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Endocrine disrupting chemicals: impacts on human fertility and fecundity during the peri-conception period

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ABSTRACT

It is becoming increasingly difficult to avoid exposure to man-made endocrine disrupting chemicals (EDCs) and environmental toxicants. This escalating yet constant exposure is postulated to partially explain the concurrent decline in human fertility that has occurred over the last 50 years. Controversy however remains as to whether causal associations exist, with conflicting findings commonly reported for all major EDC classes. The primary aim of this extensive work was to identify and review strong peer-reviewed evidence regarding the effects of environmentally-relevant EDC concentrations on adult male and female fertility during the critical periconception period on reproductive hormone concentrations, gamete and embryo characteristics, as well as the time to pregnancy. Secondly, to highlight where little or no data exists that prevents strong associations being identified. Lastly, to ascertain whether individuals or couples diagnosed as sub-fertile exhibit higher EDC or toxicant concentrations. From the greater than 1480 known EDCs, substantial evidence supports a negative association between exposure to phthalates, PCBs, PBDEs, pyrethroids, organochloride pesticides and male fertility and fecundity. Only moderate evidence exists for a negative association between BPA, PCBs, organochloride pesticides and female fertility and fecundity. Overall fewer studies were reported in women than men, with knowledge gaps generally evident for both sexes for all the major EDC classes, as well as a paucity of female fertility studies following exposure to parabens, triclosans, dioxins, PFAS, organophosphates and pyrethroids. Generally, sub-fertile individuals or couples exhibit higher EDC concentrations, endorsing a causal association between EDC exposure and sub-fertility. This review also discusses confounding and limiting factors that hamper our understanding of EDC exposures on fertility and fecundity. Finally, it highlights future research areas, as well as government, industry and social awareness strategies required to mitigate the negative effects of EDC and environmental toxicant exposure on human fertility and fecundity.

Keywords: toxicant, reproduction, periconception, IVF, infertility

1. INTRODUCTION

Over the last 40 years an increasing number of publications have reported and debated the potential associations between endocrine disrupting chemicals (EDCs) and declining human fertility, however a comprehensive review of research on the effects during the critical peri-conception period is lacking. This is arguably the time where potential effects on human fertility are the greatest. While a substantial number of environmental factors affect the fertility and fecundity of couples during the peri-conception period, including naturally-occurring compounds, the greatest concerns surround the increasing use of man-made chemicals, with 1482 currently deemed to be EDCs [1]. These EDCs are found in everyday items including plastic food containers, personal care items, food products, and those used within manufacturing, industrial and agricultural processes (see review [2]). Their wide range of uses means their possible routes of uptake in the body are also broad, encompassing absorption through inhalation, across the skin, and ingestion of contaminated water and food, impacting both the concentration and duration of exposure. Consequently, which, and/or how many of these various routes of exposure is of significance, and the rate at which these chemicals are metabolised in individuals [3], represent a major hurdle in determining consistent consequences of exposure in humans. Therefore, the aims of this comprehensive work assessing human data are to, a) review strong evidence for positive and/or negative effects of the main EDC families, specifically around the periconception period, on adult male and female fertility and fecundity. b) highlight where little or no data exists, as well as possible reasons for this, and c) determine whether individuals or couples diagnosed as sub-fertile have higher EDC concentrations in their blood, urine or reproductive tissues, thus highlighting a possible causal association between EDCs and sub-fertility. Ultimately, this review informs researchers and clinicians of the current data available and knowledge gaps that can be the focus of future research studies.

2. METHODS

PubMed, ISI Web of Science and Cochrane database searches were performed for each EDC and toxicant, limited to human fertility and fecundity studies, published in English up to 31st January 2020. Fertility was defined by inclusion of data on reproductive hormone concentrations, gamete (sperm and oocyte) or embryo parameters (quantity and quality measures). Fecundability was defined by time to pregnancy (TTP), and where data were available, pregnancy and miscarriage rates. The search terms employed in combination with a specific chemical were; AND infertility, AND human, AND fertility AND human, AND sperm AND human, as well as AND oocyte AND human. Studies given preference for inclusion were large-scale accidental/occupational exposures or epidemiological studies, prospective or retrospective cross-sectional and cohort studies with sufficient sample size (> 100 people). Case studies were excluded. In addition, studies were excluded if accidental/occupational exposure involved undefined mixtures of compounds. Specific toxicological measures, such as ED50, were not employed to define quality of the studies as the focus of this review is on physiologically and environmentally relevant doses that nevertheless elicit relevant effects. Consequently, the evidence assessed in this review is largely limited to the effects on circulating, urinary and reproductive tract hormone concentrations, as well as the characteristics of gametes and embryos where known. The potential association of EDCs to clinical reproductive disorders and diseases (e.g. cryptorchidism or endometriosis) is outside the scope of this review but should be noted as potential contributors to altered fertility and fecundity in the peri-conception period as a result of exposure to EDCs.

3. ENVIRONMENTAL CHEMICALS AFFECTING MALE AND FEMALE FERTILITY AND FECUNDITY

Most EDCs interfere with or mimic steroid hormone action; predominantly by engaging oestrogen, androgen and thyroid hormone signalling pathways [2; 4]. In animal models it has been found that the actions of EDCs can also act centrally in the hypothalamic-pituitary-gonadal axis, by modifying secretion of and/or response to gonadotrophin-releasing hormone (GnRH) and gonadotrophins [2; 4]. However, the influence of this on human fertility has been poorly studied in humans, due to the inherent difficulty in its assessment that requires extensive sampling for accuracy. This gap represents an important avenue for future research on the effects of EDCs on human reproduction.

The EDC concentrations required to elicit effects on steroid hormone action can be far lower than endogenous hormones and may not conform to predictable dose-response curves [5]. Furthermore, it is unclear whether humans have the biochemical capacity to easily detoxify or excrete these compounds [2; 5]. Herein lies one of the great challenges for scientists and clinicians in reproductive endocrinology who are trying to unravel whether causal links exist between EDC exposure and altered fertility and fecundity. Human data are currently limited, particularly for individual chemical effects on adults in the general population, and this is complicated by often conflicting findings and a lack of longitudinal assessment or *in vivo* measures of chemical levels and their metabolites. Hence, defining adverse effects and setting 'safe' exposure limits have been, and continue to be, problematic. However, research output on the impact of EDC on fertility has increased significantly in recent years with results warranting greater investigation in this area.

3.1 Dietary Phytoestrogens; awaiting more data

Phytoestrogens are naturally occurring plant-derived compounds found in a variety of foods that possess oestrogenic and anti-oestrogenic properties [6] which can be categorised into five main groups: isoflavonoids, flavonoids, coumestans, stilbenes and lignans [6; 7]. Dietary consumption of phytoestrogens is highly variable between populations [6; 8], reflected by differences in circulating concentrations, with the highest levels reported in Asian populations [7]. To date, the majority of human studies have investigated effects on the fetus, neonate, and around puberty (as reviewed in [9; 10]). In contrast, only a limited number of studies have focussed on whether phytoestrogen consumption, predominantly the isoflavone genistein found in legumes and soy products, affects human fertility and/or fecundity [9; 11; 12; 13; 14; 15; 16].

3.1.1 **Inconsistent effects of Phytoestrogens on male fertility**

Of the few studies that have evaluated the effects of phytoestrogens on semen quantity and quality, or male fertility, contradictory findings have been reported [9; 11; 14; 17], likely due to differences in consumption levels and periods of exposure. A small pilot study in which fifteen fertile men received soy supplements for two months identified no changes in circulating hormones or semen parameters (volume, count, motility and morphology)[18], however this period of time would not be sufficient to impact a full cycle of spermatogenesis. In another study, male phytoestrogen intake as part of 184 couples receiving fertility treatment was not associated with reproductive outcomes [17]. Likewise, urinary phytoestrogen concentrations were not associated with a change in the time to TTP of fertile couples trying to conceive [19]. In contrast, a prospective study of 501 men from Michigan and Texas, USA, found that men with higher urinary levels of genistein and/or

diadzein (both isoflavones) had reduced sperm number and altered morphology but no abnormalities in other sperm parameters [14].

Numerous animal study findings support the inconsistent effects of phytoestrogen intake on male reproductive hormone concentrations, fertility and fecundity (as reviewed in [9]). Altered spermatogenesis, reduced steroidogenic enzyme activity and suppressed fertility has been reported in male rats exposed to genistein during development from embryonic day 12 to 19 [20]. Significantly, this timing corresponds with the initiation of meiosis and germ stem cell differentiation in vivo [21]. However, the incidence of reduced daily sperm production, epididymal sperm density and quality as well as reduced number of implantations and live births reported in this study varied by dose. In contrast, genistein and/or daidzein treatment increased sperm number, motility, cholesterol and testosterone levels in adult mice [22]. The conflicting findings may represent species-specific differences or differing windows of sensitivity during discrete developmental stages versus adulthood. The latter is consistent with the effects of other environmental pollutants on fertility and highlights the urgency with which further human and/or comparative studies should be undertaken in this area.

3.1.2 **Phytoestrogens may positively regulate female fertility, though insufficient data exists**

Only limited evidence exists to support any effects of phytoestrogens on human female fertility and fecundity. A meta-analysis of 47 soy and/or isoflavone consumption studies identified that women that were premenopausal (11 of 47 studies) had reduced circulating LH and FSH concentrations, and an increase in menstrual cycle length with increasing phytoestrogen intake [12], findings which are relevant to those choosing to establish a family later in life. Conversely, a prospective study of 315 women found soy isoflavone intake to be positively associated with live birth ratio in women attending a fertility clinic [15], although at higher doses a reduction in this benefit was observed. Notably, recent data supports the premise that soy intake may protect against adverse effects of other EDCs, particularly bisphenol A (BPA)-induced effects on implantation, clinical pregnancy and live birth rates in women undergoing fertility treatment [16]; as outlined in Section 3.2. It remains to be determined whether these effects are a direct result of phytoestrogen intake or indirect by reflecting a general difference in lifestyle of women consuming a phytoestrogen-rich diet.

Plants containing high levels of genistein are routinely used as traditional treatments for a variety of reproductive ailments [23; 24]. When coupled with the worldwide burgeoning interest in herbal remedies, as alternative therapies for reproductive conditions, such as endometriosis (reviewed in [25]), this provides a unique research resource that can be harnessed to better understand the mechanistic basis of fertility-associated effects of phytoestrogens. This also highlights a potential source of new clinical compounds that may be drawn upon given the historical use of a naturally occurring EDCs in ancient and traditional medicine. In contrast to studies in the human, the potential for phytoestrogens to reduce fertility, increase spontaneous abortion and induce reproductive abnormalities is reported in clover-fed sheep [26], along with a reduction in fertility, reported in captive cheetahs fed a diet containing high levels of daidzein and genistein, which could be reversed by diet substitution [27].

Overall, contradictory evidence exists for phytoestrogens altering fertility and fecundity, though emerging data points towards a potential detrimental effect for sperm number and

morphology in men with extended exposure and alterations in reproductive hormones in women. Additional prospective studies would help clarify the nature and severity of negative or beneficial effects, and the length of exposure and dose at which they occur.

3.2 Bisphenols; a class of EDC with high relevance to human fertility

Bisphenol A (BPA) is one of the highest volume chemicals produced worldwide and one of the most well-studied EDCs. Amongst its many uses, it is utilised to make plastics, resins, dental fillings and thermal receipt paper [28], and is known to leach from a broad range of products thereby entering the body via multiple routes. Consequently, exposure to BPA can be considered virtually constant, as evidenced by its presence in urine samples in up to 95% of people tested [29; 30; 31]. Epidemiological studies have identified a strong correlation between high adult urine BPA concentrations and an increased incidence of obesity, type II diabetes and cardiovascular disease [32; 33]. Limited prospective studies of BPA and human fertility and fecundity exist. Equally, few human reproductive studies exist on bisphenol analogues (e.g. BPS and BPF), introduced as replacements in 'BPA-free' products under the assumption these analogues were safer. However, findings from recent animal studies indicate this may not be the case [3]. Therefore, each bisphenol analogue, including BPA, requires their own extensive risk assessment and epidemiological study before clear statements can be made regarding their effects on fertility and fecundity. Also of relevance is the consideration that additive reproductive consequences may result from cumulative effects of multiple related bisphenol chemicals derived from different sources.

3.2.1 **Bisphenol negatively impacts male sperm quality**

Epidemiological studies have identified an association between urinary BPA and perturbed oestrogen, androgen, gonadotrophin and sex hormone binding globulin (SHBG) concentrations (which sequesters steroid hormone action and may mask consequences where only absolute serum steroid measurements are made), although few consistent relationships have been observed [30; 34; 35; 36; 37]. Higher BPA levels in the urine of occupationally exposed men are associated with higher self-reported sexual dysfunction [38; 39], as well as reduced sperm concentration, count, motility and vitality [40]. However, occupationally exposed individuals have a greater exposure level than the general population and therefore the changes to sperm quality may be an extreme representation.

Most recently, a cross-sectional study assessing 215 healthy 18 to 23 year old men found a significant positive correlation between urinary BPA and serum LH, as well as an inverse association with sperm concentration and count [41]. Another recent study measured BPA concentrations of 50 infertile and 50 matched fertile men found no significant differences in urinary BPA, however total BPA levels were negatively associated with semen quality and antioxidant levels, as well as being positively correlated with DNA damage and multiple semen profile defects [42]. Furthermore, a study of 191 men seeking assisted reproduction found that seminal, but not serum, BPA was negatively associated with sperm concentration, count and morphology [43]. Within the general population, studies support a greater negative effect of BPA in obese men [44; 45; 46], however, another study of 375 fertile males whose partners were pregnant failed to identify an association between BMI and urinary BPA concentration [36]. While these studies suggest BPA exposure is correlated with negative sperm and hormone characteristics in males, quantification of BPA levels will need to encompass a range of measures given the variability in detecting a correlation based on a single sample.

Studies of BPA effects on couple fecundity are limited, of small sample size, with contrasting results, potentially explained by differences in fertility status and demographics of the cohorts screened. Studies have failed to determine an association between paternal urinary BPA concentration and poor reproductive outcomes (TTP, fertilisation and live birth rates) of couples trying to conceive [34; 47], although as noted, quantification of urinary levels may not be ideal. In further support of this, one study of 27 couples receiving fertility treatment identified an inverse correlation between paternal, but not maternal, serum BPA concentrations and embryo cell number and quality [48]. In addition, low-level antenatal BPA exposure in 496 Chinese women was associated with increased birth length in male but not female babies [49], further illustrating the potential for sex-specific effects of BPA. Likewise, a small study of 146 couples undergoing fertility treatment failed to identify an association between BPA and pregnancy, embryo quality, normally fertilised oocytes, fertilisation, sperm concentration or sperm motility [50]. The potential for effects of bisphenols on fertility during embryonic development is further highlighted by a recent study where exposure of male embryos to BPA, as determined by maternal serum at 18 and 34-weeks gestation, was associated with reduced sperm concentration and motility in adulthood, but not correlated with serum hormone profiles (LH, FSH, inhibin, androgen or oestrogen), of male offspring at 20 to 22 years of age [51].

A ban on the use of BPA in products such as baby bottles [52] led to its replacement by related bisphenols S and F [53], proposed as safer alternatives by the industry, though due to their structural similarity, recent studies have determined both to have EDC effects [31; 54; 55; 56]. As a result, little is known about their potential to impact fertility and fecundity. A recent study of 158 men seeking fertility treatment identified reduced semen volume in individuals with detectable levels of urinary BPS, with sperm concentration, total count and motility also reduced in obese males [57]. These data highlight the potential for other lifestyle factors to exacerbate subtle changes in reproductive parameters with bisphenol exposure.

3.2.2 **BPA negatively impacts female fertility**

The majority of BPA studies have been undertaken in sub-fertile females, with higher serum BPA concentrations reported in infertile, compared with fertile women [58; 59]. Overall, data suggest a negative association between urine BPA concentration and circulating oestrogen levels [35; 60; 61], although one cohort study failed to determine an association between BPA and steroid hormone concentrations in women in the general population [62]. Further effects on oocyte yield and quality [61; 63; 64], and blastocyst formation [65], as well as increased rates of implantation failure [66] and miscarriage [67; 68] have also been reported, though data from a recent study of 146 couples in South Korea suggests no association between urinary, plasma or follicular fluid BPA levels and oocyte retrieval or peak E2 [50].

Similar to findings in men, BPA exposure has not been associated with a change in TTP [59; 69; 70] and notably one study found no association with fecundity in generally healthy women [59]. By contrast, in a study of 700 Chinese women attempting pregnancy and followed for 12 months, urinary BPA levels were associated with a 13% reduction in fecundability [31]. In addition, women with a high likelihood of occupational BPA exposure during pregnancy exhibit an increased risk of low birth weight at term [71].

Altogether, clear associations between BPA and serum hormones or sperm parameters are reported, and significant data has mounted for a negative consequence of BPA exposure

on folliculogenesis and events around conception, as outlined above. Notably, numerous rodent studies corroborate these findings, reporting reduced sperm count, motility and quality [34; 72] after exposure to BPA at levels deemed safe by relevant regulatory bodies in Europe and the USA (i.e. at or below the lowest observed adverse effect level (LOAEL; 50 mg/kg)). Similarly, substantial data from animal studies strongly supports a direct negative effect of BPA exposure on follicle number and growth, oocyte ploidy and development, steroidogenesis [28; 35; 73], uterine morphology and endometrial health, embryo number and metabolism [74], implantation [75; 76] and fertility [58], including potential transgenerational effects [77]. Concerningly, paternal BPA exposure appears to preferentially affect male offspring, including the documentation of generational effects, hinting at potential long-term consequences of exposure. Based on these findings, individuals trying to conceive should minimise the use of products containing BPA, and strongly supports the need for further human studies to encourage governments to further legislate in this area.

3.3 Phthalates are major disruptors of male fertility and fecundity that warrant greater legislation against human exposure

Phthalates, such as the di-esters di(2-ethylhexyl) phthalate (DEHP), dibutyl phthalate (DBP) and diethyl phthalate (DEP), are added to plastics to increase their flexibility and durability. Products containing phthalates include toys, footwear, food packing, medical devices, perfumes and personal care products [78; 79]. Predominantly, exposure occurs via ingestion and is generally ubiquitous in developed countries, with studies detecting blood and urinary phthalates in >95% of those screened, as well as being detectable in reproductive [80; 81] and amniotic fluids [82], however the majority of anti-androgenic and oestrogenic effects of phthalates are exerted by their mono-ester metabolites [83]. Common mono-esters include mono(2-ethylhexyl) phthalate (MEHP), monobutyl phthalate (MBP), monoethyl phthalates (MEP), and monobenzyl phthalate (MBzP) [81]. Therefore, as with other classes of EDC, it is important to note that broad statements regarding phthalate actions as a single collective group may be inappropriate, potentially explaining discrepancies between studies, and may be dependent on the isoforms measured. This is reflected in temporal- and sex-specific actions of different phthalate metabolites identified in the studies below.

3.3.1 **Phthalates alter male fertility by contributing to poor sperm motility and quality**

Given the complexities stated above, readers are directed elsewhere for a systematic review of the epidemiological evidence [84]. In short, several large epidemiological and fertility centre studies report altered reproductive hormones, predominantly decreased testosterone, oestradiol and increased SHBG, in men exposed to DEHP or certain mono-ester metabolites (e.g. MBP and MEHP [85; 86; 87; 88; 89; 90; 91; 92; 93; 94; 95]). The vast majority of studies and meta-analyses associate high urinary levels of mono-ester phthalates in men with poor sperm motility and quality [78; 91; 92; 96; 97; 98; 99; 100; 101; 102; 103; 104], low sperm concentration and morphology [94; 99; 100; 104; 105; 106; 107; 108; 109; 110; 111; 112; 113], and decreased semen volume [114]. It is worth highlighting, contrary to the majority of published work, a small number of studies have found a positive association between low-level antenatal DEHP exposure and sperm motility, as well as adult serum testosterone levels [115; 116], though the latter findings may reflect a response to reduced androgen receptor activity.

An inverse relationship between male urinary phthalate metabolite concentrations and the generation of high-quality embryos in an IVF clinic has also been reported [117]. In

contrast, cross-sectional studies have failed to find any association between urinary mono-ester concentrations and any semen parameters of sub-fertile [118] or fertile men [119; 120]. In addition, one study of 153 young Canadian men found no association between phthalate levels detected in hair, and sperm count or motility, though associations with thyroid hormone levels were reported [120]. However, urinary mono-ester phthalate metabolites in male but not female partners have been associated with a longer TTP in the general population [47; 69], and a reduced implantation and live-birth rate in couples receiving fertility treatment [121]. In contrast, a recent systematic review concluded that no association exists between phthalates and male or female fecundability or TTP [122], though their analysis is complicated by the equivocal results derived from different phthalate chemicals.

3.3.2 **Phthalates reduce oocyte yield, alter reproductive hormones and may affect clinical pregnancy rates in females**

Contrasting effects are similarly evident in females with phthalate exposure. Higher urinary mono-ester concentrations, especially DEHP metabolites, have been associated with decreased antral follicle counts [123; 124] and lower oocyte yield [125; 126; 127] in women seeking fertility treatment. However, no association was identified between follicular fluid or urine mono-ester metabolite concentration and oocyte yield or peak oestradiol concentration in another study [128]. A study of urinary mono-ester concentrations and changes in menstrual cycle length identified only monocarboxyoctyl concentration as being associated with a shorter luteal phase in women trying to conceive [129].

Conflicting evidence however exists regarding the possible effects of phthalates on TTP, as urinary MEP concentration has been associated with a longer TTP in one cohort study of 229 Danish women over 430 pregnancies [130], although more generally, large cohort studies have found no association between urine or serum mono-ester phthalate concentrations and a longer TTP [69; 70; 129; 131]. Within specific studies, DEHP mono-ester metabolites levels were suggestive of a shorter TTP [70; 131]. High urine levels of specific DEHP metabolites have been correlated with a lower rate of clinical pregnancy and live birth in women undergoing IVF [123; 124; 125; 126; 127; 132]. In a study of 663 women receiving fertility treatment, urinary MBP was inversely associated with normal fertilization, as were moderate levels of MEP and mono (2-ethyl-5-oxohexyl) phthalate (MEOHP) [133]. The same study found phthalate metabolites, including DEHP, were not correlated with day 3 embryo quality, clinical pregnancy rate, live birth rate, or early miscarriage rate, though moderate levels of MEP and MMP reduced good quality blastocyst formation [133]. In contrast to the study by Deng et al (2020), no association was identified between follicular fluid or urine mono-ester metabolite concentration and fertilisation rate or embryo quality [128], or phthalate concentrations of either partner and fertilisation rate in couples receiving fertility treatment [134]. In the same study however, male but not female MEP concentrations were positively associated with cleavage stage embryo quality, and MBzP and MBP concentrations were negatively associated with blastocyst quality [134].

Equally, conflicting reports exist with regards to urine mono-esters concentrations and early pregnancy loss. MEHP has been associated with a higher occurrence of pregnancy loss [135; 136], whereas other DEHP metabolites are associated with reduced pregnancy loss [129]. These studies employed comparable participant numbers and it is worth noting that both investigated couples without proven reproductive capacity. It is however likely

that such conflicts reflect differences in the mechanism of action by specific phthalate chemicals. Perhaps greater insight of possible effects of phthalates can be gleaned from individuals exposed after an intentional contamination of 900 food and drink products with DEHP in 2011 in Taiwan [137]. Studies are beginning to emerge that investigate the long-term effect on parameters of fertility in this unique cohort, with the earliest finding of high DEHP exposure estimated at the time of contamination being associated with a reduction in serum FSH and increase in serum SHBG [138]. Follow-up studies of reproductive success will be highly informative.

Overall, a growing number of epidemiological studies provide evidence for an effect of mono-ester phthalate exposure on reproductive hormones, semen volume, and TTP, with stronger evidence for detrimental effects on sperm concentration, motility and quality. These findings are supported by many animal studies (reviewed in [139]) and therefore the topic of phthalate effects on male fertility requires greater government and social attention. Despite only a limited number of studies having been undertaken in women compared with men, generally with conflicting reports, there is evidence that specific phthalates and their metabolites may negatively impact both male and female fertility and fecundity. Further study of specific phthalates will identify clearer associations. There is however a growing body of evidence highlighting negative effects from animal studies on folliculogenesis and steroidogenesis [140; 141], as well as changes in oestrous cyclicity and accelerated reproductive ageing [142; 143] and male effects (reviewed in [139]). Overall findings highlight the potential for metabolite- and time-dependent differences in the effect of phthalates [144] and the complexity of phthalate actions that include potential transgenerational epigenetic changes identified in rodents [145] among other transgenerational consequences [146; 147; 148] that necessitate further investigation in humans.

3.4 Parabens as potential regulators of human fertility and fecundity; an important research gap

These phenolic compounds exhibit weak oestrogenic activity [149; 150] and are structurally similar to bisphenols, comprising many sub-classes including methyl, propyl and butyl parabens [151]. They are often utilised as preservative and anti-microbial agents, being commonly found in food, cosmetics and personal care products [79]. Their presence has been detected in >90% of urinary samples [152] and are recorded to be more than 5-fold higher in women than in men [153]. Despite their widespread use, surprisingly few epidemiological or animal studies exist that assess paraben concentrations and their effects on fertility and fecundity. Of the studies undertaken to date, few associations have been identified in either males or females. Thus, there is an unmet need for more studies on the potential effects of parabens on fertility and fecundity in both humans and animals.

3.4.1 **Inconclusive effects of parabens in men**

The two most commonly detected sub-classes of parabens (methyl and n-propyl) are consistently found in serum, urine and seminal plasma collected from the general population [154]. In three studies, male urinary paraben concentrations were not associated with changes in plasma steroid hormone concentrations or semen parameters normally associated with infertility [155; 156; 157], however one study did identify such an association [158], and a separate study from the same group found an association with sperm disomy [159]. Likewise, butyl parabens were positively associated with sperm DNA damage in one of the aforementioned studies [155]. In contrast, paternal urinary concentrations of couples receiving fertility treatments (IVF or ICSI) have not found am

association with fertilisation rate, embryo quality, implantation rate [151] or semen quality [160].

