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Endocrine-disrupting chemicals: implications for human health

Linda G Kahn, Claire Philippat, Shoji F Nakayama, Rémy Slama, Leonardo Trasande

Since reports published in 2015 and 2016 identified 15 probable exposure–outcome associations, there has been an increase in studies in humans of exposure to endocrine-disrupting chemicals (EDCs) and a deepened understanding of their effects on human health. In this Series paper, we have reviewed subsequent additions to the literature and identified new exposure–outcome associations with substantial human evidence. Evidence is particularly strong for relations between perfluoroalkyl substances and child and adult obesity, impaired glucose tolerance, gestational diabetes, reduced birthweight, reduced semen quality, polycystic ovarian syndrome, endometriosis, and breast cancer. Evidence also exists for relations between bisphenols and adult diabetes, reduced semen quality, and polycystic ovarian syndrome; phthalates and prematurity, reduced anogenital distance in boys, childhood obesity, and impaired glucose tolerance; organophosphate pesticides and reduced semen quality; and occupational exposure to pesticides and prostate cancer. Greater evidence has accumulated than was previously identified for cognitive deficits and attention-deficit disorder in children following prenatal exposure to bisphenol A, organophosphate pesticides, and polybrominated flame retardants. Although systematic evaluation is needed of the probability and strength of these exposure–outcome relations, the growing evidence supports urgent action to reduce exposure to EDCs.

Introduction

In 1962, Rachel Carson described the effects of dichlorodiphenyltrichloroethane (DDT) on sexual development and reproduction.¹ Less than a decade later, Herbst and colleagues² documented a cluster of patients in Boston (MA, USA) with vaginal adenocarcinoma resulting from prenatal use of the medication diethylstilbestrol. During this time, two assumptions were common: the Paracelsian notion that “Solely the dose determines that a thing is not a poison”, and the belief that only rarely could synthetic chemicals disrupt hormonal and homeostatic responses and thereby contribute to disease and dysfunction.

Over the past 50 years, these two assumptions have proven flawed. Many studies have identified effects of various exogenous chemicals on endocrine processes and functions, exposing the important need for a shift in scientific theory. Many of these dose–response relations have been non-monotonic.³ Mechanistic studies explain these unconventional associations at the molecular level. These endocrine-disrupting chemicals (EDCs) are not rogue pharmaceuticals or rare contaminants. One examination by the US Food and Drug Administration identified more than 1800 chemicals that disrupt at least one of three endocrine pathways (oestrogen, androgen, and thyroid).⁴ 320 of 575 chemicals screened at the instruction of the European Commission showed evidence or potential evidence for endocrine disruption.⁵

EDCs are now recognised as serious and urgent threats to public health, potentially emerging as one of the leading environmental risks globally. Among the non-governmental organisations and governmental agencies documenting the rapidly accelerating evidence and implications for human health are the Endocrine Society,⁶ the International Federation of Gynecology and

Obstetrics,⁷ WHO and the UN Environment Programme (UNEP),⁸ and the American Academy of Pediatrics.⁹ Reports by these organisations describe the serious adverse effects of EDCs on endocrine processes during susceptible periods of human development and the long latency period between exposure and disease as a result of early-life exposure to chemicals such as DDT, which has been associated with breast cancer incidence half a century later in life.¹⁰

This Series paper seeks to update the 2015 findings of an expert panel commissioned by the Endocrine Society that led to the identification of 15 exposure–outcome associations with a probability of causation (table 1).^{11,12} The paper also aims to expand on the previous report by identifying new exposure–outcome associations of concern, especially with regard to chemicals that were not widely researched several years ago, such as perfluoroalkyl and polyfluoroalkyl substances (PFAS) and polybrominated diphenyl ethers (PBDEs), and by including several outcomes that were not specifically focused on in the WHO and UNEP report, such as anogenital distance and prostate cancer. Because our intention is to inform future research and policy, we have focused on synthetic chemicals that are currently in circulation and not on legacy compounds, such as DDT, other organochlorine pesticides, polychlorinated biphenyls (PCBs), and dioxins and furans. Where possible, we emphasise findings related to newer chemicals that are replacing chemicals that are being phased out or banned.

Subsequent sections describe evidence that supports previously identified or increasingly likely associations of EDCs with perinatal, neurodevelopmental, metabolic, and reproductive outcomes. More equivocal results and

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Department of Pediatrics

(L G Kahn PhD, Prof L Trasande MD),

Department of Environmental Medicine, and Department of Population Health, New York University Grossman School of Medicine and New York University School of Global Public Health, New York University, New York, NY, USA (Prof L Trasande); University

Grenoble Alpes, Inserm, CNRS, Team of Environmental Epidemiology applied to Reproduction and Respiratory Health, Institute for Advanced Biosciences, Grenoble, France (C Philippat PhD, R Slama PhD); and Center for Health and Environmental Risk Research, National Institute for Environmental Studies,

Tsukuba, Japan (S F Nakayama PhD)

Correspondence to: Prof Leonardo Trasande, Department of Pediatrics, New York University Grossman School of Medicine, New York University, New York, NY 10016, USA

leonardo.trasande@nyulangone.org

See Online for appendix

tables summarising all studies reviewed that reported significant or epidemiologically meaningful associations can be found in the appendix. We conclude with an overview of knowledge gaps and opportunities to address those gaps in future studies in humans.

Birth outcomes

Fetal growth and length of gestation, especially low birthweight and preterm birth, are important predictors of health in later life.¹³ Increased understanding now exists that environmental exposures (especially EDCs) can induce the so-called thrifty phenotype that was first described by Barker and colleagues,¹⁴ in which a fetal metabolism that is conservatively programmed is maladapted to the ex utero environment, resulting in increased adiposity beginning in childhood and

cardiovascular risks later in life. EDCs are increasingly shown to shorten gestation, alter intrauterine growth, and disrupt metabolic programming in laboratory studies.¹⁵ Additionally, measures of anogenital distance obtained at birth are known to track through adulthood¹⁶ and predict infertility and reduced sperm count.¹⁷ Associations between prenatal exposure to EDCs and birth outcomes were not previously assessed in terms of probable evidence for causation. This Series paper identified three associations of note: PFAS and reduced birthweight, phthalates and preterm birth, and phthalates and reduced anogenital distance in male offspring (table 2).

