B, Schmidt JS, Schaedlich K, Rhind SM, Zhang Z & Borromeo V. Effects of polychlorinated biphenyls in CD-1 mice: reproductive toxicity and intergenerational transmission. *Toxicological Sciences* 2012 **126** 213–226. (doi:10.1093/toxsci/kfr327)
- Darnerud PO. Brominated flame retardants as possible endocrine disrupters. *International Journal of Andrology* 2008 **31** 152–160. (doi:10.1111/j.1365-2605.2008.00869.x)
- Shi Z, Valdez KE, Ting AY, Franczak A, Gum SL & Petroff BK. Ovarian endocrine disruption underlies premature reproductive senescence following environmentally relevant chronic exposure to the aryl hydrocarbon receptor agonist 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *Biology of Reproduction* 2007 **76** 198–202. (doi:10.1095/biolreprod.106.053991)
- Rubin BS. Bisphenol A: an endocrine disruptor with widespread exposure and multiple effects. *Journal of Steroid Biochemistry and Molecular Biology* 2011 **127** 27–34. (doi:10.1016/j.jsbmb.2011.05.002)
- Vinas R & Watson CS. Bisphenol S disrupts estradiol-induced nongenomic signaling in a rat pituitary cell line: effects on cell functions. *Environmental Health Perspectives* 2013 **121** 352–358. (doi:10.1289/ehp.1205826)
- Hauser R & Calafat AM. Phthalates and human health. *Occupational and Environmental Medicine* 2005 **62** 806–818. (doi:10.1136/oem.2004.017590)
- Hayes TB, Anderson LL, Beasley VR, de Solla SR, Iguchi T, Ingraham H, Kestemont P, Kniewald J, Kniewald Z, Langlois VS *et al.* Demasculinization and feminization of male gonads by atrazine: consistent effects across vertebrate classes. *Journal of Steroid Biochemistry and Molecular Biology* 2011 **127** 64–73. (doi:10.1016/j.jsbmb.2011.03.015)
- Wang H, Wang SF, Ning H, Ji YL, Zhang C, Zhang Y, Yu T, Ma XH, Zhao XF, Wang Q *et al.* Maternal cypermethrin exposure during lactation impairs testicular development and spermatogenesis in male mouse offspring. *Environmental Toxicology* 2011 **26** 382–394. (doi:10.1002/tox.20566)
- Tiemann U. *In vivo* and *in vitro* effects of the organochlorine pesticides DDT, TCPM, methoxychlor, and lindane on the female reproductive tract of mammals: a review. *Reproductive Toxicology* 2008 **25** 316–326. (doi:10.1016/j.reprotox.2008.03.002)
- Fowler PA, Abramovich DR, Haites NE, Cash P, Groome NP, Al-Qahtani A, Murray TJ & Lea RG. Human fetal testis Leydig cell disruption by exposure to the pesticide dieldrin at low concentrations. *Human Reproduction* 2007 **22** 2919–2927. (doi:10.1093/humrep/dem256)
- Kavlock R & Cummings A. Mode of action: inhibition of androgen receptor function—vinclozolin-induced malformations in reproductive development. *Critical Reviews in Toxicology* 2005 **35** 721–726. (doi:10.1080/10408440591007377)
- Herbst AL, Ulfelder H & Poskanzer DC. Adenocarcinoma of the vagina. Association of maternal stilbestrol therapy with tumor appearance in young women. *New England Journal of Medicine* 1971 **284** 878–881. (doi:10.1056/NEJM197104222841604)
- Hogan NS, Currie S, LeBlanc S, Hewitt LM & MacLachy DL. Modulation of steroidogenesis and estrogen signalling in the estuarine killifish (*Fundulus heteroclitus*) exposed to ethinylestradiol. *Aquatic Toxicology* 2010 **98** 148–156. (doi:10.1016/j.aquatox.2010.02.002)
- Kristensen DM, Hass U, Lesne L, Lottrup G, Jacobsen PR, Desdoits-Lethimonier C, Boberg J, Petersen JH, Toppari J, Jensen TK *et al.* Intrauterine exposure to mild analgesics is a risk factor for development of male reproductive disorders in human and rat. *Human Reproduction* 2011 **26** 235–244. (doi:10.1093/humrep/deq323)
- Cederroth CR, Zimmermann C & Nef S. Soy, phytoestrogens and their impact on reproductive health. *Molecular and Cellular Endocrinology* 2012 **355** 192–200. (doi:10.1016/j.mce.2011.05.049)
- Iavicoli I, Fontana L & Bergamaschi A. The effects of metals as endocrine disruptors. *Journal of Toxicology and Environmental Health. Part B, Critical Reviews* 2009 **12** 206–223. (doi:10.1080/10937400902902062)
- Younglai EV, Foster WG, Hughes EG, Trim K & Jarrell JF. Levels of environmental contaminants in human follicular fluid, serum, and seminal plasma of couples undergoing *in vitro* fertilization. *Archives of Environmental Contamination and Toxicology* 2002 **43** 121–126. (doi:10.1007/s00244-001-0048-8)
- Diamanti-Kandarakis E, Palioura E, Kandarakis SA & Koutsilieris M. The impact of endocrine disruptors on endocrine targets. *Hormone and Metabolic Research* 2010 **42** 543–552. (doi:10.1055/s-0030-1252034)
- Caserta D, Mantovani A, Marci R, Fazi A, Ciardo F, La Rocca C, Maranghi F & Moscarini M. Environment and women's reproductive health. *Human Reproduction Update* 2011 **17** 418–433. (doi:10.1093/humupd/dmq061)
- Sikka SC & Wang R. Endocrine disruptors and estrogenic effects on male reproductive axis. *Asian Journal of Andrology* 2008 **10** 134–145. (doi:10.1111/j.1745-7262.2008.00370.x)
- Pazos P, Pellizzer C, Stummann TC, Hareng L & Bremer S. The test chemical selection procedure of the European Centre for the Validation of Alternative Methods for the EU Project ReProTect. *Reproductive Toxicology* 2010 **30** 161–199. (doi:10.1016/j.reprotox.2010.04.001)
- Kumar A & Xagorarakis I. Pharmaceuticals, personal care products and endocrine-disrupting chemicals in U.S. surface and finished drinking waters: a proposed ranking system. *Science of the Total Environment* 2010 **408** 5972–5989. (doi:10.1016/j.scitotenv.2010.08.048)
- Zoeller RT, Brown TR, Doan LL, Gore AC, Skakkebaek NE, Soto AM, Woodruff TJ & vom Saal FS. Endocrine-disrupting chemicals and public health protection: a statement of principles from The Endocrine Society. *Endocrinology* 2012 **153** 4097–4110. (doi:10.1210/en.2012-1422)