3.4.2 **Inconclusive effects of parabens in women**

To date, only a handful of studies are available on the effects of parabens on fertility in women. One prospective study of 192 women receiving fertility treatment reported a weak negative association between urinary propyl paraben and antral follicle count, accompanied by a positive association with day 3 FSH concentrations [161]. In the same cohort, no association was identified between urinary paraben concentrations and mature oocyte counts, number of high-quality embryos, fertilisation rates, implantation or pregnancy rates [162]. A similar lack of effect on IVF outcomes was recently reported in a study of 420 women [132]. In a separate study of 501 women, a 34% reduction in fecundity was identified in women with a urinary paraben concentration in the highest quartile [163]. A recent systematic review of a range of suspected EDCs also provides preliminary support for an association between exposure of women to parabens and longer TTP [122], however data continues to emerge that demonstrate no association [164], or only a weak association with specific parabens [165].

Altogether there is inadequate evidence to make judgements regarding the potential for specific parabens to modify normal female fertility, though minimising exposure it likely to be better than assuming no risk. Insufficient data from animal studies exists to corroborate a definitive effect of parabens on either male or female fertility.

3.5 Triclosan; emerging negative impacts in men and a lack of consistent findings in women highlights the importance of more research in this area

Triclosan (TCS) is a phenolic compound that, like parabens, is structurally similar to bisphenols, but also PCBs and thyroid hormones [2]. It is an anti-bacterial and anti-fungal compound commonly included in many personal care, industrial and household products. Unsurprisingly, TCS is found in over 75% and up to 98% of urine samples of cohorts surveyed [166; 167; 168; 169], including those of pregnant women [170; 171]. Studies of aquatic invertebrates, fish and marine mammals highlight the potential of TCS to disrupt thyroid hormone homeostasis, in part through competitive inhibition of thyroid hormone inactivation via sulfation, as well as the reproductive axis by mimicking or interfering with the action of androgens and oestrogens [172; 173; 174]. However, conflicting findings exist from rodent studies [175] and few epidemiological studies focusing on fertility have been undertaken in humans.

3.5.1 **Triclosan negatively impacts sperm quality and androgen profiles in men**

In a large cohort (877 infertile, 713 fertile) and smaller case-controlled study (163 men), urinary TCS concentrations were not associated with semen parameters or idiopathic infertility [37; 156] though associations were identified for a raft of other phenolic compounds [156]. However, urinary TCS concentrations were negatively associated with plasma testosterone, inhibin B and LH concentrations in the small-case controlled study [37]. Also in contrast to the large cohort study by Chen [156], another large cohort study of 471 men found urinary TCS concentration to be negatively associated with sperm quality, most notably motility [176] and a second study of 419 men from the LIFE study found high TCS concentration to be associated with lower sperm concentration and count [177]. A similar association between high urinary TCS and abnormal sperm morphology was found in a study of 315 men from an infertility clinic [178] and in 262 men enrolled in the EARTH study [179]. Data from *in vitro* and animal studies, although equally

conflicting, generally demonstrate TCS to decrease androgen synthesis and sperm production, mediated by changes in FSH and LH concentrations [180].

3.5.2 **Conflicting studies of triclosan effects in women**

Retrospective analysis of 2,000 Canadian women identified that those in the highest quartile for urinary TCS concentration had an increased TTP when compared to those in other quartiles [70]. In support of this, a study of 109 women from a fertility clinic in the United States of America found that urinary TCS concentrations were inversely associated with ovarian reserve [181], and antral follicle count in a second study of 511 polish women attending a fertility clinic [182]. A study of 156 Chinese women seeking IVF with urinary TCS concentrations above the median value found significant reductions in embryo formation and implantation rates [183]. Furthermore, urinary TCS levels have been negatively associated with placental weight in 473 European women [184]. In contrast, other studies have found no association between TCS exposure and fertility and fecundity in women. One, a prospective study of 501 couples, reported no association between female, male or couple TCS exposure and TTP [163]. Finally, a study of 496 mother-infant prospective cohort pairs in China found no association between antenatal TCS urine levels and any measure of birth outcome [49], although whether reproductive effects are apparent in exposed children remains to be determined and pre-pregnancy levels were not determined. Overall, the majority of studies have shown an association between urinary TCS and fecundity of women with the highest TCS levels, however further research is needed to identify other risks and clarify the extent of effects on pregnancy.

Altogether, a number of findings suggest that there may be a negative effect of TCS on both male and female fertility and fecundity, inconsistencies emphasise the need for further study in this area. This is particularly true given that many of the conflicting studies represent large cohorts, hence better stratification of sub-cohorts within these may help delineate consistent findings.

3.6 Persistent Organic Pollutants (POPs)

As their name suggests, these compounds reside in the environment for extensive periods of time and often become concentrated in the adipose tissues of humans and animals [2]. These chemicals are comprised of superfamilies, each containing many isoforms or congeners that share a common chemical structure, yet can have vastly different biological effects [185]. As with phthalates, this goes some way to explaining conflicting reports on their action as endocrine disruptors, as outlined below, as studies often make broad conclusions irrespective of whether a specific isoform, combination of isoforms or whole superfamilies have been utilised.

3.6.1 Polybrominated biphenyls (PBBs) and diphenyl ethers (PBDEs): mounting evidence indicates negative impacts on female fertility and fecundity

PBBs and PBDEs are used in flame retardants, including those used in clothing, furniture and mattresses, hence high concentrations are often found in house dust [186]. Some PBDEs, including penta- and octa-PBDE and deca-BDE were banned or restricted in the European Union, or voluntarily phased out in the USA and other countries [187]. PBBs and PBDEs are reported to affect fertility and fecundity in both males and females, though both negative and positive effects have been observed. The exact mechanisms of action are unclear, presumably due to the large number of different congeners and their metabolites with varying toxicities, but PBB and PBDEs have known oestrogen, anti-androgen and/or thyroid actions which can affect fertility (see review [2]).

3.6.1.1 **PBB- and PBDE-induced alterations in male fertility**

Few studies have investigated the relationship of PBB concentrations and male fertility. Of these, one large cohort study (468 men in the LIFE study) determined that serum PBB concentrations were positively associated with sperm concentration and negatively with sperm morphology, yet had no association with other sperm parameters (motility and DNA integrity) [188]. Conversely, when subfertile men were studied and classified by sperm motility, no relationship was identified between serum PBBs and reproductive hormones or sperm parameters [37].

A number of studies have investigated the relationship between PBDE concentrations and male fertility. A positive association was identified between PBDE congeners found in house dust and serum LH, testosterone, oestradiol and SHBG concentrations in men attending a fertility clinic [187], but a negative association between PBDE and FSH and inhibin B concentrations in two studies [187; 189]. However, other cohort studies found, with respect to circulating reproductive hormone concentration, either contradictory findings [190] or no changes [37; 120; 191]. Several cohort studies have determined a negative association between serum PBDE and sperm concentration and motility [120; 186; 192; 193] or morphology [188], but generally inconsistent findings exist as to the effects of PBDEs on human sperm characteristics in vivo [37; 186; 188; 191; 193]. In the context of IVF, high paternal urinary flame retardant levels were associated with an 8-12% reduction in the proportion of fertilised oocytes from the first to second quartile of male urinary retardant levels [194].

3.6.1.2 **PBDEs, in limited studies, decrease fertilisation rates, embryo quality and increase implantation failure and TTP in females**

Compared with men, fewer studies have been undertaken into PBB and PBDE effects on fertility in women. Serum PBDE concentrations have been negatively associated with FSH levels [195] but were not associated with changes in menstrual cycle characteristics [196]. In women receiving fertility treatment, PBDE concentrations were identified in follicular fluid [197; 198], although not all PBDE congener concentrations were correlated between serum and follicular fluids, suggesting serum levels may not provide a good indicator of local ovarian exposures. Notably, follicular PBDE congeners, such as BDE 153, were associated with decreased fertilisation rates, lower rates of high-quality embryos and increased implantation failure [197; 198]. Equally, increasing concentrations of four congeners (BDE 47, 99, 100 and 153) in blood were associated with a longer TTP and reduced fecundability (BDE 100 and 153) [196]. Further, congener BDE-28 was associated with a longer TTP, and congener BDE-153 with an increased risk of miscarriage and premature birth [195] but not lower birth weight [199]. Similarly, maternal preconception serum concentrations of congeners BDE-17, -28, -66 and homologue triBDE are associated with a higher risk of pregnancy loss [200]. Notably, two prospective studies measuring 10 PBBs failed to find an association between PBB serum concentrations with a longer TTP in 501 couples trying to conceive [47; 201], though in a follow-up study of the same cohort, increased maternal preconception serum PBDE concentrations were associated with a higher risk of pregnancy loss [200].

Overall, limited studies on PBB have been reported, however studies have begun to emerge in the last 5 years that appear to identify PBDE exposure as being negatively associated with sperm motility and concentration in males, and embryo development, implantation failure and TTP in females. Studies in animals are equally limited, but generally support

negative effects of PBDEs on male fertility [202; 203] and offspring neurobehaviour [203] and induces mitochondrial dysfunction and oxidative stress in mouse oocytes [204]. These preliminary findings however highlight the need for further investigation.

3.6.2 Polychlorinated biphenyls (PCBs); still a major disruptor of human fertility and fecundity

PCBs comprise 209 different chemicals that were used in fluids for electrical devices, industrial lubricants, paints and copy paper until their worldwide ban in 1979 (see review [2]). However, their persistence in the environment means there is ongoing exposure to PCBs from water and soil. PCBs are known to inhibit enzymes that regulate the excretion of many chemicals, including phthalates [205], thereby increasing the body's chemical burden. The exact mechanisms of action are unclear, presumably due to the large number of different PCBs and their metabolites with varying chemical structures and toxicities, though some are known to interact with the aryl hydrocarbon receptor (AhR). As with other POPs, PCBs are known to have oestrogen, anti-androgen and thyroid hormone actions that can affect fertility and fecundity in both men and women (see review [2]).

3.6.2.1 **PCB exposure reduces sperm motility and DNA integrity**

Modelling using LIFE study data suggests that male PCB exposure may be a significant determinant of infertility risk [206; 207]. A number of studies have reported negative associations between PCB exposure and serum testosterone and SHBG concentrations [43; 208; 209; 210; 211]. While conflicting findings exist as to the effects of PCBs on human sperm characteristics in vivo (see reviews [2; 43; 99; 212; 213]), the majority of these studies identified PCB exposure as being negatively associated with sperm motility and DNA integrity. This has been consistently reported for PCB 138 and 153 [193; 205; 214; 215; 216; 217; 218]. Notably, the 1978-79 large scale PCB exposure of *in utero* and adult males in Taiwan to contaminated cooking oil resulted in decreased sperm motility and altered morphology in both cohorts [219; 220]. Evidence suggests that PCB exposure predominantly interferes with the last stage of sperm development; their maturation in the epididymis, as few studies report reductions in total sperm count or concentration [43; 221]. Indeed, human sperm exposed to a PCB mixture (Aroclor 1254) for 3 or 6 hours demonstrate reduced sperm motility, increased reactive oxygen species levels and increases in a surrogate marker of mitochondrial dysfunction [222]. However, the extent to which the chosen test concentrations reflect concentrations present in human semen is unknown as the authors merely emulate doses from previous in vitro studies. Nevertheless, higher plasma concentrations of certain PCBs (101, 138, 156, 157, 167, 170, 172, 207 and 209) have been associated with a longer TTP [47; 201]. This finding was supported by a more recent study of 501 couples from 16 countries but now living in the USA, where 7 of 36 PCBs tested in serum and urine were associated with a 17% to 29% reduction in couple fecundability [223]. To date, the most robust evidence for a negative effect of PCBs (especially PCB 138 and 153) on sperm exists for motility and DNA integrity, with weak evidence for effects of PCBs on hormone concentrations, other sperm parameters and fecundity.

3.6.2.2 **PCB exposure alters hormone and cycle characteristics in women, and is associated with reduced implantation, fertilisation and embryo quality, and increased TTP**

Studies have associated high PCB exposure, especially those with oestrogenic activity, with changes in menstrual cycle characteristics [224; 225; 226; 227], with up to a three day increase in cycle length [227]. A very large (31,575) cross-sectional study also associated

increased levels of nine specific PCBs, including PCBs 118, 138, 153 and 170, with early onset menopause [228]. Furthermore, in women receiving fertility treatment, PCB concentrations were identified in follicular fluid [229; 230] and associated with decreased fertilisation rates, lower rates of high-quality embryos and increased implantation failure [198; 231].

As a potential insight into the mechanistic basis of pregnancy loss, a study of 94 IVF participants found a negative correlation between PCB levels (PCB 28, 52, 138 and 180) in follicular fluid with endometrial thickness [232]. In the same study, individual PCBs were found to be independent predictors, with a negative association for other clinical measures of IVF success. These included PCB 28 and the number of eggs retrieved, PCB 180 and the number of fertilised oocytes or cleaved embryos and PCB 52 and the number of implantation sites [232]. Likewise, a study of urinary PCB levels in 58 female patients undergoing their first IVF cycle found an inverse association between higher PCB levels and antral follicle count, the follicular response to gonadotrophins, including oestradiol, the number of oocytes retrieved and endometrial thickness, as well as fertilisation rates, embryo quality and clinical IVF outcome in terms of embryo implantation and live birth [233]. Longitudinal studies have identified a longer TTP for women relative to exposure to certain PCBs (particularly 118, 167 and 209) [47; 201; 234; 235]. Of note, some of the effects of PCB have been associated with transplacental actions, such as reduced fecundability in the daughters of mothers exposed to relatively high PCB levels during pregnancy [236].

Generally, the majority of studies undertaken provide robust evidence that supports that PCBs are negatively associated with fertility and fecundity in both men and women, with considerable effects on both sperm and oocytes, as well as the resultant embryo culminating in implantation failure and a longer TTP. Studies in animals are limited, but generally support negative effects of PCBs and PBDEs on male fertility but again less evidence is available for female animals (see reviews [2; 4]).

3.6.3 Polychlorinated dibenzo-p-dioxins (PCDDs or Dioxins); the devil we don't know

Dioxins are by-products of industrial processes, including the production of herbicides, metal and paper, waste and wood incineration, as well as being released by microwaving plastic containers [237; 238; 239]. Dioxins are lipophilic and are not easily eliminated by the body, leading to bioaccumulation. Well-known examples of dioxins include tetrachlodibenzo-*p*-dioxin (TCDD), a contaminant present in Agent Orange [221]. Dioxins exert their effect in part through their interaction with the AhR, with reproductive effects amongst the most sensitive. Even at background levels, dioxins exert adverse effects on oestrogen, androgen and thyroid hormone regulation [240] and reviewed in [241].

3.6.3.1 Exposure to dioxins reduces pre- and peri-pubescent male sperm count

Exposure of chemical production workers to dioxin has been associated with increased gonadotrophins and decreased testosterone in serum [242]. Likewise, a substantial accidental exposure to dioxin in Seveso Italy in 1976 was followed by the analysis of 135 boys up to the age of 18 at the time of the event and demonstrated lower oestradiol and higher FSH concentrations in adulthood, compared with unexposed contemporaries [243]. Moreover, men who were breastfed [244] or were pre-pubertal at the time of the event [243] had reduced sperm count and motility as adults. In contrast, no association between adult exposure and semen quality was found, highlighting the potential for a developmentally sensitive window of exposure during childhood and adolescence. A more

recent longitudinal study of 516 Russian boys aged 18 to 19 years old associated higher peripubertal serum TCDD concentrations with poorer semen parameters, including concentration, count and motile count [245]. However, no further data exists on the actions of PCDD or dioxin on male fertility and fecundity, particularly with regards to possible effects of environmentally relevant dioxin concentrations. Similarly, animal studies examining the peri-conception period are extremely limited.

3.6.3.2 **Insufficient data on dioxin effects in women**

No clear evidence exists to allow conclusions of possible dioxin effects on female fertility and fecundity. Follow-up of ovarian function in women accidentally exposed during the aforementioned incident in Italy (section 3.6.3.1), identified no evidence of altered ovarian function or changes in menstrual cycles [246]. However, a dose-dependent association between circulating dioxin and TTP was found in women exposed while trying to conceive [247]. It is possible that, like the study of semen quality in adult men exposed during the same incident, the lack of changes in ovarian function of adult women reflects a window of sensitivity during earlier development not investigated in these studies. Animal studies have determined TCDD alters folliculogenesis, blocks ovulation and inhibits production of oestrogen while reducing ovarian weight, although effects differ between species [185; 248].

Overall, limited but direct associations can be made between dioxin exposure and sexual development in males that may alter fertility and fecundity. It is likely that the same is true for females, given data from animal studies, although investigations are yet to be undertaken to confirm this relationship in humans. Further, the persistence of these chemicals in the environment highlight the potential for dioxins to have ongoing effects, well beyond the time they are banned from use.

3.6.4 Perfluoroalkyl and Polyfluroalkyl substances (PFAS)

PFAS are a group of chemicals, containing more than 4,700 congeners, including the perfluoroalkyl acids (PFAAs) perflurooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) (see review [249]). Their hydrophobic and lipophilic properties make them desirable for use in a wide range of consumer products including teflon, textiles, pesticides, carpet and personal care products, and various manufacturing processes such as industry surfactants, and fire-fighting foams (see review [249]). The two most commonly used and studied groups are PFOA and PFOS, with few studies on human health with respective to other PFAS. PFAS are often referred to as ‘forever chemicals’, as they are very resistant to heat and to degradation in the environment, so persist for decades, often in ground and drinking water, and bio-accumulate in the body [249; 250]. These compounds are known to alter the expression of nuclear receptors involved in steroid metabolism, such as peroxisome proliferator-activated receptors (PPARs) [251; 252] and bind to oestrogen receptor alpha [253]. However, there is still a great deal of research required to identify the mechanisms by which PFAS can elicit biological effects. An extensive systematic review of the available literature was recently undertaken of PFAS effects on reproductive hormones, fertility and fecundity in humans [249].

3.6.4.1 **Significant conflicting data highlights the need for more research on effects of PFAS in men**

Several cohort studies report no effect of PFAS exposure on plasma hormone concentrations (testosterone, oestradiol, SHBG, LH or FSH) in healthy young men [254; 255; 256], although one cohort study of 257 young Danish men did identify a negative

association between PFAS and testosterone [257], and two other studies reported a positive correlation between plasma PFOA and LH and SHBG levels [211; 258]. Thus, based on these few studies, the consensus is that no substantial evidence exists to support effects of PFAS on reproductive hormones in men. The caveat however, it that all these studies were conducted on young men (< 30 years old), so potentially effects in older reproductively active men remain to be determined.

In total, fewer than 15 studies have investigated an association between PFAS exposure and sperm parameters (see review [249]). Six studies identified that a higher serum concentration of several PFAS congeners was associated with low sperm count and concentration [259], as well as sperm quality, including unfavourable morphological characteristics [260; 261; 262] and fewer normal sperm in ejaculates [255; 260]. Equally, six studies found no association between PFAS and sperm quality or DNA global methylation [211; 257; 258; 263; 264; 265]. Notably, no study has consistently found the same sperm parameters to change with PFAS exposure.

3.6.4.2 **Insufficient and conflicting data on effects of PFAS in women**

Two studies report negative associations between plasma oestradiol and PFOA and perflurooctanesulfonamide (PFOSOA) concentrations but not for other PFAS [266; 267]. Aside from these studies, very few have investigated the effects of PFAS exposure on female reproductive hormones; those that have find no changes in hormone concentrations (see review [249]). Conflicting evidence also exists for menstrual cycle length, with some studies finding that exposure to specific PFAS are associated with an altered menstrual cycle length [268; 269; 270], while another study has found no association [271]. A recent study of 146 young (18 to 21 year old) females in the Veneto region in Italy, one of the most heavily PFAS polluted areas in the world, identified an increase in the age at menarche and the frequency of irregular periods [272]. Several large cohort studies, both prospective and retrospective, report a longer TTP, reduced fecundity or infertility associated with higher maternal plasma concentrations of certain PFAS [201; 273; 274; 275], although most studies have found that the majority of PFAS congeners measured showed no associations [269; 274; 276; 277; 278; 279]. These contrasting findings may be explained by a shorter peri-conception monitoring time, correction for different confounding factors or the variety of geographical locations of the studied cohorts.

In terms of PFAS exposure and either miscarriage or preterm birth rates, data are conflicting, with only four and ten studies being undertaken respectively (see review [249]). Generally, inadequate evidence exists that precludes the ability to make any statement on maternal blood PFAS concentrations and changes in miscarriage or preterm birth rates, however, a correlation between higher PFOS (but not other PFAS) umbilical cord concentrations and increased preterm birth is evident [280; 281]. Strong evidence from the very large cross-sectional NHANES study in the USA [282], as well as a substantial systematic review [283] have identified that PFOA is associated with low birth weights. However, conflicting evidence exists relating to maternal blood concentrations of other PFAS and changes in birth weight [249]. Further, analysis of the Avon Longitudinal Study of Parents and Children, a British pregnancy cohort comprising 446 mother-daughter pairs, found no association between in utero PFAS exposure and AMH levels in female adolescents [284].

Currently, the collective findings from human studies do not support a consistent effect of PFAS on sperm. No association is evident from animal studies, as administration of PFOA

for two generations to rats at levels much higher than those found in humans showed no effect on semen parameters [285; 286]. For women, nearly all measured fertility traits result in contrasting findings from the less than 20 studies collectively undertaken. Equally, relatively few animal studies have been conducted, with conflicting findings or no effects on fertility [285] to lower implantation rates [287]. Hence, the current data cannot provide any firm conclusions for possible PFAS effects.

3.6.5 Pesticides, herbicides and insecticides; clear reductions in fertility and fecundity by specific chemicals highlights that greater research and political action is urgently required

These chemicals can be divided into several categories, with organochlorines (OC), organophosphates (OP) and pyrethroids being the most widely recognised [288]. Data on the effects of pesticide and herbicide exposure on fertility are equivocal in humans and experimental animal studies [2; 212; 288; 289]. The principle reason for this is the vast number of chemicals classified under these categories that can act via a multitude of hormonal pathways. In addition, the majority of studies do not include actual measurements of pesticide exposure, concentration and/or duration of exposure. Individuals are often simultaneously exposed to multiple chemicals and concentrations, including chemical accelerants in commercial products that can have their own detrimental effects, with limited quantitation of direct exposure levels, where the potential effects of individual or specific categories of chemicals are often not considered. Nonetheless, the clear and strong effect on human fertility in some studies of specific chemicals in this group, highlight the importance of a global effort to undertake studies of sufficient power to make unequivocal conclusions about their effects.

3.6.5.1 **Organochlorines (DDT/DDE); major disruptors of human fertility**

Probably the most studied and well-known OC in terms of their effects on fertility and fecundity are dichlorodiphenyltrichloroethane (DDT) and its breakdown product dichlorodiphenyldichloroethylene (DDE). DDT acts like oestrogen when it enters the body, while DDE blocks male hormones such as testosterone (see reviews [2; 4]). In 1972, DDT was banned in the USA and subsequently many other countries, however it is still used in areas prone to malaria [4]. Limited studies exist on the direct impacts upon fertility in humans, although many studies find significant effects in areas that have been chronically exposed to DDT.

3.6.5.1.1 **DDE compromises male fertility**

In populations where DDT is used against malaria, increased levels of DDE in the blood are associated with reduced testosterone [290], FSH and LH concentrations, and higher oestradiol and SHBG levels [290; 291], as well as changes to semen volume and sperm count [290], motility and morphology [292; 293], and sperm DNA structure [292; 294]. Consequently, androgen concentrations and semen quality are adversely affected by DDE. In contrast, some studies have identified no association between DDE and hormone concentrations and sperm parameters [2; 215], though results of these studies showed clear trends. In a large prospective cohort, a negative association between plasma concentrations of DDE and TTP was determined in male partners of couples trying to conceive for 12 months [201].

3.6.5.1.2 **DDE perturbs female reproduction**

Serum DDT and DDE concentrations are associated with changes in menstrual cycle length [295; 296] and decreased oestrogen and progesterone concentrations [297; 298]. Despite

measurement of these compounds in follicular fluid [230; 299], the majority of studies have not identified a relationship between DDE in serum and follicular fluid with fertilisation rate or pregnancy in women seeking fertility treatment [300; 301; 302]. However, several studies have associated higher serum concentrations with a longer TTP [234], lower ovarian reserve [233] and implantation rates [232] as well as early pregnancy loss [303; 304; 305], with increased DDE levels also associated with early onset menopause [228]. Additionally, low birth weight, congenital malformations and stillbirths were more prevalent in babies from women exposed to higher levels of a range of OC pesticides [306].

Collectively, studies demonstrate strong correlations between DDT and DDE exposure and male and female fertility and fecundity, particularly in areas where their use continues. Animal study findings corroborate substantial negative effects of DDT and DDE exposure on male fertility and fecundity, including data that indicates transgenerational effects [307], as well as the negative effects of these compounds on female fertility [308].

3.6.5.2 Other organochlorines can disrupt human fertility

Additional OC pesticides with potential relevance to human fertility include the pesticides methoxychlor, chlordane, dieldrin, mirex, chlordecone (kepone), heptachlor, toxaphene, as well as hexachlorobenzene (perchlorobenzene) and hexachlorocyclohexanes (e.g. lindane); though relatively little is known about these overall. In general, these compounds have similar modes of action to DDT and DDE, via modifications of steroid production and/or action (reviewed in [309]), though animal studies indicate the effects of dieldrin and mirex may be independent of their ability to modify oestrogen action (reviewed in [310]). Aside from the paucity of recent studies, difficulty in determining the influence of specific OC pesticides on fertility stems from the fact that several studies have associated only the sum of OC exposure to fertility measures. However, a strong association has been observed in females, as detailed below.

3.6.5.2.1 Specific organochlorines negatively impact male fertility

After the banning of DDT, methoxychlor was promoted as a suitable replacement but has since also been banned due to its acute toxicity and ability to modify androgen and oestrogen receptor signalling (reviewed in [311; 312; 313]) that includes potential transgenerational effects identified in animal studies [314; 315; 316]. However, animal studies to date have used doses higher than typical human environmental exposure levels and therefore the specific contributions of methoxychlor to modifying human fertility in the general population remain to be established.

