HHS Public Access

Author manuscript

Fertil Steril. Author manuscript; available in PMC 2024 December 01.

Published in final edited form as:

Fertil Steril. 2023 December ; 120(6): 1138–1149. doi:10.1016/j.fertnstert.2023.10.008.

Endocrine disrupting chemicals and male reproductive health

Lidia Mínguez-Alarcón[a,b], **Audrey J. Gaskins**[e], **John D. Meeker**[f], **Joseph M. Braun**[g], **Jorge E. Chavarro**[a,c,d]

[a]Channing Division of Network Medicine, Harvard Medical School and Brigham and Women's Hospital, Boston, MA, USA

[b]Departments of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, MA, USA

[c]Departments of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA

[d]Departments of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, USA

[e]Department of Epidemiology, Rollins School of Public Health, Emory University, 1518 Clifton Road, Atlanta, GA, 30322, USA.

[f]Department of Environmental Health Sciences, University of Michigan School of Public Health, Ann Arbor, Michigan, USA

[g]Department of Epidemiology, Brown University, Providence, RI, USA

Abstract

Modifiable factors, such as environmental exposures, can impact human fertility. The objective of this review is to summarize the potential effects of exposure to important endocrine disrupting chemicals on male reproductive health. The vast majority of experimental and animal data demonstrates strong evidence for negative effects of exposure to phenols, phthalates, pesticides and per- and poly-fluoroalkyl substances (PFAS) on male reproductive health. While evidence of negative associations in humans was overall strong for phthalates and pesticides, limited and inconclusive relationships were found for the other examined chemical biomarkers. Reasons for the discrepancies in results include, but are not limited to, differences in study populations, exposure concentrations, number of sample collected, sample sizes, study design and residual confounding. Additional studies are needed, particularly for newer phenols and PFAS, given the scarce literature on the topic and increasing exposures over time.

Correspondence: Lidia Mínguez-Alarcón, PhD. Department of Environmental Health, Harvard T. H. Chan School of Public Health, 665 Huntington Ave., Boston, MA 02115 (lminguez@hsph.harvard.edu).

Competing financial interests: None of the authors has any conflicts of interest to declare. Dr. Braun was financially compensated for serving as an expert witness for plaintiffs in litigation related to tobacco smoke exposures and received a honoraria for serving on an advisory board to Quest Diagnostics. Dr. Braun's institution was financially compensated for his services as an expert witness for plaintiffs in litigation related to PFAS-contaminated drinking water; these funds were not paid to JMB directly.

Introduction

Infertility, a disease characterized by the inability to achieve a pregnancy after more than 12 months of attempted conception, is estimated to affect about 10–15% of all couples worldwide.(1, 2) Male factor infertility, defined according to World Health Organization (WHO) reference values for semen quality, is the most prevalent cause accounting for 40% of infertility cases.(3) Poor testicular function has been also associated with higher risk of common chronic diseases and mortality, highlighting their public health importance beyond fertility and reproduction.(4–8) Attention to modifiable factors, such as environmental exposures, has emerged since they can impact human fertility.(9–12) In this review, we summarize available literature on exposure to important endocrine disrupting chemicals and male reproductive health.

Phenols

Environmental phenols include a wide range of chemicals such as bisphenols, parabens, and triclosan. Bisphenol A (BPA) is one of the most widely utilized and studied phenols, present in synthetic polymers (13, 14) building materials, thermal paper (15), toys, dental products (13, 16) and food packaging (17, 18). Given the endocrine disrupting activities associated with BPA (19–23), the replacement chemicals bisphenol S (BPS) and bisphenol F (BPF) were introduced in the market as potentially safer alternatives. Parabens — such as methylparaben, butylparaben, propylparaben, and ethylparaben — are used as food preservatives and shelf stabilizers (24, 25) and within personal care products such as shampoos, creams (26) and pharmaceutical products (27, 28). Triclosan and triclocarban are antimicrobial agents (29) used in personal hygiene products such as soaps, mouthwashes, toothpastes, and hand sanitizers (30). Benzophenone-3 is widely used in a variety of cosmetic products as a sunscreen agent that absorbs and dissipates ultraviolet (UV) radiation (31). Given their uses, phenols are most commonly absorbed through ingestion, dermal contact (32, 33), inhalation (34–38) or mucosal absorption (39–41) through the use of personal care and household products (42–45). Urine is the optimal matrix for quantifying phenols biomarkers because of their short half-lives (<24 hours), their metabolism and excretion, as well as being a non-invasive and convenient medium for biological monitoring (46).

These phenols have demonstrated endocrine disruption mechanisms. For example, aglycone (unconjugated) BPA has weak estrogenic activity through binding with different estrogen receptors (23, 47–50). BPA has also been shown in experimental animal studies to bind to the androgen receptor, peroxisome proliferator–activated receptor γ, and thyroid hormone receptor (51). In male rodents, the majority of studies on exposure to BPA and reproductive outcomes have confirmed these endocrine-disrupting activities leading to altered sperm counts, DNA damage and testosterone levels (52). Given their chemical structure, BPS and BPF have not surprisingly a similar toxicological profile to BPA based on in vivo and in vitro models (53). Specifically, animal models have demonstrated that BPS has similar endocrine disruption mechanisms to BPA, and can affect for example testosterone levels (54). Mechanisms of BPA analogues' effects have been found to be similar to those of BPA, including oxidative stress, anti-androgenic activity, genotoxicity, and mutagenicity

(54, 55). Parabens are suspected endocrine disrupting chemicals that are estrogenic (24, 56, 57), and have been shown to bind to both estrogen receptor (ER)α and (ER)β (58, 59). The estrogenic activity of parabens increases with increasing length and branching of the alkyl chain (e.g. BP > PP > MP) (57, 60, 61). Animal studies have found evidence between triclosan exposure with reproductive and developmental changes (62). In-vitro studies have demonstrated that triclosan could bind with estrogen and androgen receptors (with low affinity) to act as an agonist, antagonist, or to result in no action (63), altering testosterone production and overall leading to testicular damage (64–66) and even lower semen production (66). However, these results were not reproducible in two in-vivo studies in the same animal species (67, 68). Several benzophenones show estrogenic and antiandrogenic properties in vitro (69). These endocrine-disrupting properties appeared to lead to adverse reproductive outcomes in animal models (70, 71). For example, dermal and oral exposure to benzophenone-3 in rodents was associated with decreased sperm density and increased cycle length.

While the vast majority of *in vitro* and animal studies have confirmed endocrine-disrupting properties of the examined phenols on male reproductive outcomes, human studies have found mixed results. For example, three reviews found heterogeneous results on the relationship between exposure to BPA in men in relation to fertility, semen quality and reproductive hormone levels (52, 72, 73). Although the epidemiologic literature is growing, there is a stronger evidence supporting associations between urinary concentrations of BPA replacements (e.g. BPS and BPF) and male reproductive health in men (74–77). Only a handful of studies have evaluated male exposure to parabens in relation to semen quality and DNA fragmentation and results were also mixed and inconclusive (72, 78). Inconsistent results on environmental exposure to triclosan and semen quality/testosterone levels were also found in an overview of the epidemiological evidence (79) as well as in other individual studies (80, 81). However, other studies found that higher concentrations of triclosan were associated a few semen parameters or reproductive hormones (82–84). Only a handful of epidemiological studies have evaluated exposure to benzophenones in relation to semen quality and reproductive hormones and although suggestive associations were found, it was unclear whether these are of clinical importance (85, 86). The inconsistent results in the epidemiologic literature on environmental phenol biomarkers and male reproductive health may be due to different methodological aspects such as dose, exposure route, timing, and outcomes. Therefore, further studies in men are needed to clarify the role of these phenol biomarkers on male reproductive health. In addition, studies evaluating other phenols (e.g. other benzophenones, triclorocarban) are warranted given the scarce literature on the topic.

Phthalates

Phthalates are a group of chemicals that are used in a wide variety of products, including plastics, personal care products, and food packaging. High molecular weight phthalates, such as di-2-ethylhexyl phthalate (DEHP), diisononyl phthalate (DINP), diisodecyl phthalate (DIDP), and benzylbutyl phthalate (BzBP), have been used as plasticizers in flexible PVC commonly found in consumer products, food packaging, home furnishings, and other building materials, while low molecular weight phthalates (e.g., di-n-butyl phthalate [DnBP], diisobutyl phthalate [DiBP], and diethyl phthalate [DEP]) are used in personal care

products, certain dietary supplements and medications, and other consumer goods.(87, 88) These common and widespread uses result in ubiquitous exposure to phthalates. Ingestion, inhalation, and dermal contacts are possible routes of exposure for the general population, and that extends to *in utero* exposure to the developing fetus through the mother.(89) There is evidence that exposure levels of some commonly used phthalates for which health concerns have arisen, such as DEHP and DnBP, have been declining in the U.S. and in other populations.(88, 90–93) However, biomarkers of exposure to these phthalates can still be detected in most people.(88) On the other hand, for some common non-phthalate chemicals being used as phthalate replacements (e.g., DINCH, DEHTP), exposure has increased in recent years but health research remains limited.(88, 90–92, 94–97)

Experimental animal and *in vitro* studies have demonstrated that several phthalates possess anti-androgenic activity, and in rodents phthalate exposure causes reduced circulating testosterone and male reproductive tract abnormalities.(98) In fact, the collection of adverse reproductive effects that have been observed in male rats, including reduced testis weight, impaired spermatogenesis, and external genital malformations (shortened anogenital distance, hypospadias, and cryptorchidism), has been termed “phthalate syndrome” and has been hypothesized to manifest as testicular dysgenesis syndrome (TDS) in humans following phthalate-induced androgen deficiency *in utero*.(99, 100) However, variability in the presence and severity of these effects have been reported across specific phthalate chemicals and test species.(101, 102) In addition to endocrine disruption and decreased testosterone levels, oxidative stress is another biological pathway that has been associated with phthalate exposure and could have subsequent adverse impacts on male reproduction. (72, 103)

Numerous human studies have been conducted on exposure to phthalates in relation to male reproductive endpoints over the past couple of decades. However, studies have varied in design, study population, life stage, and reproductive health endpoints being studied, including time to pregnancy, semen quality parameters, sperm DNA damage, circulating hormone levels, anogenital distance, reproductive tract abnormalities (hypospadias/cryptorchidism), and pubertal development.

