Published in final edited form as:

Curr Opin Obstet Gynecol. 2017 August ; 29(4): 202–211. doi:10.1097/GCO.0000000000000373.

Female exposure to endocrine disrupting chemicals and fecundity: a review

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Abstract

Purpose of review—Endocrine disrupting chemicals (EDCs) have been known for their ability to interfere with aspects of hormone action resulting in adverse health consequences among animals and humans, however, the effects of EDCs on human fecundity have shown inconsistent findings. This review summarizes the most recent epidemiologic literature from humans on the potential effects of female exposure to non-persistent EDCs, specifically bisphenol A (BPA), phthalates, parabens and triclosan, on fecundity, measured by markers of reproductive hormones, markers of ovulation or ovarian reserve, in vitro fertilization outcomes, and time-to-pregnancy.

Recent findings—While the epidemiologic literature on this topic is growing, the evidence supporting an association between female urinary concentrations of BPA, phthalates, parabens, and triclosan and fecundity remains unclear. The heterogeneous results could be due to methodological differences in recruitment populations (fertile vs. subfertile), study designs (prospective vs. retrospective), assessment of exposure (including differences in the number and timing of urine samples and differences in the analytical methods used to assess the urinary concentrations), residual confounding due to diet or other lifestyle factors, and co-exposures to other chemicals.

Summary—At present there is limited evidence to conclude that female exposure to non-persistent EDCs affect fecundity in humans. Further studies focusing on exposure to mixtures of EDCs is needed.

Keywords

endocrine disrupting chemicals; fecundity; phthalates; bisphenol A; parabens

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Conflicts of interest: None.

1. Introduction

Endocrine disrupting chemicals (EDCs) are a group exogenous chemicals or mixture of chemicals that alter the hormonal and homoeostatic systems of organisms resulting in adverse health effects [1]. Due to their ability to interfere with aspects of hormone action, it has been shown that exposure to EDCs can result in a wide range of adverse health consequences [1] with annual costs of EDC exposure amounting to more than $340 billion in the US (2% of the GDP) [2] and $217 billion in the European Union (1% of the GDP) [3]. Of particular concern is the potential influence of EDCs on female fecundity, or a woman's ability to become pregnant, given the rising rates of infertility worldwide [4] and the ubiquitous exposure of reproductive aged women to EDCs [5–7]. Because female fecundity lacks a biomarker, it is assessed by a variety of different endpoints including reproductive hormones, markers of ovulation or ovarian reserve, *in vitro* fertilization (IVF) outcomes, and time-to-pregnancy (TTP) [8]. This review summarizes the most recent epidemiologic literature from humans on the potential effects of female exposure to EDCs on fecundity. While the term EDC encompasses both persistent and non-persistent chemicals, we have chosen to focus on the research pertaining to short-lived or non-persistent EDCs such as phenols (e.g. bisphenol A (BPA), parabens, triclosan) and phthalates due to the recent uptick in research studies in this area.

2. Bisphenol A

BPA is a high production volume chemical widely used in the manufacture of a variety of consumer products such as polycarbonate plastics, epoxy resin liners of canned foods, some dental sealants and composites, and thermal receipts [9]. The half-life of BPA is short, with almost complete excretion via urine in 24 hours [10]. BPA is a known endocrine disruptor with the ability to affect multiple hormonal pathways [11]. Experimental studies in animals suggest that BPA adversely affects female fecundity yet whether these same adverse effects are observed in humans remains to be determined [12, 13].

In humans, BPA is one of the most researched non-persistent EDCs in relation to fecundity with studies focusing on endpoints from menstrual cycle characteristics [14], early IVF outcomes [15, 16] and ovarian reserve [17, 18] to TTP [14, 19, 20] (Table 1). One of the first studies to assess the effects of BPA on female fecundity was the Environmental and Reproductive Health (EARTH) Study which measured BPA in urine collected twice during ovarian stimulation in relation to early outcomes of IVF. In two separate papers (n=84 and 174 women), researchers showed the female urinary BPA concentrations were negatively associated with peak serum estradiol levels, number of total and mature oocytes retrieved, and number of normally fertilized oocytes [15, 16]. They also found that higher urinary BPA concentrations were associated with a suggestive decrease in the likelihood of implantation [21]. The adverse effects of female exposure to BPA on clinical outcomes of IVF, including implantation, clinical pregnancy and live birth were not confirmed in an updated analysis which included a larger group of women (n= 256 women) from the same study cohort [22]. However, two recent papers from the EARTH Study suggest that this association could be significantly modified by a woman's soy and folate intake [23, 24]. Specifically, urinary BPA levels were negatively related to implantation, clinical pregnancy, and live birth among

women who consumed no soy foods and <400 μg/day of food folate, but not among women consuming soy or higher levels of folate.

The EARTH Study also explored the association between female exposure to BPA on markers of ovarian reserve [18]. Among 209 women seeking fertility treatment, Souter and colleagues found a significant trend toward lower antral follicle count (AFC) with higher urinary concentrations of BPA; however, no associations were found between BPA and follicle stimulating hormone (FSH) or ovarian volume. Similar to results in the aforementioned study, a more recent study among 268 infertile Chinese women diagnosed with polycystic ovary syndrome (PCOS) also found that female urinary BPA levels were inversely associated with AFC, however no associations were observed with antimullerian hormone, FSH, and inhibin B [17].