In one small Icelandic study of 27 fertile men attending a fertility clinic for female factor sub-fertility, metabolites of chlordane or a mixture of some 200 organochlorines were not associated with sperm count, concentration or motility [317]. Similarly, hexachlorobenzene was not associated with semen parameters in the same or a second study of 65 men from a Netherlands fertility clinic, or another study from a hospital andrology laboratory in the USA [318; 319], nor in 90 sub-fertile men from an Indian fertility clinic [320]. Animal model studies generally support the aforementioned human data [308].

Insight into the effects of chlordecone (kepone) on male fertility was afforded through two poisoning episodes, occurring first in 1975 at an industrial production facility in Virginia USA. Exposed men exhibited reduced sperm counts and motility lasting approximately four to six months [321; 322], suggesting a significant, albeit transient, negative effect on

fertility. Though use was banned in 1975 in the USA, it was still used in less developed nations. Subsequently, significant environmental pollution was discovered in the West Indies in 1999. Fortuitously, one year before the discovery of pollution, blood and semen samples were collected from 100 male agricultural workers in this region. These men showed higher kepone levels than non-agricultural workers but exhibited no difference in TTP, semen volume, sperm concentration, output, motility, or morphology, nor significant changes in hormone concentrations (FSH, LH, Inhibin B, testosterone and oestradiol) [309; 323; 324]. These limited findings suggest that while transient effects on fertility may result from moderate or high kepone exposures, typical environmental exposure in the general community is unlikely to result in significant impacts on fertility or fecundity in the longer term.

Very few studies exist that investigate the effects of mirex, dieldrin, lindane, heptachlor and hexachlorobenzene on male fertility. One study of 21 Canadian couples found that mirex was undetectable in seminal plasma of husbands from couples unable to conceive but was present in couples that did conceive [230]. Similarly, a small study of dieldrin exposure in 31 women and 16 men from Tanzania found no association between serum or semen lindane levels and pregnancy rate or semen quality [325]. In contrast, a study of 278 men visiting a fertility clinic in India where couples were unable to conceive with no known fertility disorders exhibited significantly higher semen lindane levels and lower sperm motility when compared to couples who had conceived within one year [326]. Blood and semen hexachlorobenzene analysis of 589 spouses of pregnant women from Greenland, Poland and Ukraine found a positive association with SHBG, and negative association with free androgen levels, without major consequences in semen quality [327].

3.6.5.2.2 **Other OCs significantly impair female fertility**

While fewer studies of OC pesticides have been conducted in women, recent data largely supports a role for OC pesticides in diminishing fertility and fecundity. As part of the Hokkaido Study Sapporo Cohort encompassing 514 women enrolled between 23 and 35 weeks of gestation, linear regression modelling found that chlordanes, hexachlorobenzene, hepatachlor, mirex and toxaphenes levels in maternal blood were negatively associated with testosterone, SHBG and prolactin, while being positively associated with dehydroepiandrostenedione and FSH levels in cord blood of male offspring [328]. This illustrates the potential for a range of OC compounds to modulate endocrine hormone production in women.

Human studies on methoxychlor have principally been performed *in vitro*. However, in mouse studies, methoxychlor was found to induce follicular atresia and reduce follicular growth [329], principally via effects on oestrogen production and action (reviewed in [310; 330]), although conflicting data regarding rodent follicular development exists (reviewed in [308]).

In further support of OC effects in women, high follicular fluid lindane concentrations in 94 women was recently associated with a lower implantation rate [232]. Furthermore, lindane isomer concentrations in blood samples of 30 women in India who had experienced more than three miscarriages were significantly higher when compared to a similarly sized fertile cohort [331] and higher lindane plasma concentrations were detected in 68 Taiwanese women seeking fertility treatment [332]. Moreover, high lindane concentrations in the blood of women living in agricultural areas of Kazakhstan have been associated with low concentrations of gonadotrophins, oestradiol and IGF-I [333], supporting a link

between lindane accumulation and changes in female fertility and fecundity. Animal studies similarly support human findings, with reductions in ovulation rates in rabbits, and oestradiol levels, implantation rates, and mitosis in mice, as well as impacting granulosa cell integrity, vaginal opening, cyclicity and LH and FSH concentrations (reviewed in [185; 308]).

Chlordecone levels in women were associated with a decrease in gestational length and an increased risk of pre-term birth in a study of 818 pregnant women from the West Indies [334]. Accidental heptachlor exposure during the peri-conception period was associated with longer luteal phase length and stunted the reduction in the oestradiol:progesterone ratio post-ovulation in 457 Hawaiian women [335]. In animal studies the relatively high OC doses used raises question regarding the relevance of findings to human exposures and fertility [310; 330], however significant data using rats and mice demonstrate the ability of chlordecone to alter reproductive function and fertility through its actions as a relatively weak oestrogen receptor agonist (reviewed in [336]). Overall, solid evidence exists to support a negative effect of OCs on female fertility.

The array of OC chemicals and their varied effects on fertility and fecundity reported to date stands as a testament to the need for standardisation in research and better classifications to inform clinicians and government regulators in assessing the endocrine-disrupting potential of each chemical. Beyond varied results in males, accumulating evidence supports the view that OC exposure in women has a negative impact on female fertility, making this class of EDCs a prime candidate for minimisation strategies in women seeking to become pregnant.

3.6.5.3 **Organophosphates (OP); is restricted use working?**

Organophosphate (OP) pesticides, such as chlorpyrifos, malathion and diazinon, were first developed in the 1940s and rapidly became widely used both industrially and residentially [337]. Residential use has become restricted in recent years, particularly in developed countries, though agricultural use remains a major concern with 93% of pregnant women in Canada having at least one OP metabolite in their urine [338]. The presence of OP exposure in the general population is associated with the consumption of fruits and vegetables [338; 339], as well as with higher education and income [338; 340]. This raises the question of whether limiting use to agricultural areas is an effective means of minimising exposure to these chemicals. Exposure to OP is also reflected in differences in culture, diet, lifestyle and the regulatory oversights of pesticides in different geographical areas [341]. Predictably, those working in agricultural areas have higher urinary OP metabolites compared with the general American population [342]. This is in addition to the significant incidental exposure of those living near agricultural areas but not being directly involved in commercial agricultural activities [343]. Therefore, while reductions in OP exposure of the general population have been achieved due to tighter regulations on residential use [344], exposure persists and highlights the relevance of OP research in the context of human fertility.

3.6.5.3.1 **OPs decrease male fertility and perturb sperm parameters**

Most of the evidence regarding OP effects on male fertility comes from studies of occupationally exposed men. Urinary OP levels were associated with lowered sperm parameters in six studies (see systematic review [345]). However, these include only weak evidence from relatively small pilot studies ($n < 100$) that specific OP metabolites had negative effects on sperm concentration [346; 347], count [348], volume [349], DNA or

morphology [350; 351; 352], and were associated with increased sperm aneuploidy; effects that may be attributed to increases in oxidative damage (reviewed in [353; 354]). In a larger study of 227 men occupationally exposed to OP, sperm chromatin condensation was compromised in 75% of semen samples [355]. Furthermore, in a large questionnaire-based study of Canadian farming couples involving 3984 pregnancies, focusing on farming activities of males in the three months prior to conception through to the month of conception, OP use generated an odds ratio > 2 for miscarriage and pre-term delivery but only where it was used in combination with other pesticides (e.g. thiocarbamates) [356]. Further, in a study of 578 partners of male Finnish greenhouse employers and employees, a suggestion of decrease in TTP was identified, with this effect only apparent in those men ineffectively protected from OP [357].

3.6.5.3.2 **Limited data to date associates high OP levels in women with increased TTP**

Similar negative effects of OP on fertility and fecundity are observed in females, though more data are required. Of 615 Chinese women planning a pregnancy and followed for one year, those in the highest quartile of OP urinary metabolite concentration had a longer TTP and lower fertility compared with women in the lowest quartile [358]. In another study of 94 couples undergoing ICSI for male factor infertility, a significant negative association between follicular fluid chlorpyrifos concentration and endometrial thickness, oocyte retrieval and implantation rate was determined, with the same associations identified for another OP pesticide, diazinon [232]. It is useful to recognise that several of the effects of OP pesticides on fertility and birth outcomes are evident in studies of flame retardants [359] (see section 3.6.4). This likely reflects their shared molecular structures and potentially, therefore, mechanisms of action. Though evidence is sparse in humans, one potential mechanism for the effect of OP on female fertility and fecundity is via alterations in thyroid function [360].

Data associating occupational exposure of men to OP with fertility are therefore broadly consistent, identifying a negative influence on various semen parameters, though large robust studies in this area are lacking. Some confidence in the view of a negative influence of OP can be drawn from many animal studies that consistently report multiple effects on sperm including reduced density, counts, motility, viability, as well as increased DNA fragmentation, plasma membrane destruction, apoptosis, and cell death. Further effects include reductions in plasma testosterone, changes in serum gonadotrophin concentrations and decreased activity of antioxidant enzymes (reviewed in [353; 354]). While fewer studies have explored the effects of OP in females, data suggest a longer TTP potentially related to reduced oocyte numbers and implantation rates.

It is worthwhile noting one study making strident conclusions of a lack of any endocrine-modulating activity for an important OP pesticide, chlorpyrifos. This study, investigating both male and female animals [361], was undertaken exclusively by the Dow Chemical company that manufactures Chlorpyrifos. This seemingly exhaustive analysis should be interpreted with an abundance of caution, due to the overt conflict of interest. The work from Dow is inconsistent with a growing number of published *in vivo* animal studies [362; 363; 364; 365], not to mention the exhaustive studies in aquatic organisms [366; 367].

Given their extensive use in agriculture and the likelihood of negative effects on fertility and fecundity, OP pesticides represent an important class of EDC on which future research should focus, the results of which will be of importance to fertility specialists seeking mechanisms to explain fertility of unknown aetiology. Thus, government health panels

should invest significantly in promoting legislation aimed at minimising and replacing OP pesticides, in the interests of reproductive health.

3.6.5.4 **Pyrethroids**

Pyrethroids, derived from naturally occurring pyrethrins in plants, are commonly used around the home as aerosol insecticides, as well as in agricultural production systems [368] under the assumption that their 'natural' origin makes them safer. These include bifenthrin, cypermethrin, permethrin and tetramethrin. Consequently, pyrethroid use has increased considerably over the last twenty-five years, resulting in widespread and greater opportunity for human exposure [368; 369]. To date, relatively few studies have investigated adverse effects on human reproduction, with most focused on male effects [345; 370; 371]. In line with studies on certain pesticide classes, a recent substantial review of pyrethroids and human epidemiology studies failed to identify any study that collectively demonstrated a robust experimental design, as well as high-quality endpoint measures and evidence, or findings that were concordant with those of toxicological animal studies [368]. Even in animal toxicity studies, only weak effects are detected in steroid and thyroid hormone concentrations, as well as sperm parameters (see review [368]). This is underpinned by conflicting evidence as to whether pyrethroids have the potential to act via or modulate oestrogen pathways [372; 373; 374]. Thus, the mechanisms of action of pyrethroids remains elusive.

3.6.5.4.1 **Pyrethroid exposure negatively impacts sperm DNA quality and concentration**

Only a small number of studies have examined pyrethroid exposure and hormone concentrations. Urinary concentrations of the pyrethroid (3-phenoxybenzoic acid, 3-PBA) were associated with increased serum LH and reduced oestrogen concentrations in a study of 212 non-occupationally exposed Chinese men, but did not relate to FSH, testosterone or prolactin concentrations [375]. Similar relationships were determined in another study of 161 men (18 to 54 years old) from an infertility clinic that investigated a number of urinary metabolites and plasma hormone concentrations. However, a positive relationship with FSH and a negative relationship with inhibin and the ratio of testosterone to SHBG were also observed [376]. In contrast to these studies, no association between urinary 3-PBA concentration and serum hormone levels was identified in a study of 322 Japanese university students [377].

Fifteen cross-sectional studies have reported negative associations between urinary pyrethroid metabolite concentrations and sperm parameters (see reviews [345; 368; 370; 371]), mainly with respect to chromatin and DNA quality, as well as aneuploidy rates [378; 379; 380; 381]. Several studies also identified that a higher 3-PBA urine concentration is negatively associated with sperm concentration [346; 375; 379; 380; 382]. Comparisons between quartiles within studies have found sperm count, motility and morphology to be negatively associated with high urinary pyrethroid metabolite concentrations [379; 383], while another study found the Y:X ratio of sperm to be negatively associated with urinary pyrethroid metabolites in healthy fertile men in Japan [384]. The majority of studies however rely on single sample time points of varying duration relative to exposure or self-reported occupational exposure from men working in greenhouses [357] and fenvalerate factories in China [378; 385], as well as those exposed to various pyrethroids in the general population [346; 379; 381; 386; 387; 388; 389]. Despite this, moderate evidence suggests that environmental concentrations of pyrethroids negatively impact reproduction, particularly sperm DNA quality and concentration, in non-occupationally exposed men.

3.6.5.4.2 **Pyrethroid effects on female fertility and fecundity is understudied**

Available data on the fertility and fecundity of women with pyrethroid exposure is sparse compared with data on men. This highlights the urgent need for research in this area, given the emerging negative consequences identified in men. Furthermore, cross-sectional studies have shown pyrethroid metabolites to be consistently present in the urine of women, and that these were from non-dietary pathways e.g. from domestic pesticide use and proximity to crop fields [390].

Few studies have explored a relationship between pyrethroid and reproductive hormone concentrations, although one study of South African women reported indoor use of pyrethroids was associated with decreased plasma anti-Mullerian hormone concentration [391] suggestive of poor reproductive outcomes. In terms of fertility studies, a prospective cohort study of 615 Chinese women seeking to conceive determined increasing urinary pyrethroid metabolite 3-PBA concentration to be associated with a longer TTP and decreased fertility [358].

The very low number of fertility and fecundity studies in women overall, means no firm conclusions can be made on the possible effects of pyrethroids. Animal data on the effects of environmental pyrethroid concentrations on female reproduction are minimal with findings conflicted [373]. In comparison, animal studies using toxicological doses have identified altered hormone concentration (estrogen and progesterone), morphometric and structural changes in the female reproductive tract, perturbed ovulation, increased atresia of follicles, oocytes and corpora lutea, as well as changes in endometrial glands [373; 392], suggesting the potential for adverse effects at lower doses.

Combined, the assumption that concentrated natural pesticide chemicals will have no impact on male or female fecundity is potentially naïve. Growing evidence supports a negative impact on male sperm characteristics, although more studies are required to assess effects in females. Until such time, pyrethroid use should likely be minimised, particularly by those trying to conceive.

4. SUMMARY

This review encapsulates the available robust human data for the effects of several common EDC classes on adult male and female fecundity and fertility around the time of conception. Accumulating data suggests that several EDCs have a negative effect in men and women [2; 4; 393], with important differences between the temporal activity of specific EDCs, where some EDCs have actions during discrete phases of reproduction, while others act more broadly. Examples include those of PCBs and chlordecone with effects at the last stages of spermatogenesis, compared with phthalates and DDT/DDE that influence both reproductive hormone levels and multiple semen parameters in men, as well as BPA influencing multiple measures of oocyte reserve/quality and measures of embryo quality in women. It is likely that the broader influence of the latter EDCs reflects their ability to bind and modulate the actions of the AR and/or ER and the diverse function of these hormone receptors in regulating normal aspects of fertility.

Based on the information reviewed, there is strong evidence to support a negative association between male fertility (measured by sperm count, motility, morphology and DNA integrity) and exposure to phthalates (MEHP and MBP), BPAs, PCBs, PCDD/Dioxins, pyrethroids as well as pesticides including DDE (Table 1). Equally, for

male fecundity (TTP), moderate evidence supports a negative association with exposure to mono-ester phthalates, PCBs and pesticides including DDE, especially in the context of couples seeking assistance through IVF clinics. In contrast to studies in men, substantially fewer studies have been undertaken in women. Consequently, only a moderate negative association is evident for oocyte quality, implantation rate and/or miscarriage rates with BPA or PCBs exposure. There is also a negative association with fecundity (TTP) and menstrual cycle length apparent for PCBs, BPA, and pesticides (including DDE) (Table 2). It is however anticipated that more associations between EDCs and female fertility and fecundity will become apparent with further study. In addition, the lower number of robust fertility effects identified in women compared with men likely reflects the difficulty in accessing and studying oocytes compared with sperm, rather than a lack of actual effects. Overall, this review not only integrates the current human literature to determine those EDCs for which strong associations with fertility and fecundity are evident, it identifies gaps in our knowledge of the effects of EDC classes. Thus, it suggests critical focus areas for future research as a foundation from which meaningful changes can be made to improve human fertility and fecundity, by placing the issue of investigating EDC exposures firmly on the social and political agenda.

4.1 Limitations of this review and EDC field

In deciding whether to include studies in this review, the authors decided to exclude many of the studies that investigate EDCs in cohorts of less than 100 individuals, except in cases where no or very little data are available for a particular EDC. The aim being to focus on studies with a higher likelihood of comprising meaningful results and to minimise small sample size-induced inflation of apparent data conflicts. This approach possibly excludes some studies with varying experimental and statistic strength that could have influenced the conclusions drawn but their inclusion would more likely have confounded the final conclusions. Nevertheless, this is a clear limitation in this review. Recently, Chung et al. [394] calculated a minimum effect size nearing 2700 to be able to establish clear significant links between EDCs and sperm parameters, highlighting that existing studies consisting of only a few hundreds of participants are underpowered. Notably, if the effect of a chemical is not discussed in this review, it is most likely due to a lack of study rather than an absence of association. Where possible, a lack of effect determined with data of sufficient robustness has been highlighted, however this is unlikely to have captured all negative data in existence, due to the inherent issue in publishing all negative study results.

Whether effects have or have not been identified in this review may be complicated by reliance on one-off urine or blood samples as a biomarker of exposures by most studies, combined with a lack of standardisation. These one-off samples also give no indication of life-stage or life-long exposure, particularly as the impacts of *in utero* exposure may only manifest in adulthood. Also, given the short half-life of some chemicals, it is the measurement of their more potent metabolites that should be the focus to more accurately determine a person's true exposure, not simply the measurement of the free or total parent chemical concentration. Without these data, it is possible that measurement of the parent chemical may be inaccurate or confounded when attempting to identify association with fertility and fecundity. Equally, the time from sampling to evaluating a biological difference in reproductive outcomes may be too short or large in some cases, for example within the approximate three-month duration for the full process of spermatogenesis [395]. It is also worth noting that concentrations of EDCs in urine may not faithfully reflect the concentrations present in reproductive organs. Studies that, for example, measure semen EDC content [396] may allow more direct relationships to emerge. This is not withstanding

the generally lower level of EDC metabolites found in semen, and the large number of study participants that would be required for an investigation of sufficient statistical strength [394]. Likewise, a significant limitation of the analysis presented herein is that this review has not made attempts to draw direct comparisons between study quality based on specific dose and exposure context used in each. Such analyses are relevant to the field but outside the scope of the current analysis.

Probably the largest confounder when interpreting study findings is determining the more realistic day-to-day exposure of humans to not just one EDC but a dynamic mixture of EDCs across a lifetime, often with EDCs working synergistically or antagonistically to result in physiological effects. Hence, simply measuring only one EDC at a time, with respect to a physiological endpoint measure, is a very narrow view and likely may explain some of the conflicting findings reported. Linked to this is the complication in obtaining experimental evidence for the direct and indirect physiological interactions between different EDCs across numerous endocrine systems in vivo, let alone the sheer difficulty of performing such analyses. Therefore arguably, the effects reviewed herein may only be the tip of the iceberg.

In addition to the specific limitations highlighted above, the EDC field as a whole has major limitations. Despite the suspected role of environmental toxicants in various human reproductive disorders and diseases, there are obviously no randomised control trials investigating their direct effects. Equally, relatively few systematic reviews and meta-analyses exist, therefore studies in humans instead often comprise large-scale accidental or occupational exposures, or alternatively cross-sectional epidemiological studies.

Available research is therefore open to confounding issues including unknown levels and duration of exposure, measurement relative to time of exposure, selection of study populations with abnormally high exposure levels, and variation in the sex, metabolism, age, health and fertility status of subjects. Stage-specific sensitivities at discrete stages of germ cell development are also likely to manifest differently and contribute to conflicting literature. In contrast, a relatively large number of animal studies exist, although exposure levels are often much higher than occur in human populations, and species-specific differences, especially in terms of sensitivity at specific developmental stages, raises questions about whether results are directly relevant to humans [4]. Far more research is thus required to establish their effects on reproductive function, particularly during the peri-conceptional period.

4.2 Challenges and clinical recommendations

Currently, it remains unclear whether exposure to EDCs and toxicants results in one, some or all of the following; an increase in sub-fertility and infertility, accentuation of underlying fertility issues, and/or whether sub-fertile individuals are more susceptible to, or unable to detoxify, these chemicals as efficiently from their bodies, which likely depend greatly on the individual, their genetics, and the presence of other existing pathologies. For individuals or couples receiving fertility treatment, particularly those diagnosed with idiopathic infertility, promoting lifestyle awareness and modification principles, as outlined above, represents an easy intervention for probable short-term gains in fertility and fecundity. It is therefore recommended that detailed information on their lifestyle, and possible occupational and general exposure to environmental chemicals be obtained. It may also prove informative to analyse blood, urine, reproductive fluids and tissues, as well as non-reproductive tissues (hair and adipose) for current and cumulative environmental

chemical loads. The major challenge therein is to balance the desires of the patient and clinician to understand the reasons behind individual cases of infertility, with the high financial burden associated with making such detailed investigations. The challenge for researchers is to undertake robust studies that are, ideally, executed in a more standardised fashion, allowing for stronger conclusions to be drawn from results that will better inform and guide clinicians in their decision making.

There is a perception by the public and even some scientists and clinicians that EDCs have little to no physiologically relevant effect at low doses. Often purportedly justified by the conflicting findings reported for several well-studied compounds. This contributes to the laissez-faire attitude and the most significant challenge related to their use: establishing minimal criteria to underpin regulation and legislative change. Legislation is highly variable, even for chemicals with demonstrated effects, including BPA, which while banned in many countries for use in specific items, such as baby bottles [52], it is still used in the same countries in other products, or remains as a voluntary phase-out in other countries. Even when certain congeners are removed, i.e. BPA, its replacements (BPS and BPF) are usually less well-studied and likely later found to have similar detriment physiological effects [31; 54; 55]. A lack of not only forethought, but also consistency, in legislating change, along with a paucity of research, contributes to a failure to protect future generations. Failure to establish appropriate tests and for more subtle endpoint measures, such as fertility, using environmentally relevant concentrations remains a significant obstacle to enacting change, with more significant consequences likely to become more apparent in future generations.

Based on the existing evidence outlined in this review, it is recommended that specific EDCs are avoided by all individuals, in particular couples trying to conceive, and by families with children. These include BPA, phthalates and pesticides, such as specific organochlorides, that have clear negative impacts on fertility and fecundity. In men, exposure to pyrethroids should also be avoided as these appear to show effects on semen quality, and while insufficient data in women has been generated, it is logical that a similar avoidance is suggested to women seeking to become pregnant. While conflicting data exists for other EDCs, the balance of evidence suggests that general avoidance principles should be practiced by all individuals until definitive data emerges. While the evidence is limited, reduced exposure may be beneficial not only in terms of improving fertility and fecundity but is also likely to benefit an individual's general health. This recommendation aligns with those of the United Nations & World Health Organization [4], the Endocrine Society [2], International Federation of Gynecology and Obstetrics [397], American College of Obstetricians and Gynaecologists [398], Royal College of Obstetricians & Gynaecologists [399], and the American Academy of Paediatrics [400], amongst a growing number of other professional organisations, societies and entities.

Clinical advice as to the lifestyle choices and management strategies that may help lower exposures to EDCs and improve fertility and fecundity success rates include: 1) avoid drinking out of, or heating food in, soft plastic containers, 2) limiting consumption of processed, pre-canned, and pre-packaged foods, 3) washing fresh produce prior to consumption, 4) limiting the consumption of fatty or oily fish, beyond amounts sufficient to reap the benefits, 5) reducing the use of EDC-laden personal care products (e.g. make-up, shampoos, hair colourings) or avoid those with high concentrations of EDCs, 6) avoid handling receipts (coated in BPA), exposure to strong solvent-based chemicals (paints,

cleaning products, glues) and industrial processing chemicals, and 7) frequently ventilate homes and offices to remove airborne particles from furniture and fittings.

Worryingly, population-based change to EDC exposure is limited by several major factors. The fact that many of our modern conveniences rely heavily on the use of such chemicals, and that the influence of chemical exposure can be a generation in front of observed consequences. Utilising these chemicals in production and manufacturing is heavily driven by consumer demand and commercial profits, something that is difficult to counter without government oversight combined with public awareness campaigns. For example, forcing producers and manufacturers to supply alternatives to EDCs may make little difference where consumers are ill-informed as to the source, type and logistics of EDC exposure. Equally, the replacement of EDCs with analogues (e.g. BPA replaced with BPS and BPF) does not necessarily mean these are safe alternatives, given their structural similarity, though advertising may give this impression. Thus, it is likely that government intervention will be required firstly, to enforce broad adherence to the replacement of EDCs with safe alternatives, due to the potential cost implications of changing current chemicals for the manufacturing industries. Secondly, to improve social awareness through government and medical practitioner campaigns. Thirdly, to focus more funds, research and resources on filling knowledge gaps in determining the effects of EDC exposure, while addressing the needs of agriculture and manufacturing industries in identifying and testing cost-effective alternative safe processes and products. Collectively, these represent substantial future challenges of how to effectively tackle EDC and toxicant usage and their associated effects on human health, including reproduction. Governments, regulators and legislators must balance the business needs of producers with the evolving stance of medical researchers around the impact of specific EDCs on human health.