Birthweight

Human studies have rightly given substantial attention to associations of prenatal exposure to EDCs with fetal growth and birthweight. Previous research that identified decreases in birthweight in relation to maternal prenatal concentrations of PFAS has been further corroborated by a study published in 2017,¹⁸ which suggested that changes in concentrations of maternal glucose act as a mediator. Measurement of PFAS in the blood spots of neonates has not yielded the same findings, perhaps because of temporality and imprecision in measuring exposure.¹⁹ A meta-analysis²⁰ of 24 studies reported a change in birthweight of -10.5 g (95% CI -16.7 to -4.4) per ng/mL increase in perfluorooctanoic acid (PFOA) concentration in maternal blood or umbilical cord blood, with a greater effect size in studies that measured exposure in late pregnancy (ie, the second or third trimester) compared with those that measured exposure preconceptionally or during early pregnancy (ie, predominantly in the first trimester). The increased effect size is notable given the potential for confounding or reverse causation, or both, in studies that rely on assessment of exposure in late pregnancy.

Evidence for associations of PBDEs, phenols, and phthalates with birthweight is not as strong, including various studies that did not show significant results and, in the case of the non-persistent chemicals, studies that did not have repeated measures of exposure (appendix pp 2–4, 7).

	Outcome	Strength of human evidence	Probability of causation, %
Prenatal PBDEs	IQ loss and intellectual disability	Moderate to high	70–100%
Prenatal organophosphate pesticides	IQ loss and intellectual disability	Moderate to high	70–100%
Multiple prenatal exposures	Attention-deficit disorder	Low to moderate	20–69%
Multiple prenatal exposures	Autism spectrum disorder	Low	20–39%
Prenatal DDE	Childhood obesity	Moderate	40–69%
Prenatal BPA	Childhood obesity	Very low to low	20–69%
Adult DEHP	Adult obesity	Low	40–69%
Adult DEHP	Adult diabetes	Low	40–69%
Prenatal DDE	Adult diabetes	Low	20–39%
Prenatal PBDEs	Cryptorchidism	Low	40–69%
Prenatal PBDEs	Testicular cancer	Very low to low	0–19%
Adult phthalates	Low testosterone, resulting in increased early mortality	Low	40–69%
Adult benzyl and butyl phthalates	Male infertility, resulting in increased use of assisted reproductive technology	Low	40–69%
Adult DEHP	Endometriosis	Low	20–39%
Lifetime DDE	Fibroids	Low	20–39%

Adapted from the data first reported in Trasande et al (2015)¹¹ and updated in Trasande et al (2016).¹² PBDE=polybrominated diphenyl ether. IQ=intelligence quotient. DDE=dichlorodiphenyldichloroethylene. BPA=bisphenol A. DEHP=di-2-ethylhexyl phthalate.

Table 1: Exposure–outcome associations with a probability of evidence for causation identified up to 2015

	Outcome	Strength of human evidence (2015)	Probability of causation (2015), %	Updates to literature (since 2015)
Prenatal PFAS	Low birthweight	Not assessed	Not assessed	Large body of evidence; no significant association at highest levels of (modelled) exposure; weaker associations with exposure measurements in early pregnancy
Prenatal phthalates	Preterm birth	Not assessed	Not assessed	Multiple studies identify associations with DEHP metabolites
Prenatal phthalates	Reduced anogenital distance in male offspring	Not assessed	Not assessed	Five studies show reduced anogenital distance or anogenital index score; two studies show increased anogenital distance; three studies show no association

Adapted from the data first reported in Trasande et al (2015)¹¹ and updated in Trasande et al (2016).¹² See appendix for full list of studies mentioned here that have updated the literature (appendix pp 2–6). PFAS=perfluoroalkyl and polyfluoroalkyl substances. DEHP=di-2-ethylhexyl phthalate.

Table 2: Updates to assessment of probable associations between prenatal exposures and birth outcomes

Preterm birth

Preterm birth is a multifactorial condition that can sometimes lead to severe consequences in the long term.²¹ Studying preterm birth raises many specific challenges. In particular, studies in humans generally do not distinguish between preterm births on the basis of different proximal causes or clinical contexts,²² potentially reducing the ability to discern effects related to EDCs that might act along specific biological pathways.

Strong evidence exists for a relation between di-2-ethylhexyl phthalate (DEHP) and preterm birth,^{23–25} with associations observed in several studies of high quality, including some studies relying on repeated samples taken during pregnancy to assess exposures. In the LIFECODES study,²⁶ several phthalates were shown to be associated with oxidative stress markers in pregnancy, which mediated part of the associations observed between DEHP metabolites and preterm birth observed in this population. Adverse effects of dibutyl phthalate (DBP) were reported in at least two studies that used biomarkers of exposure.^{24,27} Another study noted an increased rate of preterm birth in women with high exposure to DBP from taking mesalazine during pregnancy.²⁸ Other phthalate compounds, such as diisobutyl phthalate and diethyl phthalate, have also been associated with an increased risk of preterm birth, but in fewer studies of high quality.

Studies of associations of PFAS and phenols with preterm birth were inconsistent, and there was not enough evidence regarding organophosphate pesticides, pyrethroids, PBDEs, or organophosphorus flame retardants (OPFRs) to draw conclusions (appendix pp 4–5, 7–8).

Anogenital distance

Many studies have examined the relation between EDCs and anogenital distance, the distance between the anus and genitals (scrotum or penis in boys, clitoris or fourchette in girls), which is hypothesised to reflect the androgenicity of the in utero environment. In boys, most studies of phthalates of both high and low molecular weight measured in prenatal urine (n=8) or umbilical cord blood (n=1) reported associations with shorter anogenital

distance (a feminising effect) or lower anogenital index (a measure that takes the child's weight into account).^{29–33} Additionally, one study showed an association between longer anogenital distance and exposure to phthalates of low molecular weight,³⁴ one study noted associations between shorter anogenital distance and exposure to mono-2-ethylhexyl phthalate (MEHP; a metabolite of DEHP) and between longer anogenital distance and the summed metabolites of DBP (low molecular weight),³⁵ and one study found no associations.³⁶ Results for bisphenol A (BPA) were inconsistent, and there was too little evidence regarding triclosan, PFAS, PBDEs, or other EDCs to discern any significant associations (appendix pp 5–6, 8–9). In girls, anogenital distance and anogenital index were not clearly associated with in utero exposure to EDCs.