- Hoffmann J & Sommer A. Steroid hormone receptors as targets for the therapy of breast and prostate cancer – recent advances, mechanisms of resistance, and new approaches. *Journal of Steroid Biochemistry and Molecular Biology* 2005 **93** 191–200. (doi:10.1016/j.jsbmb.2004.12.002)
- De Coster S & van Larebeke N. Endocrine-disrupting chemicals: associated disorders and mechanisms of action. *Journal of*



- Environmental and Public Health* 2012 **2012** 713696. (doi:10.1155/2012/713696)
- 33 Takeuchi S, Shiraiishi F, Kitamura S, Kuroki H, Jin K & Kojima H. Characterization of steroid hormone receptor activities in 100 hydroxylated polychlorinated biphenyls, including congeners identified in humans. *Toxicology* 2011 **289** 112–121. (doi:10.1016/j.tox.2011.08.001)
- 34 Svobodova K, Plackova M, Novotna V & Cajthaml T. Estrogenic and androgenic activity of PCBs, their chlorinated metabolites and other endocrine disruptors estimated with two *in vitro* yeast assays. *Science of the Total Environment* 2009 **407** 5921–5925. (doi:10.1016/j.scitotenv.2009.08.011)
- 35 Hamers T, Kamstra JH, Sonneveld E, Murk AJ, Kester MH, Andersson PL, Legler J & Brouwer A. *In vitro* profiling of the endocrine-disrupting potency of brominated flame retardants. *Toxicological Sciences* 2006 **92** 157–173. (doi:10.1093/toxsci/kfj187)
- 36 Kuiper GG, Lemmen JG, Carlsson B, Corton JC, Safe SH, van der Saag PT, van der Burg B & Gustafsson JA. Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor β . *Endocrinology* 1998 **139** 4252–4263. (doi:10.1210/en.139.10.4252)
- 37 Fang H, Tong W, Branham WS, Moland CL, Dial SL, Hong H, Xie Q, Perkins R, Owens W & Sheehan DM. Study of 202 natural, synthetic, and environmental chemicals for binding to the androgen receptor. *Chemical Research in Toxicology* 2003 **16** 1338–1358. (doi:10.1021/tx030011g)
- 38 Molina-Molina JM, Amaya E, Grimaldi M, Saenz JM, Real M, Fernandez MF, Balaguer P & Olea N. *In vitro* study on the agonistic and antagonistic activities of bisphenol-S and other bisphenol-A congeners and derivatives via nuclear receptors. *Toxicology and Applied Pharmacology* 2013 **272** 127–136. (doi:10.1016/j.taap.2013.05.015)
- 39 Jobling S, Reynolds T, White R, Parker MG & Sumpter JP. A variety of environmentally persistent chemicals, including some phthalate plasticizers, are weakly estrogenic. *Environmental Health Perspectives* 1995 **103** 582–587. (doi:10.1289/ehp.95103582)
- 40 Kojima H, Katsura E, Takeuchi S, Niyama K & Kobayashi K. Screening for estrogen and androgen receptor activities in 200 pesticides by *in vitro* reporter gene assays using Chinese hamster ovary cells. *Environmental Health Perspectives* 2004 **112** 524–531. (doi:10.1289/ehp.6649)
- 41 Lemaire G, Mnif W, Mauvais P, Balaguer P & Rahmani R. Activation of α - and β -estrogen receptors by persistent pesticides in reporter cell lines. *Life Sciences* 2006 **79** 1160–1169. (doi:10.1016/j.lfs.2006.03.023)
- 42 Lemaire G, Terouanne B, Mauvais P, Michel S & Rahmani R. Effect of organochlorine pesticides on human androgen receptor activation *in vitro*. *Toxicology and Applied Pharmacology* 2004 **196** 235–246. (doi:10.1016/j.taap.2003.12.011)
- 43 Yoshioka W, Peterson RE & Tohyama C. Molecular targets that link dioxin exposure to toxicity phenotypes. *Journal of Steroid Biochemistry and Molecular Biology* 2011 **127** 96–101. (doi:10.1016/j.jsbmb.2010.12.005)
- 44 Beischlag TV, Luis Morales J, Hollingshead BD & Perdew GH. The aryl hydrocarbon receptor complex and the control of gene expression. *Critical Reviews in Eukaryotic Gene Expression* 2008 **18** 207–250. (doi:10.1615/CritRevEukarGeneExpr.v18.i3.20)
- 45 Ohtake F, Fujii-Kuriyama Y, Kawajiri K & Kato S. Cross-talk of dioxin and estrogen receptor signals through the ubiquitin system. *Journal of Steroid Biochemistry and Molecular Biology* 2011 **127** 102–107. (doi:10.1016/j.jsbmb.2011.03.007)
- 46 Phillips KP & Foster WG. Key developments in endocrine disrupter research and human health. *Journal of Toxicology and Environmental Health. Part B, Critical Reviews* 2008 **11** 322–344. (doi:10.1080/10937400701876194)
- 47 Whitehead SA & Rice S. Endocrine-disrupting chemicals as modulators of sex steroid synthesis. *Best Practice & Research. Clinical Endocrinology & Metabolism* 2006 **20** 45–61. (doi:10.1016/j.beem.2005.09.003)
- 48 Craig ZR, Wang W & Flaws JA. Endocrine-disrupting chemicals in ovarian function: effects on steroidogenesis, metabolism and nuclear receptor signaling. *Reproduction* 2011 **142** 633–646. (doi:10.1530/REP-11-0136)
- 49 Boukari K, Ciampi ML, Guiochon-Mantel A, Young J, Lombes M & Meduri G. Human fetal testis: source of estrogen and target of estrogen action. *Human Reproduction* 2007 **22** 1885–1892. (doi:10.1093/humrep/dem091)
- 50 Arase S, Ishii K, Igarashi K, Aisaki K, Yoshio Y, Matsushima A, Shimohigashi Y, Arima K, Kanno J, Sugimura Y *et al.* Endocrine disrupter bisphenol A increases *in situ* estrogen production in the mouse urogenital sinus. *Biology of Reproduction* 2011 **84** 734–742. (doi:10.1095/biolreprod.110.087502)
- 51 Holloway AC, Anger DA, Crankshaw DJ, Wu M & Foster WG. Atrazine-induced changes in aromatase activity in estrogen sensitive target tissues. *Journal of Applied Toxicology* 2008 **28** 260–270. (doi:10.1002/jat.1275)
- 52 Kristensen DM, Skalkam ML, Audouze K, Lesne L, Desdoits-Lethimonier C, Frederiksen H, Brunak S, Skakkebaek NE, Jegou B, Hansen JB *et al.* Many putative endocrine disruptors inhibit prostaglandin synthesis. *Environmental Health Perspectives* 2011 **119** 534–541. (doi:10.1289/ehp.1002635)
