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Exposure to non-persistent chemicals in consumer products and fecundability: a systematic review

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BACKGROUND: Exposure to non-persistent chemicals in consumer products is ubiquitous and associated with endocrine-disrupting effects. These effects have been linked to infertility and adverse pregnancy outcomes in some studies and could affect couple fecundability, i.e. the capacity to conceive a pregnancy, quantified as time to pregnancy (TTP).

OBJECTIVE AND RATIONALE: Few epidemiologic studies have examined the impact of non-persistent chemicals specifically on TTP, and the results of these studies have not been synthesized. We undertook a systematic review to summarize the strength of evidence for associations of common non-persistent chemicals with couple fecundability and to identify gaps and limitations in the literature, with the aim of informing policy decisions and future research.

SEARCH METHODS: We performed an electronic search of English language literature published between 1 January 2007 and 25 August 2017 in MEDLINE, EMBASE.com, Global Health, DART/TOXLINE, POPLINE and DESTAF. We included human retrospective and prospective cohort, cross-sectional and case–control studies that examined phthalates, bisphenol A, triclosan, triclocarban, benzophenones, parabens and glycol ethers in consumer products, and considered TTP or fecundability as an outcome among women, men and couples conceiving without medical assistance. We excluded editorials, opinion pieces, introductions to special sections, articles that described only lifestyle (e.g. caffeine, stress) or clinical factors (e.g. semen parameters, IVF success). Standardized forms for screening, data extraction and study quality were developed using DistillerSR software and completed in duplicate. We used the Newcastle–Ottawa Scale to assess risk of bias and devised additional quality metrics based on specific methodological features of fecundability studies.

OUTCOMES: The search returned 3456 articles. There were 15 papers from 12 studies which met inclusion criteria, of which eight included biomarkers of chemical exposure. Studies varied widely in terms of exposure characterization, precluding a meta-analytic approach. Among the studies that measured exposure using biospecimens, results were equivocal for associations between either male or female phthalate exposure and TTP. There was preliminary support for associations of female exposure to some parabens and glycol ethers and of male exposure to benzophenone with longer TTP, but further research and replication of these results are needed. The results provided little to no indication that bisphenol A, triclocarban or triclosan exposure was associated with TTP.

WIDER IMPLICATIONS: Despite a growing literature on couple exposure to non-persistent endocrine-disrupting chemicals and fecundability, evidence for associations between biologically measured exposures and TTP is limited. Equivocal results with different non-persistent chemical compounds and metabolites complicate the interpretation of our findings with respect to TTP, but do not preclude action, given the documented endocrine disrupting effects on other reproductive outcomes as well as fetal development. We therefore advocate for common-sense lifestyle changes in which both females and males seeking to conceive minimize their exposure to non-persistent chemicals.

SYSTEMATIC REVIEW REGISTRATION NUMBER: CRD42018084304.

Key words: time to pregnancy / couple fecundability / endocrine-disrupting chemicals / systematic review / environmental effects / phthalates / phenols / parabens

Introduction

Fecundity refers to the physiological capacity to produce live offspring irrespective of whether a pregnancy is planned or children are born. Impaired fecundity commonly manifests as delayed conception or as diagnosed infertility, defined as the inability to conceive a child within 12 months of unprotected intercourse (Zegers-Hochschild *et al.*, 2009), and affects between 37 and 70 million couples worldwide (Boivin *et al.*, 2007). According to the most recent analysis of National Survey of Family Growth data, between 2006 and 2010, an estimated 17% of US women (7.3 million) aged 25–44 years or their partners had sought services for infertility at some point in their lives (Chandra *et al.*, 2014). Yet this figure underestimates the population prevalence of reduced fecundity, because many individuals or couples with impaired fecundity do not pursue or undergo recommended treatments (Kessler *et al.*, 2013) and many cases are undetected because individuals or couples are not seeking to become pregnant.

The personal, financial and physical costs of reduced fecundity can be significant. For example, there may be negative effects on couples' interpersonal, social and sexual life (Galhardo *et al.*, 2011; Luk and Loke, 2015), economic consequences from the high costs of treatment and loss of earnings (Wu *et al.*, 2013), and health risks associated with medical intervention (Mocanu *et al.*, 2007). A number of studies have also shown that a history of impaired fecundity is associated with increased risk of adverse pregnancy outcomes (Messerlian *et al.*, 2012; Wise *et al.*, 2015; Seggers *et al.*, 2016) and developmental problems in the child (Diop *et al.*, 2016). Furthermore, research suggests that reduced fecundity may be a biomarker of poorer general health and shorter life expectancy and is linked to greater risks of reproductive and non-reproductive cancers (Eisenberg *et al.*, 2016; Hanson *et al.*, 2018), cardiovascular disease (Eisenberg *et al.*, 2016; Latif *et al.*, 2017) and earlier mortality in men and women (Jensen *et al.*, 2009; Eisenberg *et al.*, 2014).

Fecundability, the per-cycle probability of conception given unprotected intercourse, is considered a marker of couple fecundity, albeit an approximate one, given that multiple genetic/epigenetic or biological conditions may interfere with progression from conception to live birth. In epidemiologic studies, fecundability is generally quantified as time to pregnancy (TTP), defined as the number of calendar months or menstrual cycles it takes to become pregnant with unprotected intercourse or since stopping contraception (Baird *et al.*, 1986; Joffe, 1997; Smarr *et al.*, 2017a). TTP studies may be prospective, enrolling couples around the time they stop using contraception and following them until they achieve a recognized pregnancy, or

retrospective, enrolling pregnant or previously pregnant women and asking how many months they had unprotected intercourse for before conceiving.

As a couple-based measure, TTP is influenced by both male and female factors, including age (Wood and Weinstein, 1988; Wesselink *et al.*, 2017), work-related and lifestyle factors (e.g. diet, stress, physical activity, tobacco, alcohol or caffeine consumption, drug abuse) (Sharma *et al.*, 2013; Nargund, 2015; Talmor and Dunphy, 2015; Hart, 2016) and physiological factors (e.g. menstrual cycle characteristics (Rattan *et al.*, 2017) or ovarian reserve (Steiner, 2013; Vabre *et al.*, 2017; Messerlian *et al.*, 2015) in women and semen quality (Phillips and Tanphaichitr, 2008; Hauser, 2008) or hormonal profiles (Witorsch and Thomas, 2010; Kay *et al.*, 2014; Olsen and Ramlau-Hansen, 2014) in men). Mounting evidence suggests that synthetic and naturally occurring environmental chemicals in food, water, air and consumer products may also contribute to impaired fecundity, leading to recent calls by the American Society for Reproductive Medicine and the International Federation of Gynecology and Obstetrics for greater attention to the impact of environmental pollutants on human reproductive health (Zoeller *et al.*, 2012; Di Renzo *et al.*, 2015). Of particular concern are endocrine-disrupting chemicals (EDCs), exogenous compounds that can affect hormonal pathways involved in the development and function of both male and female reproductive systems (Rogers *et al.*, 2013). EDCs disrupt endocrine function through interaction with hormone receptors, interference with hormone action or alteration of hormone synthesis, transport or metabolic processes (Gore *et al.*, 2015). We present a schema of the effects of EDCs on couple fecundability in Fig. 1. Specifically, consumption, inhalation and/or absorption of these environmental chemicals may directly affect the functioning of the ovaries and testes by disrupting ovulation and oocyte quality as well as spermatogenesis and sperm quality. Endocrine disruption can also occur at the brain level, affecting the hypothalamus–pituitary (HP)–gonadal, HP–adrenal and/or HP–thyroid axes, resulting in immune–endocrine–metabolome–microbiome–epigenome interactions that may impact not only gonadal function and gametes but also endometrial receptivity and other aspects of biological aging, thereby reducing fecundability and increasing TTP.

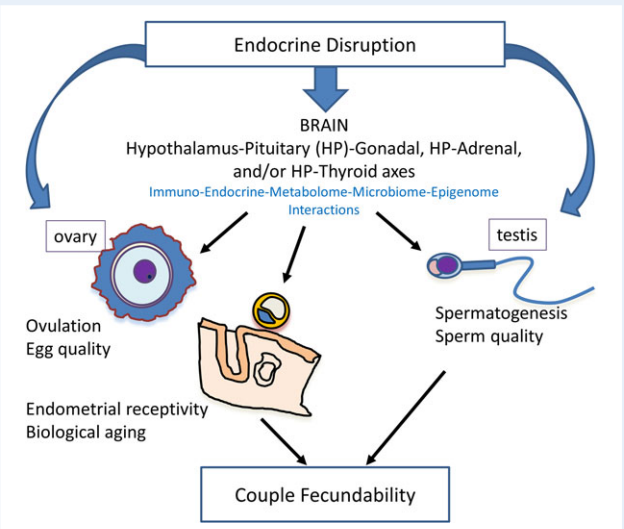

Figure 1 The effects of endocrine-disrupting chemicals (EDCs) on couple fecundability.

In general, EDCs are either persistent and accumulate in tissues (e.g. adipose tissue for organochlorine compounds), or they are non-persistent and are rapidly metabolized and excreted. There has been growing concern about the endocrine-disrupting effects of non-persistent chemicals such as phthalates, bisphenol A (BPA), parabens and other chemicals found in consumer products such as plastics, personal care products and cleaning supplies (Gore *et al.*, 2015). In the following section, we briefly summarize the common uses of these non-persistent chemicals and their associations with reproductive health outcomes. A list of chemical abbreviations is provided in Table I.