5. CONCLUSIONS

The increasing issue of exposure to EDCs and environmental toxicants resulting in a negative effect on human fertility and fecundity is arguably the major reproductive health concern of our time. Following an extensive review of the current literature substantial evidence exists to support a negative association between adult male fertility and fecundity and exposure to BPA, phthalates, PCBs, PBDEs, pyrethroids, DDE, as well as other organochloride pesticides. Whilst only moderate evidence exists of a negative association between adult female fertility and fecundity and exposure to BPA, PCBs and organochloride pesticides. The difference in the quantity of evidence between sexes is likely explained by relatively few studies on women compared with men, presumably partially due to the difficulty in accessing and studying female gametes. In addition to identifying fewer studies in women and knowledge gaps being evident generally for both sexes for all the major EDC classes, there exists a paucity of female fertility studies following exposure to parabens, triclosans, dioxins, PFAS, organophosphates and pyrethroids. Irrespective of the concerning population-wide increase in EDC exposure, sub-fertile individuals or couples commonly exhibited higher EDC and toxicant concentrations in their urine, blood and reproductive tract. Thus, a causal association between exposure to EDCs and sub-fertility is probable. Notably, this review was also able to ascertain common methodological issues, confounding and limiting factors that certainly hamper the ability to determine more than just an association between EDC exposure and sub-fertility and reduced fecundity. Finally, this review highlighted critical focus areas for future research, government regulation and social awareness campaigns to mitigate the

negative effects of EDC and environmental toxicant exposure on human fertility and fecundity.

6. DECLARATION OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

7. AUTHOR CONTRIBUTIONS

All authors undertook the searching of the literature. MPG, GAT and AJH drafted the manuscript. GAT prepared the tables. All authors contributed to the final manuscript version and approved it for submission.

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9. REFERENCES

[1] The Endocrine Exchange, List of potential endocrine disruptors, TEDX, Eckert, Co. U.S.A. (2020) https://endocrinedisuption.org Accessed 2nd October 2020.

[2] A.C. Gore, V.A. Chappell, S.E. Fenton, J.A. Flaws, A. Nadal, G.S. Prins, J. Toppari, and R.T. Zoeller, EDC-2: The Endocrine Society's second scientific statement on Endocrine-Disrupting Chemicals. Endocrine Reviews 36 (2015) E1-E150.

[3] C.V. Sartain, and P.A. Hunt, An old culprit but a new story: bisphenol A and ''NextGen'' bisphenols. Fertility and Sterility 106 (2016) 820-826.

[4] United Nations Environmental Programme & World Heath Organization, State of the science of endocrine disrupting chemicals- 2012. In: A. Bergman, J.J. Heindel, S. Jobling, K.A. Kidd, and R.T. Zoeller, (Eds.), United Nations Environmental Programme & World Health Organization, Geneva, Switzerland, (2013), pp. 1-289.

[5] L.N. Vandenberg, T. Colborn, T.B. Hayes, J.J. Heindel, D.R. Jacobs, Jr., D.-H. Lee, T. Shioda, A.M. Soto, F.S. vom Saal, W.V. Welshons, R.T. Zoeller, and J.P. Myers, Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses. Endocrine Reviews 33 (2012) 378-455.

[6] L. Strauss, R. Santti, N. Saarinen, T. Streng, S. Joshi, and S. Makela, Dietary phytoestrogens and their role in hormonally dependent disease. Toxicology Letters 102-103 (1998) 349-354.

[7] W. Mazur, and H. Adlercreutz, Overview of naturally occurring endocrine-active substances in the human diet in relation to human health. Nutrition 16 (2000) 654-658.

[8] O.K. Chun, S.J. Chung, and W.O. Song, Urinary isoflavones and their metabolites validate the dietary isoflavone intakes in US adults. Journal of the American Dietetic Association 109 (2009) 245-254.

[9] C.R. Cederroth, C. Zimmermann, and S. Nef, Soy, phytoestrogens and their impact on reproductive health. Molecualr and Cellular Endocrinology 355 (2012) 192-200.

[10] W.N. Jefferson, H.B. Patisaul, and C.J. Williams, Reproductive consequences of developmental phytoestrogen exposure. Reproduction 143 (2012) 247-60.

[11] J.E. Chavarro, T.L. Toth, S.M. Sadio, and R. Hauser, Soy food and isoflavone intake in relation to semen quality parameters among men from an infertility clinic. Human Reproduction 23 (2008) 2584-2590.

[12] L. Hooper, J.J. Ryder, M.S. Kurzer, J.W. Lampe, M.J. Messina, W.R. Phipps, and A. Cassidy, Effects of soy protein and isoflavones on circulating hormone concentrations in pre- and post-menopausal women: a systematic review and meta-analysis. Human Reproduction Update 15 (2009) 423-440.

[13] A. Giwercman, Estrogens and phytoestrogens in male infertility. Current Opinion in Urology 21 (2011) 519-526.

[14] S.L. Mumford, S. Kim, Z. Chen, D.B. Barr, and G.M.B. Louis, Urinary phytoestrogens are associated with subtle indicators of semen quality among male partners of couples desiring pregnancy. Journal of Nutrition 145 (2015) 2535-2541.

[15] J.C. Vanegas, M.C. Afeiche, A.J. Gaskins, L. Minguez-Alarcon, P.L. Williams, D.L. Wright, T.L. Toth, R. Hauser, and J.E. Chavarro, Soy food intake and treatment outcomes of women undergoing assisted reproductive technology. Fertility and Sterility 103 (2015) 749-U467.

[16] J.E. Chavarro, L. Minguez-Alarcon, Y.H. Chiu, A.J. Gaskins, I. Souter, P.L. Williams, A.M. Calafat, R. Hauser, and E.S. Team, Soy intake modifies the relation between urinary bisphenol A concentrations and pregnancy outcomes among women undergoing assisted reproduction. Journal of Clinical Endocrinology & Metabolism 101 (2016) 1082-1090.

[17] L. Minguez-Alarcon, M.C. Afeiche, Y.H. Chiu, J.C. Vanegas, P.L. Williams, C. Tanrikut, T.L. Toth, R. Hauser, and J.E. Chavarro, Male soy food intake was not associated with invitro fertilization outcomes among couples attending a fertility center. Andrology 3 (2015) 702-708.

[18] J.H. Mitchell, E. Cawood, D. Kinniburgh, A. Provan, A.R. Collins, and D.S. Irvine, Effect of a phytoestrogen food supplement on reproductive health in normal males. Clinical Science 100 (2001) 613-618.

[19] S.L. Mumford, R. Sundaram, E.F. Schisterman, A.M. Sweeney, D.B. Barr, M.E. Rybak, J.M. Maisog, D.L. Parker, C.M. Pfeiffer, and G.M.B. Louis, Higher urinary lignan concentrations in women but not men are positively associated with shorter time to pregnancy. Journal of Nutrition 144 (2014) 352-358.

[20] R. Meena, C. Supriya, K. Pratap Reddy, and P. Sreenivasula Reddy, Altered spermatogenesis, steroidogenesis and suppressed fertility in adult male rats exposed to genistein, a non-steroidal phytoestrogen during embryonic development. Food and Chemical Toxicology 99 (2017) 70-77.

[21] D. Saiti, and O. Lacham-Kaplan, Mouse germ cell development in-vivo and in-vitro. Biomarker Insights 2 (2007) 241-252.

[22] G. Eumkeb, S. Tanphonkrang, K. Sirichaiwetchakoon, T. Hengpratom, and W. Naknarong, The synergy effect of daidzein and genistein isolated from Butea superbaRoxb. on the reproductive system of male mice. Natural Product Research 31 (2017) 672-675.

[23] A. Moteetee, and L. Seleteng Kose, Medicinal plants used in Lesotho for treatment of reproductive and post reproductive problems. Journal of Ethnopharmacology 194 (2016) 827-849.

[24] M.A. Mvondo, A.J.T. Sakock, S.B. Ateba, C.F. Awounfack, T.N. Gueyo, and D. Njamen, Emmenagogue properties of Milicia excelsa (Welw.) CC Berg (Moraceae) based, at least in part, on its ability to correlate the activity of.the hypothalamic-pituitary axis to that of the ovaries. Journal of Ethnopharmacology 206 (2017) 283-289.

[25] F. Bina, S. Soleymani, T. Toliat, M. Hajimahmoodi, M. Tabarrai, M. Abdollahi, and R. Rahimi, Plant-derived medicines for treatment of endometriosis_ A comprehensive review of molecular mechanisms. Pharmacological Research 139 (2018) 76-90.

[26] H.W. Bennetts, and E.J. Underwood, The oestrogenic effects of subterranean clover (trifolium subterraneum); uterine maintenance in the ovariectomised ewe on clover grazing. Australian Journal of Experimental Biology and Medical Science 29 (1951) 249-253.

[27] K.D. Setchell, S.J. Gosselin, M.B. Welsh, J.O. Johnston, W.F. Balistreri, L.W. Kramer, B.L. Dresser, and M.J. Tarr, Dietary estrogens: a probable cause of infertility and liver disease in captive cheetahs. Gastroenterology 93 (1987) 225-233.

[28] M.S. Bloom, E. Mok-Lin, and V.Y. Fujimoto, Bisphenol A and ovarian steroidogenesis. Fertility and Sterility 106 (2016) 857-863.

[29] H.L. Ji, M.H. Miao, H. Liang, H.J. Shi, D.S. Ruan, Y.B. Li, J. Wang, and W. Yuan, Exposure of environmental Bisphenol A in relation to routine sperm parameters and sperm movement characteristics among fertile men. Scientific Reports 8 (2018) 17548.

[30] M. Radwan, B. Wielgomas, E. Dziewirska, P. Radwan, P. Kałużny, A. Klimowska, W. Hanke, and J. Jurewicz, Urinary Bisphenol A levels and male fertility. American Journal of Men's Health 12 (2018) 2144-2151.

[31] Y.X. Wang, C. Liu, Y. Shen, Q. Wang, A. Pan, P. Yang, Y.J. Chen, Y.L. Deng, Q. Lu, L.M. Cheng, X.P. Miao, S.Q. Xu, W.Q. Lu, and Q. Zeng, Urinary levels of bisphenol A, F and S and markers of oxidative stress among healthy adult men: Variability and association analysis. Environment International 123 (2019) 301-309.

[32] B. Liu, H.J. Lehmler, Y. Sun, G. Xu, Q. Sun, L.G. Snetselaar, R.B. Wallace, and W. Bao, Association of bisphenol A and its substitutes, bisphenol F and bisphenol S, with obesity in United States children and adolescents. Diabetes & Metabolism Journal 43 (2019) 59-75.

[33] C. Yang, H.K. Lee, A.P.S. Kong, L.L. Lim, Z. Cai, and A.C.K. Chung, Early-life exposure to endocrine disrupting chemicals associates with childhood obesity. Annals of Pediatric Endocrinology & Metabolism 23 (2018) 182-195.

[34] L. Minguez-Alarcon, R. Hauser, and A.J. Gaskins, Effects of bisphenol A on male and couple reproductive health: a review. Fertility and Sterility 106 (2016) 864-870.
[35] J. Peretz, L. Vrooman, W.A. Ricke, P.A. Hunt, S. Ehrlich, R. Hauser, V. Padmanabhan, H.S. Taylor, S.H. Swan, C.A. VandeVoort, and J.A. Flaws, Bisphenol A and reproductive health: Update of experimental and human evidence, 2007-2013. Environmental Health Perspectives 122 (2014) 775-786.
[36] J. Mendiola, N. Jorgensen, A.-M. Andersson, A.M. Calafat, X. Ye, J.B. Redmon, E.Z. Drobnis, C. Wang, A. Sparks, S.W. Thurston, F. Liu, and S.H. Swan, Are environmental levels of Bisphenol A associated with reproductive function in fertile men? Environmental Health Perspectives 118 (2010) 1286-1291.
[37] E. Den Hond, H. Tournaye, P. De Sutter, W. Ombelet, W. Baeyens, A. Covaci, B. Cox, T.S. Nawrot, N. Van Larebeke, and T. D'Hooghe, Human exposure to endocrine disrupting chemicals and fertility: A case–control study in male subfertility patients. Environment International 84 (2015) 154-160.
[38] D. Li, Z. Zhou, D. Qing, Y. He, T. Wu, M. Miao, J. Wang, X. Weng, J.R. Ferber, L.J. Herrinton, Q. Zhu, E. Gao, H. Checkoway, and W. Yuan, Occupational exposure to bisphenol-A (BPA) and the risk of self-reported male sexual dysfunction. Human Reproduction 25 (2010) 519-527.
[39] D.-K. Li, Z. Zhou, M. Miao, Y. He, D. Qing, T. Wu, J. Wang, X. Weng, J. Ferber, L.J. Herrinton, Q. Zhu, E. Gao, and W. Yuan, Relationship between urine bisphenol-A level and declining male sexual function. Journal of Andrology 31 (2010) 500-506.
[40] D.-K. Li, Z. Zhou, M. Miao, Y. He, J. Wang, J. Ferber, L.J. Herrinton, E. Gao, and W. Yuan, Urine bisphenol-A (BPA) level in relation to semen quality. Fertility and Sterility 95 (2011) 625-U616.
[41] E. Adoamnei, J. Mendiola, F. Vela-Soria, M.F. Fernández, N. Olea, N. Jørgensen, S.H. Swan, and A.M. Torres-Cantero, Urinary bisphenol A concentrations are associated with reproductive parameters in young men. Environmental Research 161 (2018) 122-128.
[42] G.A. Omran, H.D. Gaber, N.A.M. Mostafa, R.M. Abdel-Gaber, and E.A. Salah, Potential hazards of bisphenol A exposure to semen quality and sperm DNA integrity among infertile men. Reproductive Toxicology 81 (2018) 188-195.
[43] J. Vitku, J. Heracek, L. Sosvorova, R. Hampl, T. Chlupacova, M. Hill, V. Sobotka, M. Bicikova, and L. Starka, Associations of bisphenol A and polychlorinated biphenyls with spermatogenesis and steroidogenesis in two biological fluids from men attending an infertility clinic. Environment International 89-90 (2016) 166-173.
[44] W. Hu, T. Dong, L. Wang, Q. Guan, L. Song, D. Chen, Z. Zhou, M. Chen, Y. Xia, and X. Wang, Obesity aggravates toxic effect of BPA on spermatogenesis. Environment International 105 (2017) 56-65.
[45] A.M. Martinez, A. Cheong, J. Ying, J. Xue, K. Kannan, Y.-K. Leung, M.A. Thomas, and S.-M. Ho, Effects of high-butterfat diet on embryo implantation in female rats exposed to Bisphenol A. Biology of Reproduction 93 (2015) 147.
[46] P. Tarapore, M. Hennessy, D. Song, J. Ying, B. Ouyang, V. Govindarajah, Y.-K. Leung, and S.-M. Ho, High butter-fat diet and bisphenol A additively impair male rat spermatogenesis. Reproductive Toxicology 68 (2017) 191-199.
[47] G.M.B. Louis, D.B. Barr, K. Kannan, Z. Chen, S. Kim, and R. Sundaram, Paternal exposures to environmental chemicals and time-to-pregnancy: overview of results from the LIFE study. Andrology 4 (2016) 639-647.
[48] M.S. Bloom, F.S.v. Saal, D. Kim, J.A. Taylor, J.D. Lamb, and V.Y. Fujimoto, Serum unconjugated bisphenol A concentrations in men may influence embryo quality indicators during in vitro fertilization. Environmental Toxicology and Pharmacology 32 (2011) 319-323.
[49] G. Ding, C. Wang, A. Vinturache, S. Zhao, R. Pan, W. Han, L. Chen, W. Wang, T. Yuan, Y. Gao, and Y. Tian, Prenatal low-level phenol exposures and birth outcomes in China. Science of the Total Environment 607-608 (2017) 1400-1407.

[50] H.K. Kim, D.H. Ko, W. Lee, K.R. Kim, S. Chun, J. Song, and W.K. Min, Body fluid concentrations of bisphenol A and their association with in vitro fertilization outcomes. Human Fertility in press (2020).
[51] R.J. Hart, D.A. Doherty, J.A. Keelan, N.S. Minaee, E.B. Thorstensen, J.E. Dickinson, C.E. Pennell, J.P. Newnham, R. McLachlan, R.J. Norman, and D.J. Handelsman, The impact of antenatal Bisphenol A exposure on male reproductive function at 20–22 years of age. Reproductive BioMedicine Online 36 (2018) 340-347.
[52] T.F. Register, Indirect food additives: adhesives and components of coatings. in: F.a.D. Administration, (Ed.), Docket No. FDA-2012-F-0728, Food and Drug Administration, Washington D.C., U.S.A., 2013, pp. 41840-41843.
[53] A. Usman, and M. Ahmad, From BPA to its analogues: Is it a safe journey? Chemosphere 158 (2016) 131-142.
[54] S. Eladak, T. Grisin, D. Moison, M. Guerquin, T. N'Tumba-Byn, S. Pozzi-Gaudin, A. Benachi, G. Livera, V. Rouiller-Fabre, and R. Habert, A new chapter in the bisphenol A story: bisphenol S and bisphenol F are not safe alternatives to this compound. Fertility and Sterility 103 (2015) 11-21.
[55] M. Verbanck, M. Canouil, A. Leloire, V. Dhennin, X. Coumoul, L. Yengo, P. Froguel, and O. Poulain-Godefroy, Low-dose exposure to bisphenols A, F and S of human primary adipocyte impacts coding and non-coding RNA profiles. PLoS One 12 (2017) e0179583.
[56] A. Ullah, M. Pirzada, S. Jahan, H. Ullah, G. Shaheen, H. Rehman, M.F. Siddiqui, and M.A. Butt, Bisphenol A and its analogs bisphenol B, bisphenol F, and bisphenol S: Comparative in vitro and in vivo studies on the sperms and testicular tissues of rats. Chemosphere 209 (2018) 508-516.
[57] R.A. Ghayda, P.L. Williams, J.E. Chavarro, J.B. Ford, I. Souter, A.M. Calafat, R. Hauser, and L. Minguez-Alarcon, Urinary bisphenol S concentrations: Potential predictors of and associations with semen quality parameters among men attending a fertility center. Environment International 131 (2019) 105050.
[58] D. Caserta, N. Di Segni, M. Mallozzi, V. Giovanale, A. Mantovani, R. Marci, and M. Moscarini, Bisphenol A and the female reproductive tract: an overview of recent laboratory evidence and epidemiological studies. Reproductive Biology and Endocrinology 12 (2014) 37.
[59] A. Ziv-Gal, and J.A. Flaws, Evidence for bisphenol A-induced female infertility: a review (2007-2016). Fertility and Sterility 106 (2016) 827-856.
[60] M.S. Bloom, D. Kim, F.S. vom Saal, J.A. Taylor, G. Cheng, J.D. Lamb, and V.Y. Fujimoto, Bisphenol A exposure reduces the estradiol response to gonadotropin stimulation during in vitro fertilization. Fertility and Sterility 96 (2011) 672-699.
[61] E. Mok-Lin, S. Ehrlich, P.L. Williams, J. Petrozza, D.L. Wright, A.M. Calafat, X. Ye, and R. Hauser, Urinary bisphenol A concentrations and ovarian response among women undergoing IVF. Internatinal Journal of Andrology 33 (2010) 385-393.
[62] T. Galloway, R. Cipelli, J. Guralnik, L. Ferrucci, S. Bandinelli, A.M. Corsi, C. Money, P. McCormack, and D. Melzer, Daily bisphenol A excretion and associations with sex hormone concentrations: Results from the InCHIANTI adult population study. Environmental Health Perspectives 118 (2010) 1603-1608.
[63] V.Y. Fujimoto, D. Kim, F.S. vom Saal, J.D. Lamb, J.A. Taylor, and M.S. Bloom, Serum unconjugated bisphenol A concentrations in women may adversely influence oocyte quality during in vitro fertilization. Fertility and Sterility 95 (2011) 1816-1819.
[64] J. Shen, Q. Kang, Y. Mao, M. Yuan, F. Le, X. Yang, X.P. Xu, and F. Jin, Urinary bisphenol A concentration is correlated with poorer oocyte retrieval and embryo implantation outcomes in patients with tubal factor infertility undergoing in vitro fertilisation. Ecotoxicology and Environmental Safety 187 (2020) 109816.

[65] S. Ehrlich, P.L. Williams, S.A. Missmer, J.A. Flaws, X. Ye, A.M. Calafat, J.C. Petrozza, D. Wright, and R. Hauser, Urinary Bisphenol A concentrations and early reproductive health outcomes among women undergoing IVF. Human Reproduction 27 (2012) 3583-92.

[66] S. Ehrlich, P.L. Williams, S.A. Missmer, J.A. Flaws, K.F. Berry, A.M. Calafat, X. Ye, J.C. Petrozza, D. Wright, and R. Hauser, Urinary Bisphenol A concentrations and implantation failure among women undergoing in vitro fertilization. Environmental Health Perspectives 120 (2012) 978-983.

[67] R.B. Lathi, C.A. Liebert, K.F. Brookfield, J.A. Taylor, F.S. vom Saal, V.Y. Fujimoto, and V.L. Baker, Conjugated Bisphenol A in maternal serum in relation to miscarriage risk. Fertility and Sterility 102 (2014) 123-128.

[68] M. Sugiura-Ogasawara, Y. Ozaki, S.I. Sonta, T. Makino, and K. Suzumori, Exposure to bisphenol A is associated with recurrent miscarriage. Human Reproduction 20 (2005) 2325-2329.

[69] G.M. Buck Louis, R. Sundaram, A.M. Sweeney, E.F. Schisterman, J. Maisog, and K. Kannan, Urinary bisphenol A, phthalates, and couple fecundity: the Longitudinal Investigation of Fertility and the Environment (LIFE) Study. Fertility and Sterility 101 (2014) 1359-66.

[70] M.P. Velez, T.E. Arbuckle, and W.D. Fraser, Female exposure to phenols and phthalates and time to pregnancy: the Maternal-Infant Research on Environmental Chemicals (MIREC) Study. Fertility and Sterility 103 (2015) 1011-U210.

[71] L. Birks, M. Casas, A.M. Garcia, J. Alexander, H. Barros, A. Bergström, J.P. Bonde, A. Burdorf, N. Costet, A. Danileviciute, M. Eggesbø, M.F. Fernández, M.C. González-Galarzo, R. Gražulevičienė, W. Hanke, V. Jaddoe, M. Kogevinas, I. Kull, A. Lertxundi, V. Melaki, A.M.N. Andersen, N. Olea, K. Polanska, F. Rusconi, L. Santa-Marina, A.C. Santos, T. Vrijkotte, D. Zugna, M. Nieuwenhuijsen, S. Cordier, and M. Vrijheid, Occupational exposure to endocrine-disrupting chemicals and birth weight and length of gestation: A European meta-analysis. Environmental Health Perspectives 124 (2016) 1785-1793.

[72] G.L. Zhang, X.F. Zhang, Y.M. Feng, L. Li, E. Huynh, X.F. Sun, Z.Y. Sun, and W. Shen, Exposure to Bisphenol A results in a decline in mouse spermatogenesis. Reproduction, fertility, and development 25 (2012) 847-859.

[73] K.A. Campen, K.M. Kucharczyk, B. Bogin, J.M. Ehrlich, and C.M.H. Combelles, Spindle abnormalities and chromosome misalignment in bovine oocytes after exposure to low doses of bisphenol A or bisphenol S. Human Reproduction 33 (2018) 895-904.

[74] B.I. Choi, A.J. Harvey, and M.P. Green, Bisphenol A affects early bovine embryo development and metabolism that is negated by an oestrogen receptor inhibitor. Scientific Reports 6 (2016) 1-11.

[75] X. Li, Y. Wang, P. Wei, D. Shi, S. Wen, F. Wu, L. Liu, N. Ye, and H. Zhou, Bisphenol A affects trophoblast invasion by inhibiting CXCL8 expression in decidual stromal cells. Molecular and Cellular Endocrinology 470 (2018) 38-47.

[76] M. Yuan, M. Hu, Y. Lou, Q. Wang, L. Mao, Q. Zhan, and F. Jin, Environmentally relevant levels of bisphenol A affect uterine decidualization and embryo implantation through the estrogen receptor/serum and glucocorticoid-regulated kinase 1/epithelial sodium ion channel α-subunit pathway in a mouse model. Fertility and Sterility 109 (2018) 735-744.e1.

[77] A. Ziv-Gal, W. Wang, C. Zhou, and J.A. Flaws, The effects of in utero bisphenol A exposure on reproductive capacity in several generations of mice. Toxicology and Applied Pharmacology 284 (2015) 354-362.

[78] N. Pant, A.B. Pant, M. Shukla, N. Mathur, Y.K. Gupta, and D.K. Saxena, Environmental and experimental exposure of phthalate esters: The toxicological consequence on human sperm. Human & Experimental Toxicology 30 (2011) 507-514.

[79] Y. Guo, and K. Kannan, A survey of phthalates and parabens in personal care products from the United States and its implications for human exposure. Environmental Science & Technology 47 (2013) 14442-14449.

[80] M. Wittassek, G.A. Wiesmuller, H.M. Koch, R. Eckard, L. Dobler, J. Muller, J. Angerer, and C. Schluter, Internal phthalate exposure over the last two decades - A retrospective human biomonitoring study. International Journal of Hygiene and Environmental Health 210 (2007) 319-333.

[81] M.J. Silva, D.B. Barr, J.A. Reidy, N.A. Malek, C.C. Hodge, S.P. Caudill, J.W. Brock, L.L. Needham, and A.M. Calafat, Urinary levels of seven phthalate metabolites in the US population from the National Health and Nutrition Examination Survey (NHANES) 1999-2000. Environmental Health Perspectives 112 (2004) 331-338.

[82] I. Katsikantami, M.N. Tzatzarakis, A.K. Alegakis, V. Karzi, E. Hatzidaki, A. Stavroulaki, E. Vakonaki, P. Xezonaki, S. Sifakis, A.K. Rizos, and A. Tsatsakis, Phthalate metabolites concentrations in amniotic fluid and maternal urine: Cumulative exposure and risk assessment. Toxicological Reports 7 (2020) 529-538.