Among women conceiving naturally, there have been several studies on the link between urinary BPA levels and fecundity. Using 501 couples recruited from Michigan and Texas who were trying to get pregnant and enrolled in the Longitudinal Investigation of Fertility and the Environmental (LIFE) Study, Buck Louis and colleagues found that female urinary BPA concentrations at baseline were not associated with TTP [20]. Similarly, Velez and coworkers found no effect of first trimester female urinary BPA levels on recalled TTP among 2,001 women in the Maternal-Infant Research on Environmental Chemicals (MIREC) Study, a retrospective study among pregnant Canadian women [19]. Finally, most recently, Jukic and collaborators found that increased urinary concentrations of BPA were associated with shorter luteal phases among 221 women attempting pregnancy in the North Carolina Early Pregnancy Study (EPS); however, they did not observe any associations with TTP or early pregnancy loss [14].

Taken together, the available research in humans suggests that female exposure to BPA might have adverse effects on markers of fecundity, such as AFC and possibly oocyte quality and luteal phase length as well as IVF outcomes after accounting for dietary intake of soy and folate; however there was not sufficient evidence supporting a link between female exposure to BPA and TTP. While the women from infertility clinic studies tended to have higher BPA concentrations than the women enrolled in the LIFE and MIREC studies which might possibly explain why stronger effects were observed in those studies, the EPS found no association between BPA and TTP and they reported the highest median BPA concentration. Therefore, it is unlikely that a lower level of BPA is explaining the lack of associations observed in the LIFE and MIREC studies. As BPA levels continue to decrease in many populations and replacement chemicals are introduced into commerce, future research should focus on not only evaluating the reproductive effects of BPA but also bisphenols S and F [25]

3. Phthalates

Phthalates, a class of synthetic chemicals with a wide spectrum of commercial uses, is ubiquitous and human exposure can occur through ingestion, inhalation, dermal contact, and parenteral exposure from medical devices [26]. High-molecular-weight phthalates such as di(2-ethylhexyl) phthalate (DEHP), diisodecyl phthalate (DiDP) and diisononyl phthalate

(DiNP), are primarily used as plasticizers in the manufacture of flexible vinyl, which is used in consumer products, flooring and wall coverings, food contact applications, and medical devices [26]. The low molecular weight phthalates, such as diethyl phthalate (DEP), di-n-butyl phthalate (DnBP), and di-iso-butyl phthalate (DiBP), are primarily used in cosmetics and personal care products and in varnishes and coatings, including those used for the time release of some orally administered medications. Similar to BPA, phthalates have short half-lives and are quickly metabolized in the body. However, despite this rapid excretion, several animal studies have implicated phthalates as female reproductive toxicants with specific effects on disrupting ovarian function [27–29].

In humans, there is accumulating evidence on the effects of phthalates on female fecundity as measured by IVF outcomes [30], ovarian reserve [31] and TTP [14, 19, 20, 32] (Table 2). Hauser and colleagues found that urinary metabolites of DEHP and DiDP were associated with decreased total and mature oocyte yield during IVF, and metabolites of DiNP and DiDP were associated with reduced fertilization rates [30]. Higher urinary concentrations of the DEHP metabolites were also associated with reduced probability of clinical pregnancy and live birth following IVF. The urinary concentrations of the other measured phthalate metabolites were not significantly associated with IVF outcomes, although almost all showed negative trends with increasing urinary concentrations. The EARTH Study also investigated the effect of female exposure to phthalates on ovarian reserve as measured by AFC [31]. Messerlian and coworkers found that higher urinary concentrations of DEHP were associated with decreased AFC, with the association being strongest among women <37 years. There were no associations between the remaining phthalate metabolite concentrations and AFC.

In contrast to the striking effects of high molecular weight phthalates on markers of fecundity that were observed among subfertile women seeking fertility treatment, studies among women conceiving naturally were not consistent. Three studies including the LIFE Study [20], the MIREC Study [19] and the EPS [14], found no associations between female urinary phthalate concentrations and TTP; however, in the EPS, when nonconception cycles were compared with the conception cycle from the same woman, MnBP and ΣDEHP levels were higher in the nonconception cycles. Most recently, the Danish First Pregnancy Planner cohort, which included 229 Danish women planning pregnancy from 1992 to 1994, found that higher urinary concentrations of MEP were associated with a longer TTP [32]. Similar to the previous studies, however, these authors found no significant associations between urinary MBP, MBzP and MEHP concentrations and TTP [32].

Thus, while studies from infertility clinics suggest that high molecular weight phthalates, specifically DHEP, may have adverse effects on female fecundity, this association was not found among couples conceiving without medical assistance. The differences in results across studies may suggest that couples from an infertility clinic represent a sensitive sub-population to environmental chemicals, specifically phthalates. The EARTH study also relied on multiple spot urine samples to characterized pre-conception phthalate exposure as opposed to a spot urine which was used in many of the TTP studies which may better characterize long-term exposure given the low reproducibility of urinary levels of phthalate metabolites over time [33]. Differences in urinary concentrations of phthalates could also be

an explanation for why the Danish First Pregnancy Planner cohort found adverse effects of MEP as their levels were substantially higher than any of the other cohorts. Taken together, there is evidence for potential adverse effects of low level exposure to some phthalates on female fecundity.