The largest number of studies have been conducted for relationships of phthalate exposure with semen quality and/or circulating hormone levels among adult men. Among studies of semen quality parameters, a systematic review of the human epidemiological data concluded that there was moderate to robust evidence for reductions in semen quality in relation to DEHP, DnBP, BzBP, and DINP exposure levels based on generally consistent findings across up to 14 different studies (depending on the specific phthalate).(102) The authors of that review also reported a moderate level of evidence for associations between exposure to DEHP, DINP, and DiBP and reduced testosterone levels based on results from up to 13 different studies of adult men. Overall conclusions for other phthalates in relation to semen quality or testosterone levels were less clear due to inconsistent results across studies. For other reproductive endpoints in adult men, such as delayed time to pregnancy in relation to male phthalate exposure or sperm DNA damage and sperm aneuploidy, there is some evidence for associations with certain phthalates but studies have been more limited in number.(72, 102, 104)

Among studies investigating early life (e.g., gestational) exposure to phthalates and male reproductive health, several studies have reported associations with decreased anogenital distance (AGD), developmental anomalies of the reproductive tract, and altered circulating hormone levels during infancy. A recent systematic review and meta-analysis of 19 studies involving phthalate exposures during pregnancy and male reproductive disorders concluded that *in utero* exposures to DEHP, DnBP, BzBP, and DEP were associated with reductions in AGD, whereas DEHP and DIDP were associated with increased risk of cryptorchidism and hypospadias.(105) Exposure to phthalates during pregnancy or in childhood may also be associated with impacts on pubertal development in boys, with several studies reporting later onset or slower pubertal development in association with phthalate exposure which may be consistent with their anti-androgenic activity.(106–111) However, not all studies of phthalate exposure and pubertal development have reported similar associations.(112, 113)

Taken together, there is substantial evidence from both animal and human studies that multiple phthalates adversely impact male reproduction. Inconsistencies in specific results between human studies could be due to a wide range of factors including differences in underlying study populations related to demographics, susceptibility, exposure levels, and other risk factors, varying approaches to assessing exposure, differences in the ages at which exposure and endpoints are being assessed, or numerous other reasons. Additional well-designed studies, particularly those focused on early life exposure and later impacts on reproductive health, would further aid in risk assessment, as would studies offering robust insight into dose-response relationships and detailed investigations of other phthalates or non-phthalate chemicals being increasingly used as replacements.

Pesticides

Pesticides - which include herbicides, insecticides and fungicides - are defined as any substance or mixture of substances intended for preventing, destroying, repelling or mitigating any pest.(114) Pesticide use in agriculture accounts for approximately 90% of the total pesticide usage.(115) This utilization pattern would suggest that any health effects of exposure to pesticides would be primarily an occupational health concern limited to individuals directly involved in the manufacture or the application of pesticides. However, nationally representative surveillance data shows that nearly all Americans have detectable levels of pesticides or pesticides metabolites in urine or blood (116) suggesting ubiquitous sources of exposure to pesticides in the general. Although residential use of pesticides is one of these sources of exposure, diet, and in particular consumption of fruits and vegetables, is the primary source of exposure to pesticides and pesticide metabolites in the general population. (117, 118) The Food and Drug Administration’s (FDA) Pesticide Residue Monitoring Program has shown that a considerable proportion of domestic fruits and vegetables had detectable pesticide residue or had residue levels exceeding the EPA standards.(119, 120) Further evidence of the importance of diet to pesticide exposure are randomized trials of conventionally grown vs. organically grown produce, which have consistently shown that switching from conventionally grown to organically grown diets significantly reduces urinary levels of pesticides residues, including cross-over trials where urinary levels increase again after the intervention ends. (121–124) Although the ubiquity of exposure to pesticides in the general population and the importance of diet in determining

exposure are settled matters, an important question is the extent to which exposure to pesticides, whether it be at high occupational exposure levels or at background general population levels, carries any risks to men's reproductive health.

There is strong experimental evidence in animal models that exposure to organophosphate (OP) and pyrethroid (PYR) insecticides such as diazinon,(125–128) chlorpyrifos(129–133) and permethrin,(132, 134–139) as well as the herbicide 2,4-D,(140–146) negatively impact men's reproductive health through a variety of mechanisms including inducing oxidative stress, disrupting hormonal pathways and altering the chromatin structure of sperm DNA (147–149). For example, oral administration of cis-permethrin,(135) 2,4-D,(143) or chlorpyrifos(131) resulted in testicular toxicity by altering Leydig cells and testosterone biosynthesis and production in rodent models. Moreover, one study in mice found that chlorpyrifos-methyl exposure during the organogenesis period disrupted DNA methylation of the imprinted *H19* gene in sperm and impaired offspring's early development.(150) Another study found that chlorpyrifos-methyl exposure was associated with bovine sperm epigenetic gene methylation patterns affecting fertilization and embryo development.(151)

In humans, pesticides gained attention as potential male reproductive toxicants in the late 1970s after linking occupational exposure to 1,2-dibromo-3-chloropropane (DBCP) to azoospermia, oligospermia and higher serum levels of FSH and LH among men working in a pesticide factory. (152) Subsequent work has documented associations between biomarkers of exposure to other pesticides with poor semen quality in non-occupational settings. Chlorpyrifos has been associated to lower sperm concentration and motility,(153) reduced testosterone(154) and estradiol(155) levels, and increased sperm DNA damage.(156) Other biomarkers of exposure to OP, such as TCPY(157) and IMPY,(158) as well as pyrethroids, (159–161) and 2,4-D,(158) have been also negatively associated with either semen quality parameters or sperm DNA damage, as previously reviewed.(162) Since biomarkers of exposure cannot differentiate between exposure from dietary sources and exposure from non-dietary sources, such as the use of pesticides in home gardening or other residential uses, a particularly difficult to answer yet important question is the extent to which exposure to pesticides through diet specifically has an impact on men's fertility. Although data addressing this specific issue is scarce, it suggests that exposure to pesticides through intake of fruits and vegetables specifically can have a deleterious impact on men's fertility. Using a data from the USDA Pesticide Data Program, Chiu and colleagues developed a classification method that distinguishes between produce with low and high presence of pesticide residues in the US food supply (163, 164) (Table 1). Using this classification method, they found that intake of high-pesticide residue fruits and vegetables is related to lower sperm count and normal morphology, whereas intake of low-pesticide residue fruits and vegetables is related to higher sperm count (165, 166). Taken together, there is cumulative evidence proving associations between occupational and environmental pesticide exposure in relation to male reproductive health.

Per- and Polyfluoroalkyl Substance Exposure

Per- and polyfluoroalkyl substances (PFAS) include thousands of environmentally persistent and bioaccumulative anthropogenic chemicals used in oil and water repellant textiles,

food contact materials, cleaning products, firefighting foams, cosmetics, and hundreds of other products since the 1950s.(167–169) Human exposure is primarily derived from contaminated food and drinking water.(170–175) Experimental studies in animals show that exposure to PFAS during gestation or adulthood may adversely affect reproductive health by altering sperm membrane permeability, increasing oxidative stress and inducing sperm apoptosis, reducing expression of gonadotropin releasing hormone and production of testosterone, disrupting or destroying of the blood-testis-barrier, and altering Leydig and Sertoli cell gene expression.(176–179)

We identified 14 epidemiological studies examining the association of serum PFAS concentrations with semen parameters and reproductive hormone concentrations.(180–193) Two papers from one study also quantified PFAS levels in seminal plasma. Sample sizes ranged from 105 to 1,041.(194, 195) Notably, most studies were cross-sectional and conducted in China or Scandinavian countries. Two prospectively measured PFAS concentrations during pregnancy in relation to these outcomes in young adult males. Finally, four studies examined associations between PFAS exposure and germ cell cancers diagnosis or mortality using prospective cohort, ecological, or nested case-control designs. Nearly all of these studies controlled for potential confounding factors related to PFAS exposure or reproductive health.

Generally, the associations of serum PFAS with semen parameters in cross-sectional studies were inconsistent. In fact, several studies suggested positive associations between some PFAS and semen parameters (e.g., higher sperm concentration).(185) A case-control study reported that higher serum perfluorooctanoic acid (PFOA) and perfluorosulfonic acid (PFOS) concentrations were associated with lower odds of having low sperm motility.(191) In a study of 664 Chinese men semen concentrations of five different PFAS, but not serum concentrations, were associated with lower sperm progressive motility and higher DNA fragmentation; these associations exhibited monotonic dose-response relations.(194) Other semen parameters were not monotonically related to semen PFAS levels. There were moderate correlations between PFAS in serum and semen (Pearson r=0.58 to 0.83) The results of this study, in conjunction with the relatively null associations among studies using serum PFAS biomarkers, suggests that PFAS exposure measures at the target tissue of interest (i.e., gonads) may be better indicators of the potential reproductive toxicity of PFAS.

Several studies suggest that exposure to some PFAS were associated with reproductive hormone levels in young men. In six studies, serum perfluorooctanoic acid (PFOA), perfluorosulfonic acid (PFOS), or perfluorohexanoic acid concentrations were associated with lower testosterone, higher luteinizing hormone (LH), and higher follicle stimulating hormone (FSH); although the specific PFAS-hormone associations were inconsistent. (180–182, 188, 189, 192) In two nationally representative samples of US boys, PFAS concentrations were not associated with lower reproductive hormone levels. In a study with both serum and semen PFAS measures, the same PFAS associated with lower sperm progressive motility and higher DNA fragmentation were also associated with lower testosterone concentrations. In models adjusted for both serum and semen PFAS, the serum PFAS associations were attenuated to null, suggesting that associations between PFAS exposure and testosterone is mediated by PFAS concentrations in semen.

Two studies prospectively examined the association of prenatal PFAS exposure with semen parameters and reproductive hormones in young men. Vested et al. reported that maternal PFOA concentrations during pregnancy were associated with lower sperm count and concentrations and higher LH and FSH 164 young Danish men.(193) In a separate cohort of 864 Danish men, higher concentrations of a mixture of seven PFAS were associated with lower sperm count and concentration, and more nonprogressive and immotile sperm.(190) They also observed suggestive positive associations between this mixture and LH. These mixture associations were primarily due to perfluoroheptanoic acid (PFHpA, 42–65%) and to a lesser extent (PFOS, 6–17%) and perfluoroundecanoic acid (11–15%).