- 53 Foster WG, Neal MS, Han MS & Dominguez MM. Environmental contaminants and human infertility: hypothesis or cause for concern? *Journal of Toxicology and Environmental Health. Part B, Critical Reviews* 2008 **11** 162–176. (doi:10.1080/10937400701873274)
- 54 Vandenberg LN, Colborn T, Hayes TB, Heindel JJ, Jacobs DR Jr, Lee DH, Shioda T, Soto AM, vom Saal FS, Welshons WV *et al.* Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses. *Endocrine Reviews* 2012 **33** 378–455. (doi:10.1210/er.2011-1050)
- 55 Newbold RR, Jefferson WN & Padilla-Banks E. Prenatal exposure to bisphenol A at environmentally relevant doses adversely affects the murine female reproductive tract later in life. *Environmental Health Perspectives* 2009 **117** 879–885. (doi:10.1289/ehp.0800045)
- 56 vom Saal FS, Akingbemi BT, Belcher SM, Crain DA, Crews D, Guidice LC, Hunt PA, Lerner C, Myers JP, Nadal A *et al.* Flawed experimental design reveals the need for guidelines requiring appropriate positive controls in endocrine disruption research. *Toxicological Sciences* 2010 **115** 612–613 (author reply 614–620). (doi:10.1093/toxsci/kfq048)
- 57 Schug TT, Janesick A, Blumberg B & Heindel JJ. Endocrine disrupting chemicals and disease susceptibility. *Journal of Steroid Biochemistry and Molecular Biology* 2011 **127** 204–215. (doi:10.1016/j.jsbmb.2011.08.007)
- 58 Watson CS, Jeng YJ & Guptarak J. Endocrine disruption via estrogen receptors that participate in nongenomic signaling pathways. *Journal of Steroid Biochemistry and Molecular Biology* 2011 **127** 44–50. (doi:10.1016/j.jsbmb.2011.01.015)
- 59 Do RP, Stahlhut RW, Ponzi D, vom Saal FS & Taylor JA. Non-monotonic dose effects of *in utero* exposure to di(2-ethylhexyl) phthalate (DEHP) on testicular and serum testosterone and anogenital distance in male mouse fetuses. *Reproductive Toxicology* 2012 **34** 614–621. (doi:10.1016/j.reprotox.2012.09.006)
- 60 Rhomberg LR & Goodman JE. Low-dose effects and nonmonotonic dose-responses of endocrine disrupting chemicals: has the case been made? *Regulatory Toxicology and Pharmacology* 2012 **64** 130–133. (doi:10.1016/j.yrtph.2012.06.015)
- 61 Darnerud PO & Risberg S. Tissue localisation of tetra- and pentabromodiphenyl ether congeners (BDE-47, -85 and -99) in perinatal and adult C57BL mice. *Chemosphere* 2006 **62** 485–493. (doi:10.1016/j.chemosphere.2005.04.004)
- 62 Stahlhut RW, Welshons WV & Swan SH. Bisphenol A data in NHANES suggest longer than expected half-life, substantial nonfood exposure, or both. *Environmental Health Perspectives* 2009 **117** 784–789. (doi:10.1289/ehp.0800376)



- 63 Schiliro T, Gorrasi I, Longo A, Coluccia S & Gilli G. Endocrine disrupting activity in fruits and vegetables evaluated with the E-screen assay in relation to pesticide residues. *Journal of Steroid Biochemistry and Molecular Biology* 2011 **127** 139–146. (doi:10.1016/j.jsbmb.2011.03.002)
- 64 Calafat AM, Ye X, Wong LY, Reidy JA & Needham LL. Exposure of the U.S. population to bisphenol A and 4-tertiary-octylphenol: 2003–2004. *Environmental Health Perspectives* 2008 **116** 39–44. (doi:10.1289/ehp.10753)
- 65 Muncke J. Endocrine disrupting chemicals and other substances of concern in food contact materials: an updated review of exposure, effect and risk assessment. *Journal of Steroid Biochemistry and Molecular Biology* 2011 **127** 118–127. (doi:10.1016/j.jsbmb.2010.10.004)
- 66 Mercea P. Physicochemical processes involved in migration of bisphenol A from polycarbonate. *Journal of Applied Polymer Science* 2009 **112** 579–593. (doi:10.1002/app.29421)
- 67 Wagner M & Oehlmann J. Endocrine disruptors in bottled mineral water: estrogenic activity in the E-screen. *Journal of Steroid Biochemistry and Molecular Biology* 2011 **127** 128–135. (doi:10.1016/j.jsbmb.2010.10.007)
- 68 Stark A & Madar Z. Phytoestrogens: a review of recent findings. *Journal of Pediatric Endocrinology & Metabolism* 2002 **15** 561–572. (doi:10.1515/JPEM.2002.15.5.561)
- 69 Bhatia J, Greer F & American Academy of Pediatrics Committee on N. Use of soy protein-based formulas in infant feeding. *Pediatrics* 2008 **121** 1062–1068. (doi:10.1542/peds.2008-0564)
- 70 Setchell KD, Zimmer-Nechemias L, Cai J & Heubi JE. Isoflavone content of infant formulas and the metabolic fate of these phytoestrogens in early life. *American Journal of Clinical Nutrition* 1998 **68** 1453S–1461S.
- 71 Dinsdale EC & Ward WE. Early exposure to soy isoflavones and effects on reproductive health: a review of human and animal studies. *Nutrients* 2010 **2** 1156–1187. (doi:10.3390/nu2111156)
- 72 Crain DA, Janssen SJ, Edwards TM, Heindel J, Ho SM, Hunt P, Iguchi T, Juul A, McLachlan JA, Schwartz J *et al.* Female reproductive disorders: the roles of endocrine-disrupting compounds and developmental timing. *Fertility and Sterility* 2008 **90** 911–940. (doi:10.1016/j.fertnstert.2008.08.067)
- 73 Ge RS, Chen GR, Tanrikut C & Hardy MP. Phthalate ester toxicity in Leydig cells: developmental timing and dosage considerations. *Reproductive Toxicology* 2007 **23** 366–373. (doi:10.1016/j.reprotox.2006.12.006)
- 74 Barker DJ. The developmental origins of adult disease. *Journal of the American College of Nutrition* 2004 **23** 588S–595S. (doi:10.1080/07315724.2004.10719428)
- 75 Ben-Shlomo Y & Kuh D. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. *International Journal of Epidemiology* 2002 **31** 285–293. (doi:10.1093/ije/31.2.285)