Neurodevelopment

Prenatal exposure to EDCs can affect fetal neurodevelopment via at least two distinct hormonal pathways. Because the fetus relies on transplacental supply of thyroid hormone until the second trimester, maternal thyroid imbalance can result in permanent and lifelong neurodevelopmental consequences for children, including attention-deficit disorder, autism spectrum disorder, and cognitive and behavioural dysfunction.³⁷ Disruption of the function of sex hormones can also induce dimorphic effects on brain development.³⁸ Epidemiological studies have built on a substantial amount of toxicological literature documenting EDCs that affect these key pathways in animals, and have generally yielded similar findings in humans. This Series paper identified additional evidence to support associations of prenatal exposure to PBDEs and organophosphate pesticides with decreases in intelligence quotient (IQ); PBDEs, BPA, organophosphate pesticides, and pyrethroids with behavioural outcomes; and organophosphate pesticides, and pyrethroid pesticides with autism spectrum disorder (table 3).

Prenatal and perinatal exposure and child cognition

Evidence in humans for the cognitive effects of prenatal and perinatal exposure to EDCs is strongest for

	Outcome	Strength of human evidence (2015)	Probability of causation (2015), %	Updates to literature (since 2015)
Prenatal PBDEs	IQ loss and intellectual disability	Moderate to high	70–100%	Additional longitudinal evidence supporting high probability of causation
Prenatal organophosphate pesticides	IQ loss and intellectual disability	Moderate to high	70–100%	Additional longitudinal evidence supporting high probability of causation
Multiple prenatal exposures	Attention-deficit disorder and behaviour problems	Low to moderate	20–69%	Multiple longitudinal studies identify associations with BPA, PBDEs, organophosphate pesticides, and pyrethroids; results not uniform
Multiple prenatal exposures	Autism spectrum disorder	Low	20–39%	Evidence for organophosphate and pyrethroid pesticides; other exposures show more inconsistent associations

Adapted from the data first reported in Trasande et al (2015)³¹ and updated in Trasande et al (2016).³² See appendix for full list of studies mentioned here that have updated the literature (appendix pp 10–21). PBDE=polybrominated diphenyl ether. IQ=intelligence quotient. BPA=bisphenol A.

Table 3: Updates to assessment of probable associations between prenatal exposures and neurodevelopmental outcomes

organophosphate pesticides and PBDEs. Although one longitudinal study of prenatal exposure to organophosphate pesticide did not find an association with child cognition,³⁹ six studies showed decreases in IQ^{40–43} or IQ subscales,^{44,45} and one of these studies also noted parietal and cortical changes matching the neuropsychological deficits found.⁴⁶ Organophosphate pesticides have increasingly been replaced by pyrethroids, for which one longitudinal study reported an adverse association between prenatal exposure and child cognition,⁴³ whereas another study did not.⁴⁷ With respect to PBDEs, except for two small studies ($n < 70$),^{48,49} all studies showed consistent negative associations with IQ.^{50–54} PBDEs are increasingly being replaced by OPFRs, which have already raised concerns, with two studies showing decreases in IQ in relation to prenatal exposure.^{43,55} Overall, studies of environmental phenols and PFAS have yielded discordant findings with respect to measures of cognition (appendix pp 10–13, 22).

Prenatal exposure and autism spectrum disorder

Studies of prenatal exposure to EDCs and clinical outcomes such as attention-deficit disorder and autism spectrum disorder have been limited in part by the relative infrequency of these conditions. For autism spectrum disorder, the strongest evidence exists for a relation with organophosphate pesticides. Studies from California,^{56–59} New York State,⁶⁰ and Cincinnati (OH, USA)⁶¹ have reported an association between exposure to organophosphate pesticides, as estimated by pesticide-use registries or urinary concentrations of pesticide metabolites, and increased risk of autism spectrum disorder or increased scores on the Social Responsiveness Scale, a parental questionnaire used to evaluate signs of autism spectrum disorder. One study identified effect modification by paraoxonase genotype, suggesting differential effects in relation to detoxification of organophosphate pesticides.⁶¹ Three studies of pyrethroids have suggested an increased risk of autism spectrum disorder in Californian children living near areas with higher pyrethroid use estimated by pesticide registries.^{56,58,59} Altogether, studies of other EDCs have not yielded much clarity with respect to autism spectrum disorder (appendix pp 13–14, 22).

Prenatal exposure and child behavioural outcomes

Scales used to measure attention-deficit disorder and related behavioural outcomes have shown more consistent evidence for association with prenatal exposure to EDCs than have scales used for autism spectrum disorder. Adverse associations were identified with prenatal exposure to PBDEs in the Salinas Valley (CA, USA)⁵² Cincinnati (OH, USA)⁶² and New York City (NY, USA).⁶³ Dutch⁴⁹ and Spanish⁶⁴ studies did not identify associations, although the difference in results could be explained by the higher prevalence of exposure to PBDEs in the USA compared with in Europe. A South Korean study⁶⁵ reported increased scores for children on scales for attention-deficit disorder in mothers who had been exposed to higher

concentrations of PBDEs, and a Norwegian study⁶⁶ noted divergent associations with different PBDE congeners in breastmilk. In utero exposure to organophosphate pesticides has been associated with higher scores on the Child Behavior Checklist in California⁶⁷ and New York State (USA),⁴² supported by evidence in Mexican boys,⁶⁸ although a Danish longitudinal study did not identify any association.⁶⁹ Cohorts from France, USA, and Denmark reported that increases in attention-deficit hyperactivity disorder scores,⁶⁹ internalising symptoms (eg, anxiety, depression, and somatisation),^{60,70} and externalising symptoms (eg, aggression, hyperactivity, and conduct problems)⁶⁰ were related to concentrations of urinary pyrethroids. Among 16 analyses of the relations between prenatal exposure to BPA and child behaviour, 13 articles (representing seven different cohorts) reported deleterious associations.^{62,71–82} A randomised trial of bisphenol-based dental amalgam versus mercury amalgam in children showed higher self-reported Behaviour Assessment System for Children scores on emotional symptoms and clinical maladjustment and lower scores on personal adjustment, which indicates worse functioning in the bisphenol group.⁸³ Cohorts that have examined sex-specific associations with prenatal exposure to BPA have noted either increased externalising behaviours^{77,78,82} or other behavioural effects in boys,^{76,79} whereas few studies have reported effects in girls.⁶² Overall, evidence for associations between OPFRs and behavioural problems is sparse but consistent, whereas numerous studies of phthalates and behaviour have reported diverse findings (appendix pp 14–21, 23).