There is consistent evidence that exposure to PFOA or PFOS is associated with testicular cancer in men. Two studies of Ohio and West Virginia residents living in communities with PFOA-contaminated drinking found that serum PFOA concentrations were associated with elevated risk of testicular cell cancer,(196, 197) with evidence of a monotonic dose-response relation in one study.(196) In an ecological study, the risk of testicular cancer mortality was elevated among male Italians residing in 24 municipalities with PFOA/PFOS-contaminated drinking compared to residents in 56 uncontaminated municipalities.(198) In a study of 530 case-control pairs of US Air Force servicemen, PFOS concentrations before cancer diagnosis were monotonically associated with elevated odds of testicular cancer (OR for 4^{th} vs. 1^{st} quartile: 4.6, 95% CI: 1.4, 15.1).(199)

The results of epidemiological studies to date suggest that young adulthood exposure to some PFAS may be associated with increased risk of testicular cancer and subtle alterations in reproductive hormones, but the impact of PFAS on semen parameters is less conclusive. There is emerging evidence that prenatal exposure to individual PFAS and their mixture is associated with altered reproductive hormones and reduced semen quality. Additional prospective studies using semen PFAS biomarkers are needed to determine if and when exposure to PFAS impacts semen parameters and risk of testicular cancer, if alterations in reproductive hormones mediate this association, and estimate the aggregate impact of PFAS mixtures on reproductive health.

Air Pollution

Several animal studies have demonstrated that air pollution, particularly due to diesel exhaust, has harmful effects on sperm quality including decreased production of spermatozoa and increased sperm DNA damage (200, 201). Other animal studies have also observed structural changes in Leydig cells, a reduction in the number of Sertoli cells, decreases in testosterone concentrations, and increases in luteinizing hormone (LH) concentrations after exposure to diesel exhaust (202–204).

A systematic review published in 2023 identified 22 studies on the association between air pollution and semen quality.(205) After excluding studies who reported data in an incongruent fashion and who examined exposure time windows outside of the 90 days prior to semen collection, 11 studies including over 60,000 men and 80,000 semen samples were retained for the meta-analysis. These 11 studies were diverse in their geographic region of origin (15 from Asia, 3 from North America, 3 from Europe, and 1 from South America), study design (13 longitudinal and 9 cross-sectional), and patient populations

(13 from the general population and 9 from men attending fertility clinics). After pooling data from the eligible studies, the authors concluded that a 10 μg/m^3 increase in ambient exposure to PM_{10} and SO_2 during the 90 days prior to semen analysis was associated with a 2.2% (95% CI 0.1, 4.2%) and 8.6% (95% CI 1.0–15.6%) lower sperm concentration, respectively. No associations were identified for $PM_{2.5}$, NO_2, CO, or O_3. Similar results were observed for total sperm count. Regarding motility, the meta-analyses showed that a 10 μg/m^3 increase in ambient exposure to $PM_{2.5}$ and PM_{10} was associated with a 1.1% (95% CI 0.3, 1.8%) and 0.8% (0.4, 1.1%) lower total motility, respectively. Results were similar, albeit slightly attenuated for progressive motility. There were no associations between the gaseous pollutants and total or progressive sperm motility. Although beyond the scope of this meta-analysis, several studies have also pointed to an inverse association between exposure to ambient air pollutants, especially PM_{10}, $PM_{2.5}$, and SO_2, and decreased testosterone levels,(206–208) further suggesting that air pollution might be disrupting the function of hypothalamus pituitary gonadal axis.

Despite these consistent observations of a negative association between ambient air pollution and semen quality parameters, it still remains to be determined whether this translates into effects on couple-based fertility endpoints. Conducting epidemiologic studies on paternal air pollution exposure and fecundability is challenging because the majority of couples trying to conceive (with or without medical assistance) reside at the same address and are assigned the same air pollution exposures. This makes differentiating the influence of maternal versus paternal exposures virtually impossible in the absence of personal or occupational exposure assessment. A single study found a higher risk of spontaneous abortion, stillbirth, and neonatal death in wives of traffic policemen versus matched controls.(209) These findings, along with data linking DNA fragmentation to higher rates of miscarriage,(210, 211) suggest that paternal air pollution could have an independent, detrimental effect on couple fertility, yet studies directly addressing this hypothesis are limited. Future studies could also focus on wildfire smoke and personal exposure reduction techniques (e.g. use of masks or personal home filters) in relation to male reproductive health given increasing the importance of these exposures and the lack of studies directly evaluating them.

Conclusions

We have reviewed the available literature on the association of exposure to selected endocrine disrupting chemicals with male reproductive health (Table 2). The vast majority of experimental and animal data demonstrated strong evidence for negative effects of exposure to phenols, phthalates, pesticides and PFAS on male reproductive health. While the human evidence supporting associations with male exposure to phthalates and pesticide biomarkers is strong, associations with several phenols, PFAS and air pollution remains limited and inconclusive. Additional studies are needed, particularly for newer phenols and PFAS, given the scarce literature on the topic and increasing exposures over time.

Funding:

The project was funded by grants R01ES022955 and R01ES009718, R01ES033651, and R01ES034700 from the National Institute of Environmental Health Sciences (NIEHS).

References

1. Inhorn MC, Patrizio P. Infertility around the globe: new thinking on gender, reproductive technologies and global movements in the 21st century. Human reproduction update 2015;21:411–26. [PubMed: 25801630]
2. Mascarenhas MN, Flaxman SR, Boerma T, Vanderpoel S, Stevens GA. National, regional, and global trends in infertility prevalence since 1990: a systematic analysis of 277 health surveys. PLoS medicine 2012;9:e1001356. [PubMed: 23271957]
3. Legare C, Droit A, Fournier F, Bourassa S, Force A, Cloutier F et al. Investigation of male infertility using quantitative comparative proteomics. Journal of proteome research 2014;13:5403–14. [PubMed: 25355644]
4. Eisenberg ML, Li S, Behr B, Cullen MR, Galusha D, Lamb DJ et al. Semen quality, infertility and mortality in the USA. Human reproduction (Oxford, England) 2014;29:1567–74. [PubMed: 24838701]
5. Choy JT, Eisenberg ML. Male infertility as a window to health. Fertility and sterility 2018;110:810–4. [PubMed: 30316415]
6. Eisenberg ML, Li S, Cullen MR, Baker LC. Increased risk of incident chronic medical conditions in infertile men: analysis of United States claims data. Fertility and sterility 2016;105:629–36. [PubMed: 26674559]
7. Jensen TK, Jacobsen R, Christensen K, Nielsen NC, Bostofte E. Good semen quality and life expectancy: a cohort study of 43,277 men. American journal of epidemiology 2009;170:559–65. [PubMed: 19635736]
8. Latif T, Kold Jensen T, Mehlsen J, Holmboe SA, Brinth L, Pors K et al. Semen Quality as a Predictor of Subsequent Morbidity: A Danish Cohort Study of 4,712 Men With Long-Term Follow-up. American journal of epidemiology 2017;186:910–7. [PubMed: 28498890]
9. Kahn LG, Philippat C, Nakayama SF, Slama R, Trasande L. Endocrine-disrupting chemicals: implications for human health. The lancet Diabetes & endocrinology 2020;8:703–18. [PubMed: 32707118]
10. Rattan S, Zhou C, Chiang C, Mahalingam S, Brehm E, Flaws JA. Exposure to endocrine disruptors during adulthood: consequences for female fertility. The Journal of endocrinology 2017;233:R109–r29. [PubMed: 28356401]
11. Minguez-Alarcon L, Gaskins AJ. Female exposure to endocrine disrupting chemicals and fecundity: a review. Current opinion in obstetrics & gynecology 2017;29:202–11. [PubMed: 28557831]
12. Laws MJ, Neff AM, Brehm E, Warner GR, Flaws JA. Endocrine disrupting chemicals and reproductive disorders in women, men, and animal models. Adv Pharmacol 2021;92:151–90. [PubMed: 34452686]
13. Flint S, Markle T, Thompson S, Wallace E. Bisphenol A exposure, effects, and policy: a wildlife perspective. In: J Environ Manage. Vol. 104, 2012:19–34.
14. Hoekstra EJ, Simoneau C. Release of bisphenol A from polycarbonate: a review. Crit Rev Food Sci Nutr 2013;53:386–402. [PubMed: 23320909]
15. Ehrlich S, Calafat AM, Humblet O, Smith T, Hauser R. Handling of thermal receipts as a source of exposure to bisphenol A. JAMA 2014;311:859–60. [PubMed: 24570250]
16. Huang YQ, Wong CK, Zheng JS, Bouwman H, Barra R, Wahlstrom B et al. Bisphenol A (BPA) in China: a review of sources, environmental levels, and potential human health impacts. Environ Int 2012;42:91–9. [PubMed: 21596439]
17. Niu Y, Zhang J, Wu Y, Shao B. Analysis of bisphenol A and alkylphenols in cereals by automated on-line solid-phase extraction and liquid chromatography tandem mass spectrometry. J Agric Food Chem 2012;60:6116–22. [PubMed: 22646661]
18. Yoshida T, Horie M, Hoshino Y, Nakazawa H. Determination of bisphenol A in canned vegetables and fruit by high performance liquid chromatography. Food Addit Contam 2001;18:69–75. [PubMed: 11212549]