[83] A.J. Martino-Andrade, and I. Chahoud, Reproductive toxicity of phthalate esters. Molecular Nutrition & Food Research 54 (2010) 148-157.

[84] J.P. Bonde, E.M. Flachs, S. Rimborg, C.H. Glazer, A. Giwercman, C.H. Ramlau-Hansen, K.S. Hougaard, B.B. Høyer, K.K. Hærvig, S.B. Petersen, L. Rylander, I.O. Specht, G. Toft, and E.V. Bräuner, The epidemiologic evidence linking prenatal and postnatal exposure to endocrine disrupting chemicals with male reproductive disorders: a systematic review and meta-analysis. Human Reproduction Update 23 (2016) 104-125.

[85] U.N. Joensen, H. Frederiksen, M.B. Jensen, M.P. Lauritsen, I.A. Olesen, T.H. Lassen, A.-M. Andersson, and N. Jorgensen, Phthalate excretion pattern and testicular function: A study of 881 healthy Danish men. Environmental Health Perspectives 120 (2012) 1397-1403.

[86] J.D. Meeker, A.M. Calafat, and R. Hauser, Urinary metabolites of di(2-ethylhexyl) phthalate are associated with decreased steroid hormone levels in adult men. Journal of Andrology 30 (2009) 287-297.

[87] J.D. Meeker, and K.K. Ferguson, Urinary phthalate metabolites are associated with decreased serum testosterone in men, women, and children from NHANES 2011-2012. Journal of Clinical Endocrinology & Metabolism 99 (2014) 4346-4352.

[88] J. Mendiola, J.D. Meeker, N. Jorgensen, A.-M. Andersson, F. Liu, A.M. Calafat, J.B. Redmon, E.Z. Drobnis, A.E. Sparks, C. Wang, R. Hauser, and S.H. Swan, Urinary concentrations of di(2-ethylhexyl) phthalate metabolites and serum reproductive hormones: pooled analysis of fertile and infertile men. Journal of Andrology 33 (2012) 488-498.

[89] G. Pan, T. Hanaoka, M. Yoshimura, S. Zhang, P. Wang, H. Tsukino, K. Inoue, H. Nakazawa, S. Tsugane, and K. Takahashi, Decreased serum free testosterone in workers exposed to high levels of di-n-butyl phthalate (DBP) and di-2-ethylhexyl phthalate (DEHP): A cross-sectional study in China. Environmental Health Perspectives 114 (2006) 1643-1648.

[90] I.O. Specht, G. Toft, K.S. Hougaard, C.H. Lindh, V. Lenters, B.A.G. Jonsson, D. Heederik, A. Giwercman, and J.P.E. Bonde, Associations between serum phthalates and biomarkers of reproductive function in 589 adult men. Environment International 66 (2014) 146-156.

[91] Y.X. Wang, Q. Zeng, Y. Sun, L. You, P. Wang, M. Li, P. Yang, J. Li, Z. Huang, C. Wang, S. Li, Y. Dan, Y.F. Li, and W.Q. Lu, Phthalate exposure in association with serum hormone levels, sperm DNA damage and spermatozoa apoptosis: A cross-sectional study in China. Environmental Research 150 (2016) 557-565.

[92] J. Jurewicz, M. Radwan, W. Sobala, D. Ligocka, P. Radwan, M. Bochenek, W. Hawula, L. Jakubowski, and W. Hanke, Human urinary phthalate metabolites level and main semen parameters, sperm chromatin structure, sperm aneuploidy and reproductive hormones. Reproductive Toxicology 42 (2013) 232-241.

[93] J. Mendiola, N. Jorgensen, A.M. Andersson, A.M. Calafat, M.J. Silva, J.B. Redmon, A. Sparks, E.Z. Drobnis, C. Wang, F. Liu, and S.H. Swan, Associations between urinary metabolites of di(2-ethylhexyl) phthalate and reproductive hormones in fertile men. International Journal of Andrology 34 (2011) 369-378.

[94] I. Al-Saleh, S. Coskun, I. Al-Doush, T. Al-Rajudi, M. Abduljabbar, R. Al-Rouqi, H. Palawan, and S. Al-Hassan, The relationships between urinary phthalate metabolites, reproductive hormones and semen parameters in men attending in vitro fertilization clinic. Science of the Total Environment 658 (2019) 982-995.
[95] M.P. Tian, L.P. Liu, J. Zhang, Q.Y. Huang, and H.Q. Shen, Positive association of low-level environmental phthalate exposure with sperm motility was mediated by DNA methylation: A pilot study. Chemosphere 220 (2019) 459-467.
[96] S.M. Duty, M.J. Silva, D.B. Barr, J.W. Brock, L. Ryan, Z.Y. Chen, R.F. Herrick, D.C. Christiani, and R. Hauser, Phthalate exposure and human semen parameters. Epidemiology 14 (2003) 269-277.
[97] S.M. Duty, A.M. Calafat, M.J. Silva, J.W. Brock, L. Ryan, Z.Y. Chen, J. Overstreet, and R. Hauser, The relationship between environmental exposure to phthalates and computer-aided sperm analysis motion parameters. Journal of Andrology 25 (2004) 293-302.
[98] R. Hauser, J.D. Meeker, N.P. Singh, M.J. Silva, L. Ryan, S. Duty, and A.M. Calafat, DNA damage in human sperm is related to urinary levels of phthalate monoester and oxidative metabolites. Human Reproduction 22 (2007) 688-695.
[99] C. Wang, L. Yang, S. Wang, Z. Zhang, Y. Yu, M. Wang, M. Cromie, W. Gao, and S.-L. Wang, The classic EDCs, phthalate esters and organochlorines, in relation to abnormal sperm quality: a systematic review with meta-analysis. Scientific Reports 6 (2016).
[100] R. Hauser, J.D. Meeker, S. Duty, M.J. Silva, and A.M. Calafat, Altered semen quality in relation to urinary concentrations of phthalate monoester and oxidative metabolites. Epidemiology 17 (2006) 682-691.
[101] B.A.G. Jonsson, J. Richthoff, L. Rylander, A. Giwercman, and L. Hagmar, Urinary phthalate metabolites and biomarkers of reproductive function in young men. Epidemiology 16 (2005) 487-493.
[102] J. Axelsson, L. Rylander, A. Rignell-Hydbom, B.A.G. Jönsson, C.H. Lindh, and A. Giwercman, Phthalate exposure and reproductive parameters in young men from the general Swedish population. Environment International 85 (2015) 54-60.
[103] L. Liu, H. Wang, M. Tian, J. Zhang, P. Panuwet, P.E. D'Souza, D.B. Barr, Q. Huang, Y. Xia, and H. Shen, Phthalate metabolites related to infertile biomarkers and infertility in Chinese men. Environmental Pollution 231 (2017) 291-300.
[104] Y. Pan, J. Jing, F. Dong, Q. Yao, W. Zhang, H. Zhang, B. Yao, and J. Dai, Association between phthalate metabolites and biomarkers of reproductive function in 1066 Chinese men of reproductive age. Journal of Hazardous Materials 300 (2015) 729-736.
[105] J.J. Wirth, M.G. Rossano, R. Potter, E. Puscheck, D.C. Daly, N. Paneth, S.A. Krawetz, B.M. Protas, and M.P. Diamond, A pilot study associating urinary concentrations of phthalate metabolites and semen quality. Systems Biology in Reproductive Medicine 54 (2008) 143-154.
[106] L. Liu, H. Bao, F. Liu, J. Zhang, and H. Shen, Phthalates exposure of Chinese reproductive age couples and its effect on male semen quality, a primary study. Environment International 42 (2012) 78-83.
[107] X. Han, Z.H. Cui, N.Y. Zhou, M.F. Ma, L.B. Li, Y.F. Li, H. Lin, L. Ao, W.Q. Shu, J.Y. Liu, and J. Cao, Urinary phthalate metabolites and male reproductive function parameters in Chongqing general population, China. International Journal of Hygiene and Environmental Health 217 (2014) 271-278.
[108] Y.X. Wang, L. You, Q. Zeng, Y. Sun, Y.H. Huang, C. Wang, P. Wang, W.C. Cao, P. Yang, Y.F. Li, and W.Q. Lu, Phthalate exposure and human semen quality: Results from an infertility clinic in China. Environmental Research 142 (2015) 1-9.
[109] M.S. Bloom, B.W. Whitcomb, Z. Chen, A. Ye, K. Kannan, and G.M. Buck Louis, Associations between urinary phthalate concentrations and semen quality parameters in a general population. Human Reproduction 30 (2015) 2645-2657.

[110] W.-H. Chang, M.-H. Wu, H.-A. Pan, P.-L. Guo, and C.-C. Lee, Semen quality and insulin-like factor 3: Associations with urinary and seminal levels of phthalate metabolites in adult males. Chemosphere 173 (2017) 594-602.
[111] A. Broe, A. Pottegard, J. Hallas, T.P. Ahern, J. Fedder, and P. Damkier, Association between use of phthalate-containing medication and semen quality among men in couples referred for assisted reproduction. Human Reproduction 33 (2018) 503-511.
[112] M.M. Smarr, K. Kannan, L.P. Sun, M. Honda, W. Wang, R. Karthikraj, Z. Chen, J. Weck, and G.M.B. Louis, Preconception seminal plasma concentrations of endocrine disrupting chemicals in relation to semen quality parameters among male partners planning for pregnancy. Environmental Research 167 (2018) 78-86.
[113] D. Zamkowska, A. Karwacka, J. Jurewicz, and M. Radwan, Environmental exposure to non-persistent endocrine disrupting chemicals and semen quality: an overview of the currrent epidemiological evidence. International Journal of Occupational Medicine and Environmental Health 31 (2018) 377-414.
[114] Y.X. Wang, Q. Zeng, Y. Sun, P. Yang, P. Wang, J. Li, Z. Huang, L. You, Y.H. Huang, C. Wang, Y.F. Li, and W.Q. Lu, Semen phthalate metabolites, semen quality parameters and serum reproductive hormones: A cross-sectional study in China. Environmental Pollution 211 (2016) 173-182.
[115] R.J. Hart, H. Frederiksen, D.A. Doherty, J.A. Keelan, N.E. Skakkebaek, N.S. Minaee, R. McLachlan, J.P. Newnham, J.E. Dickinson, C.E. Pennell, R.J. Norman, and K.M. Main, The possible impact of antenatal exposure to ubiquitous phthalates upon male reproductive function at 20 years of age. Frontiers in Endocrinology 9 (2018) 288.
[116] M.P. Tian, L.P. Liu, H. Wang, X.F. Wang, F.L. Martin, J. Zhang, Q.Y. Huang, and H.Q. Shen, Phthalates induce androgenic effects at exposure levels that can be environmentally relevant in humans. Environmental Science & Technology Letters 5 (2018) 232-236.
[117] H.T. Wu, L. Ashcraft, B.W. Whitcomb, T. Rahil, E. Tougias, C.K. Sites, and J.R. Pilsner, Parental contributions to early embryo development: influences of urinary phthalate and phthalate alternatives among couples undergoing IVF treatment. Human Reproduction 32 (2017) 65-75.
[118] C. Herr, A. zur Nieden, H.M. Koch, H.-C. Schuppe, C. Fieber, J. Angerer, T. Eikmann, and N.I. Stilianakis, Urinary di(2-ethylhexyl)phthalate (DEHP)-metabolites and male human markers of reproductive function. International Journal of Hygiene and Environmental Health 212 (2009) 648-653.
[119] S.W. Thurston, J. Mendiola, A.R. Bellamy, H. Levine, C. Wang, A. Sparks, J.B. Redmon, E.Z. Drobnis, and S.H. Swan, Phthalate exposure and semen quality in fertile US men. Andrology 4 (2016) 632-8.
[120] O. Albert, J.Y. Huang, K. Aleksa, B.F. Hales, C.G. Goodyer, B. Robaire, J. Chevrier, and P. Chan, Exposure to polybrominated diphenyl ethers and phthalates in healthy men living in the greater Montreal area: A study of hormonal balance and semen quality. Environment International 116 (2018) 165-175.
[121] L.E. Dodge, P.L. Williams, M.A. Williams, S.A. Missmer, I. Souter, A.M. Calafat, R. Hauser, and E.S. Team, Associations between paternal urinary phthalate metabolite concentrations and reproductive outcomes among couples seeking fertility treatment. Reproductive Toxicology 58 (2015) 184-193.
[122] A.E. Hipwell, L.G. Kahn, P. Factor-Litvak, C.A. Porucznik, E.L. Siegel, R.N. Fichorova, R.F. Hamman, M. Klein-Fedyshin, K.G. Harley, and O. program collaborators for Environmental influences on Child Health, Exposure to non-persistent chemicals in consumer products and fecundability: a systematic review. Human Reproduction Update 25 (2019) 51-71.
[123] C. Messerlian, I. Souter, A.J. Gaskins, P.L. Williams, J.B. Ford, Y.-H. Chiu, A.M. Calafat, R. Hauser, and T. Earth Study, Urinary phthalate metabolites and ovarian reserve among women seeking infertility care. Human Reproduction 31 (2016) 75-83.

[124] H. Yi, H. Gu, T. Zhou, Y. Chen, G. Wang, Y. Jin, W. Yuan, H. Zhao, and L. Zhang, A pilot study on association between phthalate exposure and missed miscarriage. European Review for Medical and Pharmacological Sciences 20 (2016) 1894-1902.
[125] R. Hauser, A.J. Gaskins, I. Souter, K.W. Smith, L.E. Dodge, S. Ehrlich, J.D. Meeker, A.M. Calafat, P.L. Williams, and E.S. Team, Urinary phthalate metabolite concentrations and reproductive outcomes among women undergoing in vitro fertilization: results from the EARTH study. Environmental Health Perspectives 124 (2016) 831-839.
[126] R. Machtinger, T. Berman, M. Adir, A. Mansur, A.A. Baccarelli, C. Racowsky, A.M. Calafat, R. Hauser, and R. Nahum, Urinary concentrations of phthalate metabolites, bisphenols and personal care product chemical biomarkers in pregnant women in Israel. Environment International 116 (2018) 319-325.
[127] R. Machtinger, A.J. Gaskins, C. Racowsky, A. Mansur, M. Adir, A.A. Baccarelli, A.M. Calafat, and R. Hauser, Urinary concentrations of biomarkers of phthalates and phthalate alternatives and IVF outcomes. Environment International 111 (2018) 23-31.
[128] Y.Y. Du, Y.L. Fang, Y.X. Wang, Q. Zeng, N. Guo, H. Zhao, and Y.F. Li, Follicular fluid and urinary concentrations of phthalate metabolites among infertile women and associations with in vitro fertilization parameters. Reproductive Toxicology 61 (2016) 142-150.
[129] A.M. Jukic, A.M. Calafat, D.R. McConnaughey, M.P. Longnecker, J.A. Hoppin, C.R. Weinberg, A.J. Wilcox, and D.D. Baird, Urinary concentrations of phthalate metabolites and bisphenol A and associations with follicular-phase length, luteal-phase length, fecundability, and early pregnancy loss. Environmental Health Perspectives 124 (2016) 321-328.
[130] A.M.L. Thomsen, A.H. Riis, J. Olsen, B.A.G. Jönsson, C.H. Lindh, N.H. Hjollund, T.K. Jensen, J.P. Bonde, and G. Toft, Female exposure to phthalates and time to pregnancy: a first pregnancy planner study. Human Reproduction 32 (2017) 232-238.
[131] I.O. Specht, J.P. Bonde, G. Toft, C.H. Lindh, B.A.G. Jonsson, and K.T. Jorgensen, Serum phthalate levels and time to pregnancy in couples from Greenland, Poland and Ukraine. PLoS One 10 (2015) e120070.
[132] L. Minguez-Alarcon, C. Messerlian, A. Bellavia, A.J. Gaskins, Y.H. Chiu, J.B. Ford, A.R. Azevedo, J.C. Petrozza, A.M. Calafat, R. Hauser, P.L. Williams, and T. Earth Study, Urinary concentrations of bisphenol A, parabens and phthalate metabolite mixtures in relation to reproductive success among women undergoing in vitro fertilization. Environment International 126 (2019) 355-362.
[133] T.R. Deng, Y.Y. Du, Y.X. Wang, X.M. Teng, X. Hua, X.Q. Yuan, Y.C. Yao, N. Guo, and Y.F. Li, The associations of urinary phthalate metabolites with the intermediate and pregnancy outcomes of women receiving IVF/ICSI treatments: A prospective single-center study. Ecotoxicology and Environmental Safety 184 (2020) 109295.
[134] H. Wu, L. Ashcraft, B.W. Whitcomb, T. Rahil, E. Tougias, C.K. Sites, and J.R. Pilsner, Parental contributions to early embryo development: influences of urinary phthalate and phthalate alternatives among couples undergoing IVF treatment. Human Reproduction in press (2017).
[135] G. Toft, B.A.G. Jonsson, C.H. Lindh, T.K. Jensen, N.H. Hjollund, A. Vested, and J.P. Bonde, Association between pregnancy loss and urinary phthalate levels around the time of conception. Environmental Health Perspectives 120 (2012) 458-463.
[136] K.-W. Liao, P.-L. Kuo, H.-B. Huang, J.-W. Chang, H.-C. Chiang, and P.-C. Huang, Increased risk of phthalates exposure for recurrent pregnancy loss in reproductive-aged women. Environmental Pollution 241 (2018) 969-977.
[137] M.-T. Wu, C.-F. Wu, J.-R. Wu, B.-H. Chen, E.K. Chen, M.-C. Chao, C.-K. Liu, and C.-K. Ho, The public health threat of phthalate-tainted foodstuffs in Taiwan: the policies the government implemented and the lessons we learned. Environment International 44 (2012) 75-79.
[138] H.J. Wen, C.C. Chen, M.T. Wu, M.L. Chen, C.W. Sun, W.C. Wu, I.W. Huang, P.C. Huang, T.Y. Yu, C.A. Hsiung, S.L. Wang, and R. Grp, Phthalate exposure and reproductive hormones and sex-

hormone binding globulin before puberty - Phthalate contaminated-foodstuff episode in Taiwan. PLoS One 12 (2017) e0175536.
[139] M.M. Dobrzyńska, Phthalates - widespread occurrence and the effect on male gametes. Part 2. The effects of phthalates on male gametes and on the offspring. Roczniki Panstwowego Zakladu Higieny 67 (2016) 209-221.
[140] P.R. Hannon, and J.A. Flaws, The effects of phthalates on the ovary. Frontiers in Endocrinology 6 (2015) 1-19.
[141] T. Zhang, W. Shen, M. De Felici, and X.F. Zhang, Di(2-ethylhexyl)phthalate: Adverse effects on folliculogenesis that cannot be neglected. Environmental and Molecular Mutagenesis 57 (2016) 579-588.
[142] P.R. Hannon, S. Niermann, and J.A. Flaws, Acute exposure to di(2-Ethylhexyl) phthalate in adulthood causes adverse reproductive outcomes later in life and accelerates reproductive aging in female mice. Toxicological Sciences 150 (2016) 97-108.
[143] S. Niermann, S. Rattan, E. Brehm, and J.A. Flaw, Prenatal exposure to di-(2-ethylhexyl) phthalate (DEHP) affects reproductive outcomes in female mice. Reproductive Toxicology 53 (2015) 23-32.
[144] D.J. Watkins, B.N. Sánchez, M.M. Téllez-Rojo, J.M. Lee, A. Mercado-García, C. Blank-Goldenberg, K.E. Peterson, and J.D. Meeker, Impact of phthalate and BPA exposure during in utero windows of susceptibility on reproductive hormones and sexual maturation in peripubertal males. Environmental Health 16 (2017) 69.
[145] D.B. Martinez-Arguelles, and V. Papadopoulos, Prenatal phthalate exposure: epigenetic changes leading to lifelong impact on steroid formation. Andrology 4 (2016) 573-584.
[146] P. Pocar, N. Fiandanese, A. Berrini, C. Secchi, and V. Borromeo, Maternal exposure to di(2-ethylhexyl)phthalate (DEHP) promotes the transgenerational inheritance of adult-onset reproductive dysfunctions through the female germline in mice. Toxicology and Applied Pharmacology 322 (2017) 113-121.
[147] C. Zhou, L. Gao, and J.A. Flaws, Exposure to an environmentally relevant phthalate mixture causes transgenerational effects on female reproduction in mice. Endocrinology 158 (2017) 1739-1754.
[148] E. Brehm, S. Rattan, L. Gao, and J.A. Flaws, Prenatal exposure to di(2-ethylhexyl) phthalate causes long-term transgenerational effects on female reproduction in mice. Endocrinology 159 (2018) 795-809.
[149] E.J. Routledge, J. Parker, J. Odum, J. Ashby, and J.P. Sumpter, Some alkyl hydroxy benzoate preservatives (parabens) are estrogenic. Toxicology and Applied Pharmacology 153 (1998) 12-19.
[150] R.S. Tavares, F.C. Martins, P.J. Oliveira, J. Ramalho-Santos, and F.P. Peixoto, Parabens in male infertility-Is there a mitochondrial connection? Reproductive Toxicology 27 (2009) 1-7.
[151] L.E. Dodge, P.L. Williams, M.A. Williams, S.A. Missmer, T.L. Toth, A.M. Calafat, and R. Hauser, Paternal urinary concentrations of parabens and other phenols in relation to reproductive outcomes among couples from a fertility clinic. Environmental Health Perspectives 123 (2015) 665-671.
[152] A.M. Calafat, X.Y. Ye, L.Y. Wong, A.M. Bishop, and L.L. Needham, Urinary concentrations of four parabens in the US population: NHANES 2005-2006. Environmental Health Perspectives 118 (2010) 679-685.
[153] K.W. Smith, J.M. Braun, P.L. Williams, S. Ehrlich, K.F. Correia, A.M. Calafat, X. Ye, J. Ford, M. Keller, J.D. Meeker, and R. Hauser, Predictors and variability of urinary paraben concentrations in men and women, including before and during pregnancy. Environmental Health Perspectives 120 (2012) 1538-1543.
[154] H. Frederiksen, N. Jorgensen, and A.M. Andersson, Parabens in urine, serum and seminal plasma from healthy Danish men determined by liquid chromatography-tandem mass

spectrometry (LC-MS/MS). Journal of Exposure Science and Environmental Epidemiology 21 (2011) 262-271.
[155] J.D. Meeker, T. Yang, X. Ye, A.M. Calafat, and R. Hauser, Urinary concentrations of parabens and serum hormone levels, semen quality parameters, and sperm DNA damage. Environmental Health Perspectives 119 (2011) 252-257.
[156] M.J. Chen, R. Tang, G.B. Fu, B. Xu, P.F. Zhu, S.L. Qiao, X.J. Chen, B. Xu, Y.F. Qin, C.C. Lu, B. Hang, Y.K. Xia, and X.R. Wang, Association of exposure to phenols and idiopathic male infertility. Journal of Hazardous Materials 250 (2013) 115-121.
[157] E. Adoamnei, J. Mendiola, M. Moñino-García, F. Vela-Soria, L.M. Iribarne-Durán, M.F. Fernández, N. Olea, N. Jørgensen, S.H. Swan, and A.M. Torres-Cantero, Urinary concentrations of parabens and reproductive parameters in young men. The Science of the Total Environment 621 (2018) 201-209.
[158] J. Jurewicz, M. Radwan, B. Wielgomas, E. Dziewirska, A. Karwacka, A. Klimowska, P. Kałużny, P. Radwan, M. Bochenek, and W. Hanke, Human semen quality, sperm DNA damage, and the level of reproductive hormones in relation to urinary concentrations of parabens. Journal of Occupational and Environmental Medicine 59 (2017) 1034-1040.
[159] J. Jurewicz, M. Radwan, B. Wielgomas, A. Klimowska, P. Kałużny, P. Radwan, L. Jakubowski, and W. Hanke, Environmental exposure to parabens and sperm chromosome disomy. International Journal of Environmental Health Research 27 (2017) 332-343.
[160] Y. Nishihama, H. Toshima, J. Yoshinaga, Y. Mizumoto, M. Yoneyama, D. Nakajima, H. Shiraishi, and S. Tokuoka, Paraben exposure and semen quality of Japanese male partners of subfertile couples. Environmental Health and Preventive Medicine 22 (2017) 5.
[161] K.W. Smith, I. Souter, I. Dimitriadis, S. Ehrlich, P.L. Williams, A.M. Calafat, and R. Hauser, Urinary paraben concentrations and ovarian aging among women from a fertility center. Environmental Health Perspectives 121 (2013) 1299-1305.
[162] L. Minguez-Alarcon, Y.-H. Chiu, C. Messerlian, P.L. Williams, M.E. Sabatini, T.L. Toth, J.B. Ford, A.M. Calafat, R. Hauser, and E.S. Team, Urinary paraben concentrations and in vitro fertilization outcomes among women from a fertility clinic. Fertility and Sterility 105 (2016) 714-721.
[163] M.M. Smarr, R. Sundaram, M. Honda, K. Kannan, and G.M.B. Louis, Urinary concentrations of parabens and other antimicrobial chemicals and their association with couples' fecundity. Environmental Health Perspectives 125 (2017) 730-736.
[164] U.N. Joensen, N. Jørgensen, J.P. Thyssen, P.B. Szecsi, S. Stender, J.H. Petersen, A.-M. Andersson, and H. Frederiksen, Urinary excretion of phenols, parabens and benzophenones in young men: Associations to reproductive hormones and semen quality are modified by mutations in the Filaggrin gene. Environment International 121 (2018) 365-374.
[165] M.T. Aung, K.K. Ferguson, D.E. Cantonwine, T.F. McElrath, and J.D. Meeker, Preterm birth in relation to the bisphenol A replacement, bisphenol S, and other phenols and parabens. Environmental Research 169 (2019) 131-138.
[166] H. Frederiksen, T.K. Jensen, N. Jorgensen, H.B. Kyhl, S. Husby, N.E. Skakkebaek, K.M. Main, A. Juul, and A.M. Andersson, Human urinary excretion of non-persistent environmental chemicals: an overview of Danish data collected between 2006 and 2012. Reproduction 147 (2014) 555-565.
[167] C. Han, Y.H. Lim, and Y.C. Hong, Ten-year trends in urinary concentrations of triclosan and benzophenone-3 in the general US population from 2003 to 2012. Environmental Pollution 208 (2016) 803-810.
[168] J. Yin, L. Wei, Y. Shi, J. Zhang, Q.Q. Wu, and B. Shao, Chinese population exposure to triclosan and triclocarban as measured via human urine and nails. Environmental Geochemistry and Health 38 (2016) 1125-1135.