Obesity and metabolism

EDCs have been shown to disrupt peroxisome proliferator-activated receptors, oestrogen receptors, and thyroid hormone receptors, among other metabolic signalling pathways, in prospective studies with measurements of exposure in utero and in cross-sectional studies in adults. Additionally, EDCs might produce a maladaptive so-called thrifty phenotype, which increases cardiometabolic risk in later life. New data reinforce previous evidence of a link between prenatal exposure to BPA and childhood obesity, and suggest associations of prenatal exposure to PFAS and phthalates with child adiposity. Evidence is increasing that exposure to PFAS and phthalates in adulthood might be associated with gestational diabetes, impaired glucose tolerance, and obesity, and that these chemicals, as well as bisphenols, could be linked to type 2 diabetes (table 4).

Prenatal exposure and child adiposity

Among the studies that we reviewed, prenatal exposure to PFAS was associated with increases in child adiposity in multiple birth cohorts, although frequently with sexual dimorphism.^{84–89} Longer-chain PFAS have increasingly been replaced in consumer products by shorter-chain PFAS, such as perfluorobutane sulfonic acid, although

	Outcome	Strength of human evidence (2015)	Probability of causation (2015), %	Updates to literature (since 2015)
Prenatal DDE	Childhood obesity	Moderate	40–69%	Not reassessed
Prenatal PFAS	Childhood obesity	Not assessed	Not assessed	Multiple cohorts report positive findings consistent with Barker hypothesis ¹⁴ and possible mechanism of impaired glucose tolerance; less consistent associations than with birthweight
Prenatal BPA	Childhood obesity	Very low to low	20–69%	Increases in body fat measures (more consistent results than BMI); highly variable approaches to exposure assessment complicate interpretation; pattern of sexual dimorphism not consistent
Prenatal and peripubertal phthalates	Childhood obesity	Not assessed	Not assessed	Pattern of association across studies with increases in BMI and fat mass measures; one longitudinal study showed associations with peripubertal exposure
Pregnancy PFAS	Impaired glucose tolerance	Not assessed	Not assessed	Multiple studies with consistent associations; others with gestational diabetes
Prenatal phthalates	Impaired glucose tolerance	Not assessed	Not assessed	Multiple studies with consistent associations; others with gestational diabetes
Adult DEHP	Adult obesity	Low	40–69%	Positive findings strengthen existing evidence
Adult PFAS	Adult obesity	Not assessed	Not assessed	No significant association at highest levels of (modelled) exposure; associations with lower levels of exposure in multiple cohorts with mechanistic insight and effect modification by diet
Adult DEHP	Adult diabetes	Low	40–69%	One study in adults modestly supports existing evidence of association
Prenatal DDE	Adult diabetes	Low	20–39%	Not reassessed
Pregnancy PFAS	Adult diabetes	Not assessed	Not assessed	Two longitudinal studies of low exposures show associations with indices of insulin resistance; inverse association in higher range of exposure noted in one study
Adult BPA and BPS	Adult diabetes	Not assessed	Not assessed	Case-control, small-scale intervention, and longitudinal studies all consistent with associations found in laboratory studies

Adapted from the data first reported in Trasande et al (2015)¹¹ and updated in Trasande et al (2016).¹² See appendix for full list of studies mentioned here that have updated the literature (appendix pp 24–29). DDE=dichlorodiphenyltrichloroethane. PFAS=perfluoroalkyl substances. BPA=bisphenol A. DEHP=di-2-ethylhexyl phthalate. BPS=bisphenol S.

Table 4: Updates to assessment of probable associations between exposures and metabolic outcomes

evidence from a birth cohort in Shanghai, China, suggests that short-chain PFAS are obesogens and thus are a regrettable substitute.⁹⁰ A meta-analysis⁹¹ of ten cohort studies found an overall 25·0% increase in children who are overweight (95% CI 4·0–50·0; $I^2=40·5\%$) and 0·10 unit increase in BMI Z score per ng/mL of PFOA in maternal blood (95% CI 0·03–0·15; $I^2=27·9\%$).

Compared with studies of prenatal exposure to PFAS, studies of prenatal exposure to phthalates and bisphenols have not shown as consistent associations with measurements of child adiposity. The links for phthalates appear to be strongest in girls, with three studies noting associations between prenatal exposure to phthalates and BMI Z score,^{92–94} and another cohort study of young girls reporting associations between childhood exposure to phthalates at age 6–8 years and increased BMI and waist circumference over the subsequent years of follow-up.⁹⁵ Two other studies identified associations between prenatal exposure to phthalates and increases in adiposity that do not appear to differ by sex.^{96,97} The phthalates that induce effects on adiposity vary across studies, emphasising the complexity of this chemical category, which is known to contain molecules with different antiandrogenic and oestrogenic properties¹⁵ and differential peroxisome proliferator-activated receptor activity.⁹⁸ Four cohorts reported increased childhood adiposity in relation to

prenatal exposure to BPA,^{93,99–101} whereas two studies of childhood exposure did not report significant findings.^{102,103} Few studies have examined longitudinal effects of prenatal exposure to other chemicals on postnatal growth (appendix pp 24–25).

Pregnancy exposure and gestational diabetes

Six cohort studies and two case-control studies have raised compelling concerns about exposure to PFAS during pregnancy, including short-chain replacements,¹⁰⁴ contributing to gestational diabetes and impaired glucose tolerance in pregnant women from China,^{104–106} USA,^{107,108} Canada,¹⁰⁹ Denmark,¹¹⁰ or Spain.¹¹¹ Four studies identified impairments in glucose tolerance, changes in glucose concentrations, or gestational diabetes associated with phthalate exposure during pregnancy,^{112–115} but one well designed Canadian cohort study did not identify any association with gestational diabetes.¹¹⁶ Bisphenols and parabens have also been identified as chemicals that might cause gestational diabetes, but the evidence for this association is sparse (appendix pp 25–26, 30).