19. Rezg R, El-Fazaa S, Gharbi N, Mornagui B. Bisphenol A and human chronic diseases: current evidences, possible mechanisms, and future perspectives. Environ Int 2014;64:83–90. [PubMed: 24382480]
20. Rochester JR. Bisphenol A and human health: a review of the literature. Reprod Toxicol 2013;42:132–55. [PubMed: 23994667]
21. Bonefeld-Jorgensen EC, Long M, Hofmeister MV, Vinggaard AM. Endocrine-disrupting potential of bisphenol A, bisphenol A dimethacrylate, 4-n-nonylphenol, and 4-n-octylphenol in vitro: new data and a brief review. Environmental health perspectives 2007;115 Suppl 1:69–76. [PubMed: 18174953]
22. De Coster S, van Larebeke N. Endocrine-disrupting chemicals: associated disorders and mechanisms of action. J Environ Public Health 2012;2012:713696. [PubMed: 22991565]
23. Matsushima A, Kakuta Y, Teramoto T, Koshiba T, Liu X, Okada H et al. Structural evidence for endocrine disruptor bisphenol A binding to human nuclear receptor ERR gamma. J Biochem 2007;142:517–24. [PubMed: 17761695]
24. Soni MG, Carabin IG, Burdock GA. Safety assessment of esters of p-hydroxybenzoic acid (parabens). Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association 2005;43:985–1015. [PubMed: 15833376]
25. Soni MG, Taylor SL, Greenberg NA, Burdock GA. Evaluation of the health aspects of methyl paraben: a review of the published literature. Food Chem Toxicol 2002;40:1335–73. [PubMed: 12387298]
26. Guo Y, Wang L, Kannan K. Phthalates and parabens in personal care products from China: concentrations and human exposure. Arch Environ Contam Toxicol 2014;66:113–9. [PubMed: 23880707]
27. Ma WL, Zhao X, Lin ZY, Mohammed MO, Zhang ZF, Liu LY et al. A survey of parabens in commercial pharmaceuticals from China and its implications for human exposure. Environ Int 2016;95:30–5. [PubMed: 27476643]
28. Moreta C, Tena MT, Kannan K. Analytical method for the determination and a survey of parabens and their derivatives in pharmaceuticals. Environ Res 2015;142:452–60. [PubMed: 26252961]
29. Alfhili MA, Lee MH. Triclosan: An Update on Biochemical and Molecular Mechanisms. Oxid Med Cell Longev 2019;2019:1607304. [PubMed: 31191794]
30. Weatherly LM, Gosse JA. Triclosan exposure, transformation, and human health effects. J Toxicol Environ Health B Crit Rev 2017;20:447–69. [PubMed: 29182464]
31. Calafat AM, Wong LY, Ye X, Reidy JA, Needham LL. Concentrations of the sunscreen agent benzophenone-3 in residents of the United States: National Health and Nutrition Examination Survey 2003−-2004. Environmental health perspectives 2008;116:893–7. [PubMed: 18629311]
32. Chedgzoy P, Winckle G, Heard CM. Triclosan: release from transdermal adhesive formulations and in vitro permeation across human epidermal membranes. Int J Pharm 2002;235:229–36. [PubMed: 11879757]
33. Moss T, Howes D, Williams FM. Percutaneous penetration and dermal metabolism of triclosan (2,4, 4'-trichloro-2'-hydroxydiphenyl ether). Food Chem Toxicol 2000;38:361–70. [PubMed: 10722890]
34. Bledzka D, Gromadzinska J, Wasowicz W. Parabens. From environmental studies to human health. Environ Int 2014;67:27–42. [PubMed: 24657492]
35. Loganathan SN, Kannan K. Occurrence of bisphenol A in indoor dust from two locations in the eastern United States and implications for human exposures. Arch Environ Contam Toxicol 2011;61:68–73. [PubMed: 21221962]
36. Matsumoto H, Adachi S, Suzuki Y. Bisphenol A in ambient air particulates responsible for the proliferation of MCF-7 human breast cancer cells and Its concentration changes over 6 months. Arch Environ Contam Toxicol 2005;48:459–66. [PubMed: 15883673]
37. Moos RK, Angerer J, Dierkes G, Bruning T, Koch HM. Metabolism and elimination of methyl, iso- and n-butyl paraben in human urine after single oral dosage. Arch Toxicol 2016;90:2699–709. [PubMed: 26608183]

38. Rudel RA, Camann DE, Spengler JD, Korn LR, Brody JG. Phthalates, alkylphenols, pesticides, polybrominated diphenyl ethers, and other endocrine-disrupting compounds in indoor air and dust. Environmental science & technology 2003;37:4543–53. [PubMed: 14594359]
39. Bagley DM, Lin YJ. Clinical evidence for the lack of triclosan accumulation from daily use in dentifrices. Am J Dent 2000;13:148–52. [PubMed: 11763951]
40. Lin YJ. Buccal absorption of triclosan following topical mouthrinse application. Am J Dent 2000;13:215–7. [PubMed: 11763935]
41. Sandborgh-Englund G, Adolfsson-Erici M, Odham G, Ekstrand J. Pharmacokinetics of triclosan following oral ingestion in humans. J Toxicol Environ Health A 2006;69:1861–73. [PubMed: 16952905]
42. Hauser R, Calafat AM. Phthalates and human health. Occupational and environmental medicine 2005;62:806–18. [PubMed: 16234408]
43. Schettler T Human exposure to phthalates via consumer products. International journal of andrology 2006;29:134–9; discussion 81–5. [PubMed: 16466533]
44. Silva MJ, Barr DB, Reidy JA, Malek NA, Hodge CC, Caudill SP et al. Urinary levels of seven phthalate metabolites in the U.S. population from the National Health and Nutrition Examination Survey (NHANES) 1999–2000. Environ Health Perspect 2004;112:331–8. [PubMed: 14998749]
45. Zota AR, Calafat AM, Woodruff TJ. Temporal trends in phthalate exposures: findings from the National Health and Nutrition Examination Survey, 2001–2010. Environmental health perspectives 2014;122:235–41. [PubMed: 24425099]
46. Calafat AM, Longnecker MP, Koch HM, Swan SH, Hauser R, Goldman LR et al. Optimal Exposure Biomarkers for Nonpersistent Chemicals in Environmental Epidemiology. Environmental health perspectives 2015;123:A166–8. [PubMed: 26132373]
47. Gould JC, Leonard LS, Maness SC, Wagner BL, Conner K, Zacharewski T et al. Bisphenol A interacts with the estrogen receptor alpha in a distinct manner from estradiol. Molecular and cellular endocrinology 1998;142:203–14. [PubMed: 9783916]
48. Kuiper GG, Lemmen JG, Carlsson B, Corton JC, Safe SH, van der Saag PT et al. Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor beta. Endocrinology 1998;139:4252–63. [PubMed: 9751507]
49. Dong S, Terasaka S, Kiyama R. Bisphenol A induces a rapid activation of Erk1/2 through GPR30 in human breast cancer cells. Environmental pollution (Barking, Essex : 1987) 2011;159:212–8. [PubMed: 20875696]
50. Okada H, Tokunaga T, Liu X, Takayanagi S, Matsushima A, Shimohigashi Y. Direct evidence revealing structural elements essential for the high binding ability of bisphenol A to human estrogen-related receptor-gamma. Environ Health Perspect 2008;116:32–8. [PubMed: 18197296]
51. Richter CA, Birnbaum LS, Farabollini F, Newbold RR, Rubin BS, Talsness CE et al. In vivo effects of bisphenol A in laboratory rodent studies. Reproductive Toxicology 2007;24:199–224. [PubMed: 17683900]
52. Mínguez-Alarcón L, Hauser R, Gaskins AJ. Effects of bisphenol A on male and couple reproductive health: a review. Fertility and sterility 2016;106:864–70. [PubMed: 27498136]
53. Rochester JR, Bolden AL. Bisphenol S and F: A Systematic Review and Comparison of the Hormonal Activity of Bisphenol A Substitutes. Environmental health perspectives 2015;123:643–50. [PubMed: 25775505]
54. Ullah H, Jahan S, Ain QU, Shaheen G, Ahsan N. Effect of bisphenol S exposure on male reproductive system of rats: A histological and biochemical study. Chemosphere 2016;152:383–91. [PubMed: 26994432]
55. Fic A, Žegura B, Sollner Dolenc M, Filipič M, Peterlin Mašič L. Mutagenicity and DNA damage of bisphenol A and its structural analogues in HepG2 cells. Arhiv za higijenu rada i toksikologiju 2013;64:189–200. [PubMed: 23819927]
56. Golden R, Gandy J, Vollmer G. A review of the endocrine activity of parabens and implications for potential risks to human health. Critical reviews in toxicology 2005;35:435–58. [PubMed: 16097138]

57. Routledge EJ, Parker J, Odum J, Ashby J, Sumpter JP. Some alkyl hydroxy benzoate preservatives (parabens) are estrogenic. Toxicology and applied pharmacology 1998;153:12–9. [PubMed: 9875295]
58. Okubo T, Yokoyama Y, Kano K, Kano I. ER-dependent estrogenic activity of parabens assessed by proliferation of human breast cancer MCF-7 cells and expression of ERalpha and PR. Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association 2001;39:1225–32. [PubMed: 11696396]
59. Gomez E, Pillon A, Fenet H, Rosain D, Duchesne MJ, Nicolas JC et al. Estrogenic activity of cosmetic components in reporter cell lines: parabens, UV screens, and musks. Journal of toxicology and environmental health Part A 2005;68:239–51. [PubMed: 15799449]
60. Byford JR, Shaw LE, Drew MG, Pope GS, Sauer MJ, Darbre PD. Oestrogenic activity of parabens in MCF7 human breast cancer cells. The Journal of steroid biochemistry and molecular biology 2002;80:49–60. [PubMed: 11867263]
61. Vo TT, Yoo YM, Choi KC, Jeung EB. Potential estrogenic effect(s) of parabens at the prepubertal stage of a postnatal female rat model. Reproductive toxicology (Elmsford, NY) 2010;29:306–16.
62. Johnson PI, Koustas E, Vesterinen HM, Sutton P, Atchley DS, Kim AN et al. Application of the Navigation Guide systematic review methodology to the evidence for developmental and reproductive toxicity of triclosan. Environment international 2016;92–93:716–28. [PubMed: 26562560]
63. Witorsch RJ. 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 2014;44:535–55. [PubMed: 24897554]
64. Kumar V, Balomajumder C, Roy P. Disruption of LH-induced testosterone biosynthesis in testicular Leydig cells by triclosan: Probable mechanism of action. Toxicology 2008;250:124–31. [PubMed: 18655822]
65. Forgacs AL, Ding Q, Jaremba RG, Huhtaniemi IT, Rahman NA, Zacharewski TR. BLTK1 Murine Leydig Cells: A Novel Steroidogenic Model for Evaluating the Effects of Reproductive and Developmental Toxicants. Toxicological Sciences 2012;127:391–402. [PubMed: 22461451]
66. Kumar V, Chakraborty A, Kural MR, Roy P. Alteration of testicular steroidogenesis and histopathology of reproductive system in male rats treated with triclosan. Reproductive Toxicology 2009;27:177–85. [PubMed: 19118620]
67. Zorrilla LM, Gibson EK, Jeffay SC, Crofton KM, Setzer WR, Cooper RL et al. The Effects of Triclosan on Puberty and Thyroid Hormones in Male Wistar Rats. Toxicological Sciences 2008;107:56–64. [PubMed: 18940961]
68. Axelstad M, Boberg J, Vinggaard AM, Christiansen S, Hass U. Triclosan exposure reduces thyroxine levels in pregnant and lactating rat dams and in directly exposed offspring. Food and Chemical Toxicology 2013;59:534–40. [PubMed: 23831729]
69. Kim S, Choi K. Occurrences, toxicities, and ecological risks of benzophenone-3, a common component of organic sunscreen products: a mini-review. Environment international 2014;70:143–57. [PubMed: 24934855]
70. Kinnberg KL, Petersen GI, Albrektsen M, Minghlani M, Awad SM, Holbech BF et al. Endocrine-disrupting effect of the ultraviolet filter benzophenone-3 in zebrafish, Danio rerio. Environmental toxicology and chemistry 2015;34:2833–40. [PubMed: 26118430]
71. French JE. NTP technical report on the toxicity studies of 2-Hydroxy-4-methoxybenzophenone (CAS No. 131–57-7) Adminstered Topically and in Dosed Feed to F344/N Rats and B6C3F1 Mice. Toxicity report series 1992;21:1–e14. [PubMed: 12209185]
72. Virant-Klun I, Imamovic-Kumalic S, Pinter B. From Oxidative Stress to Male Infertility: Review of the Associations of Endocrine-Disrupting Chemicals (Bisphenols, Phthalates, and Parabens) with Human Semen Quality. Antioxidants (Basel) 2022;11.
73. Barbonetti A, D'Andrea S, Bernabò N, Volle DH. Editorial: Bisphenols and Male Reproductive Health. Frontiers in endocrinology 2020;11:597609. [PubMed: 33133026]
74. Ghayda RA, Williams PL, Chavarro JE, Ford JB, Souter I, Calafat AM et al. Urinary bisphenol S concentrations: Potential predictors of and associations with semen quality parameters among men attending a fertility center. Environment international 2019;131:105050. [PubMed: 31376593]