[169] X. Wang, F. Ouyang, L. Feng, X. Wang, Z. Liu, and J. Zhang, Maternal urinary triclosan concentration in relation to maternal and neonatal thyroid hormone levels: a prospective study. Environmental Health Perspectives 125 (2017) 067017.
[170] T.E. Arbuckle, L. Marro, K. Davis, M. Fisher, P. Ayotte, P. Belanger, P. Dumas, A. LeBlanc, R. Berube, E. Gaudreau, G. Provencher, E.M. Faustman, E. Vigoren, A.S. Ettinger, M. Dellarco, S. MacPherson, and W.D. Fraser, Exposure to free and conjugated forms of Bisphenol A and Triclosan among pregnant women in the MIREC cohort. Environmental Health Perspectives 123 (2015) 277-284.
[171] L. Weiss, T.E. Arbuckle, M. Fisher, T. Ramsay, R. Mallick, R. Hauser, A. LeBlanc, M. Walker, P. Dumas, and C. Lang, Temporal variability and sources of triclosan exposure in pregnancy. International Journal of Hygiene and Environmental Health 218 (2015) 507-513.
[172] K.C. Ahn, B. Zhao, J. Chen, G. Cherednichenko, E. Sanmarti, M.S. Denison, B. Lasley, I.N. Pessah, D. Kültz, D.P.Y. Chang, S.J. Gee, and B.D. Hammock, In vitro biologic activities of the antimicrobials triclocarban, its analogs, and triclosan in bioassay screens: receptor-based bioassay screens. Environmental Health Perspectives 116 (2008) 1203-1210.
[173] R.H. Gee, A. Charles, N. Taylor, and P.D. Darbre, Oestrogenic and androgenic activity of triclosan in breast cancer cells. Journal of Applied Toxicology 28 (2008) 78-91.
[174] A.B. Dann, and A. Hontela, Triclosan: environmental exposure, toxicity and mechanisms of action. Journal of Applied Toxicology 31 (2011) 285-311.
[175] R.J. Witorsch, Critical analysis of endocrine disruptive activity of triclosan and its relevance to human exposure through the use of personal care products. Critical Reviews in Toxicology 44 (2014) 535-555.
[176] W.T. Zhu, H. Zhang, C.L. Tong, C. Xie, G.H. Fan, S.S. Zhao, X.G. Yu, Y. Tian, and J. Zhang, Environmental exposure to triclosan and semen quality. International Journal of Environmental Research and Public Health 13 (2016) 224.
[177] M.M. Smarr, M. Honda, K. Kannan, Z. Chen, S. Kim, and G.M.B. Louis, Male urinary biomarkers of antimicrobial exposure and bi-directional associations with semen quality parameters. Reproductive Toxicology 77 (2018) 103-108.
[178] J. Jurewicz, M. Radwan, B. Wielgomas, P. Kaluzny, A. Klimowska, P. Radwan, and W. Hanke, Environmental levels of triclosan and male fertility. Environmental Science and Pollution Research 25 (2018) 5484-5490.
[179] F.L. Nassan, L. Minguez-Alarcon, P.L. Williams, R. Dadd, J.C. Petrozza, J.B. Ford, A.M. Calafat, R. Hauser, and E.S. Team, Urinary triclosan concentrations and semen quality among men from fertility clinic. Environmental Research 177 (2019).
[180] V. Kumar, A. Chakraborty, M.R. Kural, and P. Roy, Alteration of testicular steroidogenesis and histopathology of reproductive system in male rats treated with triclosan. Reproductive Toxicology 27 (2009) 177-185.
[181] L. Mínguez-Alarcón, G. Christou, C. Messerlian, P.L. Williams, C.C. Carignan, I. Souter, J.B. Ford, A.M. Calafat, R. Hauser, E.S. Team, M.G. Keller, X. Ye, X. Zhou, and T. Jia, Urinary triclosan concentrations and diminished ovarian reserve among women undergoing treatment in a fertility clinic. Fertility and Sterility 108 (2017) 312-319.
[182] J. Jurewicz, B. Wielgomas, M. Radwan, A. Karwacka, A. Klimowska, E. Dziewirska, K. Korczak, R. Zajdel, P. Radwan, and W. Hanke, Triclosan exposure and ovarian reserve. Reproductive Toxicology 89 (2019) 168-172.
[183] R. Hua, Y. Zhou, B. Wu, Z. Huang, Y. Zhu, Y. Song, Y. Yu, H. Li, and S. Quan, Urinary triclosan concentrations and early outcomes of in vitro fertilization-embryo transfer. Reproduction 153 (2017) 319-325.
[184] C. Philippat, B. Heude, J. Botton, N. Alfaidy, A.M. Calafat, R. Slama, and t.E.M.C.C.S. Group, Prenatal exposure to select phthalates and phenols and associations with fetal and placental weight among male births in the EDEN cohort (France). Environmental Health Perspectives 127 (2019) 017002-8.

[185] P. Pocar, T.A.L. Brevini, B. Fischer, and F. Gandolfi, The impact of endocrine disruptors on oocyte competence. Reproduction 125 (2003) 313-325.
[186] Y.J. Yu, B.G. Lin, W.B. Liang, L.Z. Li, Y.D. Hong, X.C. Chen, X.Y. Xu, M.D. Xiang, and S. Huang, Associations between PBDEs exposure from house dust and human semen quality at an e-waste areas in South China-A pilot study. Chemosphere 198 (2018) 266-273.
[187] P.I. Johnson, H.M. Stapleton, B. Mukherjee, R. Hauser, and J.D. Meeker, Associations between brominated flame retardants in house dust and hormone levels in men. Science of the Total Environment 445 (2013) 177-184.
[188] S.L. Mumford, S. Kim, Z. Chen, R.E. Gore-Langton, D.B. Barr, and G.M.B. Louis, Persistent organic pollutants and semen quality: The LIFE Study. Chemosphere 135 (2015) 427-435.
[189] C.M. Makey, M.D. McCleana, L.E. Braverman, E.N. Pearce, A. Sjodin, J. Weinberg, and T.F. Webster, Polybrominated diphenyl ether exposure and reproductive hormones in North American men. Reproductive Toxicology 62 (2016) 46-52.
[190] J.D. Meeker, P.I. Johnson, D. Camann, and R. Hauser, Polybrominated diphenyl ether (PBDE) concentrations in house dust are related to hormone levels in men. Science of the Total Environment 407 (2009) 3425-3429.
[191] G. Toft, V. Lenters, R. Vermeulen, D. Heederik, C. Thomsen, G. Becher, A. Giwercman, D. Bizzaro, G.C. Manicardi, M. Spano, L. Rylander, H.S. Pedersen, P. Strucinski, V. Zviezdai, and J.P. Bonde, Exposure to polybrominated diphenyl ethers and male reproductive function in Greenland, Poland and Ukraine. Reproductive Toxicology 43 (2014) 1-7.
[192] K. Akutsu, S. Takatori, S. Nozawa, M. Yoshiike, H. Nakazawa, K. Hayakawa, T. Makino, and T. Iwamoto, Polybrominated diphenyl ethers in human serum and sperm quality. Bulletin of Environmental Contamination and Toxicology 80 (2008) 345-350.
[193] N. Abdelouahab, Y. AinMelk, and L. Takser, Polybrominated diphenyl ethers and sperm quality. Reproductive Toxicology 31 (2011) 546-550.
[194] C.C. Carignan, L. Mínguez-Alarcón, P.L. Williams, J.D. Meeker, H.M. Stapleton, C.M. Butt, T.L. Toth, J.B. Ford, R. Hauser, and E.S. Team, Paternal urinary concentrations of organophosphate flame retardant metabolites, fertility measures, and pregnancy outcomes among couples undergoing in vitro fertilization. Environment International 111 (2018) 232-238.
[195] Y. Gao, L.M. Chen, C.F. Wang, Y.J. Zhou, Y.W. Wang, Y. Zhang, Y. Hu, L. Ji, R. Shi, C. Cui, G.D. Ding, J. Jin, and Y. Tian, Exposure to polybrominated diphenyl ethers and female reproductive function: A study in the production area of Shandong, China. Science of the Total Environment 572 (2016) 9-15.
[196] K.G. Harley, A.R. Marks, J. Chevrier, A. Bradman, A. Sjodin, and B. Eskenazi, PBDE concentrations in women's serum and fecundability. Environmental Health Perspectives 118 (2010) 699-704.
[197] P.I. Johnson, L. Altshul, D.W. Cramer, S.A. Missmer, R. Hauser, and J.D. Meeker, Serum and follicular fluid concentrations of polybrominated diphenyl ethers and in-vitro fertilization outcome. Environment International 45 (2012) 9-14.
[198] E.M. Petro, J.L. Leroy, A. Covaci, E. Fransen, D. De Neubourg, A.C. Dirtu, I. De Pauw, and P.E. Bols, Endocrine-disrupting chemicals in human follicular fluid impair in vitro oocyte developmental competence. Human Reproduction 27 (2012) 1025-33.
[199] Y.K. Serme-Gbedo, N. Abdelouahab, J.C. Pasquier, A.A. Cohen, and L. Takser, Maternal levels of endocrine disruptors, polybrominated diphenyl ethers, in early pregnancy are not associated with lower birth weight in the Canadian birth cohort GESTE. Environmental Health 15 (2016).
[200] G. Choi, Y.-B. Wang, R. Sundaram, Z. Chen, D.B. Barr, G.M.B. Louis, and M.M. Smarr, Polybrominated diphenyl ethers and incident pregnancy loss: The LIFE Study. Environmental Research 168 (2019) 375-381.

[201] G.M.B. Louis, R. Sundaram, E.F. Schisterman, A.M. Sweeney, C.D. Lynch, R.E. Gore-Langton, J. Maisog, S. Kim, Z. Chen, and D.B. Barr, Persistent environmental pollutants and couple fecundity: The LIFE study. Environmental Health Perspectives 121 (2013) 231-236.
[202] M. Czerska, M. Zielinski, J. Kaminska, and D. Ligocka, Effects of polybrominaed diphenyl ethers on thyroid hormone, neuordevelopment and fertility in rodents and humans. International Journal of Occupational Medicine and Environmental Health 26 (2013) 498-510.
[203] S.N. Kuriyama, C.E. Talsness, K. Grote, and I. Chahoud, Developmental exposure to low-dose PBDE-99: Effects on male fertility and neurobehavior in rat offspring. Environmental Health Perspectives 113 (2005) 149-154.
[204] M.H. Sun, X.H. Li, Y. Xu, Y. Xu, and S.C. Sun, Exposure to PBDE47 affects mouse oocyte quality via mitochondria dysfunction-induced oxidative stress and apoptosis. Ecotoxicology and Environmental Safety 198 (2020).
[205] R. Hauser, P. Williams, L. Altshul, and A.M. Calafat, Evidence of interaction between polychlorinated biphenyls and phthalates in relation to human sperm motility. Environmental Health Perspectives 113 (2005) 425-430.
[206] B.S. Hwang, Z. Chen, G.M.B. Louis, and P.S. Albert, A Bayesian multi-dimensional couple-based latent risk model with an application to infertility. Biometrics 75 (2019) 315-325.
[207] W. Zhang, Z. Chen, A.Y. Liu, and G.M.B. Louis, A weighted kernel machine regression approach to environmental pollutants and infertility. Statistics in Medicine 38 (2019) 809-827.
[208] M.E. Turyk, H.A. Anderson, S. Freels, R. Chatterton, L.L. Needham, D.G. Patterson, D.N. Steenport, L. Knobeloch, P. Imm, V.W. Persky, and C. Great Lakes, Associations of organochlorines with endogenous hormones in male Great Lakes fish consumers and nonconsumers. Environmental Research 102 (2006) 299-307.
[209] A. Goncharov, R. Rej, S. Negoita, M. Schymura, A. Santiago-Rivera, G. Morse, D.O. Carpenter, and E. Akwesasne Task Force, Lower serum testosterone associated with elevated polychlorinated biphenyl concentrations in Native American men. Environmental Health Perspectives 117 (2009) 1454-1460.
[210] K.K. Ferguson, R. Hauser, L. Altshul, and J.D. Meeker, Serum concentrations of p, p '-DDE, HCB, PCBs and reproductive hormones among men of reproductive age. Reproductive Toxicology 34 (2012) 429-435.
[211] M.S. Petersen, J. Hailing, N. Jorgensen, F. Nielsen, P. Grandjean, T.K. Jensen, and P. Weihe, Reproductive function in a population of young Faroese men with elevated exposure to polychlorinated biphenyls (PCBs) and perfluorinated alkylate substances (PFAS). International Journal of Environmental Research and Public Health 15 (2018).
[212] R.S. Tavares, S. Escada-Rebelo, M. Correia, P.C. Mota, and J. Ramalho-Santos, The non-genomic effects of endocrine-disrupting chemicals on mammalian sperm. Reproduction 151 (2016) R1-R13.
[213] R. Paul, J. Moltó, N. Ortuño, A. Romero, C. Bezos, J. Aizpurua, and M.J. Gómez-Torres, Relationship between serum dioxin-like polychlorinated biphenyls and post-testicular maturation in human sperm. Reproductive Toxicology 73 (2017) 312-321.
[214] J. Richthoff, L. Rylander, B.A.G. Jonsson, H. Akesson, L. Hagmar, P. Nilsson-Ehle, M. Stridsberg, and A. Giwercman, 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 111 (2003) 409-413.
[215] A. Rignell-Hydbom, L. Rylander, A. Giwercman, B.A.G. Jonsson, P. Nilsson-Ehle, and L. Hagmar, Exposure to CB-153 and p,p '-DDE and male reproductive function. Human Reproduction 19 (2004) 2066-2075.
[216] M. Spano, G. Toft, L. Hagmar, P. Eleuteri, M. Rescia, A. Rignell-Hydbom, E. Tyrkiel, V. Zvyezday, J.P. Bonde, and Inuendo, Exposure to PCB and p,p '-DDE in European and Inuit populations: impact on human sperm chromatin integrity. Human Reproduction 20 (2005) 3488-3499.

[217] A. Stronati, G.C. Manicardi, M. Cecati, M. Bordicchia, L. Ferrante, M. Spano, G. Toft, J.P. Bonde, B.A.G. Jonsson, A. Rignell-Hydbom, L. Rylander, A. Giwercman, H.S. Pedersen, E.C. Bonefeld-Jorgensen, J.K. Ludwicki, V. Lesovoy, D. Sakkas, and D. Bizzaro, Relationships between sperm DNA fragmentation, sperm apoptotic markers and serum levels of CB-153 and p,p '-DDE in European and Inuit populations. Reproduction 132 (2006) 949-958.

[218] G. Toft, A. Rignell-Hydbom, E. Tyrkiel, M. Shvets, A. Giwercman, C.H. Lindh, H.S. Pedersen, J.K. Ludwicki, K. Lesovoy, L. Hagmar, M. Spano, G.C. Manicardi, E.C. Bonefeld-Jorgensen, A.M. Thulstrup, and J.P. Bonde, Semen quality and exposure to persistent organochlorine pollutants. Epidemiology 17 (2006) 450-458.

[219] Y.L. Guo, P.C. Hsu, C.C. Hsu, and G.H. Lambert, Semen quality after prenatal exposure to polychlorinated biphenyls and dibenzofurans. Lancet 356 (2000) 1240-1241.

[220] P.C. Hsu, W.Y. Huang, W.J. Yao, M.H. Wu, Y.L. Guo, and G.H. Lambert, Sperm changes in men exposed to polychlorinated biphenyls and dibenzofurans. Jama-Journal of the American Medical Association 289 (2003) 2943-2944.

[221] K.P. Phillips, and N. Tanphaichitr, Human exposure to endocrine disrupters and semen quality. Journal of Toxicology and Environmental Health-Part B-Critical Reviews 11 (2008) 188-220.

[222] L.-G. Jiang, L.-Y. Cheng, S.-H. Kong, Y. Yang, Y.-J. Shen, C. Chen, X.-H. Deng, S.-Z. Liu, and L. Chao, Toxic effects of polychlorinated biphenyls (Aroclor 1254) on human sperm motility. Asian Journal of Andrology 19 (2017) 561-566.

[223] G.M. Buck Louis, D.B. Barr, K. Kannan, Z. Chen, S. Kim, and R. Sundaram, Paternal exposures to environmental chemicals and time-to-pregnancy: overview of results from the LIFE study. Andrology 4 (2016) 639-647.

[224] G.S. Cooper, M.A. Klebanoff, J. Promislow, J.W. Brock, and M.P. Longnecker, Polychlorinated biphenyls and menstrual cycle characteristics. Epidemiology 16 (2005) 191-200.

[225] S.L. Farr, G.S. Cooper, J. Cai, D.A. Savitz, and D.P. Sandler, Pesticide use and menstrual cycle characteristics among premenopausal women in the agricultural health study. American Journal of Epidemiology 160 (2004) 1194-1204.

[226] M.L. Yu, Y.L.L. Guo, C.C. Hsu, and W.J. Rogan, Menstruation and reproduction in women with polychlorinated biphenyl (PCB) poisoning: long-term follow-up interviews of the women from the Taiwan Yucheng cohort. International Journal of Epidemiology 29 (2000) 672-677.

[227] G.M. Buck Louis, L.I. Rios, A. McLain, M.A. Cooney, P.J. Kostyniak, and R. Sundaram, Persistent organochlorine pollutants and menstrual cycle characteristics. Chemosphere 85 (2011) 1742-1748.

[228] N.M. Grindler, J.E. Allsworth, G.A. Macones, K. Kannan, K.A. Roehl, and A.R. Cooper, Persistent organic pollutants and early menopause in US women. PLoS One 10 (2015).

[229] H. Schlebusch, U. Wagner, H. Vanderven, S. Alhasani, K. Diedrich, and D. Krebs, Polychorinated-biphenyls- The occurence of the main congeners in follicular and sperm fluids. Journal of Clinical Chemistry and Clinical Biochemistry 27 (1989) 663-667.

[230] E.V. Younglai, W.G. Foster, E.G. Hughes, K. Trim, and J.F. Jarrell, Levels of environmental contaminants in human follicular fluid, serum, and seminal plasma of couples undergoing in vitro fertilization. Archives of Environmental Contamination and Toxicology 43 (2002) 121-126.

[231] J.D. Meeker, A. Maity, S.A. Missmer, P.L. Williams, S. Mahalingaiah, S. Ehrlich, K.F. Berry, L. Altshul, M.J. Perry, D.W. Cramer, and R. Hauser, Serum concentrations of Polychlorinated Biphenyls in relation to in vitro fertilization outcomes. Environmental Health Perspectives 119 (2011) 1010-1016.

[232] T.K. Al-Hussaini, A.A. Abdelaleem, I. Elnashar, O.M. Shabaan, R. Mostafa, M.A.H. El-Baz, S.E.M. El-Deek, and T.A. Farghaly, The effect of follicullar fluid pesticides and polychlorinated biphenyls concentrations on intracytoplasmic sperm injection (ICSI) embryological and clinical outcome. European Journal of Obstetrics and Gynecology 220 (2018) 39-43.

[233] M.S. Bloom, V.Y. Fujimoto, R. Storm, L. Zhang, C.D. Butts, D. Sollohub, and R.L. Jansing, Persistent organic pollutants (POPs) in human follicular fluid and in vitro fertilization outcomes, a pilot study. Reproductive Toxicology 67 (2017) 165-173.
[234] D.C.G. Law, M.A. Klebanoff, J.W. Brock, D.B. Dunson, and M.P. Longnecker, Maternal serum levels of polychlorinated Biphenyls and 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (DDE) and time to pregnancy. American Journal of Epidemiology 162 (2005) 523-532.
[235] G.M. Buck Louis, J. Dmochowski, C. Lynch, P. Kostyniak, B.M. McGuinness, and J.E. Vena, Polychlorinated biphenyl serum concentrations, lifestyle and time-to-pregnancy. Human Reproduction 24 (2009) 451-458.
[236] L. Han, W.-W. Hsu, D. Todem, J. Osuch, A. Hungerink, and W. Karmaus, In utero exposure to polychlorinated biphenyls is associated with decreased fecundability in daughters of Michigan female fisheaters: a cohort study. Environmental Health (2016) 1-13.
[237] M. Harnly, R. Stephens, C. McLaughlin, J. Marcotte, M. Petreas, and L. Goldman, Polychlorinated dibenzo-p-dioxin and dibenzofuran contamination at metal recovery facilites, open burn sites, and a railroad car incineration facility. Environmental Science & Technology 29 (1995) 677-684.
[238] K. Tuppurainen, I. Halonen, P. Ruokojarvi, J. Tarhanen, and J. Ruuskanen, Formation of PCDDs and PCDFs in municipal waste incineration and its inhibition mechanisms: A review. Chemosphere 36 (1998) 1493-1511.
[239] R.A. Hites, Dioxins: An Overview and History. Environmental Science & Technology 45 (2011) 16-20.
[240] F. Ohtake, Y. Fujii-Kuriyama, K. Kawajiri, and S. Kato, Cross-talk of dioxin and estrogen receptor signals through the ubiquitin system. Journal of Steroid Biochemistry and Molecular Biology 127 (2011) 102-107.
[241] L. Fabelova, C.A. Loffredo, J. Klanova, K. Hilscherova, M. Horvat, J. Tihanyi, D. Richterova, L.P. Murinova, S. Wimmerova, R. Sisto, A. Moleti, and T. Trnovec, Environmental ototoxicants, a potential new class of chemical stressors. Environmental Research 171 (2019) 378-394.
[242] G.M. Egeland, M.H. Sweeney, M.A. Fingerhut, K.K. Wille, T.M. Schnorr, and W.E. Halperin, Total serum testosterone and gonadotrophins in workers exposed to dioxin. American Journal of Epidemiology 139 (1994) 272-281.
[243] P. Mocarelli, P.M. Gerthoux, D.G. Patterson, S. Milani, G. Limonta, M. Bertona, S. Signorini, P. Tramacere, L. Colombo, C. Crespi, P. Brambilla, C. Sarto, V. Carreri, E.J. Sampson, W.E. Turner, and L.L. Needham, Dioxin exposure, from infancy through puberty, produces endocrine disruption and affects human semen quality. Environmental Health Perspectives 116 (2008) 70-77.
[244] P. Mocarelli, P.M. Gerthoux, L.L. Needham, D.G. Patterson, Jr., G. Limonta, R. Falbo, S. Signorini, M. Bertona, C. Crespi, C. Sarto, P.K. Scott, W.E. Turner, and P. Brambilla, Perinatal exposure to low doses of dioxin can permanently impair human semen quality. Environmental Health Perspectives 119 (2011) 713-718.
[245] L. Minguez-Alarcon, O. Sergeyev, J.S. Burns, P.L. Williams, M.M. Lee, S.A. Korrick, L. Smigulina, B. Revich, and R. Hauser, A longitudinal study of peripubertal serum organochlorine concentrations and semen parameters in young men: the Russian children's study. Environmental Health Perspectives 125 (2017) 460-466.
[246] M. Warner, B. Eskenazi, D.L. Olive, S. Samuels, S. Quick-Miles, P. Vercellini, P.M. Gerthoux, L. Needham, D.G. Patterson, and P. Mocarelli, Serum dioxin concentrations and quality of ovarian function in women of seveso. Environmental Health Perspectives 115 (2007) 336-340.
[247] B. Eskenazi, M. Warner, A.R. Marks, S. Samuels, L. Needham, P. Brambilla, and P. Mocarelli, Serum Dioxin concentrations and time to pregnancy. Epidemiology 21 (2010) 224-231.
[248] S. Patel, C.Q. Zhou, S. Rattan, and J.A. Flaws, Effects of Endocrine-Disrupting Chemicals on the ovary. Biology of Reproduction 93 (2015).

[249] M. Kirk, K. Smurthwaite, J. Braunig, S. Trevenar, C. D'Este, R. Lucas, A. Lal, R. Korda, A. Clements, J. Mueller, and B. Armstrong, The PFAS health study: systematic literature review, The Australian National University, Canberra, 2018, pp. 1-256.

[250] J. Holzer, O. Midasch, K. Rauchfuss, M. Kraft, R. Reupert, J. Angerer, P. Kleeschulte, N. Marschall, and M. Wilhelm, Biomonitoring of perfluorinated compounds in children and adults exposed to perfluorooctanoate-contaminated drinking water. Environmental Health Perspectives 116 (2008) 651-657.

[251] M.L. Takacs, and B.D. Abbott, Activation of mouse and human peroxisome proliferator-activated receptors (alpha, beta/delta, gamma) by perfluorooctanoic acid and perfluorooctane sulfonate. Toxicological Sciences 95 (2007) 108-117.

[252] C. La Rocca, E. Alessi, B. Bergamasco, D. Caserta, F. Ciardo, E. Fanello, S. Focardi, C. Guerranti, L. Stecca, M. Moscarini, G. Perra, S. Tait, C. Zaghi, and A. Mantovani, Exposure and effective dose biomarkers for perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) in infertile subjects: Preliminary results of the PREVIENI project. International Journal of Hygiene and Environmental Health 215 (2012) 206-211.

[253] A.D. Benninghoff, W.H. Bisson, D.C. Koch, D.J. Ehresman, S.K. Kolluri, and D.E. William, Estrogen-like activity of perfluoroalkyl acids in vivo and interaction with human and rainbow trout estrogen receptors in vitro. Toxicological Sciences 120 (2011) 42-58.

[254] G.W. Olsen, F.D. Gillard, M.M. Burlew, J.M. Burris, J.S. Mandel, and J.H. Mandel, An epidemiologic investigation of reproductive hormones in men with occupational exposure to perfluorooctanoic acid. Journal of Occupational and Environmental Medicine 40 (1998) 614-622.