4. Parabens

Parabens are EDCs mainly used as antimicrobial preservatives in cosmetics, personal care products, and pharmaceuticals [34]. The most common parabens are methyl paraben (MP), propyl paraben (PP), butyl paraben (BP) and ethyl paraben (EP). Although parabens are quickly eliminated from the body [35], methyl, propyl, and butyl paraben were detected in 99.1%, 92.7%, and 40% of the general US population, respectively [36]. Many *in vitro* studies have reported estrogen receptor binding capacity of parabens [37, 38] and a few animal toxicity studies have reported adverse effects of parabens on female reproductive function including decreased ovarian weights and histopathological changes in the ovaries [39, 40].

Four studies to date (Table 3), two utilizing women from a fertility clinic [41, 42], one including women from a prospective TTP study [43], and the other among Japanese students [44], have investigated the association between female exposure to parabens and markers of fecundity. Smith and colleagues found a borderline association between increasing tertiles of PP and diminished AFC among 192 women in the EARTH Study, but no relation with ovarian volume and day 3 FSH levels [42]. Mínguez-Alarcón and coauthors studied whether female exposure to parabens was related to IVF outcomes among 245 women from the same study cohort [41] and found no associations between MP, PP, and BP and any of the fecundity endpoints assessed. Similarly, Smarr and colleagues found no evidence that parabens were associated with couple fecundity, as measured by TTP, when the exposure was modelled continuously, among couples in the LIFE Study [43]. Nevertheless, the authors' observed an almost 40% reduction in couple fecundity when female partners had a urinary MP and EP concentration in the highest quartile as compared to the lowest quartile. Nishihama and coauthors found associations between urinary concentrations of BP and the sum of all the measured parabens (BP, PP, MP and EP) and shorter menstrual cycle lengths among 128 Japanese students [44]; however, PP, MP and EP did not have independent effects on menstrual cycle length.

At present, the evidence on the association of parabens with markers of fecundity remains very limited with inconsistent results across studies. Of important note are the large differences in urinary paraben concentrations reported in these studies. The EARTH study and the cohort of Japanese students had median MP concentrations 5 times higher than the LIFE study; however none of these studies found adverse effects of MP. PP levels were also substantially higher in the EARTH study and could explain why this study saw associations of PP with AFC but other studies failed to demonstrate any effects. Finally, only the Japanese study found a detrimental association between BP and fecundity (as measured by menstrual cycle length), despite reporting comparable urinary BP levels to the LIFE Study (which showed no association with BP and TTP) and much lower urinary BP levels compared to the EARTH Study (which showed no associations with markers of ovarian

reserve or IVF outcomes). Given the ubiquitous exposure of the general population and the limited research conducted to date, future work on parabens and fecundity is warranted.

5. Triclosan

Triclosan is a lipid-soluble phenolic compound with broad-spectrum antibacterial properties used for over forty years as an ingredient in personal care products [45]. Due to its widespread use, there is potential for the general population to be exposed to triclosan through dermal and mucosal contact with consumer products [6]. Triclosan has a similar structure to known EDCs such as polychlorinated biphenyls, polybrominated diphenyl ethers, and BPA, and to thyroid hormones. These structural similitudes, coupled with some limited evidence from experimental studies, suggest that triclosan may act as an antiestrogen and/or antiandrogen with possible adverse effects on reproductive outcomes [45].

Two studies have investigated the effect of female urinary triclosan concentrations on couple fecundability among women in the LIFE [43] and MIREC [19] studies (Table 4). Smarr and colleagues showed no association between female urinary triclosan concentrations and TTP whether the exposure was modelled as continuous variable, or categorized in quartiles, in the LIFE Study [43]. In contrast, Velez and coauthors found that higher first trimester urinary levels of triclosan were associated with a longer TTP among the Canadian pregnant women in the MIREC Study [19].

It is difficult to make strong conclusions regarding the effect of female exposure to triclosan on fecundity given there are only two human studies on this topic and they are conflicting. While these two studies appear similar in many regards– both focused on TTP and both studies had similar urinary triclosan concentrations- there are important differences worth considering. First, because the MIREC study was a pregnancy-based TTP study, the authors assumed that triclosan concentrations measured during the first trimester of pregnancy were representative of the preconception concentrations; however, it is possible that concentrations of these chemicals could be metabolized differently during pregnancy due to the physiologic changes occurring during this period. Both studies also had relatively low urinary triclosan concentrations which could explain discrepancies seen with animal studies. More research on the topic is needed to clarify the role of this non-persistent chemical on TTP, and other outcomes of human fecundity.

6. Conclusions

While the epidemiologic literature on female exposure to non-persistent EDCs and fecundity is growing, the evidence supporting an association between female urinary concentrations of most non-persistent EDCs and fecundity remains limited. As was pointed out in each of the individual sections, the heterogeneous results could be due to methodological differences in patient populations, study designs, assessment of exposure, residual confounding due to diet or other lifestyle factors, and co-exposures to other chemicals. Also given than most of the studies examined several chemicals and multiple outcomes without statistical adjustment for multiple comparisons and in many studies post hoc analyses were performed, it is also possible that chance results could be to blame for inconsistent findings. It is also being

increasingly recognized that environmental endocrine disruption is most often not due to the effect of a single compound, but rather due to exposure to mixtures of chemicals at low concentrations [46]. Thus, while none of the studies reviewed here examined the health effects of exposure to a mixture of non-persistent EDCs, this is clearly an area for future research [47, 48]. Similarly, as research accumulates on the adverse health consequences of exposure to specific EDCs, substitute chemicals are introduced into the market such as bisphenol S and F, for BPA, and di-(iso-nonyl)-cyclohexane-1,2-dicarboxylate (DINCH), for high molecular weight phthalates. Thus, while exposure to certain EDCs such as BPA and DEHP may be declining, exposure to many others are on the rise [25, 49] and early studies suggest they may not be safer alternatives [50, 51]. Future research should focus on incorporating the assessment of these newer chemicals into ongoing studies to assess the potential effects that these chemicals could have on human fecundity.