75. Chen PP, Liu C, Zhang M, Miao Y, Cui FP, Deng YL et al. Associations between urinary bisphenol A and its analogues and semen quality: A cross-sectional study among Chinese men from an infertility clinic. Environment international 2022;161:107132. [PubMed: 35149449]

76. Benson TE, Gaml-Sørensen A, Ernst A, Brix N, Hougaard KS, Hærvig KK et al. Urinary Bisphenol A, F and S Levels and Semen Quality in Young Adult Danish Men. International journal of environmental research and public health 2021;18:1742. [PubMed: 33670148]

77. Wang Y, Aimuzi R, Nian M, Zhang Y, Luo K, Zhang J. Bisphenol A substitutes and sex hormones in children and adolescents. Chemosphere 2021;278:130396. [PubMed: 33819883]

78. Shen X, Zhan M, Wang Y, Tang W, Zhang Q, Zhang J. Exposure to parabens and semen quality in reproductive-aged men. Ecotoxicology and environmental safety 2023;264:115453. [PubMed: 37688867]

79. Zamkowska D, Karwacka A, Jurewicz J, Radwan M. 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 2018;31:377–414. [PubMed: 30160090]

80. Yuan G, Ma Y, Zeng Y, Pan H, Liu P, Liu Y et al. Associations between low-dose triclosan exposure and semen quality in a Chinese population. Environmental pollution (Barking, Essex : 1987) 2022;299:118926. [PubMed: 35101560]

81. Yan J, Joseph MA, Reynolds SA, Geer LA. Association between Urinary Triclosan and Serum Testosterone Levels in U.S. Adult Males from NHANES, 2011–2012. International journal of environmental research and public health 2020;17. [PubMed: 33375123]

82. Nassan FL, Mínguez-Alarcón L, Williams PL, Dadd R, Petrozza JC, Ford JB et al. Urinary triclosan concentrations and semen quality among men from a fertility clinic. Environmental research 2019;177:108633. [PubMed: 31421444]

83. Zhu W, Zhang H, Tong C, Xie C, Fan G, Zhao S et al. Environmental Exposure to Triclosan and Semen Quality. International journal of environmental research and public health 2016;13:224. [PubMed: 26901211]

84. Pollock T, Arbuckle TE, Guth M, Bouchard MF, St-Amand A. Associations among urinary triclosan and bisphenol A concentrations and serum sex steroid hormone measures in the Canadian and U.S. Populations. Environment international 2021;146:106229. [PubMed: 33161203]

85. Joensen UN, Jørgensen N, Thyssen JP, Szecsi PB, Stender S, Petersen JH et al. 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 2018;121:365–74. [PubMed: 30245359]

86. Adoamnei E, Mendiola J, Moñino-García M, Vela-Soria F, Iribarne-Durán LM, Fernández MF et al. Urinary concentrations of benzophenone-type ultra violet light filters and reproductive parameters in young men. International journal of hygiene and environmental health 2018;221:531–40. [PubMed: 29449081]

87. Wang Y, Zhu H, Kannan K. A Review of Biomonitoring of Phthalate Exposures. Toxics 2019;7. [PubMed: 30717263]

88. CDC. National Report on Human Exposure to Environmental Chemicals. In. Vol. 2022. Atlanta, GA: US Centers for Disease Control and Prevention, 2022.

89. Johns LE, Cooper GS, Galizia A, Meeker JD. Exposure assessment issues in epidemiology studies of phthalates. Environment international 2015;85:27–39. [PubMed: 26313703]

90. Bommarito PA, Stevens DR, Welch BM, Weller D, Meeker JD, Cantonwine DE et al. Temporal trends and predictors of phthalate, phthalate replacement, and phenol biomarkers in the LIFECODES Fetal Growth Study. Environment international 2023;174:107898. [PubMed: 37001215]

91. Vogel N, Frederiksen H, Lange R, Jorgensen N, Koch HM, Weber T et al. Urinary excretion of phthalates and the substitutes DINCH and DEHTP in Danish young men and German young adults between 2000 and 2017 - A time trend analysis. International journal of hygiene and environmental health 2023;248:114080. [PubMed: 36657282]

92. Rodriguez-Carmona Y, Ashrap P, Calafat AM, Ye X, Rosario Z, Bedrosian LD et al. Determinants and characterization of exposure to phthalates, DEHTP and DINCH among pregnant women in the

PROTECT birth cohort in Puerto Rico. Journal of exposure science & environmental epidemiology 2020;30:56–69. [PubMed: 31481681]

93. Pollock T, Karthikeyan S, Walker M, Werry K, St-Amand A. Trends in environmental chemical concentrations in the Canadian population: Biomonitoring data from the Canadian Health Measures Survey 2007–2017. Environment international 2021;155:106678. [PubMed: 34118655]
94. Silva MJ, Wong LY, Samandar E, Preau JL, Calafat AM, Ye X. Exposure to di-2-ethylhexyl terephthalate in a convenience sample of U.S. adults from 2000 to 2016. Arch Toxicol 2017.
95. Bastiaensen M, Gys C, Colles A, Malarvannan G, Verheyen V, Koppen G et al. Biomarkers of phthalates and alternative plasticizers in the Flemish Environment and Health Study (FLEHS IV): Time trends and exposure assessment. Environmental pollution (Barking, Essex : 1987) 2021;276:116724. [PubMed: 33631684]
96. Kasper-Sonnenberg M, Koch HM, Apel P, Ruther M, Palmke C, Bruning T et al. Time trend of exposure to the phthalate plasticizer substitute DINCH in Germany from 1999 to 2017: Biomonitoring data on young adults from the Environmental Specimen Bank (ESB). International journal of hygiene and environmental health 2019;222:1084–92. [PubMed: 31378638]
97. Lessmann F, Kolossa-Gehring M, Apel P, Ruther M, Palmke C, Harth V et al. German Environmental Specimen Bank: 24-hour urine samples from 1999 to 2017 reveal rapid increase in exposure to the para-phthalate plasticizer di(2-ethylhexyl) terephthalate (DEHTP). Environment international 2019;132:105102. [PubMed: 31491609]
98. National Research Council (U.S.). Committee on the Health Risks of Phthalates., National Academies Press (U.S.). Phthalates and cumulative risk assessment : the task ahead. Washington, D.C.: National Academies Press, 2008.
99. Sharpe RM, Skakkebaek NE. Testicular dysgenesis syndrome: mechanistic insights and potential new downstream effects. Fertility and sterility 2008;89:e33–8. [PubMed: 18308057]
100. Hlisnikova H, Petrovicova I, Kolena B, Sidlovska M, Sirotkin A. Effects and Mechanisms of Phthalates' Action on Reproductive Processes and Reproductive Health: A Literature Review. International journal of environmental research and public health 2020;17. [PubMed: 33375123]
101. Johnson KJ, Heger NE, Boekelheide K. Of mice and men (and rats): phthalate-induced fetal testis endocrine disruption is species-dependent. Toxicological sciences : an official journal of the Society of Toxicology 2012;129:235–48. [PubMed: 22700540]
102. Radke EG, Braun JM, Meeker JD, Cooper GS. Phthalate exposure and male reproductive outcomes: A systematic review of the human epidemiological evidence. Environment international 2018;121:764–93. [PubMed: 30336412]
103. Davalos AD, Minguez-Alarcon L, van T' Erve TJ, Keil AP, Williams PL, Meeker JD et al. Associations between mixtures of urinary phthalate metabolite concentrations and oxidative stress biomarkers among couples undergoing fertility treatment. Environmental research 2022;212:113342. [PubMed: 35461852]
104. Buck Louis GM, Sundaram R, Sweeney AM, Schisterman EF, Maisog J, Kannan K. Urinary bisphenol A, phthalates, and couple fecundity: the Longitudinal Investigation of Fertility and the Environment (LIFE) Study. Fertil Steril 2014;101:1359–66. [PubMed: 24534276]
105. Yu C, Lu J, Zhao J, Zhao T, Long C, Lin T et al. Maternal phthalate exposure during pregnancy and male reproductive disorders: a systematic review and metaanalysis. Turk J Pediatr 2022;64:187–209. [PubMed: 35611408]
106. Burns JS, Sergeyev O, Lee MM, Williams PL, Minguez-Alarcon L, Plaku-Alakbarova B et al. Associations of prepubertal urinary phthalate metabolite concentrations with pubertal onset among a longitudinal cohort of boys. Environmental research 2022;212:113218. [PubMed: 35390299]
107. Burns JS, Bather JR, Sergeyev O, Lee MM, Korrick SA, Sokolov S et al. Longitudinal association of prepubertal urinary phthalate metabolite concentrations with pubertal progression among a cohort of boys. Environmental research 2023;233:116330. [PubMed: 37348639]
108. Su PH, Huang JY, Wang SJ, Chang HP. Phthalates exposure and pubertal development in a 15-year follow-up birth cohort study in Taiwan. Front Endocrinol (Lausanne) 2023;14:1065918. [PubMed: 37288299]