Adult exposure and adult weight gain

Over the past 5 years, evidence has increased to suggest that exposure to phthalates contributes to weight gain in adults, with most studies done in women. Findings from

the Women's Health Initiative¹¹⁷ have identified an association between urinary concentrations of some metabolites of phthalates, of both high and low molecular weight, and weight gain, supporting previous concerns raised by the Nurses' Health Study¹¹⁸ in the USA and the PIVUS cohort in Sweden.¹¹⁹ One study examined exposures during pregnancy and identified possible divergent effects of different phthalates in relation to post-partum weight gain.¹²⁰

Two American studies have identified an association between weight gain and serum concentrations of PFAS across both sexes. In the Diabetes Prevention Program lifestyle intervention trial,¹²¹ concentrations of total PFAS were associated with increased weight gain exclusively in the control group, whose members did not receive a lifestyle intervention. Follow-up of the POUNDS LOST trial¹²² of an energy-restricted diet gave mechanistic insights: PFAS, in particular perfluorooctane sulfonate (PFOS) and perfluorononanoic acid, were associated with reductions in resting metabolic rate. In communities surrounding a chemical plant in Washington (WV, USA) that were continuously exposed to high concentrations of PFAS, no association was reported between exposure to PFAS and weight gain in adults. However, exposure imprecision due to modelled rather than measured concentrations of PFAS, different coexposures, and different participant characteristics could explain the absence of significant findings (appendix pp 27, 30).¹²³

Adult exposure and type 2 diabetes

Occupational studies of persistent EDCs provided the first human evidence of diabetogenicity, when PFAS were identified as contributors to type 2 diabetes in a sample that was exposed to these chemicals at work.¹²⁴ Although measured exposure was not associated with diabetes in a population near Washington (WV, USA) that was consistently exposed to drinking water that was contaminated with PFAS,^{125,126} concentrations of total PFAS measured in blood samples have been associated with diabetes in Swedish¹²⁷ and American cohorts.^{128,129} A dietary intervention appeared to modify the risk of diabetes associated with PFAS in one American study.¹²⁹

The strongest associations with diabetogenicity in adults relate to bisphenols and other non-persistent chemicals. Case-control studies have associated BPA with increased risk of diabetes,^{130–132} as has the prospective Nurses' Health Study.¹³³ Two small-scale (n<25) intervention studies have identified effects of BPA on glucose, insulin, and C-peptide, suggesting that concentrations that are considered safe by US regulators alter the glucose-stimulated insulin response in humans.^{134,135} A meta-analysis¹³⁶ estimated the pooled relative risk of type 2 diabetes to be 1.45 (95% CI 1.13–1.87) for BPA and 1.48 (95% CI 0.98–2.25) for phthalates. Since then, a French case-cohort study¹³⁷ identified a near doubling of type 2 diabetes risk in relation to measured BPA glucuronide and bisphenol S (BPS) glucuronide, adding

to concerns that BPS and other replacements of BPA, which are widely used in aluminium cans and thermal paper receipts, might be regrettable substitutes. Two case-control^{131,138} and two cohort studies^{133,139} have also identified exposure to phthalates as a risk factor for type 2 diabetes. Data have suggested that PBDEs, some non-persistent pesticides and herbicides, parabens, and benzophenones could be associated with type 2 diabetes, but more research is needed in these areas (appendix pp 27–29, 30).

Male reproductive health

Testicular dysgenesis syndrome is the prevailing hypothesis linking prenatal exposure to EDCs with male reproductive health outcomes across the life course. Testicular dysgenesis syndrome posits that prenatal exposure to EDCs interferes with healthy testicular development, including differentiation and proliferation of fetal germ cells that give rise to spermatogonia, Sertoli cells that aid in the transformation of those spermatogonia to functional sperm, and Leydig cells that produce the testosterone necessary for testis descent and overall masculinisation.¹⁴⁰ In this section, we review associations of EDCs with outcomes that might result from perturbations in this developmental trajectory, including hypospadias, cryptorchidism, testicular cancer, prostate cancer, low testosterone, and poor semen quality. Studies reinforced previous findings of links between PBDEs and cryptorchidism and between phthalates of high molecular weight and reduced testosterone. Additionally, evidence is accumulating of associations of occupational exposure to persistent pesticides with prostate cancer, and of exposure to bisphenols, PFAS, phthalates, and organophosphate pesticides with reduced semen quality (table 5).

Prenatal and perinatal exposure and genital malformations

A large Canadian study that measured PBDEs in hair samples obtained from mothers 3–18 months post partum reported a positive association with cryptorchidism.¹⁴¹ Evidence for associations of prenatal and perinatal exposure to numerous other persistent and non-persistent chemicals with hypospadias and cryptorchidism was either sparse or inconsistent (appendix pp 31–32, 41).

Testicular cancer

Although much still needs to be understood about the environmental origins of testicular cancer, a condition that has increased in many countries since the middle of the 20th century,¹⁴² no new biomarker studies have been published since 2015. The few studies published since 2015 were ecological studies or were based on pesticide-use registries, and examined exposure to only PFAS and pesticides (appendix pp 32, 41–42). The scarcity of research on other chemicals included in this Series paper emphasises the need for biomarker studies that collect samples during relevant windows of

	Outcome	Strength of human evidence (2015)	Probability of causation (2015), %	Updates to literature (since 2015)
Prenatal PBDEs	Cryptorchidism	Low	40–69%	One study reports a positive association
Prenatal PBDEs	Testicular cancer	Very low to low	0–19%	No new evidence
Occupational pesticides	Prostate cancer	Not assessed	Not assessed	Evidence for increased risk with exposure to persistent pesticides from studies in diverse geographical regions
Adult phthalates	Low testosterone (resulting in increased early mortality)	Low	40–69%	Increased evidence for negative association with testosterone in cross-sectional studies (n=13; all but one for DEHP and MEHP, two for MiBP); association of prenatal exposure and testosterone in children, adolescents, and young men was not as consistent
Adult BPA and BPS	Semen quality	Not assessed	Not assessed	Six studies show negative associations with concentration of sperm and total sperm count; negative associations with motility (n=3), morphology (n=2), and reduced semen quality (n=1); two studies found no associations, one study found positive association for motility and concentration; one study of BPS shows negative associations with total sperm count, concentration, motility, and normal morphology
Adult PFAS	Semen quality	Not assessed	Not assessed	Four studies consistently associated higher concentrations of PFAS with lower semen quality (three of morphology, one of motility)
Organophosphate pesticides	Semen quality	Not assessed	Not assessed	Three studies consistently associated higher concentrations of organophosphate pesticides with lower semen quality (sperm concentration, motility, and morphology)
Adult benzyl and butyl phthalates	Male infertility (resulting in increased use of assisted reproductive technology)	Low	40–69%	22 more studies linked higher phthalate concentrations to lower sperm concentration, motility, or normal morphology; three studies had increases in these measures; three studies showed no significant association