Phthalates

Phthalates are a class of compounds used in a multitude of consumer products, including personal care products (e.g. soap, cosmetics), medications (e.g. pill capsules) and polychlorinated vinyl plastics (e.g. food packaging, medical devices, shower curtains, vinyl flooring). Phthalate exposure occurs through ingestion, inhalation or dermal absorption (Rudel *et al.*, 2011; Braun *et al.*, 2014; Langer *et al.*, 2014). Although phthalates do not persist in the body and have short biological half-lives (<24 h), repeated, episodic and long-term exposures occur. The body burden of different phthalates is usually measured via their individual urinary metabolites. Research has shown that certain phthalates are associated with perturbed thyroid function (Meeker *et al.*, 2007; Meeker and Ferguson, 2011), lower semen quality (Jurewicz and Hanke, 2011; Sedha *et al.*, 2015; Wang *et al.*, 2016) and altered sex hormones (Jurewicz and Hanke, 2011; Kay *et al.*, 2014) in men. In girls and women, phthalate exposure is associated with altered thyroid function (Morgenstern *et al.*, 2017), increased risk of endometriosis (Mariana *et al.*, 2016) and lower oocyte yield and decreased odds of implantation in IVF cycles (Dodge *et al.*, 2015; Hauser *et al.*, 2016). Phthalates have also been shown to be related to longer estrous cycles and anovulation in animal studies (Hannon *et al.*, 2014; Mariana *et al.*, 2016).

Bisphenol A

Bisphenol A (BPA) is a phenol used to produce polycarbonate plastics and resins found in a wide range of consumer products (e.g. water bottles, linings of food cans, merchandise receipts, dental sealants). Oral ingestion is the predominant exposure route, as BPA can leach into food and beverages from containers. Individuals working with BPA-containing merchandise receipts may also be susceptible to inhalation and dermal absorption (Carwile *et al.*, 2011; Ehrlich *et al.*, 2014). BPA is excreted in urine as glucuronide or sulfate conjugates, does not persist in the body, and has an estimated biological half-life of ~6 h (Thayer *et al.*, 2015). BPA may interact with a variety of hormone systems that affect reproductive function. It is a weak agonist of nuclear estrogen receptors α and β (Acconcia *et al.*, 2015), but also acts on estrogen receptors bound to plasma proteins. It can interfere with estrogenic signaling at nanomolar and picomolar concentrations (Wetherill *et al.*, 2007). *In-vitro* studies have shown that BPA can affect androgen and/or estrogen concentrations by inhibiting key enzymes involved in gonadal hormone synthesis and metabolism

Table I Summary of chemical abbreviations.

Phthalate metabolites
- MBzP: monobenzyl phthalate
- MCHP: mono-cyclo-hexyl phthalate
- MCMHP: mono-[(2-carboxymethyl) hexyl] phthalate
- MCNP: monocarboxynonyl phthalate
- MCOP: monocarboxyoctyl phthalate
- MCPP: mono (3-carboxypropyl) phthalate
- MECPP: mono-(2-ethyl-5-carboxyphentyl) phthalate
- MEHHP: mono-(2-ethyl-5-hydroxy-hexyl) phthalate
- MEHP: mono-(2-ethylhexyl) phthalate
- MEOHP: mono-(2-ethyl-5-oxo-hexyl) phthalate
- MEP: mono-ethyl phthalate
- MiBP: mono (2-isobutyl) phthalate
- MiNP: mono-isononyl phthalate
- MMP: mono-methyl phthalate
- MnBP: mono-n-butyl phthalate
- MOP: monooctyl phthalate
- BPA: bisphenol A
- TCS: triclosan
- TCC: triclocarban

Benzophenones
- BP-1: 2,4-dihydroxybenzophenone
- BP-2: 2,2′,4,4′-tetrahydroxybenzophenone
- BP-3: 2-hydroxy-4-methoxybenzophenone
- BP-8: 2,2′-dihydroxy-4-methoxybenzophenone
- 4-OH-BP: 4-hydroxybenzophenone

Parabens
- BP: butyl paraben
- BzP: benzyl paraben
- EP: ethyl paraben
- HP: heptyl paraben
- MP: methyl paraben
- OH-Et-P: ethyl-protocatechuic acid
- OH-Me-P: methyl-protocatechuic acid
- PP: propyl paraben
- 3,4-DHB: 3,4-dihydroxy benzoic acid
- 4-HB: 4-hydroxy benzoic acid

Glycol ethers
- BAA: 2-butoxyacetic acid
- EAA: ethoxyacetic acid
- EEAA: ethoxyethoxyacetic acid
- MAA: methoxyacetic acid
- MEAA: methoxyethoxyacetic acid
- PAA: *n*-propoxyacetic acid
- PhAA: phenoxyacetic acid
- 2-MPA: 2-methoxypropionic acid

(Zhang *et al.*, 2011); however, results from human studies have been inconsistent (Meeker *et al.*, 2009; Galloway *et al.*, 2010; Mendiola *et al.*, 2010). In epidemiologic studies, urinary concentrations of BPA conjugates have been associated with increased risk of polycystic ovarian syndrome and disrupted oocyte development (Huo *et al.*, 2015), as well as lower semen quality (Manfo *et al.*, 2014; Minguez-Alarcon *et al.*, 2016) and poorer IVF outcomes (Machtinger and Orvieto, 2014).

Triclosan and triclocarban

Triclosan (TCS; 5-chloro-2-[2,4-dichlorophenoxy]phenol) and triclocarban (TCC; 3,4,4′-trichlorocarbanilide) are chlorinated antimicrobial agents widely used in soaps, healthcare antiseptic scrubs and some personal hygiene products (e.g. toothpaste, mouthwash, acne cream, deodorant and lotions) (Dann and Hontela, 2011; Ye *et al.*, 2011; Rochester *et al.*, 2017). Ingestion and dermal and mucosal absorption are the most significant routes of exposure to both chemicals (Moss *et al.*, 2000; Sandborgh-Englund *et al.*, 2006; Rodricks *et al.*, 2010; Ye *et al.*, 2011). In 2016, the US Food and Drug Administration deemed both chemicals no longer 'generally recognized as safe and effective' (GRAS-GRAE) and their use in consumer products is now regulated (US Food and Drug Administration, 2013). TCS is a phenol that has been associated with antiestrogenic activity (Stoker *et al.*, 2010) and decreased serum thyroid hormone concentrations in animal studies (Paul *et al.*, 2010; Stoker *et al.*, 2010). In rodents, TCS has been shown to disrupt the synthesis of luteinizing hormone, FSH and testosterone (Kumar *et al.*, 2009), and is associated with lower ovarian and uterine weight (Rattan *et al.*, 2017). TCS is also a powerful inhibitor of estrogen sulfonation in sheep placental tissue (James *et al.*, 2010), which could interfere with the maintenance of pregnancy. In humans, TCS has been associated with lower semen quality (Zhu *et al.*, 2016) and poorer IVF outcomes (Hua *et al.*, 2017). *In-vitro* human cell-based assays have demonstrated the potential for TCS to act as an antiestrogen and/or antiandrogen (Chen *et al.*, 2007; Ahn *et al.*, 2008; Gee *et al.*, 2008). TCC is structurally similar to carbanilide pesticides. While there have been few epidemiologic studies of TCC, animal models suggest that it may augment the action of endogenous hormones rather than directly activating hormone receptors (Rochester *et al.*, 2017).

Benzophenones

Benzophenone UV light filters are used in sunscreens for skin protection and in cosmetics such as lipsticks, hairsprays, shampoos and skin lotions to prolong product durability (Schlumpf *et al.*, 2001). As a result, most human exposure occurs through dermal absorption (Jiang *et al.*, 1999; Gonzalez *et al.*, 2006). Benzophenone-3 (BP-3; 2-hydroxy-4-methoxybenzophenone, also known as oxybenzone) is particularly common, and is often detected in human urine in biomonitoring studies (Calafat *et al.*, 2008). Other benzophenone sunscreen agents used in consumer products include 2,2′,4,4′-tetrahydroxybenzophenone (BP-2), 4-hydroxybenzophenone (4-OH-BP) and 2,4-dihydroxyphenyl-phenylmethanone (BP-1; a major metabolite of BP-3 (Kunisue *et al.*, 2012; Wang and Kannan, 2013)), which is used as a UV stabilizer in plastic coatings of food packages (Suzuki *et al.*, 2005). Benzophenones have a half-life of ~15–18 h in rats (Jeon *et al.*, 2008), but because their metabolites are lipid soluble and may be stored in adipose tissue, their effective half-life may be longer and so their effects may be more persistent. Several benzophenones show estrogenic and antiandrogenic properties *in vitro* (Kawamura *et al.*, 2005;

Kim and Choi, 2014). For example, BP-3 exposure in rats leads to changes in sperm density and quality, estrous cycle length and reproductive organ weight and histopathology (Krause *et al.*, 2012). Evidence suggests that BP-1 may have greater estrogen receptor binding affinity compared to BP-3 (Molina-Molina *et al.*, 2008). In addition, BP-3 and BP-1 are believed to influence hormone-dependent diseases and are associated with adverse birth outcomes in humans (Wolff *et al.*, 2008; Kunisue *et al.*, 2012).

Parabens

Parabens are chemicals with bactericidal or fungicidal properties that are frequently used as preservatives in cosmetics, pharmaceuticals and food (Andersen, 2008). Common parabens include methyl paraben (MP), ethyl paraben (EP), propyl paraben (PP) and butyl paraben (BP). Often, mixtures of parabens are found in the same product because they act synergistically, increasing preservative activity. Exposure to parabens may occur through dermal absorption, ingestion or inhalation (Soni *et al.*, 2005; El Hussein *et al.*, 2007), and is widespread in the general population; MP and PP were detected in the urine of more than 90% of individuals participating in the 2005–2006 National Health and Nutrition Examination Survey (NHANES), with levels in women 5–10 times higher than in men (Calafat *et al.*, 2010). Although parabens do not accumulate in the body (Boberg *et al.*, 2010), they have been detected in breast tissue and breast tumors (Darbre *et al.*, 2004; Barr *et al.*, 2012). In animal studies, parabens have demonstrated weak estrogenic activity (Routledge *et al.*, 1998; Vo *et al.*, 2010) as well as antiandrogenic properties (Chen *et al.*, 2007) and thyroid effects (Vo *et al.*, 2010). Epidemiologic studies show associations of urinary parabens concentrations with lower semen quality in men (Tavares *et al.*, 2009) and sex hormone disruption (Aker *et al.*, 2016), shortened menstrual cycles and lower antral follicle counts in women (Rattan *et al.*, 2017).