- 76 Main KM, Kiviranta H, Virtanen HE, Sundqvist E, Tuomisto JT, Tuomisto J, Vartiainen T, Skakkebaek NE & Toppari J. Flame retardants in placenta and breast milk and cryptorchidism in newborn boys. *Environmental Health Perspectives* 2007 **115** 1519–1526. (doi:10.1289/ehp.9924)
- 77 Milligan SR, Khan O & Nash M. Competitive binding of xenobiotic oestrogens to rat α -fetoprotein and to sex steroid binding proteins in human and rainbow trout (*Oncorhynchus mykiss*) plasma. *General and Comparative Endocrinology* 1998 **112** 89–95. (doi:10.1006/gcen.1998.7146)
- 78 Bruckner JV. Differences in sensitivity of children and adults to chemical toxicity: the NAS panel report. *Regulatory Toxicology and Pharmacology* 2000 **31** 280–285. (doi:10.1006/rtph.2000.1393)
- 79 Toyama Y & Yuasa S. Effects of neonatal administration of 17 β -estradiol, β -estradiol 3-benzoate, or bisphenol A on mouse and rat spermatogenesis. *Reproductive Toxicology* 2004 **19** 181–188. (doi:10.1016/j.reprotox.2004.08.003)
- 80 Rajender S, Avery K & Agarwal A. Epigenetics, spermatogenesis and male infertility. *Mutation Research* 2011 **727** 62–71. (doi:10.1016/j.mrrev.2011.04.002)
- 81 Kang ER, Iqbal K, Tran DA, Rivas GE, Singh P, Pfeifer GP & Szabo PE. Effects of endocrine disruptors on imprinted gene expression in the mouse embryo. *Epigenetics* 2011 **6** 937–950. (doi:10.4161/epi.6.7.16067)
- 82 Veiga-Lopez A, Luense LJ, Christenson LK & Padmanabhan V. Developmental programming: gestational bisphenol-A treatment alters trajectory of fetal ovarian gene expression. *Endocrinology* 2013 **154** 1873–1884. (doi:10.1210/en.2012-2129)
- 83 Newbold RR. Lessons learned from perinatal exposure to diethylstilbestrol. *Toxicology and Applied Pharmacology* 2004 **199** 142–150. (doi:10.1016/j.taap.2003.11.033)
- 84 Kalfa N, Paris F, Soyer-Gobillard MO, Daures JP & Sultan C. Prevalence of hypospadias in grandsons of women exposed to diethylstilbestrol during pregnancy: a multigenerational national cohort study. *Fertility and Sterility* 2011 **95** 2574–2577. (doi:10.1016/j.fertnstert.2011.02.047)
- 85 Nayyar T, Bruner-Tran KL, Piestrzeniewicz-Ulanska D & Osteen KG. Developmental exposure of mice to TCDD elicits a similar uterine phenotype in adult animals as observed in women with endometriosis. *Reproductive Toxicology* 2007 **23** 326–336. (doi:10.1016/j.reprotox.2006.09.007)
- 86 Anway MD, Cupp AS, Uzumcu M & Skinner MK. Epigenetic transgenerational actions of endocrine disruptors and male fertility. *Science* 2005 **308** 1466–1469. (doi:10.1126/science.1108190)
- 87 Skinner MK. Role of epigenetics in developmental biology and transgenerational inheritance. *Birth Defects Research. Part C, Embryo Today: Reviews* 2011 **93** 51–55. (doi:10.1002/bdrc.20199)
- 88 Taylor JA, Richter CA, Ruhlen RL & vom Saal FS. Estrogenic environmental chemicals and drugs: mechanisms for effects on the developing male urogenital system. *Journal of Steroid Biochemistry and Molecular Biology* 2011 **127** 83–95. (doi:10.1016/j.jsbmb.2011.07.005)
- 89 Vandenberg LN, Hauser R, Marcus M, Olea N & Welshons WV. Human exposure to bisphenol A (BPA). *Reproductive Toxicology* 2007 **24** 139–177. (doi:10.1016/j.reprotox.2007.07.010)
- 90 Krysiak-Baltyn K, Toppari J, Skakkebaek NE, Jensen TS, Virtanen HE, Schramm KW, Shen H, Vartiainen T, Kiviranta H, Taboureau O *et al.* Country-specific chemical signatures of persistent environmental compounds in breast milk. *International Journal of Andrology* 2010 **33** 270–278. (doi:10.1111/j.1365-2605.2009.00996.x)
- 91 Damgaard IN, Skakkebaek NE, Toppari J, Virtanen HE, Shen H, Schramm KW, Petersen JH, Jensen TK & Main KM. Persistent pesticides in human breast milk and cryptorchidism. *Environmental Health Perspectives* 2006 **114** 1133–1138. (doi:10.1289/ehp.8741)
- 92 Schwenk M, Gundert-Remy U, Heinemeyer G, Olejniczak K, Stahlmann R, Kaufmann W, Bolt HM, Greim H, von Keutz E & Gelbke HP. Children as a sensitive subgroup and their role in regulatory toxicology: DGPT workshop report. *Archives of Toxicology* 2003 **77** 2–6. (doi:10.1007/s00204-002-0416-9)
- 93 Kortenkamp A. Low dose mixture effects of endocrine disruptors: implications for risk assessment and epidemiology. *International Journal of Andrology* 2008 **31** 233–240. (doi:10.1111/j.1365-2605.2007.00862.x)
- 94 Vinas R & Watson CS. Mixtures of xenoestrogens disrupt estradiol-induced non-genomic signaling and downstream functions in pituitary cells. *Environmental Health* 2013 **12** 26. (doi:10.1186/1476-069X-12-26)
- 95 Rider CV, Furr JR, Wilson VS & Gray LE Jr. Cumulative effects of *in utero* administration of mixtures of reproductive toxicants that disrupt common target tissues via diverse mechanisms of toxicity. *International Journal of Andrology* 2010 **33** 443–462. (doi:10.1111/j.1365-2605.2009.01049.x)
- 96 Kristensen DM, Lesne L, Le Fol V, Desdoits-Lethimonier C, Dejuqc-Rainsford N, Leffers H & Jegou B. Paracetamol



- (acetaminophen), aspirin (acetylsalicylic acid) and indomethacin are anti-androgenic in the rat foetal testis. *International Journal of Andrology* 2012 **35** 377–384. (doi:10.1111/j.1365-2605.2012.01282.x)
- 97 Foresta C, Zuccarello D, Garolla A & Ferlin A. Role of hormones, genes, and environment in human cryptorchidism. *Endocrine Reviews* 2008 **29** 560–580. (doi:10.1210/er.2007-0042)
- 98 Eustache F, Mondon F, Canivenc-Lavier MC, Lesaffre C, Fulla Y, Berges R, Cravedi JP, Vaiman D & Auger J. Chronic dietary exposure to a low-dose mixture of genistein and vinclozolin modifies the reproductive axis, testis transcriptome, and fertility. *Environmental Health Perspectives* 2009 **117** 1272–1279.