Acknowledgments

Financial support: The authors were funded by NIH grants L50-HD085359 from the National Institute of Child Health and Human Development and R01-ES009718 and K99-ES026648 from the National Institute of Environmental Health Sciences.

We would also like to thank Dr. Russ Hauser, Harvard T.H. Chan School of Public Health, for his invaluable feedback on this review.

References

1. Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, Hauser R, Prins GS, Soto AM, et al. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. Endocr Rev. 2009 Jun; 30(4):293–342. [PubMed: 19502515]
2. Attina TM, Hauser R, Sathyanarayana S, Hunt PA, Bourguignon JP, Myers JP, et al. Exposure to endocrine-disrupting chemicals in the USA: a population-based disease burden and cost analysis. Lancet Diabetes Endocrinol. 2016 Dec; 4(12):996–1003. [PubMed: 27765541]
3. Trasande L, Zoeller RT, Hass U, Kortenkamp A, Grandjean P, Myers JP, et al. Estimating burden and disease costs of exposure to endocrine-disrupting chemicals in the European union. J Clin Endocrinol Metabol. 2015 Apr; 100(4):1245–55.
4. Centers for Disease Control and Prevention (CDC). [Accessed March 30th 2017] National Public Health Action Plan for the Detection, Prevention, and Management of Infertility. 2014. Available: http://www.cdc.gov/reproductivehealth/infertility/pdf/drh_nap_final_508.pdf
5. 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 Mar; 112(3):331–8. [PubMed: 14998749]
6. Calafat AM, Ye X, Wong LY, Reidy JA, Needham LL. Urinary concentrations of triclosan in the U.S population: 2003–2004. Environ Health Perspect. 2008 Mar; 116(3):303–7. [PubMed: 18335095]
7. Calafat AM, Ye X, Wong LY, Reidy JA, Needham LL. Exposure of the U.S. population to bisphenol A and 4-tertiary-octylphenol: 2003–2004. Environ Health Perspect. 2008 Jan; 116(1):39–44. [PubMed: 18197297]
8. Smarr MM, Sapra KJ, Gemmill A, Kahn LG, Wise LA, Lynch CD, et al. Is human fecundity changing? A discussion of research and data gaps precluding us from having an answer. Hum Reprod. 2017 Jan 30.
9. 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(8):859–60. [PubMed: 24570250]

10. Volkel W, Colnot T, Csanady GA, Filser JG, Dekant W. Metabolism and kinetics of bisphenol a in humans at low doses following oral administration. Chem Res Toxicol. 2002 Oct; 15(10):1281–7. [PubMed: 12387626]

11. Vandenberg LN, Hauser R, Marcus M, Olea N, Welshons WV. Human exposure to bisphenol A (BPA). Reprod Toxicol. 2007; 24(2):139–77. [PubMed: 17825522]

12. Takai Y, Tsutsumi O, Ikezuki Y, Kamei Y, Osuga Y, Yano T, et al. Preimplantation exposure to bisphenol A advances postnatal development. Reprod Toxicol. 2001 Jan-Feb;15(1):71–4. [PubMed: 11137380]

13. Tsutsui T, Tamura Y, Yagi E, Hasegawa K, Takahashi M, Maizumi N, et al. Bisphenol-A induces cellular transformation, aneuploidy and DNA adduct formation in cultured Syrian hamster embryo cells. Int J Cancer. 1998 Jan 19; 75(2):290–4. [PubMed: 9462721]

14**. Jukic AM, Calafat AM, McConnaughey DR, Longnecker MP, Hoppin JA, Weinberg CR, et al. Urinary Concentrations of Phthalate Metabolites and Bisphenol A and Associations with Follicular-Phase Length, Luteal-Phase Length, Fecundability, and Early Pregnancy Loss. Environ Health Perspect. 2016; 124(3):321–8. This prospective study had multiple urinary BPA and phthalate assessments in each menstrual cycle understudy and were able to measure many early fecundity endpoints as well as TTP. The authors found associations between BPA and MCOP and shorter luteal phase lengths but no association with the other fecudnty endpoints. [PubMed: 26161573]

15. Mok-Lin E, Ehrlich S, Williams PL, Petrozza J, Wright DL, Calafat AM, et al. Urinary bisphenol A concentrations and ovarian response among women undergoing IVF. In J Androl. 2010 Apr; 33(2):385–93.