Glycol ethers

Glycol ethers are organic solvents used in industrial applications but also favored in a range of common consumer products (e.g. liquid soaps, cosmetics, perfumes, water-based paints, cleaning products) due to their low acute toxicity and high miscibility in water and oils. More than 30 different ethers of ethylene glycol and propylene glycol are in use, and not all have the same toxicity. Although most research on glycol ethers has focused on industrial use, particularly in the semi-conductor industry, their inclusion in cleaning products and personal care items leads to the potential for widespread exposure. In animal studies, various glycol ethers have demonstrated adverse effects on ovarian function and on sperm production and quality (Multigner *et al.*, 2005). The toxic effects of glycol ethers may be mediated by their alkoxycarboxylic metabolites, which are rapidly eliminated in urine and can be used for biomonitoring exposure (Foster *et al.*, 1987). Although few studies have been conducted in humans, in infertility patients urinary glycol ether metabolites have been associated with poor semen characteristics (Veulemans *et al.*, 1993), and in occupational studies of the semi-conductor industry glycol ether exposure has been linked to disrupted menstrual cycles (Hsieh *et al.*, 2005) and spontaneous abortion (Correa *et al.*, 1996).

Objectives

Despite the growing body of evidence for adverse effects of non-persistent chemicals on male and female reproductive systems and the public health importance of reduced fecundability, relatively few epidemiologic studies have investigated their impact on TTP in couples conceiving without medical assistance, and the results of these studies have not been synthesized. We therefore undertook a systematic review to summarize the strength of evidence for associations of common non-persistent chemicals with couple fecundability to inform policy decisions and identify gaps and limitations in the literature as a guide for future research.

Methods

The review was conducted according to the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) (Moher *et al.*, 2009, 2015; Shamseer *et al.*, 2015). The protocol is registered (CRD42018084304) on PROSPERO (www.crd.york.ac.uk/prospero).

Search strategy

We performed an electronic search of literature published between 1 January 2007 and 25 August 2017 in MEDLINE on the PubMed platform, EMBASE.com, Global Health (OvidSP), DART (Developmental and Reproductive Toxicology)/TOXLINE (National Library of Medicine, USA) and POPLINE (popline.org). A subsequent search of DESTAF (Dragon Exploration System for Toxicants and Fertility, http://cbrc.kaust.edu.sa/destaf) did not add any further articles to the results. A professional health sciences librarian (MK-F) developed and executed the bibliographic searches using subject thesaurus vocabulary (e.g. MeSH, EMTREE), keywords and text words for each of the search concepts of fecundability/fertility/TTP and various environmental exposures using each database platform's command language and search fields. Retrievals were limited to human studies in English. The full search strategy is listed in Supplemental Table SI. Search results were downloaded to EndNote software (Thomson Reuters) to merge references and remove duplicates.

Screening and eligibility

Article screening was conducted with DistillerSR software (Evidence Partners, Ontario, CA) using standardized forms for title and abstract screening and for full-text review. Each level of review (Fig. 2) was completed in duplicate by authors A.E.H., L.G.K., P.R.F.-L., C.A.P., E.L.S., K. B. and K.G.H., and any conflicts were resolved through discussion.

At the title- and abstract-screening level, we included all human studies that related to chemical exposures and TTP or fecundability and screened out editorials, opinion pieces, introductions to special sections and articles that described only lifestyle (e.g. caffeine, alcohol, illicit drugs, medication, stress) or clinical factors (e.g. semen parameters, IVF success, obesity). We obtained full-text reports for all titles that did not meet exclusion criteria or where there was any uncertainty. At the second level of screening, we included only original empirical research papers that considered TTP or fecundability as an outcome and examined exposure to non-persistent EDCs in consumer products, specifically: phthalates, phenols (BPA, TCS, benzophenones), TCC, parabens and glycol ethers. No a priori inclusion/exclusion criteria were applied according to how individuals were exposed (e.g. day-to-day activities or in the workplace) or according to study design (i.e. retrospective or prospective cohort, cross-sectional or case–control).

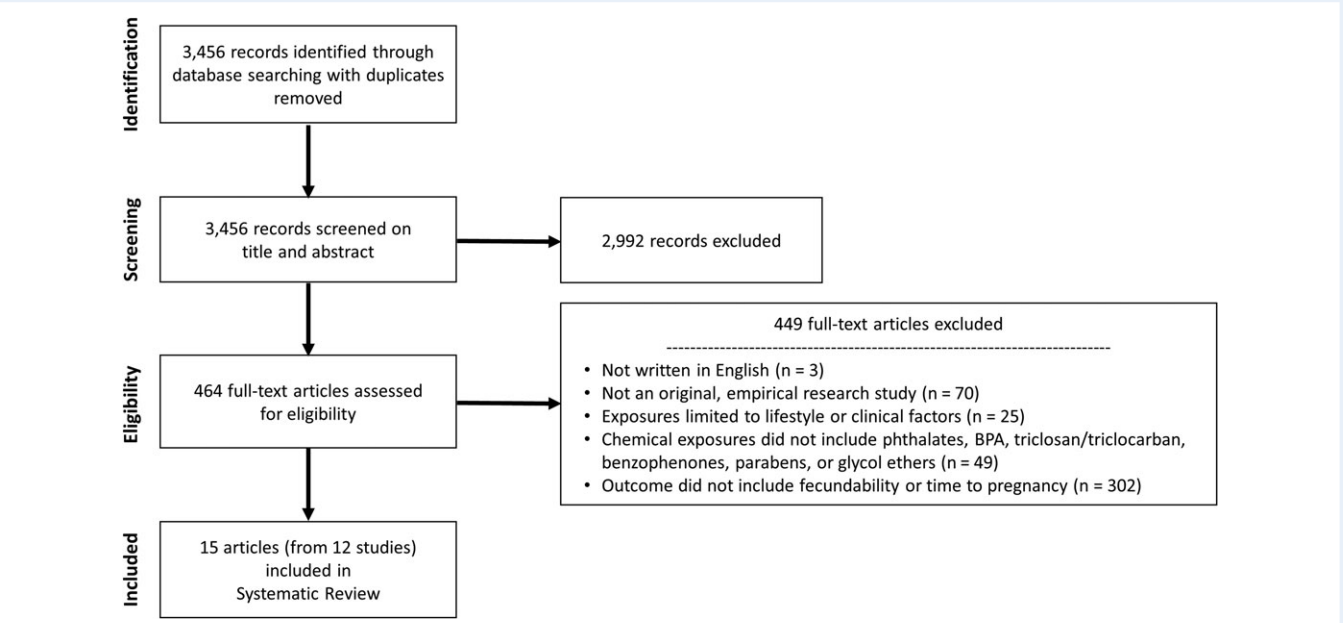

Figure 2 PRISMA flow chart.

Data extraction

We created standardized forms for data extraction in DistillerSR, which were also completed in duplicate. Where available, prior articles that described study methods in greater detail were reviewed. As done previously, coding discrepancies were recorded and resolved through discussion. None of the review authors were blind to the journal titles, study authors or institutions.

Risk of bias assessment

We used the Newcastle–Ottawa Scale (NOS) (Stang, 2010; Wells *et al.*, 2011; Zeng *et al.*, 2015) to assess risk of bias in three domains: participant selection/exposure, comparability of groups and outcome assessment (Table II). High-quality study characteristics (associated with low risk of bias) were awarded a star with a maximum of one star for each numbered item within each domain. Because selection item 4 ('demonstration that outcome [i.e. pregnancy] was not present at the start of the study') was not relevant for retrospective studies enrolling participants in the prenatal period or later, we replaced this item with 'Was exposure measured in women and men?', giving a star to studies that measured exposures in both partners as opposed to exposures in women or in men only. We followed recommendations to convert the NOS score to Agency for Healthcare Research and Quality (AHRQ) standards of good, fair and poor (Singh *et al.*, 2015). Specifically, good-quality studies were identified as those awarded 3–4 stars in the selection/exposure domain AND 1–2 stars in the comparability domain AND 2 stars in the outcome domain. Fair studies were indicated by 2 stars for selection/exposure AND 1–2 stars for comparability AND 1–2 stars for outcome, whereas poor-quality studies scored 0–1 for selection/exposure OR 0 for comparability OR 0 for outcome.

The NOS criteria apply generally to epidemiologic studies. However, there were several issues that we felt were particularly relevant to TTP studies examining non-persistent chemicals exposures that were not reflected by the NOS. Thus, we devised five additional quality metrics to identify specific methodological features of fecundability studies that further distinguished those of the highest quality (Table II).

Results

The search returned 3456 potentially relevant journal articles, of which 2992 were excluded at the title- and abstract-screening level. Of the remaining 464 full-text articles assessed for eligibility, 449 met study exclusion criteria and 15 articles from 12 different studies were included (Fig. 2). The reviewing team achieved good pairwise agreement in the selection of articles for inclusion (weighted overall kappa 0.87).

Description of studies

Characteristics of the 12 included studies are summarized in Table III. The studies examined chemical exposures and TTP in North American (n = 4), European (n = 6), Iranian (n = 1) and South African (n = 1) cohorts between 1982 and 2011. Different chemical exposures from one North American study (Longitudinal Investigation of Fertility and the Environment [LIFE]) were described in three papers, and those from one European study (Generation R) were described in two papers. There were eight residential and four occupational samples; three studies used a prospective design and nine were retrospective. Eight articles (from six studies) described associations of chemical exposures measured in either urine (n = 5) or blood (n = 1) with TTP. Three of these articles were rated as good quality and the other five were rated as fair quality according to NOS scores; additional quality metrics ranged from 0 to 5. Among the eight articles that reported associations of TTP with biomarkers of exposures measured in women (Garlantézec *et al.*, 2013; Buck Louis *et al.*, 2014a, b; Specht *et al.*, 2015; Vélez *et al.*, 2015; Jukic

Table II Assessment of risk of bias and study quality.