Adapted from the data first reported in Trasande et al (2015)¹¹ and updated in Trasande et al (2016).¹² See appendix for full list of studies mentioned here that have updated the literature (appendix pp 31–40). PBDE=polybrominated diphenyl ethers. DEHP=di-2-ethylhexyl phthalate. MEHP=mono-2-ethylhexyl phthalate. MiBP=monoisobutyl phthalate. BPA=bisphenol A. BPS=bisphenol S. PFAS=perfluoroalkyl substances.

Table 5: Updates to assessment of probable associations between exposures and outcomes in male reproductive health

biological susceptibility for testicular cancer, and the need for development of relevant animal models.

Prostate cancer

Overall, occupational exposure to pesticides was consistently associated with prostate cancer in the American Agricultural Health Study¹⁴³ and other studies from Canada, France, and elsewhere in the USA.^{144–146} Only one study, from the Netherlands, reported an inverse relation with self-reported occupational use of pesticides,¹⁴⁷ whereas another study from Australia did not find a significant association.¹⁴⁸

Findings for self-reported exposure to exclusively non-persistent pesticides were less consistent and results were sparse for other chemicals, including phthalates, BPA, PBDEs, polycyclic aromatic hydrocarbons (PAHs), and PFAS (appendix pp 32–33, 42). None of these studies were able to directly test the testicular dysgenesis syndrome hypothesis, as they were mostly cross-sectional and exposure was not measured during the prenatal period.

Testosterone

The testicular dysgenesis syndrome theory postulates that prenatal exposure to EDCs impairs proliferation and

development of fetal Leydig cells, leading to lifelong reduced production of testosterone. Most evidence from cross-sectional studies of boys and men across the life course supports a negative association of DEHP or its main metabolite MEHP, or both, with testosterone.^{149–160} Studies of prenatal exposure were less consistent. Although two studies noted negative associations of DEHP or MEHP with free testosterone at birth¹⁶¹ and at age 8–14 years,¹⁶² four studies did not find associations with testosterone in adulthood.^{160,163–165} The longitudinal Raine study¹⁶⁶ from Australia reported a positive association between prenatal exposure to DEHP, MEHP, the replacement chemical diisononyl phthalate, and monoisononyl phthalate (the main metabolite of diisononyl phthalate) with total testosterone at ages 20–22 years. However, phthalates were measured in stored maternal serum in this study, which is less reliable than measures in urine. Results were weaker for phthalates of low molecular weight, BPA, organophosphate pesticides, PFAS, and parabens, and data were sparse for benzophenones, PAHs, PBDEs, triclosan, pyrethroids, and carbamates (appendix pp 34–36, 43).

Semen quality

Most studies of semen quality are cross-sectional and do not contain information on exposure in utero and in

early life, so they cannot provide evidence to support the testicular dysgenesis syndrome hypothesis. The results of these studies are still relevant to the question of how EDCs affect sperm production, which occurs continuously beginning in puberty and affects male fecundity.

Most studies investigating phthalates reported negative associations with at least one, but often multiple, semen quality parameters, including sperm concentration, motility, and morphology. In contrast to testosterone, however, phthalates of both low and high molecular weight were implicated. Evidence is also mounting for a negative association between BPA and semen quality, including results from the Raine birth cohort, in which BPA was measured in prenatal serum;¹⁶⁶ a Chinese occupational cohort;¹⁶⁷ cohorts of young men from Denmark¹⁶⁸ and Spain;¹⁶⁹ and five studies done in men recruited from fertility clinics,^{170–174} in which BPA was measured cross-sectionally. The Boston-based Environment And Reproductive Health study¹⁷⁵ was the only one to analyse BPS, a widely prevalent replacement for BPA that shares its obesogenic properties, and reported negative associations with sperm concentration, motility, and morphology, but only in men who had overweight or obesity.

Three studies that examined organophosphate pesticides and semen quality all reported negative associations,^{176–178} as did four studies that examined PFAS.^{179–182} Results were more variable for benzophenones, triclosan, parabens, and PBDEs, and sparse for pyrethroids, carbamates, and OPFRs. Many of these studies recruited men who were part of couples seeking fertility treatment, so results might not be generalisable (appendix pp 36–40).

Female reproductive health

Paralleling the testicular dysgenesis syndrome hypothesis linking prenatal endocrine disruption to adverse outcomes in male reproductive health, the ovarian dysgenesis syndrome hypothesis suggests that prenatal exposure to

EDCs could lead to pathophysiological reproductive conditions in women, including polycystic ovarian syndrome, endometriosis, uterine fibroids, and cancers at reproductive sites.¹⁸³ Few studies have had the data for prenatal exposure that would be necessary to test this hypothesis; however, substantial evidence exists to implicate exposure to EDCs closer to the time of diagnosis. In particular, studies identified an increased risk of polycystic ovarian syndrome in association with exposure to BPA and PFAS; reinforced links between phthalates and endometriosis; and suggested associations of PFAS with endometriosis and of organophosphate pesticides and PFAS with breast cancer (table 6; appendix p 47). Similar to outcomes in male reproductive health, most epidemiological studies of female reproductive health are cross-sectional and cannot be interpreted to support causal associations, especially when participants had pre-existing conditions.

Polycystic ovarian syndrome

Among various studies examining associations between EDCs and polycystic ovarian syndrome, the evidence is strongest for an association with PFAS. Three cross-sectional studies of polycystic ovarian syndrome reported positive associations with various PFAS: a study in China with perfluorododecanoic acid,¹⁸⁴ an American study with PFOA and PFOS,¹⁸⁵ and a smaller study in the UK with only PFOS.¹⁸⁶ Evidence is also accumulating of a link between BPA and polycystic ovarian syndrome. Six cross-sectional studies reported positive associations between BPA and polycystic ovarian syndrome,^{187–192} although one of these studies identified associations only among women who had overweight or obesity, and three studies reported no associations.^{185,193,194} Overall, knowledge about other EDCs, such as PBDEs, phthalates, PAHs, and triclosan, and polycystic ovarian syndrome is just beginning to emerge, but no conclusions can be drawn about these chemicals yet (appendix pp 44–45, 49).