16. Ehrlich S, Williams PL, Missmer SA, Flaws JA, Ye X, Calafat AM, et al. Urinary bisphenol A concentrations and early reproductive health outcomes among women undergoing IVF. Hum Reprod. 2012 Dec; 27(12):3583–92. [PubMed: 23014629]

17. Zhou W, Fang F, Zhu W, Chen ZJ, Du Y, Zhang J. Bisphenol A and Ovarian Reserve among Infertile Women with Polycystic Ovarian Syndrome. In J Environ Res Public Health. 2016 Dec 27.14(1)

18. Souter I, Smith KW, Dimitriadis I, Ehrlich S, Williams PL, Calafat AM, et al. The association of bisphenol-A urinary concentrations with antral follicle counts and other measures of ovarian reserve in women undergoing infertility treatments. Reprod Toxicol. 2013 Dec.42:224–31. [PubMed: 24100206]

19. Velez MP, Arbuckle TE, Fraser WD. Female exposure to phenols and phthalates and time to pregnancy: the Maternal-Infant Research on Environmental Chemicals (MIREC) Study. Fertil Steril. 2015 Apr; 103(4):1011–20. e2. [PubMed: 25681860]

20**. 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(5):1359–66. This was the first study to prospectively investigate the relationships of BPA and phthalates on couples' fecundity and overall showed no associations with urinary BPA or any of the phthalates concentrations and TTP. [PubMed: 24534276]

21. Ehrlich S, Williams PL, Missmer SA, Flaws JA, Berry KF, Calafat AM, et al. Urinary bisphenol A concentrations and implantation failure among women undergoing in vitro fertilization. Environ Health Perspect. 2012 Jul; 120(7):978–83. [PubMed: 22484414]

22*. Minguez-Alarcon L, Gaskins AJ, Chiu YH, Williams PL, Ehrlich S, Chavarro JE, et al. Urinary bisphenol A concentrations and association with in vitro fertilization outcomes among women from a fertility clinic. Hum Reprod. 2015 Sep; 30(9):2120–8. This was the largest prospective studyamong women undergoing fertility treatment to explore whether BPA is associated with IVF outcomes among women. Overall, the authors found no significant relationships. [PubMed: 26209788]

23*. Chavarro JE, Minguez-Alarcon L, Chiu YH, Gaskins AJ, Souter I, Williams PL, et al. Soy Intake Modifies the Relation Between Urinary Bisphenol A Concentrations and Pregnancy Outcomes Among Women Undergoing Assisted Reproduction. J Clin Endocrinol Metab. 2016 Mar; 101(3): 1082–90. This was the first human study to coroborrate animal findings that dietary

phytoestrogens might protect against the negative reproductive effects of BPA exposure. [PubMed: 26815879]

24. Minguez-Alarcon L, Gaskins AJ, Chiu YH, Souter I, Williams PL, Calafat AM, et al. Dietary folate intake and modification of the association of urinary bisphenol A concentrations with in vitro fertilization outcomes among women from a fertility clinic. Reprod Toxicol. 2016 Oct. 65:104–12. [PubMed: 27423903]
25. Ye X, Wong LY, Kramer J, Zhou X, Jia T, Calafat AM. Urinary Concentrations of Bisphenol A and Three Other Bisphenols in Convenience Samples of U.S. Adults during 2000–2014. Environ Sci Technol. 2015 Oct 06; 49(19):11834–9. [PubMed: 26360019]
26. Hauser R, Calafat AM. Phthalates and human health. Occup Environ Med. 2005 Nov; 62(11):806–18. [PubMed: 16234408]
27. Lovekamp-Swan T, Davis BJ. Mechanisms of phthalate ester toxicity in the female reproductive system. Environ Health Perspect. 2003 Feb; 111(2):139–45. [PubMed: 12573895]
28. Craig ZR, Singh J, Gupta RK, Flaws JA. Co-treatment of mouse antral follicles with 17beta-estradiol interferes with mono-2-ethylhexyl phthalate (MEHP)-induced atresia and altered apoptosis gene expression. Reprod Toxicol. 2014 Jun.45:45–51. [PubMed: 24412242]
29. Hannon PR, Peretz J, Flaws JA. Daily exposure to Di(2-ethylhexyl) phthalate alters estrous cyclicity and accelerates primordial follicle recruitment potentially via dysregulation of the phosphatidylinositol 3-kinase signaling pathway in adult mice. Biol Reprod. 2014 Jun.90(6):136. [PubMed: 24804967]

30**. Hauser R, Gaskins AJ, Souter I, Smith KW, Dodge LE, Ehrlich S, et al. Urinary Phthalate Metabolite Concentrations and Reproductive Outcomes among Women Undergoing in Vitro Fertilization: Results from the EARTH Study. Environ Health Perspect. 2016 Jun; 124(6):831–9. This was the first study to prospectively investigate the associations of phthalates on IVF outcomes among women and to report negative relationships between some phthalates, particularly those of high molecular weight, and markers of female fecundity such as clinical pregnancy and live birth. [PubMed: 26545148]

31. Messerlian C, Souter I, Gaskins AJ, Williams PL, Ford JB, Chiu YH, et al. Urinary phthalate metabolites and ovarian reserve among women seeking infertility care. Hum Reprod. 2016 Jan; 31(1):75–83. [PubMed: 26573529]

32*. Thomsen AM, Riis AH, Olsen J, Jonsson BA, Lindh CH, Hjollund NH, et al. Female exposure to phthalates and time to pregnancy: a first pregnancy planner study. Hum Reprod. 2017 Jan; 32(1): 232–8. This is the most recent publication on female exposure to phthlates and fecundity and the only one yet to find a significant adverse effect of MEP on TTP (although levels were much higher than in the other studies). [PubMed: 27852689]