Newcastle–Ottawa Scale domains	Criteria for higher quality
Selection	
Representativeness of exposed cohort or occupational group	Truly or somewhat representative of the population or occupational group*
Selection of the non-exposed cohort	Drawn from the same community or occupational group as the exposed cohort and over the same time frame*
Adequacy of exposure measure	Independent, individual-level biological measure (e.g. urine, blood, semen)*
Exposure measured	Women and men*
Comparability	
Comparability of cohorts on the basis of the design (e.g. groups are matched on key variables) or analysis controls for confounders	Controls for age*
	Controls for at least one additional factor: e.g. BMI, parity, socioeconomic status, race or lifestyle factors such as smoking*
Outcome	
Assessment of outcome	Independent, biological measure of pregnancy (e.g. home pregnancy test) OR medical record confirmation*
Study design	Prospective, follow-up study*
Additional quality metrics	
Was exposure measured within the TTP window (i.e. after stopping contraception but before conception)?	Yes
Was exposure measured on more than one occasion?	Yes
Was exposure measured in urine?	Yes
Were participants actively trying to conceive?	Yes
Was pregnancy status assessed with daily pregnancy tests?	Yes

Note: *Study characteristics used to convert NOS scores to AHRQ standards of good, fair and poor.

et *al.*, 2016; Thomsen *et al.*, 2017; Smarr *et al.*, 2017b), three adjusted for male partner's exposure (Table IV); among the four articles that reported on associations with measures in men (Buck Louis *et al.*, 2014a, b; Specht *et al.*, 2015; Smarr *et al.*, 2017b), three adjusted for female partner's exposure (Table V). To facilitate comparisons of findings across the five studies (seven articles) that measured non-persistent chemicals in urine, we summarized details of the laboratory methods, limits of detection (LOD) or quantification (LOQ) and hydration adjustment in Supplemental Table SII. With one exception, all the studies used high- or ultra-performance liquid chromatography tandem-mass spectrometry consistent with methods used by the US Centers for Disease Control and Prevention (CDC; Ye *et al.*, 2005, 2006; Silva *et al.*, 2007); Velez *et al.* (2015) measured BPA with gas chromatography. Supplemental Table SIII presents data on urinary levels of all 42 non-persistent chemicals alongside data on participant age, gender and 19 urinary biomarker concentrations available from the 2013 to 2014 wave of NHANES (https://www.cdc.gov/nchs/nhanes/index.htm) to provide US population comparisons for the studies included in this review. Descriptive statistics from NHANES were calculated in Stata using sampling weights to account for the multistage sampling design. Among the four articles reporting phthalate metabolites in women (Buck Louis *et al.*, 2014b; Vélez *et al.*, 2015; Jukic *et al.*, 2016; Thomsen *et al.*, 2017), concentrations were often higher (i.e. non-overlapping confidence intervals) than in the general US population. For the three articles reporting on BPA, one reported similar levels to NHANES (Jukic *et al.*, 2016) and two reported lower levels (Buck Louis *et al.*, 2014b; Vélez *et al.*, 2015). Levels of TCS and TCC (Vélez *et al.*, 2015; Smarr *et al.*, 2017b) and urinary concentrations of parabens (Smarr *et al.*, 2017b) were generally similar to the population sample. Concentrations of non-persistent chemicals in males were measured in the LIFE study only (Buck Louis *et al.*, 2014a, b; Smarr *et al.*, 2017b): phthalate levels were generally higher than reported in NHANES, BPA levels were lower, and levels of TCC, TCS and parabens were similar.

The five studies without biomarkers measured exposures in women indirectly via air quality sampling (Attarchi *et al.*, 2012) or via coded occupation categories (Baste *et al.*, 2008; Peretz *et al.*, 2009; Ronda *et al.*, 2009; Burdorf *et al.*, 2011; Snijder *et al.*, 2011; Bello *et al.*, 2016). These studies received lower ratings on both the NOS and our additional fecundability-specific quality metrics (range: 0–2); results are summarized in Supplemental Table SIV.

A note on effect sizes

Before presenting the study findings, a note on the interpretation of effect sizes is warranted. In most cases, studies reported effect sizes as fecundability odds ratios (FORs) with 95% CIs, modeling TTP as discrete, time-to-event data in months. Analogous to a hazard ratio, an FOR represents the probability of conceiving in a specified time period (e.g. one menstrual cycle), conditional on not having become pregnant in the previous time period, per unit of change in chemical

Table III Study characteristics.

First author, year	Study acronym	Country	Period of exposure	Sample/ design	No. women	No. men	Measurement mode of chemical exposure				NOS/ quality metrics
							Urine	Blood	Air quality	Occupation	
Jukic *et al.* (2016)	EPS	USA	1982–1986	Resid Prospec	221/94[a]	0	Phthalate metabolites (MBzP, MCNP, MCOP, MCPP, MECPP, MEHHP, MEHP, MEOHP, MEP, MiBP, MnBP); BPA				Fair/5
(i) Burdorf *et al.* (2011)	Gen R	Netherlands	2002–2006	Resid Retrosp	6302	0				Job exposure coding	Poor/0
(ii) Snijder *et al.* (2011)					2774	2728				Job exposure coding	Fair/2
Baste *et al.* (2008)	HUSK	Norway	1997–1999	Occup Retrosp	10 512[b]	0				Hairdressers	Poor/0
Specht *et al.* (2015)	INUENDO	Greenland Poland Ukraine	2002–2004	Resid Retrosp	448 203 287	160 146 95		Phthalate metabolites (∑DEHP, ∑DiNP)[c]			Fair/0
(i) Buck Louis *et al.* (2014a)	LIFE	USA	2005–2009	Resid Prospec	501	501	Benzophenones (BP-1, BP-2, BP-3, BP-8, 4-OH-BP)				Good/4
(ii) Buck Louis *et al.* (2014b)							Phthalate metabolites (MBzP, MCHP, MCMHP, MCPP, MECPP, MEHHP, MEHP, MEOHP, MEP, MiBP, MiNP, MMP, MnBP, MOP); BPA				Good/4
(iii) Smarr *et al.* (2017b)							TCC, TCS; Parabens (BP, BzP, EP, MP, OH-EtP, OH-MeP, PP, 3,4-DHB, 4-HB)				Good/4
Vélez *et al.* (2015)	MIREC	Canada	2008–2011	ResidRetrosp	1597–1742	0	Phthalate metabolites (MBzP, MCPP, MEHHP, MEHP, MEOHP, MEP, MnBP); BPA; TCS				Fair/2
Garlantézec *et al.* (2013)	PELAGIE	France	2002–2006	Resid Retrosp	519	0	Glycol ether metabolites (BAA, EAA, EEAA, MAA, MEAA, PAA, PhAA, 2-MPA)				Fair/2
Peretz *et al.* (2009)	ROSE	USA	2005–2008	Occup Retrosp	956[d]	0				Cosmetologists	Poor/0
Attarchi *et al.* (2012)		Iran	2010	Occup Retrosp	406[e]	0			Formaldehyde, phenol, N-hexane, chloroform		Poor/0
Bello *et al.* (2016)		S. Africa	2008	Resid Retrosp	137[f]	0				Domestic workers	Poor/1

Ronda *et al.* (2009)	Spain	2006	Occup Retrosp	620[g]	0		Hairdressers	Poor/0	
Thomsen *et al.* (2017)	Denmark	1992–1994	Resid Prospec	229	0	Phthalate metabolites (MBzP, MEHP, MEP, MnBP)		Fair/4	

Note: EPS = North Carolina Early Pregnancy Study; Gen R = Generation R Study; HUSK = Hordaland Health Study; INUENDO = Biopersistent organochlorines in diet and human fertility; LIFE = Longitudinal Investigation of Fertility and the Environment Study; MIREC = Maternal-Infant Research on Environmental Chemicals Study; PELAGIE = Perturbateurs endocriniens: Étude Longitudinale sur les Anomalies de la Grossesse, l'Infertilité et l'Enfance; ROSE = Reproductive Outcomes in Salon Employees. Resid = Residential sample; Occup = Occupation-based sample; Prospec = prospective design; Retrosp = retrospective design.
See Fig. 2 for chemical abbreviations.
[a]Main analysis (n = 221 women), secondary 'within woman' analysis comparing non-conception cycles with clinical conception cycles in the same woman (n = 94 women).
[b]Comparisons were: n = 221 female hairdressers [83 current, 138 former] vs n = 10 291 women in other occupations, and n = 208 female hairdressers vs n = 593 shop assistants of similar socioeconomic status.
[c]∑DEHP=sum of secondary metabolites: 5OH-MEHP, 5-oxo-MEHP, and 5cx-MEPP; ∑DiNP=sum of secondary metabolites: 7OH-MMeOP, 7oxo-MMeOP, and 7cx-MMeOP.
[d]n = 448 cosmetologists vs n = 508 other occupations similar on socioeconomic status, education, stress and workplace environments.
[e]n = 205 pharmaceutical factory female laboratory workers vs n = 201 pharmaceutical factory female packing workers.
[f]n = 31 domestic workers vs n = 106 administrative (office) workers.
[g]n = 310 hairdressers vs n = 310 shop assistants and office workers.

exposure. However, because different units of change in exposure were used, it is difficult to compare FORs across studies. Some studies examined chemical exposure as a continuous variable, either on the arithmetic or logarithmic scale, and a few studies log-transformed chemical concentrations and then rescaled by the standard deviation to estimate the FOR per standard deviation increase in the log chemical concentration. Other studies characterized exposures categorically, comparing the probability of conception in the fourth quartile (Q4) to the remaining quartiles (Q1–Q3), for example. In group comparisons (e.g. exposure implied by occupation), the FOR represents the per-cycle probability of conception in the exposed group relative to the non-exposed group. A small number of studies (see Supplemental Table SIV) dichotomized TTP into a binary variable of infertility, defined as TTP > 12 months, and used logistic regression to examine associations between variables. These analyses presented odds ratios (ORs) for infertility per unit change in chemical exposure. In addition, one study reported relative risk (RR) of delayed conception (TTP > 12 months) in exposed relative to non-exposed individuals. Diminished fecundability or longer TTP is indicated by FOR <1 (reduced probability of conception in a given month) or OR >1 (greater odds of taking more than 12 months to conceive).