- 99 Lehraiki A, Messiaen S, Berges R, Canivenc-Lavier MC, Auger J, Habert R & Levacher C. Antagonistic effects of gestational dietary exposure to low-dose vinclozolin and genistein on rat fetal germ cell development. *Reproductive Toxicology* 2011 **31** 424–430. (doi:10.1016/j.reprotox.2010.12.005)
- 100 Berman T, Levine H, Gamzu R & Grotto I. Trends in reproductive health in Israel: implications for environmental health policy. *Israel Journal of Health Policy Research* 2012 **1** 34. (doi:10.1186/2045-4015-1-34)
- 101 Carlsen E, Giwercman A, Keiding N & Skakkebaek NE. Evidence for decreasing quality of semen during past 50 years. *BMJ* 1992 **305** 609–613. (doi:10.1136/bmj.305.6854.609)
- 102 Swan SH, Elkin EP & Fenster L. The question of declining sperm density revisited: an analysis of 101 studies published 1934–1996. *Environmental Health Perspectives* 2000 **108** 961–966. (doi:10.1289/ehp.00108961)
- 103 Merzenich H, Zeeb H & Blettner M. Decreasing sperm quality: a global problem? *BMC Public Health* 2010 **10** 24. (doi:10.1186/1471-2458-10-24)
- 104 Boisen KA, Kaleva M, Main KM, Virtanen HE, Haavisto AM, Schmidt IM, Chellakooty M, Damgaard IN, Mau C, Reunanen M *et al.* Difference in prevalence of congenital cryptorchidism in infants between two Nordic countries. *Lancet* 2004 **363** 1264–1269. (doi:10.1016/S0140-6736(04)15998-9)
- 105 Jorgensen N, Carlsen E, Nermoen I, Punab M, Suominen J, Andersen AG, Andersson AM, Haugen TB, Horte A, Jensen TK *et al.* East–West gradient in semen quality in the Nordic–Baltic area: a study of men from the general population in Denmark, Norway, Estonia and Finland. *Human Reproduction* 2002 **17** 2199–2208. (doi:10.1093/humrep/17.8.2199)
- 106 Hauser R, Meeker JD, Duty S, Silva MJ & Calafat AM. Altered semen quality in relation to urinary concentrations of phthalate monoester and oxidative metabolites. *Epidemiology* 2006 **17** 682–691. (doi:10.1097/01.ede.0000235996.89953.d7)
- 107 Richthoff J, Rylander L, Jonsson BA, Akesson H, Hagmar L, Nilsson-Ehle P, Stridsberg M & Giwercman A. Serum levels of 2,2',4,4',5,5'-hexachlorobiphenyl (CB-153) in relation to markers of reproductive function in young males from the general Swedish population. *Environmental Health Perspectives* 2003 **111** 409–413. (doi:10.1289/ehp.5767)
- 108 Abdelouahab N, Ainmelk Y & Takser L. Polybrominated diphenyl ethers and sperm quality. *Reproductive Toxicology* 2011 **31** 546–550. (doi:10.1016/j.reprotox.2011.02.005)
- 109 Akutsu K, Takatori S, Nozawa S, Yoshiike M, Nakazawa H, Hayakawa K, Makino T & Iwamoto T. Polybrominated diphenyl ethers in human serum and sperm quality. *Bulletin of Environmental Contamination and Toxicology* 2008 **80** 345–350. (doi:10.1007/s00128-008-9370-4)
- 110 Meeker JD, Ehrlich S, Toth TL, Wright DL, Calafat AM, Trisini AT, Ye X & Hauser R. Semen quality and sperm DNA damage in relation to urinary bisphenol A among men from an infertility clinic. *Reproductive Toxicology* 2010 **30** 532–539. (doi:10.1016/j.reprotox.2010.07.005)
- 111 Phillips KP & Tanphaichitr N. Human exposure to endocrine disruptors and semen quality. *Journal of Toxicology and Environmental Health. Part B, Critical Reviews* 2008 **11** 188–220. (doi:10.1080/10937400701873472)
- 112 Lambrot R, Muczynski V, Lecureuil C, Angenard G, Coffigny H, Pairault C, Moison D, Frydman R, Habert R & Rouiller-Fabre V. Phthalates impair germ cell development in the human fetal testis *in vitro* without change in testosterone production. *Environmental Health Perspectives* 2009 **117** 32–37. (doi:10.1289/ehp.1174c32)
- 113 Lassurguere J, Livera G, Habert R & Jegou B. Time- and dose-related effects of estradiol and diethylstilbestrol on the morphology and function of the fetal rat testis in culture. *Toxicological Sciences* 2003 **73** 160–169. (doi:10.1093/toxsci/kg065)
- 114 Murugesan P, Muthusamy T, Balasubramanian K & Arunakaran J. Polychlorinated biphenyl (Aroclor 1254) inhibits testosterone biosynthesis and antioxidant enzymes in cultured rat Leydig cells. *Reproductive Toxicology* 2008 **25** 447–454. (doi:10.1016/j.reprotox.2008.04.003)
- 115 Salian S, Doshi T & Vanage G. Neonatal exposure of male rats to bisphenol A impairs fertility and expression of Sertoli cell junctional proteins in the testis. *Toxicology* 2009 **265** 56–67. (doi:10.1016/j.tox.2009.09.012)
- 116 Nordkap L, Joensen UN, Blomberg Jensen M & Jorgensen N. Regional differences and temporal trends in male reproductive health disorders: semen quality may be a sensitive marker of environmental exposures. *Molecular and Cellular Endocrinology* 2012 **355** 221–230. (doi:10.1016/j.mce.2011.05.048)
- 117 Skakkebaek NE, Rajpert-De Meyts E & Main KM. Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects. *Human Reproduction* 2001 **16** 972–978. (doi:10.1093/humrep/16.5.972)
- 118 Vega A, Baptissart M, Caira F, Brugnon F, Lobaccaro JM & Volle DH. Epigenetic: a molecular link between testicular cancer and environmental exposures. *Frontiers in Endocrinology* 2012 **3** 150. (doi:10.3389/fendo.2012.00150)
- 119 Massart F & Saggese G. Sex steroidal targets & genetic susceptibility to idiopathic cryptorchidism. *Pediatric Endocrinology Reviews* 2009 **6** 481–490.
- 120 Joensen UN, Jorgensen N, Rajpert-De Meyts E & Skakkebaek NE. Testicular dysgenesis syndrome and Leydig cell function. *Basic Clinical Pharmacology & Toxicology* 2008 **102** 155–161. (doi:10.1111/j.1742-7843.2007.00197.x)
- 121 Andersson AM, Jorgensen N, Frydelund-Larsen L, Rajpert-De Meyts E & Skakkebaek NE. Impaired Leydig cell function in infertile men: a study of 357 idiopathic infertile men and 318 proven fertile controls. *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 3161–3167. (doi:10.1210/jc.2003-031786)
- 122 Olesen IA, Sonne SB, Høi-Hansen CE, Rajpert-De Meyts E & Skakkebaek NE. Environment, testicular dysgenesis and carcinoma *in situ* testis. *Best Practice & Research. Clinical Endocrinology & Metabolism* 2007 **21** 462–478. (doi:10.1016/j.beem.2007.04.002)
- 123 Chen M, Tang R, Fu G, Xu B, Zhu P, Qiao S, Chen X, Xu B, Qin Y, Lu C *et al.* Association of exposure to phenols and idiopathic male infertility. *Journal of Hazardous Materials* 2013 **250–251** 115–121. (doi:10.1016/j.jhazmat.2013.01.061)
- 124 Dohle GR, Colpi GM, Hargreave TB, Papp GK, Jungwirth A, Weidner W & Infertility EAUWGoM. EAU guidelines on male infertility. *European Urology* 2005 **48** 703–711. (doi:10.1016/j.eururo.2005.06.002)
- 125 Andersen HR, Schmidt IM, Grandjean P, Jensen TK, Budtz-Jorgensen E, Kjaerstad MB, Baelum J, Nielsen JB, Skakkebaek NE & Main KM. Impaired reproductive development in sons of women occupationally exposed to pesticides during pregnancy. *Environmental Health Perspectives* 2008 **116** 566–572. (doi:10.1289/ehp.10790)
- 126 Brucker-Davis F, Wagner-Mahler K, Delattre I, Ducot B, Ferrari P, Bongain A, Kurzenne JY, Mas JC, Fenichel P & Cryptorchidism Study Group from Nice A. Cryptorchidism at birth in Nice area (France) is associated with higher prenatal exposure to PCBs and DDE, as assessed by colostrum concentrations. *Human Reproduction* 2008 **23** 1708–1718. (doi:10.1093/humrep/den186)