33. Fisher M, Arbuckle TE, Mallick R, LeBlanc A, Hauser R, Feeley M, et al. Bisphenol A and phthalate metabolite urinary concentrations: Daily and across pregnancy variability. J Expo Sci Environ Epidemiol. 2015 May; 25(3):231–9. [PubMed: 25248937]
34. Braun JM, Just AC, Williams PL, Smith KW, Calafat AM, Hauser R. Personal care product use and urinary phthalate metabolite and paraben concentrations during pregnancy among women from a fertility clinic. J Expo Sci Environ Epidemiol. 2014 Sep-Oct;24(5):459–66. [PubMed: 24149971]
35. Janjua NR, Frederiksen H, Skakkebaek NE, Wulf HC, Andersson AM. Urinary excretion of phthalates and paraben after repeated whole-body topical application in humans. Int J Androl. 2008 Apr; 31(2):118–30. [PubMed: 18194284]
36. Calafat AM, Ye X, Wong LY, Bishop AM, Needham LL. Urinary concentrations of four parabens in the U.S. population: NHANES 2005–2006. Environ Health Perspect. 2010 May; 118(5):679–85. [PubMed: 20056562]
37. Golden R, Gandy J, Vollmer G. A review of the endocrine activity of parabens and implications for potential risks to human health. Crit Rev Toxicol. 2005 Jun; 35(5):435–58. [PubMed: 16097138]
38. Routledge EJ, Parker J, Odum J, Ashby J, Sumpter JP. Some alkyl hydroxy benzoate preservatives (parabens) are estrogenic. Toxicol Appl Pharmacol. 1998 Nov; 153(1):12–9. [PubMed: 9875295]
39. Taxvig C, Vinggaard AM, Hass U, Axelstad M, Boberg J, Hansen PR, et al. Do parabens have the ability to interfere with steroidogenesis? Toxicol Sci. 2008 Nov; 106(1):206–13.

40. Vo TT, Yoo YM, Choi KC, Jeung EB. Potential estrogenic effect(s) of parabens at the prepubertal stage of a postnatal female rat model. Reprod Toxicol. 2010 Jun; 29(3):306–16. [PubMed: 20132880]

41*. Minguez-Alarcon L, Chiu YH, Messerlian C, Williams PL, Sabatini ME, Toth TL, et al. Urinary paraben concentrations and in vitro fertilization outcomes among women from a fertility clinic. Fertil Steril. 2016 Mar; 105(3):714–21. This was the first study evaluating the association between cycle specific preconception paraben concentrations and IVF outcomes. Despite evaluating a large number of intermediate and clinical IVF outcomes, none were associated with parabens. [PubMed: 26654974]

42. Smith KW, Souter I, Dimitriadis I, Ehrlich S, Williams PL, Calafat AM, et al. Urinary Paraben Concentrations and Ovarian Aging among Women from a Fertility Center. Environ Health Perspect. 2013 Nov-Dec;121(11–12):1299–305. [PubMed: 23912598]

43**. Smarr MM, Sundaram R, Honda M, Kannan K, Buck Louis GM. Urinary Concentrations of Parabens and Other Antimicrobial Chemicals and Their Association with Couples' Fecundity. Environ Health Perspect. 2017 Apr; 125(4):730–736. This was the first study to prospectively investigate whether urinary parabens and triclosan concentrations were associated with couples' fecundity. The authors found that women with higher urinary concentrations of specific parabens (PP and MP) had longer TTP. [PubMed: 27286252]

44. Nishihama Y, Yoshinaga J, Iida A, Konishi S, Imai H, Yoneyama M, et al. Association between paraben exposure and menstrual cycle in female university students in Japan. ReprodToxicol. 2016 Aug.63:107–13.

45. Dann AB, Hontela A. Triclosan: environmental exposure, toxicity and mechanisms of action. J Appl Toxicol. 2011 May; 31(4):285–311. [PubMed: 21462230]

46. Sumpter JP, Johnson AC. Lessons from endocrine disruption and their application to other issues concerning trace organics in the aquatic environment. Environ Sci Technol. 2005 Jun 15; 39(12): 4321–32. [PubMed: 16047764]

47. Brian JV, Harris CA, Scholze M, Backhaus T, Booy P, Lamoree M, et al. Accurate prediction of the response of freshwater fish to a mixture of estrogenic chemicals. Environ Health Perspect. 2005 Jun; 113(6):721–8. [PubMed: 15929895]

48. Rajapakse N, Silva E, Kortenkamp A. Combining xenoestrogens at levels below individual no-observed-effect concentrations dramatically enhances steroid hormone action. Environ Health Perspect. 2002 Sep; 110(9):917–21. [PubMed: 12204827]

49. Silva MJ, Jia T, Samandar E, Preau JL Jr, Calafat AM. Environmental exposure to the plasticizer 1,2-cyclohexane dicarboxylic acid, diisononyl ester (DINCH) in U.S. adults (2000–2012). Environ Res. 2013 Oct.126:159–63. [PubMed: 23777640]

50. Minguez-Alarcon L, Souter I, Chiu YH, Williams PL, Ford JB, Ye X, et al. Urinary concentrations of cyclohexane-1,2-dicarboxylic acid monohydroxy isononyl ester, a metabolite of the non-phthalate plasticizer di(isononyl)cyclohexane-1,2-dicarboxylate (DINCH), and markers of ovarian response among women attending a fertility center. Environ Res. 2016 Nov.151:595–600. [PubMed: 27591839]