Summary of associations of chemical exposures with TTP

Associations of phthalate exposure with TTP

Associations of female phthalate exposure with TTP: Three prospective studies (Buck Louis *et al.*, 2014b; Jukic *et al.*, 2016; Thomsen *et al.*, 2017) and two retrospective studies (Specht *et al.*, 2015; Vélez *et al.*, 2015) investigated whether biomarkers of phthalate exposure in women were associated with fecundability.

Evidence for no association with TTP: Velez and colleagues measured seven phthalate metabolites (monobenzyl phthalate [MBzP], mono (3-carboxypropyl) phthalate [MCPP], mono-(2-ethyl-5-hydroxy-hexyl) phthalate [MEHHP], mono-(2-ethylhexyl) phthalate [MEHP], mono-(2-ethyl-5-oxo-hexyl) phthalate [MEOHP], mono-ethyl phthalate [MEP] and mono-*n*-butyl phthalate [MnBP]) in the urine of 1597 women in the Maternal-Infant Research on Environmental Chemicals (MIREC) study (Vélez *et al.*, 2015). The investigators reported no association with TTP when exposure was assessed continuously or divided into quartiles. This study was rated 'fair' on the NOS and met two of the five additional quality metrics (i.e. exposure was measured in urine, participants were actively trying to conceive). A moderate concern with this retrospective study is that exposure to phthalates was assessed in the first trimester of pregnancy rather than within the TTP window (i.e. after stopping contraception but before conception), and so the extent to which concentrations of prenatal phthalates correspond to exposures during the preconception period is unclear.

Evidence for longer TTP: Using data from the North Carolina Early Pregnancy Study (EPS), Jukic *et al.* (2016) examined associations of 11 urinary phthalate metabolites (MBzP, monocarboxynonyl phthalate [MCNP], monocarboxyoctyl phthalate [MCOP], MCPP, mono-(2-ethyl-5-carboxyphentyl) phthalate [MECPP], MEHHP, MEHP, MEOHP, MEP, mono (2-isobutyl) phthalate [MiBP] and MnBP) with TTP. Even though the main analysis of 221 women revealed no associations between any phthalate metabolites and fecundability, within-

Table IV Fecundability odds ratios for biological measurement of exposures in women.

First author, year	Study acronym	Analysis	Phthalates	BPA	TCS/TCC	Benzophen.	Parabens	Glycol ethers	Covariates
Jukic *et al.* (2016)	EPS	Tertiles	Betw-woman: ns	ns					a,b,c,h,n
		Third vs first tertiles	Within-woman: MnBP: FOR = 0.3 (0.1–0.8)	ns					
Specht *et al.* (2015)	INUENDO	Contin (ln)	Proxy-MEHP [All]: FOR = 1.14 (1.0–1.30) Proxy-MEHP [Gr]: FOR = 1.24 (1.01–1.53)						a,b,c,m,o,r
		Third vs first tertiles	Proxy-MEHP [Gr]: FOR = 1.32 (1.01–1.78)						
Buck Louis *et al.* (2014a)	LIFE	Q4 vs Q1–Q3				ns			a,b,d,e,f,i,k
		Q4 vs Q1–Q3				ns			a,b,d,e,f,i,k,l,t
Buck Louis *et al.* (2014b)	LIFE	Contin (ln_SD)	MCPP: FOR = 1.20 (1.0–1.43)	ns					a,b,d,e,f,i
			MCPP: FOR = 1.22 (1.02–1.47) MOP: FOR = 1.18 (1.03–1.35)	ns					a,b,d,e,f,i,l,t
Smarr *et al.* (2017b)	LIFE	Contin (ln)			ns		ns		a,b,d,e,f,g,j,l
		Above/below LOQ			ns		ns		
		Q4 vs Q1			ns		EP: FOR = 0.66 (0.46–0.95) MP: FOR = 0.66 (0.45–0.97)		
		Contin (ln)			ns		ns		a,b,d,e,f,g,j,l,t
		Above/below LOQ			ns		ns		
		Q4 vs Q1			ns		EP: FOR = 0.67 (0.46–0.98) MP: FOR = 0.63 (0.41–0.96)		
Vélez *et al.* (2015)	MIREC	Contin (ln_SD)	ns	ns	ns				a,b,c,g,h,p
		Quartiles	ns	ns	ns				
		Q4 vs Q1-Q3		ns	TCS: FOR = 0.84 (0.72–0.97)				
Garlantézec *et al.* (2013)	PELAGIE	Contin						PhAA: FOR = 0.95 (0.90–1.00)	a,b,c,q
		Q4 vs Q1-Q3						PhAA: FOR = 0.70 (0.52–0.95)	
Thomsen *et al.* (2017)		Contin (ln)	MEP: FOR = 0.79 (0.63–0.99)						a,b,c

Note: FOR = fecundability odds ratio; Contin=continuous scale, Contin (ln) = continuous natural logarithm transformed scale; Contin (ln_SD) = continuous natural logarithm transformed scale and rescaled by standard deviation; LOQ = Limit of quantification; Q1, Q2, Q3, Q4 = first, second, third and fourth quartiles, respectively. For Specht *et al.* (2015): All = Greenland, Poland, Ukraine; Gr = Greenland; Po = Poland.
Covariates in adjusted model: [a]age, [b]BMI, [c]lifestyle factors (e.g. self-reported smoking, diet, exercise), [d]serum cotinine, [e]time off contraception, [f]urine creatinine, [g]household income, [h]education level, [l]research site, [j]race, [k]season, [l]difference in partner age, [m]parity, [n]age at menarche, [o]frequency of intercourse, [p]specific gravity, [q]use of oral contraception prior to pregnancy, [r]gestational week of assessment, [s]partner age, [t]extent of partner chemical exposure.

Table V Fecundability odds ratios for biological measurement of exposures in men.

First author, year	Study acronym	Analysis	Phthalates	BPA	TCS/TCC	Benzophenone	Parabens	Covariates
Specht *et al.* (2015)	INUENDO	Contin (ln)	Proxy-MEHP [Gr]: FOR = 1.59 (1.27–2.24) Proxy-MiNP [All]: FOR = 1.23 (1.04–1.45) Proxy-MiNP [Gr]: FOR = 1.55 (1.09–2.19)					a,b,s
		Second vs first tertiles	Proxy-MEHP [Ukr]: FOR = 0.38 (0.18–0.77)					
		Third vs first tertiles	Proxy-MEHP [Gr]: FOR = 1.90 (1.16–3.09) Proxy-MiNP [Gr]: FOR = 1.73 (1.05–2.85)					
Buck Louis *et al.* (2014a)	LIFE	Q4 vs Q1–Q3				BP-2: FOR = 0.69 (0.50–0.95) 4-OH-BP: FOR = 0.74 (0.54–1.00)		a,b,d,e,f,i,k
		Q4 vs Q1–Q3				ns		a,b,d,e,f,i,k,l,t
Buck Louis *et al.* (2014b)	LIFE	Contin (ln_SD)	MnBP: FOR = 0.82 (0.70–0.97) MBzP: FOR = 0.77 (0.65–0.92) MMP: FOR = 0.80 (0.70–0.93)	ns				a,b,d,e,f,i
		Contin (ln_SD)	MBzP: FOR = 0.80 (0.67–0.97) MMP: FOR = 0.81 (0.70–0.94)	ns				a,b,d,e,f,i,l,t
Smarr *et al.* (2017b)	LIFE	Contin (ln)			ns		ns	a,b,d,e,f,g,j
		Above/below LOQ			ns		ns	
		Q4 vs Q1			ns		ns	
		Contin (ln)			ns		ns	a,b,d,e,f,g,j,l,t
		Above/below LOQ			ns		ns	
		Q4 vs Q1			ns		EP: *FOR* = 0.67 (0.46–0.98) MP: *FOR* = 0.63 (0.41–0.96)	

Note: Contin = continuous scale, Contin (ln) = continuous natural logarithm transformed scale; Contin (ln_SD) = continuous natural logarithm transformed scale and rescaled by standard deviation; LOQ = Limit of quantitation; Q1, Q2, Q3, Q4 = first, second, third, and fourth quartiles. For Specht *et al.* (2015): All = Greenland, Poland, Ukraine; Gr = Greenland; Po = Poland; Ukr = Ukraine.
Covariates in adjusted model: [a]age, [b]BMI, [d]serum cotinine, [e]time off contraception, [f]urine creatinine, [g]household income, [l]research site, [j]race, [k]season, [l]difference in partner age, [s]partner age, [t]extent of partner chemical exposure.

person sub-group analysis (n = 94, comparing non-conception cycles to conception cycles in the same woman) showed that high (third tertile) MnBP was associated with longer TTP relative to low (first tertile) MnBP (FOR = 0.3; 95% CI = 0.1–0.8). Although this study was rated 'fair' on the NOS, the prospective study design was a major strength and the study met all five additional fecundability-specific quality metrics. Of particular note, women were enrolled after stopping contraception and so were actively trying to conceive, exposure was measured three times each month within the TTP window, and pregnancy status was assessed using daily pregnancy tests, so the investigators could also detect early pregnancy loss. Nevertheless, the within-woman sample size was small so replication in future work is warranted. Furthermore, the samples were collected between 1982 and 1986, raising questions about generalizability to more recent chemical exposure levels; concentrations of phthalate metabolites were generally higher in this study, except for MCNP, MCOP and MiBP, when compared with 2013–2014 NHANES reference data (see Supplemental Table SIII).