109. Ferguson KK, Peterson KE, Lee JM, Mercado-Garcia A, Goldenberg CB, Tellez-Rojo MM et al. Prenatal and Peripubertal Phthalates and Bisphenol-A in Relation to Sex Hormones and Puberty in Boys. Reproductive toxicology 2014;47:70–6. [PubMed: 24945889]
110. Watkins DJ, Sanchez BN, Tellez-Rojo MM, Lee JM, Mercado-Garcia A, Blank-Goldenberg C et al. Impact of phthalate and BPA exposure during in utero windows of susceptibility on reproductive hormones and sexual maturation in peripubertal males. Environmental health : a global access science source 2017;16:69. [PubMed: 28637469]
111. Golestanzadeh M, Riahi R, Kelishadi R. Association of phthalate exposure with precocious and delayed pubertal timing in girls and boys: a systematic review and meta-analysis. Environ Sci Process Impacts 2020;22:873–94. [PubMed: 32091510]
112. Uldbjerg CS, Koch T, Lim YH, Gregersen LS, Olesen CS, Andersson AM et al. Prenatal and postnatal exposures to endocrine disrupting chemicals and timing of pubertal onset in girls and boys: a systematic review and meta-analysis. Hum Reprod Update 2022;28:687–716. [PubMed: 35466359]
113. Freire C, Castiello F, Lopez-Espinosa MJ, Beneito A, Lertxundi A, Jimeno-Romero A et al. Association of prenatal phthalate exposure with pubertal development in Spanish boys and girls. Environmental research 2022;213:113606. [PubMed: 35716812]
114. EPA. US Environmental Protection Agency. Pesticides Available at: https://www.epa.gov/pesticides [accessed December 2021]. 2019.
115. EPA. US Environmental Protection Agency. Pesticides Industry Sales and Usage 2008 – 2012 Market Estimates. Available at: https://www.epa.gov/sites/production/files/2017-01/documents/pesticides-industry-sales-usage-2016_0.pdf [accessed December 2021]. 2019.
116. CDC. Centers for Disease Control and Prevention. Fourth Report on Human Exposure to Environmental Chemicals, Updated Tables, (March 2018). Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. Available at https://www.cdc.gov/exposurereport/ (accessed December 2021). 2018.
117. USDA. US Department of Agriculture. Pesticide data program. Available at: https://www.ams.usda.gov/datasets/pdp [accessed December 2021] 2019.
118. Xue J, Zartarian V, Tornero-Velez R, Tulve NS. EPA's SHEDS-multimedia model: children's cumulative pyrethroid exposure estimates and evaluation against NHANES biomarker data. Environ Int 2014;73:304–11. [PubMed: 25192887]
119. FDA. US Food and Drug Administration. Pesticide Monitoring Program Fiscal Year 2012 Pesticide Report 2012 2012.
120. EPA. US Environmental Protection Agency. Food and Pesticides. Available at: https://www.epa.gov/safepestcontrol/food-and-pesticides [accessed December 2021]. 2019.
121. Curl CL, Porter J, Penwell I, Phinney R, Ospina M, Calafat AM. Effect of a 24-week randomized trial of an organic produce intervention on pyrethroid and organophosphate pesticide exposure among pregnant women. Environ Int 2019;132:104957. [PubMed: 31324402]
122. Rempelos L, Wang J, Barański M, Watson A, Volakakis N, Hoppe HW et al. Diet and food type affect urinary pesticide residue excretion profiles in healthy individuals: results of a randomized controlled dietary intervention trial. Am J Clin Nutr 2022;115:364–77. [PubMed: 34718382]
123. Hyland C, Spivak M, Sheppard L, Lanphear BP, Antoniou M, Ospina M et al. Urinary Glyphosate Concentrations among Pregnant Participants in a Randomized, Crossover Trial of Organic and Conventional Diets. Environ Health Perspect 2023;131:77005. [PubMed: 37493357]
124. Lu C, Toepel K, Irish R, Fenske RA, Barr DB, Bravo R. Organic diets significantly lower children's dietary exposure to organophosphorus pesticides. Environ Health Perspect 2006;114:260–3. [PubMed: 16451864]
125. Sarabia L, Maurer I, Bustos-Obregon E. Melatonin prevents damage elicited by the organophosphorous pesticide diazinon on mouse sperm DNA. Ecotoxicology and environmental safety 2009;72:663–8. [PubMed: 18571725]
126. Salazar-Arredondo E, de Jesus Solis-Heredia M, Rojas-Garcia E, Hernandez-Ochoa I, Quintanilla-Vega B. Sperm chromatin alteration and DNA damage by methyl-parathion, chlorpyrifos and diazinon and their oxon metabolites in human spermatozoa. Reproductive toxicology (Elmsford, NY) 2008;25:455–60.

127. Pina-Guzman B, Solis-Heredia MJ, Quintanilla-Vega B. Diazinon alters sperm chromatin structure in mice by phosphorylating nuclear protamines. Toxicology and applied pharmacology 2005;202:189–98. [PubMed: 15629194]

128. Adamkovicova M, Toman R, Martiniakova M, Omelka R, Babosova R, Krajcovicova V et al. Sperm motility and morphology changes in rats exposed to cadmium and diazinon. Reproductive biology and endocrinology : RB&E 2016;14:42. [PubMed: 27503218]

129. Sai L, Li X, Liu Y, Guo Q, Xie L, Yu G et al. Effects of chlorpyrifos on reproductive toxicology of male rats. Environmental toxicology 2014;29:1083–8. [PubMed: 23364943]

130. Peiris DC, Dhanushka T. Low doses of chlorpyrifos interfere with spermatogenesis of rats through reduction of sex hormones. Environmental science and pollution research international 2017;24:20859–67. [PubMed: 28721614]

131. Joshi SC, Mathur R, Gulati N. Testicular toxicity of chlorpyrifos (an organophosphate pesticide) in albino rat. Toxicology and industrial health 2007;23:439–44. [PubMed: 18536496]

132. Alaa-Eldin EA, El-Shafei DA, Abouhashem NS. Individual and combined effect of chlorpyrifos and cypermethrin on reproductive system of adult male albino rats. Environmental science and pollution research international 2017;24:1532–43. [PubMed: 27785720]

133. Roy TS, Andrews JE, Seidler FJ, Slotkin TA. Chlorpyrifos elicits mitotic abnormalities and apoptosis in neuroepithelium of cultured rat embryos. Teratology 1998;58:62–8. [PubMed: 9787407]

134. Zhang SY, Ueyama J, Ito Y, Yanagiba Y, Okamura A, Kamijima M et al. Permethrin may induce adult male mouse reproductive toxicity due to cis isomer not trans isomer. Toxicology 2008;248:136–41. [PubMed: 18455858]

135. Zhang SY, Ito Y, Yamanoshita O, Yanagiba Y, Kobayashi M, Taya K et al. Permethrin may disrupt testosterone biosynthesis via mitochondrial membrane damage of Leydig cells in adult male mouse. Endocrinology 2007;148:3941–9. [PubMed: 17463061]

136. Saito H, Hara K, Tanemura K. Prenatal and postnatal exposure to low levels of permethrin exerts reproductive effects in male mice. Reproductive toxicology (Elmsford, NY) 2017;74:108–15.

137. Mostafa Hel S, Abd El-Baset SA, Kattaia AA, Zidan RA, Al Sadek MM. Efficacy of naringenin against permethrin-induced testicular toxicity in rats. International journal of experimental pathology 2016;97:37–49. [PubMed: 26867500]

138. Imanishi S, Okura M, Zaha H, Yamamoto T, Akanuma H, Nagano R et al. Prenatal exposure to permethrin influences vascular development of fetal brain and adult behavior in mice offspring. Environmental toxicology 2013;28:617–29. [PubMed: 24150868]

139. Zhang Q, Zhang Y, Du J, Zhao M. Environmentally relevant levels of lambda-cyhalothrin, fenvalerate, and permethrin cause developmental toxicity and disrupt endocrine system in zebrafish (Danio rerio) embryo. Chemosphere 2017;185:1173–80. [PubMed: 28772355]

140. Pochettino AA, Hapon MB, Biolatto SM, Madariaga MJ, Jahn GA, Konjuh CN. Effects of 2,4-dichlorophenoxyacetic acid on the ventral prostate of rats during the peri-pubertal, pubertal and adult stage. Drug and chemical toxicology 2016;39:392–9. [PubMed: 26759115]

141. Marouani N, Tebourbi O, Cherif D, Hallegue D, Yacoubi MT, Sakly M et al. Effects of oral administration of 2,4-dichlorophenoxyacetic acid (2,4-D) on reproductive parameters in male Wistar rats. Environmental science and pollution research international 2017;24:519–26. [PubMed: 27734311]

142. Li K, Wu JQ, Jiang LL, Shen LZ, Li JY, He ZH et al. Developmental toxicity of 2,4-dichlorophenoxyacetic acid in zebrafish embryos. Chemosphere 2017;171:40–8. [PubMed: 28002765]

143. Harada Y, Tanaka N, Ichikawa M, Kamijo Y, Sugiyama E, Gonzalez FJ et al. PPARalpha-dependent cholesterol/testosterone disruption in Leydig cells mediates 2,4-dichlorophenoxyacetic acid-induced testicular toxicity in mice. Archives of toxicology 2016;90:3061–71. [PubMed: 26838045]

144. Aronzon CM, Sandoval MT, Herkovits J, Perez-Coll CS. Stage-dependent toxicity of 2,4-dichlorophenoxyacetic on the embryonic development of a South American toad, Rhinella arenarum. Environmental toxicology 2011;26:373–81. [PubMed: 20112415]

145. Courtney KD. Prenatal effects of herbicides: evaluation by the prenatal development index. Archives of environmental contamination and toxicology 1977;6:33–46. [PubMed: 907374]

146. Sameshima K, Kobae H, Fofana D, Yoshidome K, Nishi J, Miyata K. Effects of pure 2,4-dichlorophenoxyacetic acid on cultured rat embryos. Congenital anomalies 2004;44:93–6. [PubMed: 15198722]

147. Rahman MF, Mahboob M, Danadevi K, Saleha Banu B, Grover P. Assessment of genotoxic effects of chloropyriphos and acephate by the comet assay in mice leucocytes. Mutat Res 2002;516:139–47. [PubMed: 11943619]

148. Abdollahi M, Ranjbar A, Shadnia S, Nikfar S, Rezaie A. Pesticides and oxidative stress: a review. Med Sci Monit 2004;10:Ra141–7. [PubMed: 15173684]

149. Chen H, Xiao J, Hu G, Zhou J, Xiao H, Wang X. Estrogenicity of organophosphorus and pyrethroid pesticides. J Toxicol Environ Health A 2002;65:1419–35. [PubMed: 12396874]

150. Shin HS, Seo JH, Jeong SH, Park SW, Park YI, Son SW et al. Effect on the H19 gene methylation of sperm and organs of offspring after chlorpyrifos-methyl exposure during organogenesis period. Environmental toxicology 2015;30:1355–63. [PubMed: 25782373]

151. Pallotta MM, Barbato V, Pinton A, Acloque H, Gualtieri R, Talevi R et al. In vitro exposure to CPF affects bovine sperm epigenetic gene methylation pattern and the ability of sperm to support fertilization and embryo development. Environmental and molecular mutagenesis 2019;60:85–95. [PubMed: 30365181]

152. Whorton D, Krauss RM, Marshall S, Milby TH. Infertility in male pesticide workers. Lancet 1977;2:1259–61. [PubMed: 73955]

153. Meeker JD, Ryan L, Barr DB, Herrick RF, Bennett DH, Bravo R et al. The relationship of urinary metabolites of carbaryl/naphthalene and chlorpyrifos with human semen quality. Environmental health perspectives 2004;112:1665–70. [PubMed: 15579410]

154. Meeker JD, Ryan L, Barr DB, Hauser R. Exposure to nonpersistent insecticides and male reproductive hormones. Epidemiology (Cambridge, Mass) 2006;17:61–8. [PubMed: 16357596]

155. Meeker JD, Ravi SR, Barr DB, Hauser R. Circulating estradiol in men is inversely related to urinary metabolites of nonpersistent insecticides. Reproductive toxicology (Elmsford, NY) 2008;25:184–91.