51. Eladak S, Grisin T, Moison D, Guerquin MJ, N'Tumba-Byn T, Pozzi-Gaudin S, et al. A new chapter in the bisphenol A story: bisphenol S and bisphenol F are not safe alternatives to this compound. Fertil Steril. 2015 Jan; 103(1):11–21. [PubMed: 25475787]

Key points

- The evidence in humans supporting an association between female urinary concentrations of bisphenol A, phthalates, parabens and triclosan, and fecundity remains unclear.
- The heterogeneous results across studies could be due to methodological differences in recruitment populations, study designs, assessment of exposure, residual confounding, and co-exposures to other chemicals.
- Future research should focus on incorporating the assessment of newer non-persistent EDCs into ongoing studies and investigating the potential effects that mixtures of EDCs could have on human fecundity.

Table 1

Overview of studies on female urinary concentrations of BPA and markers of fecundity.

Citation	Years of Study	Number of Women	Type of Study	Timing of Exposure	Mean/median urinary BPA concentration (ng/mL)	Outcome(s)	Results
Mok-Lin et al. 2010	2004–2008	84	Prospective IVF study	Between day 3–9 and 10–20 of menstrual IVF cycle	Median (IQR): 1.60 (0.70, 3.10) GM (SD): 2.52 (SD 3.20)	Markers of ovarian response	Associated with decreased oocytes retrieved and peak oestradiol levels.
Ehrlich et al. 2012a	2004–2010	137	Prospective IVF study	Between day 3–9 and 10–20 of menstrual IVF cycle	Median (IQR): 1.50 (0.89, 2.40) GM (SD): 1.53 (2.22)	Implantation failure	Associated with increased implantation failure
Ehrlich et al. 2012b	2004–2010	174	Prospective IVF study	Between day 3–9 and 10–20 of menstrual IVF cycle	Median (IQR): 1.50 (0.85, 2.47) GM (SD): 1.50 (2.22)	Markers of ovarian response and early reproductive outcomes	Associated with decrease oocytes (retrieved, mature and fertilized), E2 levels, and blastocyst formation. No associations with embryo quality or cleavage rate
Souter et al. 2013	2004–2010	209	Prospective fertility patient study	Study entry, and between day 3–9 and 10–20 of menstrual cycle	Median (IQR): 1.20 (0.70, 2.30) GM (SD): 1.30 (2.50)	Markers of ovarian reserve	Associated with lower AFC. No associations with day 3 FSH levels or ovarian volume.
Buck-Louis et al. 2014a	2005–2009	501	Prospective TTP study	Study entry	GM (5^{th}, 95^{th}): 0.63 (0.54, 0.73)	Couples fecundity as TTP	No association with TTP.
Minguez-Alarcon et al. 2015	2004–2012	256	Prospective IVF study	Between day 3–9 and 10–20 of menstrual IVF cycle	Median (IQR): 1.47 (0.89, 2.40) GM (SD): 2.06 (2.20)	IVF outcomes	No association with total and mature oocytes, embryo quality, fertilization, implantation, clinical pregnancy or live birth.
Velez et al. 2015	2008–2011	1,742	Retrospective TTP Study	First trimester	GM (5^{th}, 95^{th}): 0.78 (0.73, 0.82)	Couples fecundity as TTP	No association with TTP.
Zhou et al. 2016	2014	268	Prospective study in infertile women with PCOS	Study entry	Median (IQR): 2.35 (1.47, 3.95)	Markers of ovarian reserve	Associated with lower AFC. No associations with AMH, Day 3 FSH or inhibin B levels.
Jukic et al. 2016	1982–1986	221	Prospective TTP study	3 pooled urines from each menstrual cycle	Median (IQR): 2.7 (1.8, 4.3)	Ovulation, conception and pregnancy loss.	Associated with shorter luteal phases. Not associated with mid-luteal progesterone

Citation	Years of Study	Number of Women	Type of Study	Timing of Exposure	Mean/median urinary BPA concentration (ng/mL)	Outcome(s)	Results
							levels, TTP, or early pregnancy loss.

Table 2

Overview of studies on female urinary concentrations of phthalates and markers of fecundity.