	Outcome	Strength of human evidence (2015)	Probability of causation (2015), %	Updates to literature (since 2015)
BPA	Polycystic ovarian syndrome	Not assessed	Not assessed	Multiple case-control studies identify increased risk
PFAS	Polycystic ovarian syndrome	Not assessed	Not assessed	Case-control studies identify increased risk
Adult DEHP (and metabolites)	Endometriosis	Low	20–39%	Three studies show positive associations; one study shows negative association; one study shows no significant association
PFAS	Endometriosis	Not assessed	Not assessed	Two studies report positive association; one study with mixed associations (positive for PFBS, negative for PFAS)
Lifetime DDE	Fibroids	Low	20–39%	Not reassessed
PFAS	Breast cancer	Not assessed	Not assessed	Multiple studies show positive associations for exposure at different stages of life

Adapted from the data first reported in Trasande et al (2015)¹¹ and updated in Trasande et al (2016).¹² See appendix for full list of studies mentioned here that have updated the literature (appendix pp 44–48). BPA=bisphenol A. PFAS=perfluoroalkyl and polyfluoroalkyl substances. DEHP=di-2-ethylhexyl phthalate. PFBS=perfluorobutane sulfonate. DDE=dichlorodiphenyldichloroethylene.

Table 6: Updates to assessment of probable associations between exposures and outcomes in female reproductive health

Endometriosis and uterine fibroids

Notable additions to the literature on EDCs and endometriosis have been made regarding PFAS, but results are inconsistent. An analysis of 2002–06 US NHANES data¹⁹⁵ and the ENDO study¹⁹⁶ of women recruited from Utah and California (USA) in 2007–09 reported positive associations with PFOS, PFOA, and perfluorononanoic acid. A 2017 Chinese study¹⁹⁷ suggested a positive association with perfluorobutane sulfonate and negative associations with perfluoroheptanoic acid, perfluorohexane sulfonic acid (PFHxS), and perfluorononanoic acid.

One cross-sectional study showed a positive association between serum DEHP and endometriosis, although this study did not adjust for covariates,¹⁹⁸ and another study reported a positive association between urinary mono-2-ethyl-5-carboxypentyl phthalate¹⁹⁹ (a metabolite of DEHP) and endometriosis. A third study of phthalates and endometriosis found no associations, although this study was smaller and did not adjust for covariates.²⁰⁰ Other additions to the endometriosis literature examined BPA, benzophenones, and PBDEs, but none of the evidence was conclusive (appendix pp 45, 49).

Studies of EDCs and uterine fibroids have focused on phthalates and phenols, but results have been varied (appendix pp 46, 49–50).

Breast, endometrial, and ovarian cancer

Breast cancer studies have investigated a wide range of EDCs, with several studies reporting positive associations for PFAS and organophosphate pesticides. The evidence for PFAS includes results from the Child Health and Development Studies²⁰¹ in Oakland (CA, USA) in which prenatal exposure to N-ethyl-perfluorooctane sulfonamidoacetic acid, a precursor of PFOS, was positively associated with breast cancer in daughters, whereas prenatal exposure to PFOS was protective. Other longitudinal analyses include the French E3N study²⁰² of women born between 1925 and 1950, which reported a positive association between PFOS and postmenopausal breast cancer, and the Danish National Birth Cohort study,²⁰³ in which perfluorooctane sulfonamide in first-trimester blood samples was positively associated with postnatal development of maternal breast cancer, whereas PFHxS was protective. In a cross-sectional study of Greenland Inuit women, PFOS, PFHxS, and the sum of perfluoroalkyl acids were associated with higher odds of breast cancer.²⁰⁴ Finally, an ecological study in the Veneto region of Italy reported higher mortality rates from female breast cancer in municipalities with drinking water contaminated with PFAS.²⁰⁵ The only study of PFAS not to find any associations was a large case-control analysis nested in the longitudinal California Teachers Study.²⁰⁶

All four studies that examined organophosphate pesticide exposure and breast cancer reported increased risk, specifically for chlorpyrifos, methyl parathion, terbufos, coumaphos, diazinon, fonofos, and phorate. None of these studies measured chemicals in blood or

metabolites in urine; all were studies of agricultural populations that estimated exposure from self-report or geocoded addresses linked to pesticide registries.^{143,207–209}

The literature on phthalates and breast cancer is sparse with inconsistent results. Results for studies of PBDEs, phenols, benzophenones, parabens, and carbamate and pyrethroid insecticides were scarce or were not significant (appendix pp 46–47, 50).

Among the few papers published on EDCs and other female reproductive cancers (eg, endometrial and ovarian cancer), studies examined organophosphate pesticides, diazinon, and atrazine. However, there was not enough evidence to draw conclusions (appendix pp 48, 50).

Discussion

This Series paper suggests new adverse health effects of frequently used EDCs with a probability of causation and strengthens the evidence for many other EDCs that have been previously identified by an expert panel commissioned by WHO and UNEP.¹¹ The expanding evidence for these environmental contributors to non-communicable diseases suggests that synthetic chemicals are ignored or at least underappreciated as a focus of the 2030 Sustainable Development Goals (SDGs). Decreasing exposure to synthetic chemicals with endocrine-disrupting or other adverse properties is not identified as one of the SDGs, although the SDGs rightly emphasise air pollution and climate change as global priorities.²¹⁰

The new exposure–outcome pairings proposed here have not been subject to systematic review methods²¹¹ or application of GRADE Working Group²¹² and other methods to evaluate the strength of evidence and probability of causation.²¹³ Full evaluation of the probability of causation and estimates of disease burden and costs for all of the identified exposure–outcome pairs represent a natural and logical extension of this work.