In a Danish study of 229 women who were trying to conceive, Thomsen et al. (2017) assessed four urinary phthalate metabolites (MBzP, MEHP, MEP and MnBP) and found that higher MEP (measured continuously, natural log-transformed) was associated with longer TTP (FOR = 0.79; 95% CI = 0.63–0.99). A notable strength of this prospective study was the measurement of urinary phthalates twice during the TTP window, each time on Day 10 of the menstrual cycle. Although the NOS risk of bias rating was 'fair' due to concerns about the representativeness of the sample, this study met four of the five additional quality metrics, lending weight to the reported results.

Evidence for shorter TTP: Buck Louis et al. (2014b) reported on the prospective LIFE study of 501 couples with 14 phthalate metabolites measured in urine (MBzP, mono-cyclo-hexyl phthalate [MCHP], mono-[(2-carboxymethyl) hexyl] phthalate [MCMHP], MCPP, mono-(2-ethyl-5-carboxyphentyl) phthalate [MECPP], MEHHP, MEHP, MEOHP, MEP, MiBP, mono-isononyl phthalate [MiNP], mono-methyl phthalate [MMP], MnBP and monooctyl phthalate [MOP]). For the women in the sample, the results revealed only a trend for an association of log-transformed MCPP exposure assessed continuously with TTP (FOR for each standard deviation increase=1.20; 95% CI = 1.0–1.43). The LIFE study was rated 'good' on the NOS, indicating a low risk for bias in the results. Although chemical exposure was assessed only once, it was measured within the TTP window via urine, participants were actively trying to conceive, and pregnancy was assessed with daily digital pregnancy tests enabling the detection of early pregnancy loss. Thus, the study met four of the five additional quality metrics. In further analyses that simultaneously accounted for partner exposure to the same set of phthalate metabolites, the associations between MCPP and MOP (continuously measured, standard deviation increase) and shorter TTP were statistically significant (FOR = 1.22; 95% CI = 1.02–1.47, and FOR = 1.18; 95% CI = 1.03–1.35, respectively).

Analysis of data from the multi-country European INUENDO study revealed a significant association of the sum of bis(2-ethylhexyl) phthalate (DEHP) metabolites (proxy-MEHP), measured in serum, with shorter TTP in women (n = 448) living in Greenland (continuous, log-transformed measures: FOR = 1.24; 95% CI = 1.01–1.53; high vs low tertiles: FOR = 1.32; 95% CI = 1.01–1.78) (Specht et al., 2015). However, this association was not significant in the combined sample of 938 women living in Greenland, Poland and Ukraine. There was also no reported association of the sum of the diisononyl phthalate (DiNP) metabolites (proxy-MiNP) with TTP. In this retrospective study, phthalate concentrations were measured in blood, which is a less reliable matrix than urine because of increased risk of phthalate contamination in the field, during processing or in the laboratory (Calafat et al., 2015), and because serum measures result in much lower concentrations than in urine, increasing the risk of non-detection (Calafat and Needham, 2009). Additional concerns were that biospecimens were collected during pregnancy and may not have measured exposures that occurred prior to conception, analyses included only three potential confounders (male and female age and male BMI), and it was unclear whether couples had been actively trying to conceive. As a result, the study was rated as 'fair' on the NOS and did not meet any of the additional fecundability-specific quality metrics.

Associations of male phthalate exposure with TTP: One prospective (Buck Louis et al., 2014b) and one retrospective (Specht et al., 2015) study investigated whether phthalate exposure in men (using metabolites measured in biospecimens) was associated with fecundability.

Evidence for longer TTP: In the LIFE study, Buck Louis et al. (2014b) measured the same 14 phthalate metabolites in the urine of 501 male partners. While controlling for multiple potential confounders, the investigators reported that each standard deviation increase in log-unit exposure to MnBP, MBzP, and MMP was associated with longer TTP (FOR = 0.82; 95% CI = 0.70–0.97 for MnBP, FOR = 0.77; 95% CI = 0.65–0.92 for MBzP, and FOR = 0.80; 95% CI = 0.70–0.93 for MMP). When analyses were re-run while simultaneously adjusting for the female partner's exposure, MBzP and MMP continued to show a statistically significant association with longer TTP (FOR = 0.80; 95% CI = 0.67–0.97, and FOR = 0.81; 95% CI = 0.70–0.94 respectively). As noted previously, this study had a strong design and met all additional quality metrics except that exposure was measured only once during the TTP window.

In the INUENDO study, Specht et al. (2015) reported associations of male partners' exposure to two types of phthalates (DEHP and DiNP, measured in serum as the sum of their metabolites) with TTP. Within the Ukrainian subsample (n = 95), mid-level MEHP exposure (second tertile) was associated with longer TTP when compared with the lowest group (first tertile) (FOR = 0.38; 95% CI = 0.18–0.77). However, these analyses were likely limited by the sample size, questionable generalizability (26% participation rate in the Ukrainian subsample) and the fact that exposure in the third tertile did not follow the dose response curve. As noted above, this study carried a moderate risk of bias and met none of the additional quality metrics.

Evidence for shorter TTP: In the same INUENDO study, Specht et al. (2015) reported that for the male sample as a whole (n = 401), exposure to MiNP (continuously measured on a natural log scale) was associated with shorter TTP (FOR = 1.23; 95% CI = 1.04–1.45). In the Greenland subsample (n = 160), both MiNP and MEHP were associated with shorter TTP (FOR = 1.55; 95% CI = 1.09–2.19, and FOR = 1.59; 95% CI = 1.27–2.24, respectively). The top tertiles of MiNP and MEHP were also associated with shorter TTP in the Greenland sample when compared with the lowest tertiles (FOR = 1.73; 95% CI = 1.05–2.85, and FOR = 1.90; 95% CI = 1.16–3.09, respectively). As noted above, this study had several methodological limitations.

Weight of evidence: Results from the five studies (one 'good', four 'fair') of the association between female phthalate exposure and TTP are mixed. Of the three prospective studies measuring urinary concentrations of phthalate metabolites in women, two reported that higher levels of MnBP and MEP were associated with longer TTP, and one reported that MCPP and MOP (while controlling for partner exposure) were associated with shorter TTP. In addition, one retrospective study that measured urinary concentrations during pregnancy reported no evidence of an association with TTP. The two studies (INUENDO, LIFE) examining male exposure to phthalates also reported discrepant findings, although the former measured the sum of DEHP and DiNP metabolites in serum, whereas the latter measured individual metabolites in urine. In the more rigorous prospective LIFE study, three of 14 phthalates (MnBP, MBzP and MMP) were associated with longer TTP, a result that largely held after controlling for partner exposure (although it should also be noted that there was little correlation between male and female phthalate concentrations within couples, $r = 0–0.03$).

Taken together, the study results suggest that phthalate exposure is associated with disruptions in couple fecundability, but the direction of effects may vary for women and men and/or may be specific to the metabolite. Thus, in the LIFE study, two urinary phthalates (MCPP and MOP) were associated with shorter TTP for women, whereas another three (MnBP, MBzP and MMP) were linked to longer TTP in their male partners. Of note, the results revealed that MnBP was associated with reduced fecundability in two separate studies (Jukic *et al.*, 2016 and Buck Louis *et al.*, 2014b). In the former study of women, the effect was only revealed in post-hoc person-centered analyses, and in the latter study of men, the effect became negligible after controlling for partner factors, so caution is clearly warranted. These overall equivocal findings may, in part, reflect the mode, timing and challenges of exposure measurement as well as differences between studies such as characteristics of the sample, study design and analytic approach. In summary, the relation between phthalates and TTP is not yet clear enough to make definitive recommendations.

Associations of bisphenol A exposure with TTP

Two prospective studies (Buck Louis *et al.*, 2014b; Jukic *et al.*, 2016) and one retrospective study (Vélez *et al.*, 2015) investigated whether urinary BPA exposure in women was associated with TTP. None of the studies (two rated 'fair', one 'good' on the NOS) found evidence of an association of BPA exposure with TTP whether examined continuously or categorically. In the LIFE study, Buck Louis *et al.* (2014b) also reported no association of BPA measured as a continuous, log-transformed variable with TTP in either men or women, while also controlling for partner exposure.

Weight of evidence: Neither of the two prospective studies (EPS and LIFE) that measured BPA found any association between BPA exposure and TTP. However, like phthalates, the half-life of BPA in the body is short and concentrations are extremely variable within and between days; thus, it is possible that no study has yet performed exposure assessment for BPA at a precise enough level to detect an effect on TTP.

Associations of exposure to triclosan and triclocarban with TTP

One prospective (Smarr *et al.*, 2017b) and one retrospective study (Vélez *et al.*, 2015) examined whether exposure to two common antimicrobial agents was associated with TTP. In the prospective LIFE study, Smarr *et al.* (2017b) reported no association of female, male or couple ($n = 501$) exposure to TCC and TCS with TTP in analyses that examined exposure continuously (log-transformed), above vs below the limit of quantitation (LOQ), or in Q4 vs Q1 contrasts. In a similar vein, Vélez *et al.* (2015) reported no association of TCS with retrospectively reported TTP in women in the MIREC study ($n = 1699$) when analyzed continuously (standard deviation increase in log-unit exposure) or as quartiles. However, when women with high levels (Q4) were compared with those in the lowest three quartiles (Q1–Q3), the investigators reported that TCS was associated with reduced fecundability (FOR=0.84; 95% CI = 0.72–0.97). As noted previously, urinary exposures in this study were measured in pregnancy, not during the TTP window.

Weight of evidence: Evidence from two studies mostly indicates no effect of these chlorinated antiseptic agents on fecundability. The most rigorous study (LIFE) found no evidence of association using any metric; the MIREC study similarly reported no association with TTP except for a single analysis suggesting an association between high TCS exposure and longer TTP. While this initial evidence is largely negative, further rigorous studies are required to assess the impacts of these compounds.