- 127 Fernandez MF, Olmos B, Granada A, Lopez-Espinosa MJ, Molina-Molina JM, Fernandez JM, Cruz M, Olea-Serrano F & Olea N. Human exposure to endocrine-disrupting chemicals and prenatal risk factors for cryptorchidism and hypospadias: a nested case–control study. *Environmental Health Perspectives* 2007 **115** (Suppl 1) 8–14. (doi:10.1289/ehp.9351)
- 128 Kukulvitis A, Georgiou I, Bouba I, Tzirka A, Giannouli CH, Yapijakis C, Tarlatzis B, Bontis J, Lolis D, Sofikitis N *et al.* Association of oestrogen receptor α polymorphisms and androgen receptor CAG trinucleotide repeats with male infertility: a study in 109 Greek infertile men. *International Journal of Andrology* 2002 **25** 149–152. (doi:10.1046/j.1365-2605.2002.00339.x)
- 129 McLachlan JA. Environmental signaling: what embryos and evolution teach us about endocrine disrupting chemicals. *Endocrine Reviews* 2001 **22** 319–341. (doi:10.1210/er.22.3.319)
- 130 Giwercman A, Rylander L, Rignell-Hydbom A, Jonsson BA, Pedersen HS, Ludwicki JK, Lesovoy V, Zvyezday V, Spano M, Manicardi GC *et al.* Androgen receptor gene CAG repeat length as a modifier of the association between persistent organohalogen pollutant exposure markers and semen characteristics. *Pharmacogenetics and Genomics* 2007 **17** 391–401. (doi:10.1097/01.fpc.0000236329.26551.78)
- 131 Watanabe M, Yoshida R, Ueoka K, Aoki K, Sasagawa I, Hasegawa T, Sueoka K, Kamatani N, Yoshimura Y & Ogata T. Haplotype analysis of the estrogen receptor 1 gene in male genital and reproductive abnormalities. *Human Reproduction* 2007 **22** 1279–1284. (doi:10.1093/humrep/del513)
- 132 Nassar N, Bower C & Barker A. Increasing prevalence of hypospadias in Western Australia, 1980–2000. *Archives of Disease in Childhood* 2007 **92** 580–584. (doi:10.1136/adc.2006.112862)
- 133 Schneider S, Kaufmann W, Strauss V & van Ravenzwaay B. Vinclozolin: a feasibility and sensitivity study of the ILSI–HESI F1–extended one-generation rat reproduction protocol. *Regulatory Toxicology and Pharmacology* 2011 **59** 91–100. (doi:10.1016/j.yrtph.2010.09.010)
- 134 Mylchreest E, Wallace DG, Cattley RC & Foster PM. Dose-dependent alterations in androgen-regulated male reproductive development in rats exposed to di(n-butyl) phthalate during late gestation. *Toxicological Sciences* 2000 **55** 143–151. (doi:10.1093/toxsci/55.1.143)
- 135 Virtanen HE & Toppari J. Epidemiology and pathogenesis of cryptorchidism. *Human Reproduction Update* 2008 **14** 49–58. (doi:10.1093/humupd/dmm027)
- 136 Emmen JM, McLuskey A, Adham IM, Engel W, Verhoef-Post M, Themmen AP, Grootegoed JA & Brinkmann AO. Involvement of insulin-like factor 3 (InsI3) in diethylstilbestrol-induced cryptorchidism. *Endocrinology* 2000 **141** 846–849. (doi:10.1210/en.141.2.846)
- 137 Hughes IA, Davies JD, Bunch TI, Pasterski V, Mastroyannopoulou K & MacDougall J. Androgen insensitivity syndrome. *Lancet* 2012 **380** 1419–1428. (doi:10.1016/S0140-6736(12)60071-3)
- 138 Welsh M, Saunders PT, Finken M, Scott HM, Hutchison GR, Smith LB & Sharpe RM. Identification in rats of a programming window for reproductive tract masculinization, disruption of which leads to hypospadias and cryptorchidism. *Journal of Clinical Investigation* 2008 **118** 1479–1490. (doi:10.1172/JCI34241)
- 139 Giwercman A. Estrogens and phytoestrogens in male infertility. *Current Opinion in Urology* 2011 **21** 519–526. (doi:10.1097/MOU.0b013e32834b7e7c)
- 140 El Kholy M, Hamza RT, Saleh M & Elsedfy H. Penile length and genital anomalies in Egyptian male newborns: epidemiology and influence of endocrine disruptors. *Journal of Pediatric Endocrinology & Metabolism* 2013 **26** 509–513. (doi:10.1515/jpem-2012-0350)
- 141 Parks LG, Ostby JS, Lambright CR, Abbott BD, Klinefelter GR, Barlow NJ & Gray LE Jr. The plasticizer diethylhexyl phthalate induces malformations by decreasing fetal testosterone synthesis during sexual differentiation in the male rat. *Toxicological Sciences* 2000 **58** 339–349. (doi:10.1093/toxsci/58.2.339)
- 142 Fisher JS, Macpherson S, Marchetti N & Sharpe RM. Human ‘testicular dysgenesis syndrome’: a possible model using *in-utero* exposure of the rat to dibutyl phthalate. *Human Reproduction* 2003 **18** 1383–1394. (doi:10.1093/humrep/deg273)
- 143 Swan SH, Main KM, Liu F, Stewart SL, Kruse RL, Calafat AM, Mao CS, Redmon JB, Teraand CL, Sullivan S *et al.* Decrease in anogenital distance among male infants with prenatal phthalate exposure. *Environmental Health Perspectives* 2005 **113** 1056–1061. (doi:10.1289/ehp.8100)
- 144 Salazar-Martinez E, Romano-Riquer P, Yanez-Marquez E, Longnecker MP & Hernandez-Avila M. Anogenital distance in human male and female newborns: a descriptive, cross-sectional study. *Environmental Health* 2004 **3** 8. (doi:10.1186/1476-069X-3-8)
- 145 Mendiola J, Stahlhut RW, Jorgensen N, Liu F & Swan SH. Shorter anogenital distance predicts poorer semen quality in young men in Rochester, New York. *Environmental Health Perspectives* 2011 **119** 958–963. (doi:10.1289/ehp.1103421)
- 146 Hsieh MH, Breyer BN, Eisenberg ML & Baskin LS. Associations among hypospadias, cryptorchidism, anogenital distance, and endocrine disruption. *Current Urology Reports* 2008 **9** 137–142. (doi:10.1007/s11934-008-0025-0)
- 147 Yu WJ, Lee BJ, Nam SY, Ahn B, Hong JT, Do JC, Kim YC, Lee YS & Yun YW. Reproductive disorders in pubertal and adult phase of the male rats exposed to vinclozolin during puberty. *Journal of Veterinary Medical Science* 2004 **66** 847–853. (doi:10.1292/jvms.66.847)
- 148 Roeleveld N & Bretveld R. The impact of pesticides on male fertility. *Current Opinion in Obstetrics & Gynecology* 2008 **20** 229–233. (doi:10.1097/GCO.0b013e3282fcc334)
- 149 Pierik FH, Burdorf A, Deddens JA, Juttmann RE & Weber RF. Maternal and paternal risk factors for cryptorchidism and hypospadias: a case–control study in newborn boys. *Environmental Health Perspectives* 2004 **112** 1570–1576. (doi:10.1289/ehp.7243)
- 150 Swan SH, Kruse RL, Liu F, Barr DB, Drobnis EZ, Redmon JB, Wang C, Brazil C & Overstreet JW. Semen quality in relation to biomarkers of pesticide exposure. *Environmental Health Perspectives* 2003 **111** 1478–1484. (doi:10.1289/ehp.6417)
- 151 Masse J, Watrin T, Laurent A, Deschamps S, Guerrier D & Pellerin I. The developing female genital tract: from genetics to epigenetics. *International Journal of Developmental Biology* 2009 **53** 411–424. (doi:10.1387/ijdb.082680jm)
- 152 Caserta D, Bordi G, Ciardo F, Marci R, La Rocca C, Tait S, Bergamasco B, Stecca L, Mantovani A, Guerranti C *et al.* The influence of endocrine disruptors in a selected population of infertile women. *Gynecological Endocrinology* 2013 **29** 444–447. (doi:10.3109/09513590.2012.758702)
- 153 Takeuchi T, Tsutsumi O, Ikezumi Y, Takai Y & Taketani Y. Positive relationship between androgen and the endocrine disruptor, bisphenol A, in normal women and women with ovarian dysfunction. *Endocrine Journal* 2004 **51** 165–169. (doi:10.1507/endocrj.51.165)
- 154 Cohn BA, Cirillo PM, Wolff MS, Schwingl PJ, Cohen RD, Sholtz RI, Ferrara A, Christianson RE, van den Berg BJ & Siiteri PK. DDT and DDE exposure in mothers and time to pregnancy in daughters. *Lancet* 2003 **361** 2205–2206. (doi:10.1016/S0140-6736(03)13776-2)
- 155 Rice HR & Baker BA. Workplace hazards to women’s reproductive health. *Minnesota Medicine* 2007 **90** 44–47.