[255] U.N. Joensen, R. Bossi, H. Leffers, A.A. Jensen, N.E. Skakkebaek, and N. Jorgensen, Do perfluoroalkyl compounds impair human semen quality? Environmental Health Perspectives 117 (2009) 923-927.

[256] M.S. Tsai, C.Y. Lin, C.C. Lin, M.H. Chen, S.H.J. Hsu, K.L. Chien, F.C. Sung, P.C. Chen, and T.C. Su, Association between perfluoroalkyl substances and reproductive hormones in adolescents and young adults. International Journal of Hygiene and Environmental Health 218 (2015) 437-443.

[257] U.N. Joensen, B. Veyrand, J.P. Antignac, M.B. Jensen, J.H. Petersen, P. Marchand, N.E. Skakkebaek, A.M. Andersson, B. Le Bizec, and N. Jorgensen, PFOS (perfluorooctanesulfonate) in serum is negatively associated with testosterone levels, but not with semen quality, in healthy men. Human Reproduction 28 (2013) 599-608.

[258] J.H. Raymer, L.C. Michael, W.B. Studabaker, G.W. Olsen, C.S. Sloan, T. Wilcosky, and D.K. Walmer, Concentrations of perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) and their associations with human semen quality measurements. Reproductive Toxicology 33 (2012) 419-427.

[259] A. Vested, C.H. Ramlau-Hansen, S.F. Olsen, J.P. Bonde, S.L. Kristensen, T.I. Halldorsson, G. Becher, L.S. Haug, E.H. Ernst, and G. Toft, Associations of in utero exposure to perfluorinated alkyl acids with human semen quality and reproductive hormones in adult men. Environmental Health Perspectives 121 (2013) 453-458.

[260] G. Toft, B.A.G. Jonsson, C.H. Lindh, A. Giwercman, M. Spano, D. Heederik, V. Lenters, R. Vermeulen, L. Rylander, H.S. Pedersen, J.K. Ludwicki, V. Zviezdai, and J.P. Bonde, Exposure to perfluorinated compounds and human semen quality in arctic and European populations. Human Reproduction 27 (2012) 2532-2540.

[261] L. Governini, C. Guerranti, V. De Leo, L. Boschi, A. Luddi, M. Gori, R. Orvieto, and P. Piomboni, Chromosomal aneuploidies and DNA fragmentation of human spermatozoa from patients exposed to perfluorinated compounds. Andrologia 47 (2015) 1012-1019.

[262] G.M.B. Louis, Z. Chen, E.F. Schisterman, S. Kim, A.M. Sweeney, R. Sundaram, C.D. Lynch, R.E. Gore-Langton, and D.B. Barr, Perfluorochemicals and human semen quality: The LIFE study. Environmental Health Perspectives 123 (2015) 57-63.

[263] G. Leter, C. Consales, P. Eleuteri, R. Uccelli, I.O. Specht, G. Toft, T. Moccia, A. Budillon, B.A.G. Jonsson, C.H. Lindh, A. Giwercman, H.S. Pedersen, J.K. Ludwicki, V. Zviezdai, D. Heederik, J.P.E. Bonde, and M. Spano, Exposure to perfluoroalkyl substances and sperm DNA global methylation in Arctic and European populations. Environmental and Molecular Mutagenesis 55 (2014) 591-600.

[264] I.O. Specht, K.S. Hougaard, M. Spano, D. Bizzaro, G.C. Manicardi, C.H. Lindh, G. Toft, B.A.G. Jonsson, A. Giwercman, and J.P.E. Bonde, Sperm DNA integrity in relation to exposure to environmental perfluoroalkyl substances - A study of spouses of pregnant women in three geographical regions. Reproductive Toxicology 33 (2012) 577-583.

[265] E. Emerce, and O. Cetin, Genotoxicity assessment of perfluoroalkyl substances on human sperm. Toxicology and Industrial Health 34 (2018) 884-890.

[266] E.S. Barrett, C.S. Chen, S.W. Thurston, L.S. Haug, A. Sabaredzovic, F.N. Fjeldheim, H. Frydenberg, S.F. Lipson, P.T. Ellison, and I. Thune, Perfluoroalkyl substances and ovarian hormone concentrations in naturally cycling women. Fertility and Sterility 103 (2015) 1261-1270.

[267] S.S. Knox, T. Jackson, B. Javins, S.J. Frisbee, A. Shankar, and A.M. Ducatman, Implications of early menopause in women exposed to perfluorocarbons. Journal of Clinical Endocrinology & Metabolism 96 (2011) 1747-1753.

[268] J. Lyngso, C.H. Ramlau-Hansen, B.B. Hoyer, H. Stovring, J.P. Bonde, B.A.G. Jonsson, C.H. Lindh, H.S. Pedersen, J.K. Ludwicki, V. Zviezdai, and G. Toft, Menstrual cycle characteristics in fertile women from Greenland, Poland and Ukraine exposed to perfluorinated chemicals: a cross-sectional study. Human Reproduction 29 (2014) 359-367.

[269] K.J. Lum, R. Sundaram, D.B. Barr, T.A. Louis, and G.M.B. Louis, Perfluoroalkyl chemicals, menstrual cycle length, and fecundity findings from a prospective pregnancy study. Epidemiology 28 (2017) 90-98.

[270] W. Zhou, L.L. Zhang, C.L. Tong, F. Fang, S.S. Zhao, Y. Tian, Y.X. Tao, J. Zhang, and S. Shanghai Birth Cohort, Plasma perfluoroalkyl and polyfluoroalkyl substances concentration and menstrual cycle characteristics in preconception women. Environmental Health Perspectives 125 (2017) 067012.

[271] A.B. Singer, K.W. Whitworth, L.S. Haug, A. Sabaredzovic, A. Impinen, E. Papadopoulou, and M.P. Longnecker, Menstrual cycle characteristics as determinants of plasma concentrations of perfluoroalkyl substances (PFASs) in the Norwegian Mother and Child Cohort (MoBa study). Environmental Research 166 (2018) 78-85.

[272] A. Di Nisio, M.S. Rocca, I. Sabovic, M.D. Ponce, C. Corsini, D. Guidolin, C. Zanon, L. Acquasaliente, A.R. Carosso, L. De Toni, and C. Foresta, Perfluorooctanoic acid alters progesterone activity in human endometrial cells and induces reproductive alterations in young women. Chemosphere 242 (2020) 125208.

[273] C. Fei, J.K. McLaughlin, L. Lipworth, and J. Olsen, Maternal levels of perfluorinated chemicals and subfecundity. Human Reproduction 24 (2009) 1200-1205.

[274] K.T. Jorgensen, I.O. Specht, V. Lenters, C.C. Bach, L. Rylander, B.A.G. Jonsson, C.H. Lindh, A. Giwercman, D. Heederik, G. Toft, and J.P. Bonde, Perfluoroalkyl substances and time to pregnancy in couples from Greenland, Poland and Ukraine. Environmental Health 13 (2014).

[275] M.P. Velez, T.E. Arbuckle, and W.D. Fraser, Maternal exposure to perfluorinated chemicals and reduced fecundity: the MIREC study. Human Reproduction 30 (2015) 701-709.

[276] S. Vestergaard, F. Nielsen, A.M. Andersson, N.H. Hjollund, P. Grandjean, H.R. Andersen, and T.K. Jensen, Association between perfluorinated compounds and time to pregnancy in a prospective cohort of Danish couples attempting to conceive. Human Reproduction 27 (2012) 873-880.

[277] K.W. Whitworth, L.S. Haug, D.D. Baird, G. Becher, J.A. Hoppin, R. Skjaerven, C. Thomsen, M. Eggesbo, G. Travlos, R. Wilson, and M.P. Longnecker, Perfluorinated compounds and subfecundity in pregnant women. Epidemiology 23 (2012) 257-263.

[278] C.C. Bach, B.H. Bech, E.A. Nohr, J. Olsen, N.B. Matthiesen, R. Bossi, N. Uldbjerg, E.C. Bonefeld-Jorgensen, and T.B. Henriksen, Serum perfluoroalkyl acids and time to pregnancy in nulliparous women. Environmental Research 142 (2015) 535-541.
[279] K.W. Whitworth, L.S. Haug, A. Sabaredzovic, M. Eggesbo, and M.P. Longnecker, Plasma concentrations of perfluorooctane sulfonamide and time-to-pregnancy among primiparous women. Epidemiology 27 (2016) 712-715.
[280] M.H. Chen, E.H. Ha, T.W. Wen, Y.N. Su, G.W. Lien, C.Y. Chen, P.C. Chen, and W.S. Hsieh, Perfluorinated compounds in umbilical cord blood and adverse birth outcomes. PLoS One 7 (2012) e42474.
[281] T.E. Arbuckle, C. Kubwabo, M. Walker, K. Davis, K. Lalonde, I. Kosarac, S.W. Wen, and D.L. Arnold, Umbilical cord blood levels of perfluoroalkyl acids and polybrominated flame retardants. International Journal of Hygiene and Environmental Health 216 (2013) 184-194.
[282] J. Malits, J. Blustein, L. Trasande, and T.M. Attina, Perfluorooctanoic acid and low birth weight: Estimates of US attributable burden and economic costs from 2003 through 2014. International Journal of Hygiene and Environmental Health 221 (2018) 269-275.
[283] P.I. Johnson, P. Sutton, D.S. Atchley, E. Koustas, J. Lam, S. Sen, K.A. Robinson, D.A. Axelrad, and T.J. Woodruff, The navigation guide-evidence-based medicine meets environmental health: systematic review of human evidence for PFOA effects on fetal growth. Environmental Health Perspectives 122 (2014) 1028-1039.
[284] G.M. Donley, E. Taylor, Z. Jeddy, G. Namulanda, and T.J. Hartman, Association between in utero perfluoroalkyl substance exposure and anti-Mullerian hormone levels in adolescent females in a British cohort. Environmental Research 177 (2019).
[285] J.L. Butenhoff, G.L. Kennedy, S.R. Frame, J.C. O'Connor, and R.G. York, The reproductive toxicology of ammonium perfluorooctanoate (APFO) in the rat. Toxicology 196 (2004) 95-116.
[286] R.G. York, G.L. Kennedy, G.W. Olsen, and J.L. Butenhoff, Male reproductive system parameters in a two-generation reproduction study of ammonium perfluorooctanoate in rats and human relevance. Toxicology 271 (2010) 64-72.
[287] D.J. Luebker, M.T. Case, R.G. York, J.A. Moore, K.J. Hansen, and J.L. Butenhoff, Two-generation reproduction and cross-foster studies of perfluorooctanesulfonate (PFOS) in rats. Toxicology 215 (2005) 126-148.
[288] P. Sengupta, and R. Banerjee, Environmental toxins: Alarming impacts of pesticides on male fertility. Human & Experimental Toxicology 33 (2014) 1017-1039.
[289] C.A. Snijder, E. Te Velde, N. Roeleveld, and A. Burdorf, Occupational exposure to chemical substances and time to pregnancy: a systematic review. Human Reproduction Update 18 (2012) 284-300.
[290] P. Ayotte, S. Giroux, E. Dewailly, M.H. Avila, P. Farias, R. Danis, and C.V. Diaz, DDT spraying for malaria control and reproductive function in Mexican men. Epidemiology 12 (2001) 366-367.
[291] M. Bornman, R. Delport, P. Farías, N. Aneck-Hahn, S. Patrick, R.P. Millar, and C. de Jager, Alterations in male reproductive hormones in relation to environmental DDT exposure. Environment International 113 (2018) 281-289.
[292] C. De Jager, P. Farias, A. Barraza-Villarreal, M.H. Avila, P. Ayotte, E. Dewailly, C. Dombrowski, F. Rousseau, V.D. Sanchez, and J.L. Bailey, Reduced seminal parameters associated with environmental DDT exposure and p,p '-DDE concentrations in men in Chiapas, Mexico: A cross-sectional study. Journal of Andrology 27 (2006) 16-27.
[293] N.H. Aneck-Hahn, G.W. Schulenburg, M.S. Bornman, P. Farias, and C. De Jager, Impaired semen quality associated with environmental DDT exposure in young men living in a malaria area in the Limpopo Province, South Africa. Journal of Andrology 28 (2007) 423-434.
[294] C. de Jager, N.H. Aneck-Hahn, M.S. Bornman, P. Farias, G. Leter, P. Eleuteri, M. Rescia, and M. Spano, Sperm chromatin integrity in DDT-exposed young men living in a malaria area in the Limpopo Province, South Africa. Human Reproduction 24 (2009) 2429-2438.

[295] P. Mendola, L.C. Messer, and K. Rappazzo, Science linking environmental contaminant exposures with fertility and reproductive health impacts in the adult female. Fertility and Sterility 89 (2008) e81-94.
[296] F. Ouyang, M.J. Perry, S.A. Venners, C. Chen, B. Wang, F. Yang, Z. Fang, T. Zang, L. Wang, X. Xu, and X. Wang, Serum DDT, age at menarche, and abnormal menstrual cycle length. Occupational and Environmental Medicine 62 (2005) 878-884.
[297] M.J. Perry, F. Ouyang, S.A. Korrick, S.A. Venners, C. Chen, X. Xu, B.L. Lasley, and X. Wang, A prospective study of serum DDT and progesterone and estrogen levels across the menstrual cycle in nulliparous women of reproductive age. American Journal of Epidemiology 164 (2006) 1056-1064.
[298] G.C. Windham, D. Lee, P.I. Mitchell, M. Anderson, M. Petreas, and B. Lasley, Exposure to organochlorine compounds and effects on ovarian function. Epidemiology 16 (2005) 182-190.
[299] V. Baukloh, H.G. Bohnet, M. Trapp, W. Heeschen, W. Feichtinger, and P. Kemeter, Biocides in human follicular fluid. Annals of the New York Academy of Sciences 442 (1985) 240-250.
[300] I. Al-Saleh, S. Coskun, I. El-Doush, G. Billedo, A. Mashhour, K. Jaroudi, A. Al-Shahrani, H. Al-Mayman, and G. Mohamed, Outcome of in-vitro fertilization treatment and DDT levels in serum and follicular fluid. Medical Science Monitor 15 (2009) BR320-BR333.
[301] S. Mahalingaiah, S.A. Missmer, A. Maity, P.L. Williams, J.D. Meeker, K. Berry, S. Ehrlich, M.J. Perry, D.W. Cramer, and R. Hauser, Association of Hexachlorobenzene (HCB), Dichlorodiphenyltrichloroethane (DDT), and Dichlorodiphenyldichloroethylene (DDE) with in Vitro Fertilization (IVF) Outcomes. Environmental Health Perspectives 120 (2012) 316-320.
[302] P. Kadhel, P. Monnier, I. Boucoiran, N. Chaillet, and W.D. Fraser, Organochlorine pollutants and female fertility: A systematic review focusing on in vitro fertilization studies. Reproductive Sciences 19 (2012) 1246-1259.
[303] S.A. Korrick, C.Z. Chen, A.I. Damokosh, J.T. Ni, X. Liu, S.I. Cho, L. Altshul, L. Ryan, and X.P. Xu, Association of DDT with spontaneous abortion: A case-control study. Annals of Epidemiology 11 (2001) 491-496.
[304] M.P. Longnecker, M.A. Klebanoff, D.B. Dunson, X.G. Guo, C. Zhen, H.B. Zhou, and J.W. Brock, Maternal serum level of the DDT metabolite DDE in relation to fetal loss in previous pregnancies. Environmental Research 97 (2005) 127-133.
[305] S.A. Venners, S. Korrick, X.P. Xu, C.Z. Chen, W.W. Guang, A.Q. Huang, L. Altshul, M. Perry, L.L. Fu, and X.B. Wang, Preconception serum DDT and pregnancy loss: A prospective study using a biomarker of pregnancy. American Journal of Epidemiology 162 (2005) 709-716.
[306] R.M. Toichuev, L.V. Zhilova, T.R. Paizildaev, M.S. Khametova, A. Rakhmatillaev, K.S. Sakibaev, Z.A. Madykova, A.U. Toichueva, M. Schlumpf, R. Weber, and W. Lichtensteiger, Organochlorine pesticides in placenta in Kyrgyzstan and the effect on pregnancy, childbirth, and newborn health. Environmental Science and Pollution Research (2018) 1-10.
[307] E.E. Nilsson, I. Sadler-Riggleman, and M.K. Skinner, Environmentally induced epigenetic transgenerational inheritance of disease. Environmental Epigenetics 4 (2018) dvy016.
[308] U. Tiemann, 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 25 (2008) 316-326.
[309] L. Multigner, P. Kadhel, F. Rouget, P. Blanchet, and S. Cordier, Chlordecone exposure and adverse effects in French West Indies populations. Environmental Science and Pollution Research 23 (2016) 3-8.
[310] Z.R. Craig, W. Wang, and J.A. Flaws, Endocrine-disrupting chemicals in ovarian function: effects on steroidogenesis, metabolism and nuclear receptor signaling. Reproduction 142 (2011) 633-646.
[311] A.M. Cummings, Methoxychlor as a model for environmental estrogens. Critical Reviews in Toxicology 27 (1997) 367-379.

[312] K.W. Gaido, S.C. Maness, D.P. McDonnell, S.S. Dehal, D. Kupfer, and S. Safe, Interaction of methoxychlor and related compounds with estrogen receptor alpha and beta, and androgen receptor: structure-activity studies. Molecular Pharmacology 58 (2000) 852-858.
[313] E.J. Mrema, F.M. Rubino, G. Brambilla, A. Moretto, A.M. Tsatsakis, and C. Colosio, Persistent organochlorinated pesticides and mechanisms of their toxicity. Toxicology 307 (2013) 74-88.
[314] A.S. Cupp, M. Uzumcu, H. Suzuki, H. Dirks, B. Phillips, and M.K. Skinner, Effect of transient embryonic in vivo exposure to the endocrine disruptor methoxychlor on embryonic and postnatal testis development. Journal of Andrology 24 (2003) 736-745.
[315] M.D. Anway, A.S. Cupp, M. Uzumcu, and M.K. Skinner, Epigenetic transgenerational actions of endocrine disruptors and male fertility. Science 308 (2005) 1466-1469.
[316] H. Aoyama, H. Hojo, K.L. Takahashi, N. Shimizu-Endo, M. Araki, Y. Takeuchi-Kashimoto, M. Saka, and S. Teramoto, Two-generation reproduction toxicity study in rats with methoxychlor. Congenital Anomalies 52 (2012) 28-41.
[317] E.V. Magnusdottir, T. Thorsteinsson, S. Thorsteinsdottir, M. Heimisdottir, and K. Olafsdottir, Persistent organochlorines, sedentary occupation, obesity and human male subfertility. Human Reproduction 20 (2005) 208-215.
[318] J.W. Dallinga, E.J.C. Moonen, J.C.M. Dumoulin, J.L.H. Evers, J.P.M. Geraedts, and J.C.S. Kleinjans, Decreased human semen quality and organochlorine compounds in blood. Human Reproduction 17 (2002) 1973-1979.
[319] R. Hauser, N.P. Singh, Z. Chen, L. Pothier, and L. Altshul, Lack of an association between environmental exposure to polychlorinated biphenyls and p,p '-DDE and DNA damage in human sperm measured using the neutral comet assay. Human Reproduction 18 (2003) 2525-2533.
[320] N. Pant, N. Mathur, A.K. Banerjee, S.P. Srivastava, and D.K. Saxena, Correlation of chlorinated pesticides concentration in semen with seminal vesicle and prostatic markers. Reproductive Toxicology 19 (2004) 209-214.
[321] S.B. Cannon, J.M. Veazey, R.S. Jackson, V.W. Burse, C. Hayes, W.E. Straub, P.J. Landrigan, and J.A. Liddle, Epidemic kepone poisoning in chemical workers. American Journal of Epidemiology 107 (1978) 529-537.
[322] W.J. Cohn, J.J. Boylan, R.V. Blanke, M.W. Fariss, J.R. Howell, and P.S. Guzelian, Treatment of chlordecone (kepone) toxicity with cholestyramine: results of a controlled clinical trial. New England Journal of Medicine 298 (1978) 243-248.
[323] L. Multigner, P. Kadhel, F. Huc-Terki, J. Thome, E. Janky, and J. Auger, Exposure to chlordecone and male fertility in Guadeloupe (French West Indies). Epidemiology 17 (2006) S372-S372.
[324] L. Multigner, P. Kadhel, M. Pascal, F. Huc-Terki, H. Kercret, C. Massart, E. Janky, J. Auger, and B. Jegou, Parallel assessment of male reproductive function in workers and wild rats exposed to pesticides in banana plantations in Guadeloupe. Environmental Health 7 (2008).
[325] J.M. Weiss, O. Bauer, A. Bluthgen, A.K. Ludwig, E. Vollersen, M. Kaisi, S. Al-Hasani, K. Diedrich, and M. Ludwig, Distribution of persistent organochlorine contaminants in infertile patients from Tanzania and Germany. Journal of Assisted Reproduction and Genetics 23 (2006) 393-399.
[326] N. Pant, M. Shukla, A.D. Upadhyay, P.K. Chaturvedi, D.K. Saxena, and Y.K. Gupta, Association between environmental exposure to p, p '-DDE and lindane and semen quality. Environmental Science and Pollution Research 21 (2014) 11009-11016.
[327] I.O. Specht, J.P.E. Bonde, G. Toft, A. Giwercman, M. Spano, D. Bizzaro, G.C. Manicardi, B.A.G. Jonsson, and W.A. Robbins, Environmental hexachlorobenzene exposure and human male reproductive function. Reproductive Toxicology 58 (2015) 8-14.
[328] A. Araki, C. Miyashita, T. Mitsui, H. Goudarzi, F. Mizutani, Y. Chisaki, S. Itoh, S. Sasaki, K. Cho, K. Moriya, N. Shinohara, K. Nonomura, and R. Kishi, Prenatal organochlorine pesticide exposure and the disruption of steroids and reproductive hormones in cord blood: The Hokkaido study. Environment International 110 (2018) 1-13.

[329] M.S. Basavarajappa, B.N. Karman, W. Wang, R.K. Gupta, and J.A. Flaws, Methoxychlor induces atresia by altering Bcl2 factors and inducing caspase activity in mouse ovarian antral follicles in vitro. Reproductive Toxicology 34 (2012) 545-551.
[330] S. Sifakis, V.P. Androutsopoulos, A.M. Tsatsakis, and D.A. Spandidos, Human exposure to endocrine disrupting chemicals: effects on the male and female reproductive systems. Environmental Toxicology and Pharmacology 51 (2017) 56-70.
[331] R. Pathak, M. Mustafa, R.S. Ahmed, A.K. Tripathi, K. Guleria, and B.D. Banerjee, Association between recurrent miscarriages and organochlorine pesticide levels. Clinical Biochemistry 43 (2010) 131-135.
[332] M.W. Chen, H.M. Santos, D.E. Que, Y.Y. Gou, L.L. Tayo, Y.C. Hsu, Y.B. Chen, F.A. Chen, H.R. Chao, and K.L. Huang, Association between organochlorine pesticide levels in breast milk and their effects on female reproduction in a Taiwanese population. International Journal of Environmental Research and Public Health 15 (2018) 931.
[333] G. Bapayeva, R. Issayeva, A. Zhumadilova, R. Nurkasimova, S. Kulbayeva, and R. Tleuzhan, Organochlorine pesticides and female puberty in South Kazakhstan. Reproductive Toxicology 65 (2016) 67-75.
[334] P. Kadhel, C. Monfort, N. Costet, F. Rouget, J.P. Thome, L. Multigner, and S. Cordier, Chlordecone exposure, length of gestation, and risk of preterm birth. American Journal of Epidemiology 179 (2014) 536-544.
[335] U. Luderer, J.S. Kesner, J.M. Fuller, E.F. Krieg, J.W. Meadows, S.L. Tramma, H.O. Yang, and D. Baker, Effects of gestational and lactational exposure to heptachlor epoxide on age at puberty and reproductive function in men and women. Environmental Research 121 (2013) 84-94.
[336] G.P. Daston, J.W. Gooch, W.J. Breslin, D.L. Shuey, A.I. Nikiforov, T.A. Fico, and J.W. Gorsuch, Environmental estrogens and reproductive health: A discussion of the human and environmental data. Reproductive Toxicology 11 (1997) 465-481.
[337] L.G. Costa, Organophosphorus compounds at 80: some old and new issues. Toxicological Sciences 162 (2018) 24-35.
[338] K. Sokoloff, W. Fraser, T.E. Arbuckle, M. Fisher, E. Gaudreau, A. LeBlanc, A.S. Morisset, and M.F. Bouchard, Determinants of urinary concentrations of dialkyl phosphates among pregnant women in Canada - Results from the MIREC study. Environment International 94 (2016) 133-140.
[339] A. Lewin, T.E. Arbuckle, M. Fisher, C.L. Liang, L. Marro, K. Davis, N. Abdelouahab, and W.D. Fraser, Univariate predictors of maternal concentrations of environmental chemicals: The MIREC study. International Journal of Hygiene and Environmental Health 220 (2017) 77-85.
[340] M.A. van den Dries, A. Pronk, M. Guxens, S. Spaan, T. Voortman, V.W. Jaddoe, T.A. Jusko, M.P. Longnecker, and H. Tiemeier, Determinants of organophosphate pesticide exposure in pregnant women: A population-based cohort study in the Netherlands. International Journal of Hygiene and Environmental Health 221 (2018) 489-501.
[341] Z. Abdeen, T. Berman, K. Azmi, R. Abu Seir, H. Agha, E. Ein-Mor, T. Goen, Y. Stein, E. Richter, and R. Calderon-Margalit, Urinary organophosphate metabolite levels in Palestinian pregnant women: results of the Middle East Regional Cooperation Project. International Journal of Environmental Health Research 26 (2016) 254-266.
[342] A. Bradman, B. Eskenazi, D.B. Barr, R. Bravo, R. Castorina, J. Chevrier, K. Kogut, M.E. Harnly, and T.E. McKone, Organophosphate urinary metabolite levels during pregnancy and after delivery in women living in an agricultural community. Environmental Health Perspectives 113 (2005) 1802-1807.
[343] G.D. Coronado, S. Holte, E. Vigoren, W.C. Griffith, D.B. Barr, E. Faustman, and B. Thompson, Organophosphate pesticide exposure and residential proximity to nearby fields evidence for the drift pathway. Journal of Occupational and Environmental Medicine 53 (2011) 884-891.