156. Meeker JD, Singh NP, Ryan L, Duty SM, Barr DB, Herrick RF et al. Urinary levels of insecticide metabolites and DNA damage in human sperm. Human reproduction (Oxford, England) 2004;19:2573–80. [PubMed: 15333606]

157. Dziewirska E, Radwan M, Wielgomas B, Klimowska A, Radwan P, Kaluzny P et al. Human Semen Quality, Sperm DNA Damage, and the Level of Urinary Concentrations of 1N and TCPY, the Biomarkers of Nonpersistent Insecticides. American journal of men's health 2019;13:1557988318816598.

158. Swan SH, Kruse RL, Liu F, Barr DB, Drobnis EZ, Redmon JB et al. Semen quality in relation to biomarkers of pesticide exposure. Environmental health perspectives 2003;111:1478–84. [PubMed: 12948887]

159. Perry MJ, Venners SA, Barr DB, Xu X. Environmental pyrethroid and organophosphorus insecticide exposures and sperm concentration. Reproductive toxicology (Elmsford, NY) 2007;23:113–8.

160. Jurewicz J, Radwan M, Wielgomas B, Sobala W, Piskunowicz M, Radwan P et al. The effect of environmental exposure to pyrethroids and DNA damage in human sperm. Systems biology in reproductive medicine 2015;61:37–43. [PubMed: 25376306]

161. Radwan M, Jurewicz J, Wielgomas B, Piskunowicz M, Sobala W, Radwan P et al. The association between environmental exposure to pyrethroids and sperm aneuploidy. Chemosphere 2015;128:42–8. [PubMed: 25655817]

162. Martenies SE, Perry MJ. Environmental and occupational pesticide exposure and human sperm parameters: a systematic review. Toxicology 2013;307:66–73. [PubMed: 23438386]

163. Chiu YH, Williams PL, Minguez-Alarcon L, Gillman M, Sun Q, Ospina M et al. Comparison of questionnaire-based estimation of pesticide residue intake from fruits and vegetables with urinary concentrations of pesticide biomarkers. Journal of exposure science & environmental epidemiology 2017.

164. Hu Y, Chiu YH, Hauser R, Chavarro J, Sun Q. Overall and class-specific scores of pesticide residues from fruits and vegetables as a tool to rank intake of pesticide residues in United States: A validation study. Environ Int 2016;92–93:294–300. [PubMed: 26562560]
165. Chiu YH, Afeiche MC, Gaskins AJ, Williams PL, Petrozza JC, Tanrikut C et al. Fruit and vegetable intake and their pesticide residues in relation to semen quality among men from a fertility clinic. Hum Reprod 2015;30:1342–51. [PubMed: 25824023]
166. Chiu YH, Gaskins AJ, Williams PL, Mendiola J, Jorgensen N, Levine H et al. Intake of Fruits and Vegetables with Low-to-Moderate Pesticide Residues Is Positively Associated with Semen-Quality Parameters among Young Healthy Men. J Nutr 2016;146:1084–92. [PubMed: 27075904]
167. Buck RC, Franklin J, Berger U, Conder JM, Cousins IT, de Voogt P et al. Perfluoroalkyl and polyfluoroalkyl substances in the environment: terminology, classification, and origins. Integr Environ Assess Manag 2011;7:513–41. [PubMed: 21793199]
168. OECD OfECaD. Toward a New Comprehensive Global Datbase of Per- and Polyfluoroalkyl Substances (PFAS). In: Series on Risk Management. Vol. citat. Paris, France: Organisation for Economic Co-operation and Development, 2018.
169. Gluge J, Scheringer M, Cousins IT, DeWitt JC, Goldenman G, Herzke D et al. An overview of the uses of per- and polyfluoroalkyl substances (PFAS). Environ Sci Process Impacts 2020;22:2345–73. [PubMed: 33125022]
170. Tittlemier SA, Pepper K, Seymour C, Moisey J, Bronson R, Cao XL et al. Dietary exposure of Canadians to perfluorinated carboxylates and perfluorooctane sulfonate via consumption of meat, fish, fast foods, and food items prepared in their packaging. Journal of agricultural and food chemistry 2007;55:3203–10. [PubMed: 17381114]
171. Haug LS, Huber S, Becher G, Thomsen C. Characterisation of human exposure pathways to perfluorinated compounds--comparing exposure estimates with biomarkers of exposure. Environ Int 2011;37:687–93. [PubMed: 21334069]
172. Haug LS, Salihovic S, Jogsten IE, Thomsen C, van Bavel B, Lindstrom G et al. Levels in food and beverages and daily intake of perfluorinated compounds in Norway. Chemosphere 2010;80:1137–43. [PubMed: 20599247]
173. Hlouskova V, Hradkova P, Poustka J, Brambilla G, De Filipps SP, D'Hollander W et al. Occurrence of perfluoroalkyl substances (PFASs) in various food items of animal origin collected in four European countries. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 2013;30:1918–32. [PubMed: 24107131]
174. Macheka LR, Olowoyo JO, Mugivhisa LL, Abafe OA. Determination and assessment of human dietary intake of per and polyfluoroalkyl substances in retail dairy milk and infant formula from South Africa. The Science of the total environment 2021;755:142697. [PubMed: 33065506]
175. Susmann HP, Schaider LA, Rodgers KM, Rudel RA. Dietary Habits Related to Food Packaging and Population Exposure to PFASs. Environ Health Perspect 2019;127:107003. [PubMed: 31596611]
176. Lu T, Mortimer M, Li F, Li Z, Chen L, Li M et al. Putative adverse outcome pathways of the male reproductive toxicity derived from toxicological studies of perfluoroalkyl acids. The Science of the total environment 2023;873:162439. [PubMed: 36848992]
177. Li Z, Li C, Wen Z, Yan H, Zou C, Li Y et al. Perfluoroheptanoic acid induces Leydig cell hyperplasia but inhibits spermatogenesis in rats after pubertal exposure. Toxicology 2021;448:152633. [PubMed: 33220336]
178. Qiu L, Wang H, Dong T, Huang J, Li T, Ren H et al. Perfluorooctane sulfonate (PFOS) disrupts testosterone biosynthesis via CREB/CRTC2/StAR signaling pathway in Leydig cells. Toxicology 2021;449:152663. [PubMed: 33359577]
179. Zhou Y, Sun W, Tang Q, Lu Y, Li M, Wang J et al. Effect of prenatal perfluoroheptanoic acid exposure on spermatogenesis in offspring mice. Ecotoxicology and environmental safety 2023;260:115072. [PubMed: 37262965]
180. Raymer JH, Michael LC, Studabaker WB, Olsen GW, Sloan CS, Wilcosky T et al. Concentrations of perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) and their associations with human semen quality measurements. Reproductive toxicology (Elmsford, NY 2012;33:419–27.

181. Petersen MS, Halling J, Jørgensen N, Nielsen F, Grandjean P, Jensen TK et al. 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 2018;15. [PubMed: 30577626]
182. Petersen KU, Hærvig KK, Flachs EM, Bonde JP, Lindh C, Hougaard KS et al. Per- and polyfluoroalkyl substances (PFAS) and male reproductive function in young adulthood; a cross-sectional study. Environmental research 2022;212:113157. [PubMed: 35318009]
183. Olsen GW, Gilliland FD, Burlew MM, Burris JM, Mandel JS, Mandel JH. An epidemiologic investigation of reproductive hormones in men with occupational exposure to perfluorooctanoic acid. Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine 1998;40:614–22.
184. Luo K, Liu X, Nian M, Wang Y, Qiu J, Yu H et al. Environmental exposure to per- and polyfluoroalkyl substances mixture and male reproductive hormones. Environment international 2021;152:106496. [PubMed: 33744484]
185. Luo K, Huang W, Zhang Q, Liu X, Nian M, Wei M et al. Environmental exposure to legacy poly/perfluoroalkyl substances, emerging alternatives and isomers and semen quality in men: A mixture analysis. The Science of the total environment 2022;833:155158. [PubMed: 35421474]
186. Louis GM, Chen Z, Schisterman EF, Kim S, Sweeney AM, Sundaram R et al. Perfluorochemicals and human semen quality: the LIFE study. Environmental health perspectives 2015;123:57–63. [PubMed: 25127343]
187. Lenters V, Portengen L, Smit LA, Jonsson BA, Giwercman A, Rylander L et al. Phthalates, perfluoroalkyl acids, metals and organochlorines and reproductive function: a multipollutant assessment in Greenlandic, Polish and Ukrainian men. Occupational and environmental medicine 2015;72:385–93. [PubMed: 25209848]
188. Joensen UN, Veyrand B, Antignac JP, Blomberg Jensen M, Petersen JH, Marchand P et al. PFOS (perfluorooctanesulfonate) in serum is negatively associated with testosterone levels, but not with semen quality, in healthy men. Human reproduction (Oxford, England) 2013;28:599–608. [PubMed: 23250927]
189. Joensen UN, Bossi R, Leffers H, Jensen AA, Skakkebaek NE, Jørgensen N. Do perfluoroalkyl compounds impair human semen quality? Environmental health perspectives 2009;117:923–7. [PubMed: 19590684]
190. Hærvig KK, Petersen KU, Hougaard KS, Lindh C, Ramlau-Hansen CH, Toft G et al. Maternal Exposure to Per- and Polyfluoroalkyl Substances (PFAS) and Male Reproductive Function in Young Adulthood: Combined Exposure to Seven PFAS. Environmental health perspectives 2022;130:107001. [PubMed: 36197086]
191. Den Hond E, Tournaye H, De Sutter P, Ombelet W, Baeyens W, Covaci A et al. Human exposure to endocrine disrupting chemicals and fertility: A case-control study in male subfertility patients. Environment international 2015;84:154–60. [PubMed: 26292060]
192. Cui Q, Pan Y, Wang J, Liu H, Yao B, Dai J. Exposure to per- and polyfluoroalkyl substances (PFASs) in serum versus semen and their association with male reproductive hormones. Environ Pollut 2020;266:115330. [PubMed: 32781340]
193. Vested A, Ramlau-Hansen CH, Olsen SF, Bonde JP, Kristensen SL, Halldorsson TI et al. Associations of in utero exposure to perfluorinated alkyl acids with human semen quality and reproductive hormones in adult men. Environmental health perspectives 2013;121:453–8. [PubMed: 23360585]
194. Pan Y, Cui Q, Wang J, Sheng N, Jing J, Yao B et al. Profiles of Emerging and Legacy Per/Polyfluoroalkyl Substances in Matched Serum and Semen Samples: New Implications for Human Semen Quality. Environmental health perspectives 2019;127:127005. [PubMed: 31841032]
195. Huang Q, Liu L, Wu Y, Wang X, Luo L, Nan B et al. Seminal plasma metabolites mediate the associations of multiple environmental pollutants with semen quality in Chinese men. Environment international 2019;132:105066. [PubMed: 31394396]
196. Barry V, Winquist A, Steenland K. Perfluorooctanoic acid (PFOA) exposures and incident cancers among adults living near a chemical plant. Environ Health Perspect 2013;121:1313–8. [PubMed: 24007715]