Associations of benzophenone exposure with TTP

Buck Louis and colleagues (2014a) examined associations of three benzophenone-type UV radiation filters (BP-2, BP-3, and 4-OH-BP) and two BP-3 metabolites (BP-1 and 2,2′-dihydroxy-4-methoxybenzophenone [BP-8]) with TTP in the LIFE study. The investigators reported no associations with TTP for exposure in women. In contrast, high levels of BP-2 (Q4) in men were associated with longer TTP compared with lower levels (Q1-Q3) (FOR = 0.69; 95% CI = 0.50–0.95), and there was a trend toward longer TTP for men's 4-OH-BP exposure (FOR = 0.74; 95% CI = 0.54–1.0). Couple-based analyses revealed a similar pattern of associations: high BP-2 exposure (Q4) in men was associated with longer TTP relative to lower levels (Q1–Q3) (FOR = 0.69; 95% CI = 0.49–0.97) when partner exposure was accounted for, but there were no associations for exposures in women when controlling for partner exposures. It was noteworthy that correlations between couples' urinary benzophenone concentrations were relatively low ($r \leq 0.19$).

Weight of evidence: Although the LIFE study found a clear association of male exposure to BP-2 with reduced fecundability, no other studies identified in this systematic review examined this association, and so this finding has yet to be replicated. Furthermore, despite the many methodological strengths of the study, BP-2 was only measured once during the TTP window and may not reflect ongoing exposure. As a result, while current evidence suggests that male exposure to BP-2 may be associated with impaired fecundability, additional studies are warranted to confirm this association.

Associations of paraben exposure with TTP

The associations between paraben exposure and TTP have also been examined in the LIFE study (Smarr *et al.*, 2017b): 10 parabens or paraben metabolites (MP, EP, PP, BP, benzyl paraben [BzP], heptyl paraben [HP], 4-hydroxy benzoic acid [4-HB], 3,4-dihydroxy benzoic acid [3,4-DHB], methyl-protocatechuic acid [OH-MeP], ethyl-protocatechuic acid [OH-EtP]) assessed via urine samples were

examined in 501 couples. The results showed that women's exposure to MP and EP was associated with TTP, but only when the exposures were examined dichotomously: the highest level of MP and EP exposure (Q4) was associated with longer TTP relative to the lowest level (Q1) (FOR = 0.66; 95% CI = 0.45–0.97 and FOR=0.66; 95% CI = 0.46–0.95, respectively). There were no associations when exposures were examined continuously. There was also no evidence of an association between male paraben exposure and TTP when examined continuously (log-transformed), above vs below the LOQ, or in analyses comparing the highest vs lowest levels. Couple-based analyses revealed a similar pattern: the highest female MP and EP level was associated with longer TTP relative to the lowest levels of MP and EP (FOR = 0.63; 95% CI = 0.41–0.96, and FOR = 0.67; 95% CI = 0.46–0.98, respectively) when male partner exposure was included in the statistical models, whereas this was not the case when male exposure was examined while controlling for female partner exposure. Once again, there was little correspondence ($r < 0.10$) between the chemical concentrations recorded within the couples.

Weight of evidence: The only study to examine female paraben exposure reported that high levels of exposure to MP and EP were associated with reduced TTP, results that remained statistically significant even when partner exposure was taken into account. As noted previously, the LIFE study was well designed, but included only one urine sample in the TTP window, which raises the possibility that paraben exposure window was misspecified. While these associations are suggestive of an association between paraben exposure and reduced fecundability, the results clearly need to be validated and confirmed in other cohorts.

Associations of glycol ether exposure with TTP

Associations of exposure to glycol ethers with TTP were examined in one retrospective study of 519 women (PELAGIE). Garlantézec *et al.* (2013) examined eight metabolites (methoxyacetic acid [MAA], methoxyethoxyacetic acid [MEAA], ethoxyacetic acid [EAA], ethoxyethoxyacetic acid [EEAA], 2-butoxyacetic acid [BAA], *n*-propoxyacetic acid [PAA], phenoxyacetic acid [PhAA] and 2-methoxypropionic acid [2-MPA]) and reported that the highest level of PhAA exposure (Q4) was associated with longer TTP compared to the lowest level (Q1) (FOR = 0.70; 95% CI = 0.52–0.95). There was also a trend for the same effect when PhAA exposure (untransformed) was examined continuously (FOR = 0.95; 95% CI = 0.90–1.0). None of the remaining seven glycol ether metabolites showed any statistically significant associations. This study obtained a 'fair' rating on the NOS, reflecting its retrospective design and inclusion of women only. Nevertheless, noted strengths included the high initial participation rate of 80%, a random sampling of urine specimens, a focus on women who had been actively trying to conceive, and sensitivity analyses that excluded 113 women who conceived during the first month with no change to the results.

Weight of evidence: Investigation of the effects of glycol ethers on TTP to date has been very limited. Although the results of the PELAGIE study suggest a possible link between high levels of PhAA exposure and longer TTP, further research and replication of these results are needed before conclusions can be drawn.

Studies with indirect measures of chemical exposures

As noted above, six studies met inclusion/exclusion review criteria but did not include biological measurements of chemical exposures (see Supplemental Table SIV). With one exception (Snijder *et al.*, 2011), these studies were rated 'poor' on the NOS, most ($n = 5$) met none of the additional quality metrics, one study met one of them (Bello *et al.*, 2016), and one study met two (Snijder *et al.*, 2011). For these reasons, the results are only summarized briefly here.

In a study that assessed formaldehyde, phenols, N-hexane, and chloroform in air samples within a pharmaceutical factory, Attarchi *et al.* (2012) reported longer TTP in female laboratory (exposed) workers compared with packing (non-exposed) workers (OR for TTP ≥ 12 months = 2.20; 95% CI = 1.26–4.30). However, study limitations included the lack of verification of individual exposures, retrospective design, self-reported pregnancy history and the possibility that the non-exposed group may have varied in important, unmeasured ways from the exposed group. Two analyses from the Generation R study reported on implied occupational exposure to phthalates determined by job titles coded as indicative of probable, possible, or no phthalate exposure. In one of these analyses, Burdorf *et al.* (2011) reported a greater odds of TTP > 6 months among a small group of employed women with probable phthalate exposure ($n = 41$) compared with 3678 other employed women (OR = 2.16; 95% CI = 1.02–4.57), whereas in the second, Snijder *et al.* (2011) reported no associations with TTP for women or men in occupations linked to probable or possible phthalate exposure vs non-exposure in a subsample of Generation R couples. Three other retrospective studies recruited samples of hairdressers or cosmetologists (Baste *et al.*, 2008; Peretz *et al.*, 2009; Ronda *et al.*, 2009) with mixed results. These studies were generally limited by small, select exposed samples, control groups drawn from a different population, self-report of pregnancy history and a lack of information as to whether participants were actively trying to become pregnant and whether participants were working in the specified occupations around the time of conception or while they were trying to conceive. A final study (Bello *et al.*, 2016) reported reduced fecundability in a small sample of female domestic workers ($n = 31$) compared with office workers ($n = 106$), but similar methodological limitations (e.g. questionable representativeness of the small sample and adequacy of the control group) raise concerns about the robustness and reproducibility of the results.

Discussion

There is now a substantial literature summarizing links between environmental and occupational exposures to EDCs and fecundability, but to our knowledge, no prior systematic reviews have examined the strength of evidence for associations between non-persistent chemical exposures and TTP. The results of this systematic review revealed that, although there is reason to be concerned about the effects of non-persistent chemicals in plastics, personal care products and other consumer items on the reproductive health of women and men, the dearth of research on fecundability as an outcome has left critical gaps in knowledge. Our exhaustive review of six major bibliographic databases revealed that only 12 empirical studies with articles published between 2007 and 2017 have examined associations of phthalates, BPA, TCS, TCC, benzophenones, parabens and/or glycol ethers with TTP; among these, only six used biomarkers of exposure.

Phthalates have been the most studied compounds, but evidence for their associations with TTP is conflicting. The review lends some preliminary support for adverse effects on fecundability from female exposure to some parabens and glycol ethers and from male exposure to benzophenone, but further research and replication of these results is clearly warranted to confirm these associations. Finally, our review provided little to no indication that BPA, TCS or TCC exposure in either women or men was associated with TTP, but further rigorous studies are urgently needed to fully assess the impacts of these compounds.

The studies identified in this review ranged in quality based on duplicate ratings on the widely used NOS for assessing risk of bias in epidemiologic research, as well as our own fecundability-specific quality metrics. The wide range of scores highlights a host of methodological challenges in this field, exemplified by the variety of methods and limitations we encountered across the studies. In particular, our review revealed substantial heterogeneity in terms of: participant characteristics (i.e. women only, women and men, women and men adjusting for respective partner exposure); study design (i.e. prospective vs retrospective); timing of data collection (1982–2010); the frequency, type and timing of chemical exposure measures; and the accuracy and validity of outcome measures. The studies often examined different arrays of metabolites within broad chemical groupings (e.g. phthalates) and quantified chemical concentrations in multiple ways (e.g. untransformed or log-transformed continuous scales, often in combination with ordinal and dichotomous categories), resulting in different effect sizes (FOR, OR, RR) per unit change for each study. These inconsistent approaches precluded quantitative synthesis of the data, such as meta-analysis, meaning that the absolute magnitudes of effects cannot be compared directly across studies. Finally, many studies reported a few significant results from a large number of analyses, and none adjusted for multiple testing. This approach increases the risk of Type I errors and thereby reduces the likelihood of replication.