[344] E. Ein-Mor, Z. Ergaz-Shaltiel, T. Berman, T. Goen, J. Natsheh, A. Ben-Chetrit, R. Haimov-Kochman, and R. Calderon-Margalit, Decreasing urinary organophosphate pesticide metabolites among pregnant women and their offspring in Jerusalem: Impact of regulatory restrictions on agricultural organophosphate pesticides use? International Journal of Hygiene and Environmental Health 221 (2018) 775-781.
[345] S.E. Martenies, and M.J. Perry, Environmental and occupational pesticide exposure and human sperm parameters: A systematic review. Toxicology 307 (2013) 66-73.
[346] M.J. Perry, S.A. Venners, D.B. Barr, and X.P. Xu, Environmental pyrethroid and organophosphorus insecticide exposures and sperm concentration. Reproductive Toxicology 23 (2007) 113-118.
[347] M.J. Perry, S.A. Venners, X. Chen, X. Liu, G.F. Tang, H.X. Xing, D.B. Barr, and X.P. Xu, Organophosphorous pesticide exposures and sperm quality. Reproductive Toxicology 31 (2011) 75-79.
[348] R. Recio-Vega, G. Carnpo-Gomez, V.H. Borja-Aburto, J. Moran-Martinez, and M.E. Cebrian-Garcia, Organophosphorus pesticide exposure decreases sperm quality: association between sperm parameters and urinary pesticide levels. Journal of Applied Toxicology 28 (2008) 674-680.
[349] S. Yucra, M. Gasco, J. Rubio, and G.F. Gonzales, Semen quality in Peruvian pesticide applicators: association between urinary organophosphate metabolites and semen parameters. Environmental Health 7 (2008) 59.
[350] J.D. Meeker, N.P. Singh, L. Ryan, S.M. Duty, D.B. Barr, R.F. Herrick, D.H. Bennett, and R. Hauser, Urinary levels of insecticide metabolites and DNA damage in human sperm. Human Reproduction 19 (2004) 2573-2580.
[351] E. Dziewirska, M. Radwan, B. Wielgomas, A. Klimowska, P. Radwan, P. Kaluzny, W. Hanke, M. Slodki, and J. Jurewicz, Human semen quality, sperm DNA damage, and the level of urinary concentrations of 1N and TCPY, the biomarkers of nonpersistent insecticides. American Journal of Mens Health 13 (2018).
[352] L. Miranda-Contreras, R. Gomez-Perez, G. Rojas, I. Cruz, L. Berrueta, S. Salmen, M. Colmenares, S. Barreto, A. Balza, L. Zavala, Y. Morales, Y. Molina, L. Valeri, C.A. Contreras, and J.A. Osuna, Occupational exposure to organophosphate and carbamate pesticides affects sperm chromatin integrity and reproductive hormone levels among Venezuelan farm workers. Journal of Occupational Health 55 (2013) 195-203.
[353] O. Mehrpour, P. Karrari, N. Zamani, A.M. Tsatsakis, and M. Abdollahi, Occupational exposure to pesticides and consequences on male semen and fertility: A review. Toxicology Letters 230 (2014) 146-156.
[354] A.B. Harchegani, A. Rahmani, E. Tahmasbpour, H.B. Kabootaraki, H. Rostami, and A. Shahriary, Mechanisms of diazinon effects on impaired spermatogenesis and male infertility. Toxicology and Industrial Health 34 (2018) 653-664.
[355] L.C. Sanchez-Pena, B.E. Reyes, L. Lopez-Carrillo, R. Recio, J. Moran-Martinez, M.E. Cebrian, and B. Quintanilla-Vega, Organophosphorous pesticide exposure alters sperm chromatin structure in Mexican agricultural workers. Toxicology and Applied Pharmacology 196 (2004) 108-113.
[356] D.A. Savitz, T. Arbuckle, D. Kaczor, and K.M. Curtis, Male pesticide exposure and pregnancy outcome. American Journal of Epidemiology 146 (1997) 1025-1036.
[357] M. Sallmen, J. Liesivuori, H. Taskinen, M.L. Lindbohm, A. Anttila, L. Aalto, and K. Hemminki, Time to pregnancy among the wives of Finnish greenhouse workers. Scandinavian Journal of Work Environment & Health 29 (2003) 85-93.
[358] Y. Hu, L. Ji, Y. Zhang, R. Shi, W.C. Han, L.A. Tse, R. Pan, Y.W. Wang, G.D. Ding, J. Xu, Q.Y. Zhang, Y. Gao, Y. Tian, and S. Shanghai Birth Cohort, Organophosphate and pyrethroid pesticide exposures measured before conception and associations with time to pregnancy in chinese

couples enrolled in the Shanghai birth cohort. Environmental Health Perspectives 126 (2018) 077001.
[359] K. Hoffman, H.M. Stapleton, A. Lorenzo, C.M. Butt, L. Adair, A.H. Herring, and J.L. Daniels, Prenatal exposure to organophosphates and associations with birthweight and gestational length. Environment International 116 (2018) 248-254.
[360] Y.W. Wang, L.M. Chen, C.F. Wang, Y. Hum, Y. Gao, Y.J. Zhou, R. Shi, Y. Zhang, M. Kamijima, J. Ueyama, and Y. Tian, Association between organophosphate pesticide exposure and thyroid hormones in pregnant women. Epidemiology 28 (2017) S35-S40.
[361] D.R. Juberg, S.C. Gehen, K.K. Coady, M.J. LeBaron, V.J. Kramer, H.T. Lu, and M.S. Marty, Chlorpyrifos: Weight of evidence evaluation of potential interaction with the estrogen, androgen, or thyroid pathways. Regulatory Toxicology and Pharmacology 66 (2013) 249-263.
[362] T.K. Mandal, and N.S. Das, Correlation of testicular toxicity and oxidative stress induced by chlorpyrifos in rats. Human & Experimental Toxicology 30 (2011) 1529-1539.
[363] E.E. Elsharkawy, D. Yahia, and N.A. El-Nisr, Chlorpyrifos induced testicular damage in rats: ameliorative effect of glutathione antioxidant. Environmental Toxicology 29 (2014) 1011-1019.
[364] M. Babazadeh, and G. Najafi, Effect of chlorpyrifos on sperm characteristics and testicular tissue changes in adult male rats. Veterinary Research Forum 8 (2017) 319-326.
[365] J. Li, G. Pang, F. Ren, and B. Fang, Chlorpyrifos-induced reproductive toxicity in rats could be partly relieved under high-fat diet. Chemosphere 229 (2019) 94-102.
[366] P. De Silva, and L.A. Samayawardhena, Effects of chlorpyrifos on reproductive performances of guppy (Poecilia reticulata). Chemosphere 58 (2005) 1293-1299.
[367] K.A. Sumon, M.F. Yesmin, P.J. Van den Brink, R.H. Bosma, E. Peeters, and H. Rashid, Effects of long-term chlorpyrifos exposure on mortality and reproductive tissues of Banded Gourami (Trichogaster fasciata). Journal of Environmental Science and Health Part B-Pesticides Food Contaminants and Agricultural Wastes 54 (2019) 549-559.
[368] C.J. Burns, and T.P. Pastoor, Pyrethroid epidemiology: a quality-based review. Critical Reviews in Toxicology 48 (2018) 297-311.
[369] A.J. Li, and K. Kannan, Urinary concentrations and profiles of organophosphate and pyrethroid pesticide metabolites and phenoxyacid herbicides in populations in eight countries. Environment International 121 (2018) 1148-1154.
[370] M. Koureas, A. Tsakalof, A. Tsatsakis, and C. Hadjichristodoulou, Systematic review of biomonitoring studies to determine the association between exposure to organophosphorus and pyrethroid insecticides and human health outcomes. Toxicology Letters 210 (2012) 155-168.
[371] A.M. Saillenfait, D. Ndiaye, and J.P. Sabate, Pyrethroids: Exposure and health effects: An update. International Journal of Hygiene and Environmental Health 218 (2015) 281-292.
[372] A.M. Saillenfait, D. Ndiaye, and J.P. Sabate, The estrogenic and androgenic potential of pyrethroids in vitro. Review. Toxicology in Vitro 34 (2016) 321-332.
[373] E. Marettova, M. Maretta, and J. Legath, Effect of pyrethroids on female genital system. Review. Animal Reproduction Science 184 (2017) 132-138.
[374] X.Q. Ye, and L. Liu, Effects of pyrethroid insecticides on hypothalamic-pituitary-gonadal axis: A reproductive health perspective. Environmental Pollution 245 (2019) 590-599.
[375] Y. Han, Y.K. Xia, J.Y. Han, J.P. Zhou, S.L. Wang, P.F. Zhu, R.C. Zhao, N.Z. Jin, L. Song, and X.R. Wang, The relationship of 3-PBA pyrethroids metabolite and male reproductive hormones among non-occupational exposure males. Chemosphere 72 (2008) 785-790.
[376] J.D. Meeker, D.B. Barr, and R. Hauser, Pyrethroid insecticide metabolites are associated with serum hormone levels in adult men. Reproductive Toxicology 27 (2009) 155-160.
[377] J. Yoshinaga, K. Imai, H. Shiraishi, S. Nozawa, M. Yoshiike, M.N. Mieno, A.M. Andersson, and T. Iwamoto, Pyrethroid insecticide exposure and reproductive hormone levels in healthy Japanese male subjects. Andrology 2 (2014) 416-420.

[378] Q. Bian, L.C. Xu, S.L. Wang, Y.K. Xia, L.F. Tan, J.F. Chen, L. Song, H.C. Chang, and X.R. Wang, Study on the relation between occupational fenvalerate exposure and spermatozoa DNA damage of pesticide factory workers. Occupational and Environmental Medicine 61 (2004) 999-1005.

[379] J.D. Meeker, D.B. Barr, and R. Hauser, Human semen quality and sperm DNA damage in relation to urinary metabolites of pyrethroid insecticides. Human Reproduction 23 (2008) 1932-1940.

[380] G.X. Ji, Y.K. Xia, A.H. Gu, X.G. Shi, Y. Long, L. Song, S.L. Wang, and X.R. Wang, Effects of non-occupational environmental exposure to pyrethroids on semen quality and sperm DNA integrity in Chinese men. Reproductive Toxicology 31 (2011) 171-176.

[381] H.A. Young, J.D. Meeker, S.E. Martenies, Z.I. Figueroa, D.B. Barr, and M.J. Perry, Environmental exposure to pyrethroids and sperm sex chromosome disomy: a cross-sectional study. Environmental Health 12 (2013) 111.

[382] Y.K. Xia, Y. Han, B. Wu, S.L. Wang, A.H. Gu, N.X. Lu, J.L. Bo, L. Song, N.Z. Jin, and X.R. Wang, The relation between urinary metabolite of pyrethroid insecticides and semen quality in humans. Fertility and Sterility 89 (2008) 1743-1750.

[383] M. Radwan, J. Jurewicz, B. Wielgomas, W. Sobala, M. Piskunowicz, P. Radwan, and W. Hanke, Semen quality and the level of reproductive hormones after environmental exposure to pyrethroids. Journal of Occupational and Environmental Medicine 56 (2014) 1113-1119.

[384] J. Jurewicz, M. Radwan, W. Sobala, P. Radwan, L. Jakubowski, B. Wielgomas, D. Ligocka, S. Brzenicki, and W. Hanke, Exposure, to widespread environmental endocrine disrupting chemicals and human sperm sex ratio. Environmental Pollution 213 (2016) 732-740.

[385] Y.K. Xia, Q. Bian, L.C. Xu, S.P. Cheng, L. Song, J.Y. Liu, W. Wu, S.L. Wang, and X.R. Wang, Genotoxic effects on human spermatozoa among pesticide factory workers exposed to fenvalerate. Toxicology 203 (2004) 49-60.

[386] H. Toshima, Y. Suzuki, K. Imai, J. Yoshinaga, H. Shiraishi, Y. Mizumoto, S. Hatakeyama, C. Onohara, and S. Tokuoka, Endocrine disrupting chemicals in urine of Japanese male partners of subfertile couples: A pilot study on exposure and semen quality. International Journal of Hygiene and Environmental Health 215 (2012) 502-506.

[387] K. Imai, J. Yoshinaga, M. Yoshikane, H. Shiraishi, M.N. Mieno, M. Yoshiike, S. Nozawa, and T. Iwamoto, Pyrethroid insecticide exposure and semen quality of young Japanese men. Reproductive Toxicology 43 (2014) 38-44.

[388] J. Jurewicz, M. Radwan, B. Wielgomas, W. Sobala, M. Piskunowicz, P. Radwan, M. Bochenek, and W. Hanke, The effect of environmental exposure to pyrethroids and DNA damage in human sperm. Systems Biology in Reproductive Medicine 61 (2015) 37-43.

[389] M. Radwan, J. Jurewicz, B. Wielgomas, M. Piskunowicz, W. Sobala, P. Radwan, L. Jakubowski, W. Hawula, and W. Hanke, The association between environmental exposure to pyrethroids and sperm aneuploidy. Chemosphere 128 (2015) 42-48.

[390] C. Dereumeaux, A. Saoudi, S. Goria, V. Wagner, P. De Crouy-Chanel, M. Pecheux, B. Berat, C. Zaros, and L. Guldner, Urinary levels of pyrethroid pesticides and determinants in pregnant French women from the Elfe cohort. Environment International 119 (2018) 89-99.

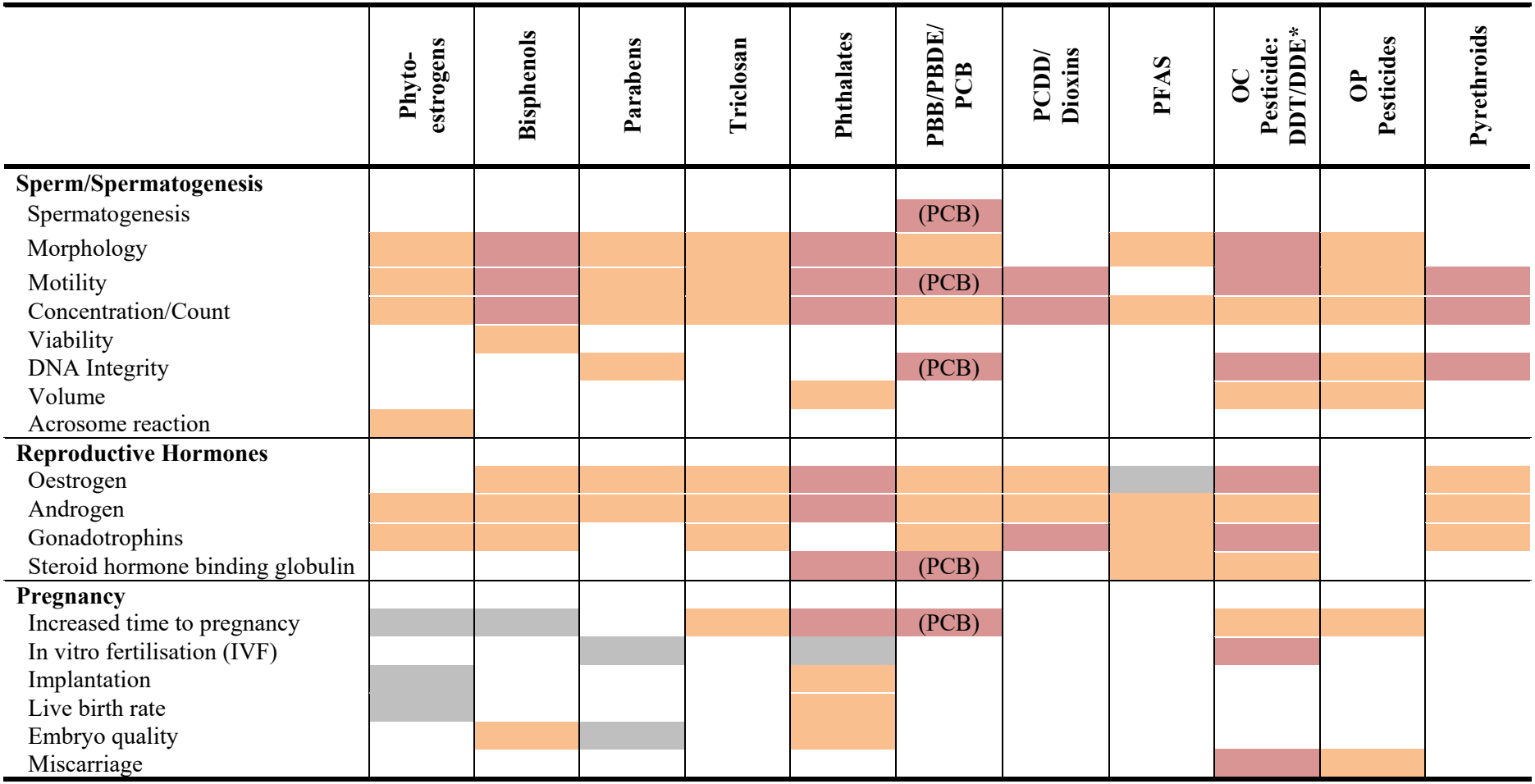
[391] K.W. Whitworth, D.D. Baird, A.Z. Steiner, R.M.S. Bornman, G.S. Travlos, R.E. Wilson, and M.P. Longnecker, Anti-Mullerian Hormone and lifestyle, reproductive, and environmental factors among women in rural South Africa. Epidemiology 26 (2015) 429-435.

[392] Y.J. Zhou, X.D. Wang, S. Xiao, D.E. Yu, L.Q. Wang, J.H. Wang, and H.Q. Zhu, Exposure to beta-cypermethrin impairs the reproductive function of female mice. Regulatory Toxicology and Pharmacology 95 (2018) 385-394.

[393] D. Zamkowska, A. Karwacka, J. Jurewicz, and M. Radwan, Environmental exposure to non-persistent endocrine disrupting chemicals and semen quality: An overview of the current epidemiological evidence. International Journal of Occupational Medicine and Environmental Health 31 (2018) 377-414.

[394] M.K. Chung, G.M. Buck Louis, K. Kannan, and C.J. Patel, Exposome-wide association study of semen quality: Systematic discovery of endocrine disrupting chemical biomarkers in fertility require large sample sizes. Environment International 125 (2019) 505-514.
[395] M.D. Griswold, Spermatogenesis: The commitment to meiosis. Physiological Reviews 96 (2016) 1-17.
[396] G.M. Buck Louis, M.M. Smarr, L. Sun, Z. Chen, M. Honda, W. Wang, R. Karthikraj, J. Weck, and K. Kannan, Endocrine disrupting chemicals in seminal plasma and couple fecundity. Environmental Research 163 (2018) 64-70.
[397] G.C. Di Renzo, J.A. Conry, J. Blake, M.S. DeFrancesco, N. DeNicola, J.N. Martin, Jr., K.A. McCue, D. Richmond, A. Shah, P. Sutton, T.J. Woodruff, S.Z. van der Poel, and L.C. Giudice, International Federation of Gynecology and Obstetrics opinion on reproductive health impacts of exposure to toxic environmental chemicals. International Journal of Gynecology & Obstetrics 131 (2015) 219-225.
[398] The American College of Obstetricians and Gynecologists Committee on Health Care for Underserved Women, and A.S.f.R.M.P. Committee, Committee Opinion: Exposure to Toxic Environmental Agents. in: T.A.C.o.O.a. Gynecologists, (Ed.), The American College of Obstetricians and Gynecologists, Washington D.C., USA, 2016, pp. 1-5.
[399] M. Bellingham, and R.M. Sharpe, Chemical exposures during pregnancy: dealing with potential, but unproven, risks to child health, Scientific Impact Paper, Royal College of Obstetricians and Gynaecologists, London, UK, 2013, pp. 1-7.
[400] L. Trasande, R.M. Shaffer, S. Sathyanarayana, and Council of Environmental, Food Additives and Child Health. Pediatrics 142 (2018) e20181410.

Table 1: Summary of studies on the influence of endocrine disrupting chemicals (EDCs) on male fertility and fecundity. Red shading indicates consistent results in ≥ 2 studies with n > 100 individuals. Orange shading indicates conflicting or inadequate sample sizes, irrespective of whether data supports an influence or not. Grey shading indicates that data support no effect in studies of sufficient statistical strength (in ≥ 2 studies with n > 100 individuals). White panels indicate studies were not available or did not meet the criterion of having n > 100 individuals in a study.



*Only data relating to dichlorodiphenyltrichloroethane (DDT) and dichlorodiphenyldichloroethylene (DDE) are captured in this table. Polybrominated biphenyls (PBB), polybrominated diphenyl ethers (PBDE), polychlorinated biphenyls (PCB), polychlorinated dibenzo-p-dioxins (PCDD), per- and poly-fluroalkyl substances (PFAS), organochlorides (OC), organophosphates (OP).

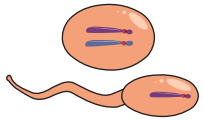
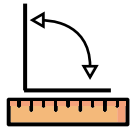
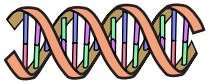
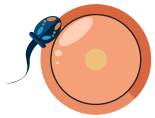
Table 2: Summary of studies on the influence of endocrine disrupting chemicals (EDCs) on female fertility and fecundity. Red shading indicates consistent results in ≥ 2 studies with n > 100 individuals. Orange shading indicates conflicting or inadequate sample sizes, irrespective of whether data supports an influence or not. Grey shading indicates that data support no effect in studies of sufficient statistical strength (in ≥ 2 studies with n > 100 individuals). White panels indicate studies were not available or did not meet the criterion of having n > 100 individuals in a study.

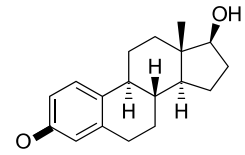
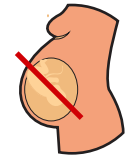
	Phyto-estrogen	Bisphenols	Parabens	Triclosan	Phthalates	PBB/PBDE/PCB	PCDD/Dioxins	PFAS	OC Pesticide: DDT/DDE*	OP Pesticides	Pyrethroids
Menstrual Cycle Characteristics											
Menstrual cycle length						(PCB)					
Age at menopause											
Oogenesis/Blastocyst											
Oocyte number/quality						(PCB)					
Ovarian response to stimulation						(PCB)					
Blastocyst formation											
Uterine Effects											
Changes in endometrium						(PCB)					
Reproductive Hormones											
Oestrogen											
Gonadotrophins											
Steroid hormone binding globulin											
Pregnancy											
Increased time to pregnancy						(PCB)					
In vitro fertilisation (IVF)											
Implantation											
Live birth rate											
Embryo quality											
Miscarriage											

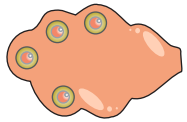
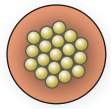
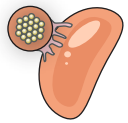
*Only data relating to dichlorodiphenyltrichloroethane (DDT) and dichlorodiphenyldichloroethylene (DDE) are captured in this table. Polybrominated biphenyls (PBB), polybrominated diphenyl ethers (PBDE), polychlorinated biphenyls (PCB), polychlorinated dibenzo-p-dioxins (PCDD), per- and poly-fluroalkyl substances (PFAS), organochlorides (OC), organophosphates (OP).

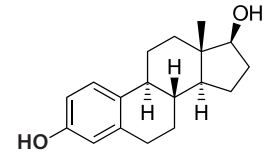
Highlights

- Strong evidence of negative associations between EDC exposure and fertility
- Male fertility is reduced by BPA, phthalate, PCB, PBDE, pyrethroid and DDE exposure
- Female fertility is reduced by BPA, PCB and organochloride pesticide exposure
- More studies on EDC exposure in men than women, with limited data for many EDCs
- Subfertile individuals or couples commonly exhibit higher EDC concentrations

	Stronger Evidence	Weaker Evidence
Sperm Motility/ Morphology 	Bisphenols OC Pesticides PCB PCDD/Dioxins Phthalates Pyrethroids	OP Pesticides Parabens PFAS Phytoestrogens Triclosan
Sperm Concentration/ Count 	Bisphenols Phthalates Pyrethroids	Triclosan OC/OP Pesticides Parabens PBB/PBDE/PCB PFAS Phytoestrogens
Semen Volume 		OC Pesticides OP Pesticides Phthalates
DNA Integrity 	PCB OC Pesticides Pyrethroids	OP Pesticides Parabens
Acrosome Reaction 		Phytoestrogens
Embryo Quality 		Bisphenols Phthalates

Weaker Evidence	Stronger Evidence
Bisphenols Parabens PFAS Pyrethroids Phytoestrogens Triclosan	**Steroid Action**  OC Pesticides PCB PCDD/Dioxin Phthalates
OC Pesticides OP Pesticides Triclosan	**Time to Pregnancy**  PCB Phthalates
OP Pesticides	**Miscarriage**  OC Pesticides

	Stronger Evidence	Weaker Evidence
Cycle Length **Age at Menopause** 	OC Pesticides PCB	PFAS Phytoestrogens Phthalates
Oocyte Number/Quality **Response to Stimulation** 	Bisphenols PCB	OC/OP Pesticides Phthalates Triclosan
Fertilisation 	PBB/PBDE/PCB	OC Pesticides Triclosan
Blastocyst Formation 	Bisphenols PCB/PBDB/PCDE	Triclosan
Implantation 	Bisphenols PBB/PBDE/PCB	Triclosan OC/OP Pesticides
Embryo Quality 	Bisphenols	Phthalates PBB/PBDE/PCB

Weaker Evidence	Stronger Evidence
OC/OP Pesticides PFAS Phytoestrogens Phthalates	**Steroid Action** Bisphenols 
Bisphenols OC/OP Pesticides Parabens PCDD/Dioxins PFAS Phthalates Pyrethroids Triclosan	**Time to Pregnancy** PCB 
Bisphenols PBB/PBDE/PCB PFAS Phthalates Triclosan	**Miscarriage** OC Pesticides