In reviewing hundreds of published studies, we have emphasised the many challenges in unravelling the complex relations of exposure to EDCs with disease and disability across the lifespan. These challenges include confounding, the complex mixtures of exposures and their inter-relationships, the variability in exposure distributions and timing across studies that could explain differences in results, the cross-sectional designs of many studies, and the imprecision of exposure assessment methods, especially for chemicals with short half-lives. Some of these challenges can be addressed through technological advances and novel study designs. In particular, given the high variability in concentrations of BPA and other non-persistent chemicals in individuals, prenatal studies relying on a spot biospecimen during pregnancy or a given pregnancy period (eg, in assessing associations with trimester-specific exposure) are likely to have strong attenuation bias and low power.²¹⁴ Studies should endeavour to collect frequent, repeated biospecimens across the duration of pregnancy to reduce measurement error. Another issue in human studies is

Search strategy and selection criteria

Using a combination of exposure and outcome keywords, we searched PubMed for articles on empirical research in humans published in English from January, 1990, to September, 2019. We used standardised searches that combined exposures (eg, organophosphorus and brominated flame retardants, phenols, phthalates, pesticides, pyrethroids, parabens, perfluoroalkyl substances, and benzophenones) and outcomes (eg, intelligence quotient, neurodevelopment, neurobehaviour, autism, attention deficit, fetal growth, birthweight, preterm birth, prematurity, obesity, diabetes, anogenital distance, cryptorchidism, hypospadias, testicular cancer, prostate cancer, testosterone, semen quality, polycystic ovarian syndrome, endometriosis, fibroids, breast cancer, uterine cancer, and ovarian cancer). As an example of our strategy, for the outcome of preterm birth, we used the search terms “(((PBDE OR brominated OR organophosphate OR chlorpyrifos OR POP OR phthalate OR DEHP OR BBP OR DBP OR DiBP OR phenol OR bisphenol OR BPA OR BPS OR BPF OR triclosan OR triclocarban OR benzophenone OR PFAS OR PFOA OR perfluoroalkyl OR perfluor* OR perfluorinated OR pyrethroid OR parabens OR paraben* OR phytoestrogen OR nonylphenol OR “endocrine disruptor*”) AND ENGLISH[Language]) AND (“1990”[Date - Publication] : “2019/09”[Date - Publication])) AND (preterm OR “premature birth” OR “gestational duration”)”. For neurodevelopmental, birth, and congenital outcomes, studies only with prenatal or perinatal exposure assessment are included in this Series paper.

the inability to readily measure chemicals in target tissues (eg, ovary) and the ongoing gaps in knowledge about the distribution and mobilisation of chemicals during physiological events, such as pregnancy and menopause.

Many of the papers described in this Series paper limit their examination to a single class of chemical exposures or their metabolites. Biostatistical developments have not yet yielded a superior method to manage the related exposures that might exist in the human body.²¹⁵ The composition of mixtures also varies across individuals, and the high cost of analytical technologies has generally restricted the needed and simultaneous study of the thousands of natural and synthetic compounds with endocrine effects.²¹⁶ Larger sample sizes are also needed to sufficiently power interaction testing across chemical mixtures. Cohorts such as the European LifeCycle or ATHLETE consortia, the Japan Environment and Children's Study, and the National Institutes of Health Environmental Influences on Child Health Outcomes programme are well poised to overcome the sample size challenge, as each cohort can contribute archived samples from tens of thousands of mother–infant pairs. Metabolomic technologies hold promise in the identification of a broad array of emerging and novel exposures, and other exposomic methods offer mechanistic insights

and opportunities to develop intermediate markers that could reliably predict disease endpoints and aggregate effects of multiple interacting exposures. Additionally, genomics and related tools can carefully examine interactions between genes (or gene expression) and exposures (eg, paroxonase polymorphisms and their influence on the health outcomes of exposure to organophosphate pesticides²¹⁷).

Intervention studies have produced rapid decreases in exposure to organophosphate pesticides, bisphenols, phthalates, parabens, and triclosans,²¹⁸ but these studies have not examined changes in disease or intermediate markers. Randomised designs of interventions to increase or decrease exposure generally have little applicability because of ethical and logistical considerations. That said, we identified crossover studies in which intentional administration of EDCs showed intermediate markers of disease risk.¹³⁵ These designs, under some circumstances, can offer promising opportunities to identify effects of EDCs more quickly, especially for conditions with long latency periods.

A theme throughout the studies reviewed is the emergence of effects on human health due to replacements of EDCs by compounds that have had little testing. These health effects include the neurodevelopmental effects of pyrethroids, which are replacing organophosphate pesticides, and of OPFRs used as substitutes for their brominated counterparts; metabolic effects of BPS and other BPA analogues as well as short-chain PFAS now being used as concern has grown regarding longer-chain versions; and reproductive effects of substituting diisononyl phthalate for DEHP. The few studies of the associations of these emerging exposures with human health, many of which have identified adverse effects, support the conclusion in the second paper in this Series²¹⁹ that regulators should treat chemicals as classes rather than individual compounds and strengthen premarketing toxicological testing.

Further research will always be needed to elaborate on the effects of EDCs and other synthetic chemicals on human health with greater precision. As Bradford Hill described in his landmark lecture on causality, actions—in this case, to reduce exposure to EDCs—require consideration of the evidence and the stakes involved in the decision.²²⁰ In many cases, alternative manufacturing practices can be applied to mitigate exposure to EDCs. Additional costs to society will need to be weighed against the economic benefits of decreased disease and disability as well as other societal effects (eg, ecosystem effects).

The past 5 years of research on EDCs have brought into sharp focus the substantial stakes involved for human health. Although there are actions that individuals can take to reduce their exposure, the definitive way to make a difference on a population level is through regulation. Regulation can eliminate environmental injustices when individuals are left to implement sometimes costly

For more on the **European LifeCycle project** see <https://lifecycle-project.eu>

For more on the **ATHLETE consortia** see <https://www.humanexposome.eu/portfolios/athlete>

For more on the **Japan Environment and Children's Study** see <https://www.env.go.jp/chemi/ceh/en>

For more on the **National Institutes of Health Environmental Influences on Child Health Outcomes programme** see <https://www.nih.gov/research-training/environmental-influences-child-health-outcomes-echo-program>

changes to their daily lives (eg, buying organic food). The second paper in this Series²¹⁹ describes how policies can reduce exposure, prevent disease, and produce economic benefits that might even outweigh the costs of safer alternatives.

Contributors

LT conceptualised the Series paper, and equally contributed with RS, CP, and LGK. LGK compiled the narrative and oversaw construction of the tables. SFN reviewed multiple draft manuscripts, providing editorial support. LT had final editorial oversight.

Declaration of interests

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