It is generally recognized that chemical exposures rarely, if ever, occur in isolation (Robinson *et al.*, 2015) and that environmental endocrine disruption is often due not to the effect of a single compound, but rather to the effect of mixtures of chemicals at low concentrations (Rajapakse *et al.*, 2002; Sumpter and Johnson, 2005). Many common non-persistent chemicals co-occur in the same consumer products; for example, phthalates, parabens and benzophenones are all used in cosmetics, so an individual's urinary concentrations of these compounds might have synergistic or cumulative associations with health (Webster, 2013), including reproductive health. Although most of the studies identified in this review controlled for multiple sociodemographic confounders (e.g. age, BMI, lifestyle factors), none accounted for the complication of mixed exposures, which might impact TTP via additive, multiplicative or interactive effects, or for exposure to other, related endocrine disruptors. These unmeasured co-exposures may have also contributed to the mixed results reported here.

Because exposures to these common non-persistent chemicals are episodic and the compounds have short biological half-lives, obtaining accurate estimates of participants' typical exposure or of their exposure at the biologically critical time vis-à-vis conception is another major challenge, especially over an extended period of months while a couple is trying to conceive. Single spot urine samples only reflect exposure at that moment in time (Baird *et al.*, 2010), and the collection of multiple urine samples is preferable to ensure accurate measures of ongoing or cumulative exposure (Braun *et al.*, 2012). In fact, a recent simulation study indicated that at least 10 estimates of exposure per individual may be needed to ensure a stable estimate of average exposure (Perrier *et al.*, 2016), especially for chemicals like BPA and DEHP, whose exposure route is partially through diet and is highly variable within individuals throughout the day and from one day to the next (Rudel *et al.*, 2011). Intraclass correlation coefficients, which quantify measurement reliability, indicate that BPA and DEHP exhibit higher variability among urinary samples than do lower molecular weight phthalates (e.g. diethyl phthalate and dibutyl phthalate), parabens and other phenols found in everyday personal care products (Townsend *et al.*, 2013; Koch *et al.*, 2014). Such data suggest that it will be particularly difficult to determine associations of BPA and certain phthalate metabolites with TTP in the absence of intensive and frequent exposure sampling.

Our review identified studies that employed both prospective and retrospective designs, methods that likely target different groups of individuals with different results and therefore impact the generalizability of results in important ways. On the one hand, prospective studies, which have the advantage of measuring TTP in real time and collecting biosamples prior to conception, must enroll couples at or near the time they begin trying to conceive, thus restricting the study population to 'pregnancy planners'. Health problems, certain lifestyle factors and irregular menstrual cycles may be additional exclusionary criteria in these studies. Furthermore, given that ~50% of pregnancies are unplanned (Wellings *et al.*, 2013; Finer and Zolna, 2016) and that prospective TTP studies involve considerable participant burden, these samples are unlikely to be representative of the general population. On the other hand, retrospective studies are susceptible to the problems of recall bias and are limited to couples who successfully conceived, thus oversampling a more fertile population. Although retrospective studies can enroll couples who experienced an unplanned pregnancy, making them more representative of the general population in some respects, self-reported preconception data may be of lower quality, as couples with unintended pregnancies may less accurately recall events and exposures during the preconception period compared with pregnancy planners. As noted above, accurate measurement of non-persistent chemicals also requires collection of urine samples (preferably multiple samples from each individual) prior to conception, which are unlikely to be available in retrospective studies that enrolled couples after they achieved a pregnancy or at a later point in life. Both types of TTP study also miss conceptions that result in fetal loss before they are clinically recognized. In theory, this can be avoided in prospective studies by collecting daily urine samples for analysis of hCG (Wilcox *et al.*, 1999) to identify even occult pregnancies, although this is expensive, time-consuming and rarely done in practice. Despite these limitations, TTP studies are a useful epidemiologic approach that have identified delays in conception (continuously measured) due to a wide variety of factors, offering greater insights into etiology, risk and protective factors than a binary indicator of infertility.

Future research

The results of the current review reveal that for evaluating associations of non-persistent chemicals with TTP, there is a clear need for

refinement and improvement in data collection methods and analytic approaches that may be applied rigorously and consistently across studies. First, the field needs more prospective studies with population-based, unselected sampling, including couples who do not successfully conceive. Second, because exposure to environmental chemicals differs according to a variety of sociodemographic variables (e.g. rural vs urban environments, age, race/ethnicity [Barr *et al.*, 2005; Kobrosly *et al.*, 2012; Nelson *et al.*, 2012]), careful consideration of these factors as probable confounders and/or effect modifiers is necessary. Future research should especially consider the heterogeneous social and economic factors that drive consumer product use (Zota and Shamasunder, 2017). Third, more effort needs to be made to identify the biological mechanisms underlying any observed associations. While animal and *in-vitro* studies can provide preliminary data, these scenarios are unlikely to fully represent the human condition. Fecundability is a complex, couple-based clinical outcome involving male and female biological factors. As shown in Fig. 1, endocrine disruption from common non-persistent chemical exposure may occur at multiple levels with direct effects on the reproductive functioning of the ovaries and testes and indirect effects via the HP–gonadal, HP–adrenal and/or HP–thyroid axes, which further impact gonadal function and gametes as well as endometrial receptivity and other aspects of biological aging. Therefore, future studies should include neuroendocrine variables, such as markers of steroid and thyroid hormones, to further our understanding of these specific and shared pathways. Fourth, as the LIFE study eloquently illustrates, while fecundability is clearly a couple phenomenon, women and men may be differentially exposed to non-persistent chemicals, so chemical concentrations need to be measured in both partners. Fifth, longitudinal studies with repeated measures and methods to identify periods of heightened vulnerability (Sánchez *et al.*, 2011) are eventually needed, as exposure to non-persistent chemicals at different points in the lifespan may have different associations with TTP. For example, critical periods for development of the reproductive system, a contributing factor to fecundity, likely occur between the fetal stage and adolescence, and not during the period when a couple is attempting conception. Sixth, future research should be designed to examine associations of mixtures of non-persistent chemical exposures with TTP. Improved analytic approaches may also address important questions about the impact of mixtures of non-persistent chemicals from consumer products with other environmental toxins (e.g. lead, carbon monoxide, pesticides) in water, air and soil. Studies should also measure exposure to chemicals such as bisphenols S and F, replacements for BPA and di-(isononyl)-cyclohexane-1,2-dicarboxylate, a replacement for high molecular weight phthalates (Caserta *et al.*, 2013; Alur *et al.*, 2015), as these new compounds are being substituted for chemicals that have been linked to adverse health outcomes. There is some evidence to suggest that their endocrine-disrupting effects may, in fact, be stronger (Eladak *et al.*, 2015; Minguez-Alarcon *et al.*, 2016), but research on their relation to TTP is currently lacking. Seventh, future studies should consider incorporating evolving 'omics' technologies (e.g. genomics, epigenomics, metabolomics, mitochondriomics), which have the potential to generate data that enhance exposure assessment to include the exposome (i.e. the totality of the lifetime exposure burden) and provide biologically based estimates of individual risks. Finally, because of the distinct challenges inherent in assessing associations between chemical exposures and TTP, targeted instruments need to be developed to evaluate risk of bias that are specific to these studies. While we estimated the quality of studies using the established NOS, we found it necessary to modify the scale to accommodate TTP studies. The five additional metrics that we developed provided additional useful criteria for evaluating TTP study quality.

Newly designed studies that address these gaps will contribute valuable data to the field as long as they are sufficiently powered to detect effects. However, the challenges of exposure measurement (i.e. repeated testing of multiple non-persistent chemicals across time) combined with the difficulties of outcome measurement (i.e. TTP) point to the need for large-scale, interdisciplinary/multi-site collaborations to accelerate the pace of discovery. Using a common protocol that ensures that collection, processing and storage are specifically designed for analytical chemistry of environmental toxicants and that biological contamination is minimized, collaborative consortia could pool data gathered from women, men and couples before, during and after pregnancy (planned and unplanned) and in the interpregnancy period. Cross-study data harmonization can be used to increase the power to detect the often subtle effects of environmental exposures and to perform mediation and interaction analyses. Furthermore, the inclusion of racially, socioeconomically and geographically diverse samples from disparate locations at national or international levels will be critical to increase the generalizability and utility of the results.

Implications for policy and practice

Reduced fecundability is associated with many personal and interpersonal costs such as increased stress, financial hardship, adverse pregnancy outcomes and poorer general health. Although equivocal results with different non-persistent chemical compounds and metabolites complicate the interpretation of our findings with respect to TTP, they do not preclude action given the growing evidence of links between EDCs and a wide range of adverse reproductive outcomes, as well as risks to fetal growth and development. Furthermore, the ubiquitous daily exposure to non-persistent chemicals across the lifespan makes it important to weigh the potential costs of continuous exposure against small behavioral changes that could be beneficial for fecundability. We therefore advocate for common-sense lifestyle changes in which both females and males seeking to conceive minimize their exposure to non-persistent chemicals, for example, by reducing their use of plastic food containers (potential sources of phthalates and BPA) and examining ingredient lists on personal care and cleaning products for phthalates, parabens, TCS, benzophenones and glycol ethers. Recent research has shown that simple steps such as choosing personal care products that are labeled free of phthalates, parabens, TCS and BP-3 is effective in lowering levels of these chemicals in the body (Harley *et al.*, 2016).

Conclusions

Despite a growing literature on non-persistent endocrine-disrupting chemicals and fecundability, evidence for associations between biomarkers of exposure and TTP remains limited. In total, 15 empirical articles published in the past decade drawing on data from 12 studies

reported associations between exposure to non-persistent chemicals in consumer products and TTP with inconsistent results. In an effort to achieve more specificity and better replication of results in this field, the next wave of prospective studies investigating associations of non-persistent chemical exposures with TTP should attempt to (i) obtain multiple urine samples over the preconception period to better characterize ongoing exposure; (ii) evaluate the effects of mixtures as well as individual chemicals; (iii) focus on both female and male exposure, since TTP is a measure of couple fecundability; and (iv) ensure adequate control for confounders, including other chemical exposures. Further human studies are necessary to clarify both the effects of non-persistent chemical exposures on reproductive health as well as the physiologic mechanisms underlying these effects.

Supplementary data

Supplementary data are available at *Human Reproduction Update* online.

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Conflicts of interest

None declared.

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