Citation	Years of Study	Number of Women	Type of Study	Timing of Exposure	Mean/median urinary phthalate concentration (ng/mL)*	Outcome(s)	Results
Buck-Louis et al. 2014a	2005–2009	501	Prospective TTP study	Study entry	GM (95% CI): MEP, 93.83 (79.57–110.64); MEHP, 4.56 (3.40–6.11) MEHHP, 15.24 (13.01–17.86); MEOHP, 8.65 (7.40–10.10); mBP, 9.97 (8.96–11.09), mBzP, 4.61 (4.06–5.23)	Couples fecundity as TTP	No association between any parent compound and TTP.
Velez et al. 2015	2008–2011	1,597	Retrospective TTP Study	First trimester	GM (95% CI): MEHHP, 9.21 (8.65–8.79); MEOHP, 6.42 (6.06–6.81); MEHP, 2.27 (2.14–2.40); MEP, 32.09 (29.67–34.70); MBzP, 5.10 (4.79–5.44); MnBP, 11.44 (10.78–12.15)	Couples fecundity as TTP	No association between any parent compound and TTP.
Jukic et al. 2016	1982–1986	221	Prospective TTP study	3 pooled urines from each menstrual cycle	Median (IQR): MnBP: 80.0 (48.7, 127.0), MEP: 134 (72.4, 296.0), MBzP: 39.5 (24.7, 68.6), MEHP: 6.6 (3.8, 11.2), MEHHP: 50.4 (31.8, 80.8), MEOHP: 30.3 (19.5, 48.9), MCOP: 3.3 (2.3, 5.2)	Ovulation, conception and pregnancy loss.	MCOP associated with shorter luteal phases. The rest of the parent compounds were not associated with mid-luteal progesterone levels, TTP or early pregnancy loss.
Hauser et al. 2016	2004–2012	256	Prospective IVF study	Between day 3–9 and 10–20 of menstrual IVF cycle	Median (IQR): DEHP, 0.20 (0.09, 0.44); MEP, 49.3 (21.5, 129); MBP, 12.9 (7.32, 20.8); MBzP, 3.44 (1.75, 7.35); MCOP, 22.8 (9.10, 57.7)	IVF outcomes	DEHP and DiDP were associated with decreased oocyte yield and number of mature oocytes. DEHP metabolites were associated with reduced probability of clinical pregnancy and live birth. The rest of the parent compounds were not associated with outcomes of IVF.
Messerlian et al. 2016	2004–2012	215	Prospective fertility patient study	Study entry, and between day 3–9 and 10–20 of menstrual cycle	Median (IQR): DEHP 0.21 (0.10, 0.46); MEP, 54.2 (27.6, 139); MBP, 12.8 (7.4, 22.5); MBzP, 3.2 (1.7, 6.4); MCOP, 14.2 (5.8, 42.8)	Markers of ovarian reserve	DEHP was associated with lower AFC. The rest of the parent compounds were not associated with AFC.
Thomsen et al. 2017	1992–1994	229	Prospective TTP study	Average of 2 urines from day 0–10 of first menstrual cycle and the	Median (Range): MEP, 225 (21.5; 7044); MBP, 178 (32.3;	Couples fecundity as TTP	MEP was associated with a decreased fecundity (longer TTP). No

Citation	Years of Study	Number of Women	Type of Study	Timing of Exposure	Mean/median urinary phthalate concentration (ng/mL)*	Outcome(s)	Results
				5th menstrual cycle (or pregnancy cycle)	1392); MBzP, 14.9 (2.5; 103); MEHP, 11.2 (0.6; 71.1)		associations were found for MBP, MBzP and MEHP.

* Concentrations are reported for the most common phthalates measured across studies.

Table 3

Overview of studies on female urinary concentrations of parabens and markers of fecundity.

Citation	Years of Study	Number of Women	Type of Study	Timing of Exposure	Median urinary paraben concentration (ng/mL)	Outcome(s)	Results
Smith et al. 2013	2004–2010	192	Prospective fertility patient study	Study entry, and between day 3–9 and 10–20 of menstrual cycle	BP-Median 2.08 (IQR 0.40, 6.58) MP-Median 210 (IQR 75.2, 520) PP-Median 49.6 (IQR 13.0, 89.3)	Markers of ovarian response	PP was weakly associated with AFC, but no with day 3 FSH levels or ovarian volume. No associations for MP or BP.
Minguez-Alarcon et al. 2016	2004–2012	245	Prospective IVF study	Between day 3–9 and 10–20 of menstrual IVF cycle	BP-Median 1.18 (IQR 0.29, 5.77) MP-Median 163 (IQR 52.2, 380) PP-Median 31.4 (IQR 8.21, 90.2)	IVF outcomes	No association with total and mature oocytes, embryo quality, fertilization, implantation, clinical pregnancy or live birth.
Smarr et al. 2016	2005–2009	501	Prospective TTP study	Study entry	BP-Median 0.59 (IQR 0.08, 2.84) MP-Median 31.9 (IQR 12.0, 104) PP-Median 12.1 (IQR 3.54, 35.6) EP-Median 1.09 (IQR 0.27 5.62)	Couples fecundity as TTP	Only associated with longer TTP when MP and EP was divided in groups.
Nishihama et al. 2016	2012–2013	128	Cross-sectional study	1–2 months after they joined the study	BP-Median 0.63 (Range <LOD, 67) MP-Median 273 (Range 2.97, 4107) PP-Median 7.38 (Range <LOD, 245) EP-Median 4.04 (Range <LOD, 166)	Menstrual cycle length	BP and sum of parabens were associated with shorter menstrual cycle length. No associations for MP, EP or PP.

Table 4

Overview of studies on female urinary concentrations of triclosan and markers of fecundity.

Citation	Years of Study	Number of Women	Type of Study	Timing of Exposure	Mean/median urinary triclosan concentrations (ng/mL)	Outcome(s)	Results
Velez et al. 2015	2008–2011	1,699	Retrospective TTP Study	First trimester	GM (5^{th}, 95^{th}): 11.93 (10.67, 13.34)	Couples fecundity as TTP	Women in the top 25^{th} percentile of triclosan had longer TTP (reduced couple fecundity)
Smarr et al. 2016	2005–2009	501	Prospective TTP study	Study entry	Median (IQR): 11.70 (3.55, 54.2)	Couples fecundity as TTP	No association between any parent compound and TTP.