- 156 Buck Louis GM, Cooney MA & Peterson CM. The ovarian dysgenesis syndrome. *Journal of Developmental Origins of Health and Disease* 2011 **2** 25–35. (doi:10.1017/S2040174410000693)
- 157 Holoch KJ & Lessey BA. Endometriosis and infertility. *Clinical Obstetrics and Gynecology* 2010 **53** 429–438. (doi:10.1097/GRF.0b013e3181db7d71)
- 158 Caserta D, Maranghi L, Mantovani A, Marci R, Maranghi F & Moscarini M. Impact of endocrine disruptor chemicals in gynaecology. *Human Reproduction Update* 2008 **14** 59–72. (doi:10.1093/humupd/dmm025)



- 159 Cobellis L, Colacurci N, Trabucco E, Carpentiero C & Grumetto L. Measurement of bisphenol A and bisphenol B levels in human blood sera from healthy and endometriotic women. *Biomedical Chromatography* 2009 **23** 1186–1190. (doi:10.1002/bmc.1241)
- 160 Reddy BS, Rozati R, Reddy BV & Raman NV. Association of phthalate esters with endometriosis in Indian women. *BJOG: an International Journal of Obstetrics and Gynaecology* 2006 **113** 515–520. (doi:10.1111/j.1471-0528.2006.00925.x)
- 161 Missmer SA, Hankinson SE, Spiegelman D, Barbieri RL, Michels KB & Hunter DJ. *In utero* exposures and the incidence of endometriosis. *Fertility and Sterility* 2004 **82** 1501–1508. (doi:10.1016/j.fertnstert.2004.04.065)
- 162 Signorile PG, Spugnini EP, Mita L, Mellone P, D'Avino A, Bianco M, Diano N, Caputo L, Rea F, Viceconte R *et al.* Pre-natal exposure of mice to bisphenol A elicits an endometriosis-like phenotype in female offspring. *General and Comparative Endocrinology* 2010 **168** 318–325. (doi:10.1016/j.ygcen.2010.03.030)
- 163 Cai LY, Izumi S, Suzuki T, Goya K, Nakamura E, Sugiyama T & Kobayashi H. Dioxins in ascites and serum of women with endometriosis: a pilot study. *Human Reproduction* 2011 **26** 117–126. (doi:10.1093/humrep/deq312)
- 164 Rier SE. Environmental immune disruption: a comorbidity factor for reproduction? *Fertility and Sterility* 2008 **89** e103–e108. (doi:10.1016/j.fertnstert.2007.12.040)
- 165 Mark-Kappeler CJ, Hoyer PB & Devine PJ. Xenobiotic effects on ovarian preantral follicles. *Biology of Reproduction* 2011 **85** 871–883. (doi:10.1095/biolreprod.111.091173)
- 166 Wang W, Craig ZR, Basavarajappa MS, Hafner KS & Flaws JA. Mono-(2-ethylhexyl) phthalate induces oxidative stress and inhibits growth of mouse ovarian antral follicles. *Biology of Reproduction* 2012 **87** 152. (doi:10.1095/biolreprod.112.102467)
- 167 Juliani CC, Silva-Zacarin EC, Santos DC & Boer PA. Effects of atrazine on female Wistar rats: morphological alterations in ovarian follicles and immunocytochemical labeling of 90 kDa heat shock protein. *Micron* 2008 **39** 607–616. (doi:10.1016/j.micron.2007.04.006)
- 168 Uzumcu M, Kuhn PE, Marano JE, Armenti AE & Passantino L. Early postnatal methoxychlor exposure inhibits folliculogenesis and stimulates anti-Mullerian hormone production in the rat ovary. *Journal of Endocrinology* 2006 **191** 549–558. (doi:10.1677/joe.1.06592)
- 169 Zhuang XL, Fu YC, Xu JJ, Kong XX, Chen ZG & Luo LL. Effects of genistein on ovarian follicular development and ovarian life span in rats. *Fitoterapia* 2010 **81** 998–1002. (doi:10.1016/j.fitote.2010.06.018)
- 170 Susiarjo M, Hassold TJ, Freeman E & Hunt PA. Bisphenol A exposure *in utero* disrupts early oogenesis in the mouse. *PLoS Genetics* 2007 **3** e5. (doi:10.1371/journal.pgen.0030005)
- 171 Fujimoto VY, Kim D, vom Saal FS, Lamb JD, Taylor JA & Bloom MS. Serum unconjugated bisphenol A concentrations in women may adversely influence oocyte quality during *in vitro* fertilization. *Fertility and Sterility* 2011 **95** 1816–1819. (doi:10.1016/j.fertnstert.2010.11.008)
- 172 Iguchi T, Kamiya K, Uesugi Y, Sayama K & Takasugi N. *In vitro* fertilization of oocytes from polyovular follicles in mouse ovaries exposed neonatally to diethylstilbestrol. *In Vivo* 1991 **5** 359–363.