197. Vieira VM, Hoffman K, Shin HM, Weinberg JM, Webster TF, Fletcher T. Perfluorooctanoic acid exposure and cancer outcomes in a contaminated community: a geographic analysis. Environ Health Perspect 2013;121:318–23. [PubMed: 23308854]

198. Mastrantonio M, Bai E, Uccelli R, Cordiano V, Screpanti A, Crosignani P. Drinking water contamination from perfluoroalkyl substances (PFAS): an ecological mortality study in the Veneto Region, Italy. Eur J Public Health 2018;28:180–5. [PubMed: 28541558]

199. Purdue MP, Rhee J, Denic-Roberts H, McGlynn KA, Byrne C, Sampson J et al. A Nested Case-Control Study of Serum Per- and Polyfluoroalkyl Substances and Testicular Germ Cell Tumors among U.S. Air Force Servicemen. Environ Health Perspect 2023;131:77007. [PubMed: 37458713]

200. Ema M, Naya M, Horimoto M, Kato H. Developmental toxicity of diesel exhaust: a review of studies in experimental animals. Reproductive toxicology (Elmsford, NY) 2013;42:1–17.

201. Jedlińska-Krakowska M, Gizejewski Z, Dietrich GJ, Jakubowski K, Glogowski J, Penkowski A. The effect of increased ozone concentrations in the air on selected aspects of rat reproduction. Pol J Vet Sci 2006;9:11–6. [PubMed: 16573270]

202. Kubo-Irie M, Oshio S, Niwata Y, Ishihara A, Sugawara I, Takeda K. Pre- and postnatal exposure to low-dose diesel exhaust impairs murine spermatogenesis. Inhalation toxicology 2011;23:805–13. [PubMed: 22017524]

203. Takeda K, Tsukue N, Yoshida S. Endocrine-disrupting activity of chemicals in diesel exhaust and diesel exhaust particles. Environ Sci 2004;11:33–45. [PubMed: 15746887]

204. Tsukue N, Toda N, Tsubone H, Sagai M, Jin WZ, Watanabe G et al. Diesel exhaust (DE) affects the regulation of testicular function in male Fischer 344 rats. Journal of toxicology and environmental health Part A 2001;63:115–26. [PubMed: 11393798]

205. Xu R, Zhong Y, Li R, Li Y, Zhong Z, Liu T et al. Association between exposure to ambient air pollution and semen quality: A systematic review and meta-analysis. Sci Total Environ 2023;870:161892. [PubMed: 36731563]

206. Zheng P, Chen Z, Shi J, Xue Y, Bai Y, Kang Y et al. Association between ambient air pollution and blood sex hormones levels in men. Environ Res 2022;211:113117. [PubMed: 35304116]

207. Wang F, Chen Q, Zhan Y, Yang H, Zhang A, Ling X et al. Acute effects of short-term exposure to ambient air pollution on reproductive hormones in young males of the MARHCS study in China. Sci Total Environ 2021;774:145691. [PubMed: 33611002]

208. Radwan M, Jurewicz J, Polańska K, Sobala W, Radwan P, Bochenek M et al. Exposure to ambient air pollution--does it affect semen quality and the level of reproductive hormones? Ann Hum Biol 2016;43:50–6. [PubMed: 26211899]

209. Devi VS, Prasad MH, Rao VD, Devi GS, Reddy PP. Reproductive Outcome in the Wives of Traffic Policemen Exposed to Automobile Exhaust. Journal of Human Ecology 2006;20:77–82.

210. Robinson L, Gallos ID, Conner SJ, Rajkhowa M, Miller D, Lewis S et al. The effect of sperm DNA fragmentation on miscarriage rates: a systematic review and meta-analysis. Human reproduction (Oxford, England) 2012;27:2908–17. [PubMed: 22791753]

211. Borges E Jr., Zanetti BF, Setti AS, Braga D, Provenza RR, Iaconelli A Jr. Sperm DNA fragmentation is correlated with poor embryo development, lower implantation rate, and higher miscarriage rate in reproductive cycles of non-male factor infertility. Fertil Steril 2019;112:483–90. [PubMed: 31200969]

Table 1.

Fruits and vegetables monitored by the USDA Pesticide Data Program between 2010 and 2018, classified according to pesticide residue status using the Pesticide Residue Burden Score* (PRBS; 162,163).

Low pesticide residue fruits and vegetables (PRBS: 0 to 3)		High pesticide residue fruits and vegetables (PRBS: 4 to 6)	
Food	**PRBS**	**Food**	**PRBS**
Avocados	0	Strawberry	6
Beets	0	Spinach, fresh or frozen	6
Corn, fresh or frozen	0	Bell peppers	6
Beans	0	Potato, fresh	6
Garbanzo beans	0	Peaches	6
Cranberries	0	Nectarines	6
Pineapple	0	Grapes or raisins	6
Orange juice	0	Kale	6
Olives	0	Cucumber	6
Dried plum	0	Cilantro	6
Sweet pea	0	Blueberry	6
Papaya	0	Apple	5
Apple juice	1	Pear	5
Cauliflower	1	Summer squash	5
Cabbage	1	Eggplant	5
Cantaloupe	1	Tomato, fresh	5
Kiwi	1	Cherry tomato	5
Mushrooms	1	Collard greens	5
Onions	1	Cherries, fresh	5
Tomato, paste or canned	1	Celery	5
Asparagus	2	Winter squash	4
Carrot	2	Snap peas	4
Green beans, canned	2	Hot peppers	4
Grape juice	2	Green beans, fresh	4
Mango	2	Cherries, frozen	4
Potato, frozen	2	Apple sauce	4
Raspberry, frozen	2		
Watermelon	2		
Green beans, frozen	3		
Cranberry	3		
Banana	3		
Broccoli	3		
Green onion	3		
Lettuce	3		
Orange or grapefruit	3		

Low pesticide residue fruits and vegetables (PRBS: 0 to 3)		High pesticide residue fruits and vegetables (PRBS: 4 to 6)	
Food	**PRBS**	**Food**	**PRBS**
Raspberry, fresh	3		
Sweet potato	3		
Soybeans (edamame)	3		
Tangerine	3		

*Low pesticide residue foods are listed in increasing PRBS score (least contaminated first) and high pesticide residue foods are listed in decreasing PRBS score (most contaminated first).

Table 2.

Overview of the relation between exposure to selected endocrine disrupting environmental exposures and male reproductive health.

Exposure	Exposure route	Experimental evidence	Human evidence	Exposure mitigation
Phenols	Dermal, oral, inhalation	Anti-androgenic / estrogenic activity. Impaired spermatogenesis and steroidogenesis	Human data for BPA and replacement products, consistent with animal data. Human data for other phenols is scarce	Avoid packaged and canned food. Use phenol-free personal care products.
Phthalates	Dermal, oral, inhalation	Anti-androgenic activity. Impaired spermatogenesis, steroidogenesis, decreased testis size. External male genitalia malformations (in utero exposure).	Lower semen quality and testosterone levels. Decreased anogenital distance. Increased risk of cryptorchidism and hypospadias	Choose fragrance-free products. Avoid vinyl products. Use phthalate-free containers.
Pesticides	Diet (fruits and vegetables). Residential or commercial use of pesticides (e.g. lawn care)	Increased oxidative stress. Altered sperm chromatin structure. Altered Leydig cell function, steroidogenesis. Alternation of sperm epigenome.	Decreased semen quality including oligospermia, azoospermia, asthenospermia. Increased LH, FSH. Decreased T, E2	Avoid direct handling of pesticides. Choose low pesticide contamination produce, including organic.
PFAS	Consumption of contaminated food and water. Water/stain/oil repellent fabrics and other household products.	Decreased expression of GnRH gene. Decreased T production. Disruption or blood-testis barrier. Altered Leydig and Sertoli cell gene expression. Altered sperm membrane permeability. Increased oxidative stress, sperm apoptosis.	Inconsistent associations with semen quality and sperm DNA damage. Increased LH, FSH, decreased T; somewhat consistent. Suggestive association with higher risk of testicular cancer.	Reduce or limit the amount of fast food, microwave food, and takeout you eat. Reduce or limit your use of non-stick cookware.
Air pollution	Inhalation	Decreased production of spermatozoa and increased sperm DNA damage. Changes in Leydig cells and reduction in the number of Sertoli cells. Decreased T and increased LH.	Lower semen quality (concentration, total count, total motility) Lower T	Use of masks and air filters in days of high exposure to ambient particulate matter.