- 173 Jefferson W, Newbold R, Padilla-Banks E & Pepling M. Neonatal genistein treatment alters ovarian differentiation in the mouse: inhibition of oocyte nest breakdown and increased oocyte survival. *Biology of Reproduction* 2006 **74** 161–168. (doi:10.1095/biolreprod.105.045724)
- 174 Valdez KE, Shi Z, Ting AY & Petroff BK. Effect of chronic exposure to the aryl hydrocarbon receptor agonist 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in female rats on ovarian gene expression. *Reproductive Toxicology* 2009 **28** 32–37. (doi:10.1016/j.reprotox.2009.03.004)
- 175 Chedrese PJ & Feyles F. The diverse mechanism of action of dichlorodiphenyldichloroethylene (DDE) and methoxychlor in ovarian cells *in vitro*. *Reproductive Toxicology* 2001 **15** 693–698. (doi:10.1016/S0890-6238(01)00172-1)
- 176 Uzumcu M & Zachow R. Developmental exposure to environmental endocrine disruptors: consequences within the ovary and on female reproductive function. *Reproductive Toxicology* 2007 **23** 337–352. (doi:10.1016/j.reprotox.2006.10.006)
- 177 Kokcu A. Premature ovarian failure from current perspective. *Gynecological Endocrinology* 2010 **26** 555–562. (doi:10.3109/09513590.2010.488773)
- 178 Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES & Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 2745–2749. (doi:10.1210/jc.2003-032046)
- 179 Kandaraki E, Chatzigeorgiou A, Livadas S, Palioura E, Economou F, Koutsilieris M, Palimeri S, Panidis D & Diamanti-Kandaraki E. Endocrine disruptors and polycystic ovary syndrome (PCOS): elevated serum levels of bisphenol A in women with PCOS. *Journal of Clinical Endocrinology and Metabolism* 2011 **96** E480–E484. (doi:10.1210/jc.2010-1658)
- 180 Couse JF & Korach KS. Estrogen receptor null mice: what have we learned and where will they lead us? *Endocrine Reviews* 1999 **20** 358–417. (doi:10.1210/er.20.3.358)
- 181 Nikaido Y, Yoshizawa K, Danbara N, Tsujita-Kyutoku M, Yuri T, Uehara N & Tsubura A. Effects of maternal xenoestrogen exposure on development of the reproductive tract and mammary gland in female CD-1 mouse offspring. *Reproductive Toxicology* 2004 **18** 803–811. (doi:10.1016/j.reprotox.2004.05.002)
- 182 Taylor HS, Vanden Heuvel GB & Igarashi P. A conserved Hox axis in the mouse and human female reproductive system: late establishment and persistent adult expression of the Hoxa cluster genes. *Biology of Reproduction* 1997 **57** 1338–1345. (doi:10.1095/biolreprod57.6.1338)
- 183 Taylor HS. Endocrine disruptors affect developmental programming of HOX gene expression. *Fertility and Sterility* 2008 **89** e57–e58. (doi:10.1016/j.fertnstert.2007.12.030)
- 184 Block K, Kardana A, Igarashi P & Taylor HS. *In utero* diethylstilbestrol (DES) exposure alters Hox gene expression in the developing Mullerian system. *FASEB Journal* 2000 **14** 1101–1108.
- 185 Abaci A, Demir K, Bober E & Buyukgebiz A. Endocrine disruptors – with special emphasis on sexual development. *Pediatric Endocrinology Reviews* 2009 **6** 464–475.
- 186 Tena-Sempere M. Kisspeptin/GPR54 system as potential target for endocrine disruption of reproductive development and function. *International Journal of Andrology* 2010 **33** 360–368. (doi:10.1111/j.1365-2605.2009.01012.x)
- 187 Smith JT, Clifton DK & Steiner RA. Regulation of the neuroendocrine reproductive axis by kisspeptin–GPR54 signaling. *Reproduction* 2006 **131** 623–630. (doi:10.1530/rep.1.00368)
- 188 Navarro VM, Sanchez-Garrido MA, Castellano JM, Roa J, Garcia-Galiano D, Pineda R, Aguilar E, Pinilla L & Tena-Sempere M. Persistent impairment of hypothalamic KiSS-1 system after exposures to estrogenic compounds at critical periods of brain sex differentiation. *Endocrinology* 2009 **150** 2359–2367. (doi:10.1210/en.2008-0580)
- 189 Bateman HL & Patisaul HB. Disrupted female reproductive physiology following neonatal exposure to phytoestrogens or estrogen specific ligands is associated with decreased GnRH activation and kisspeptin fiber density in the hypothalamus. *Neurotoxicology* 2008 **29** 988–997. (doi:10.1016/j.neuro.2008.06.008)
- 190 Gore AC, Wu TJ, Oung T, Lee JB & Woller MJ. A novel mechanism for endocrine-disrupting effects of polychlorinated biphenyls: direct effects on gonadotropin-releasing hormone neurons. *Journal of Neuroendocrinology* 2002 **14** 814–823. (doi:10.1046/j.1365-2826.2002.00845.x)
- 191 Khan IA & Thomas P. Disruption of neuroendocrine control of luteinizing hormone secretion by Aroclor 1254 involves inhibition of hypothalamic tryptophan hydroxylase activity. *Biology of Reproduction* 2001 **64** 955–964. (doi:10.1095/biolreprod64.3.955)



- 192 Rasier G, Parent AS, Gerard A, Denooz R, Lebrethon MC, Charlier C & Bourguignon JP. Mechanisms of interaction of endocrine-disrupting chemicals with glutamate-evoked secretion of gonadotropin-releasing hormone. *Toxicological Sciences* 2008 **102** 33–41. (doi:10.1093/toxsci/kfm285)
- 193 Fernandez M, Bianchi M, Lux-Lantos V & Libertun C. Neonatal exposure to bisphenol A alters reproductive parameters and gonadotropin releasing hormone signaling in female rats. *Environmental Health Perspectives* 2009 **117** 757–762. (doi:10.1289/ehp.0800267)
- 194 Warita K, Okamoto K, Mutoh K, Hasegawa Y, Yue ZP, Yokoyama T, Matsumoto Y, Miki T, Takeuchi Y, Kitagawa H *et al.* Activin A and equine chorionic gonadotropin recover reproductive dysfunction induced by neonatal exposure to an estrogenic endocrine disruptor in adult male mice. *Biology of Reproduction* 2008 **78** 59–67. (doi:10.1095/biolreprod.106.059857)
- 195 Gore AC. Neuroendocrine targets of endocrine disruptors. *Hormones* 2010 **9** 16–27.
- 196 McCarthy MM, Wright CL & Schwarz JM. New tricks by an old dogma: mechanisms of the Organizational/Activational Hypothesis of steroid-mediated sexual differentiation of brain and behavior. *Hormones and Behavior* 2009 **55** 655–665. (doi:10.1016/j.yhbeh.2009.02.012)
- 197 Weiss B. Endocrine disruptors as a threat to neurological function. *Journal of Neurological Sciences* 2011 **305** 11–21. (doi:10.1016/j.jns.2011.03.014)
- 198 Martini M, Miceli D, Gotti S, Viglietti-Panzica C, Fissore E, Palanza P & Panzica G. Effects of perinatal administration of bisphenol A on the neuronal nitric oxide synthase expressing system in the hypothalamus and limbic system of CD1 mice. *Journal of Neuroendocrinology* 2010 **22** 1004–1012. (doi:10.1111/j.1365-2826.2010.02043.x)

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