Endocrine-disrupting chemicals 1

Endocrine-disrupting chemicals: implications for human health

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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.

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This is the first in a **Series** of two papers about endocrine-disrupting chemicals

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Introduction

In 1962, Rachel Carson described the effects of dichlorodiphenyltrichloroethane (DDT) on sexual development and reproduction.[1] Less than a decade later, Herbst and colleagues[2] 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 homoeostatic 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

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 adulthood[16] 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).

	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**

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-analysis[20] 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 (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 polyfluroalkyl 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)[33] and updated in Trasande et al (2016).[12] 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] Dutch[49] and Spanish[64] 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 study[65] 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 study[66] 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 California[67] 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-analysis[91] 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 properties[15] 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 Initiative[117] 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 Study[118] 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 trial[122] 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 Swedish[127] 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-analysis[136] 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 study[137] 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)[21] 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 Study[143] 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 birth[161] and at age 8–14 years,[162] four studies did not find associations with testosterone in adulthood.[160,163–165] The longitudinal Raine study[166] 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 Denmark[168] 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 study[175] 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 data[195] and the ENDO study[196] of women recruited from Utah and California (USA) in 2007–09 reported positive associations with PFOS, PFOA, and perfluorononanoic acid. A 2017 Chinese study[197] 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 phthalate[199] (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 Studies[201] 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 study[202] 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 methods[211] or application of GRADE Working Group[212] 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 pesticides[217]).

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 Series[219] 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 Series[219] 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.

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Endocrine-disrupting chemicals 2

Endocrine-disrupting chemicals: economic, regulatory, and policy implications

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Endocrine-disrupting chemicals (EDCs) substantially cost society as a result of increases in disease and disability but—unlike other toxicant classes such as carcinogens—have yet to be codified into regulations as a hazard category. This Series paper examines economic, regulatory, and policy approaches to limit human EDC exposures and describes potential improvements. In the EU, general principles for EDCs call for minimisation of human exposure, identification as substances of very high concern, and ban on use in pesticides. In the USA, screening and testing programmes are focused on oestrogenic EDCs exclusively, and regulation is strictly risk-based. Minimisation of human exposure is unlikely without a clear overarching definition for EDCs and relevant pre-marketing test requirements. We call for a multifaceted international programme (eg, modelled on the International Agency for Research in Cancer) to address the effects of EDCs on human health—an approach that would proactively identify hazards for subsequent regulation.

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This is the second in a Series of two papers about endocrine-disrupting chemicals

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Introduction

Endocrine-disrupting chemicals (EDCs) are chemicals capable of interfering with hormone action and which thereby contribute to disease and disability across the lifespan.[1–5] EDCs are found in food and food packaging, water, personal care products, household goods, detergents, fabrics and upholstery, electronics, medical equipment,[6–9] pesticides,[1] and ambient air (table 1).[10] Although many pharmaceuticals are designed to target the endocrine system to promote therapeutic benefits, the release of these drugs into waterways and sewage sludge allows them to contaminate the environment,[11–14] also potentially leading to endocrine disruption.[15,16]

In this Series paper, we examine the approaches that have been taken to quantify economic costs of EDC exposures, describe the regulatory approaches applied to EDCs to date, particularly in the USA and the EU, and detail the strengths and weaknesses of these regulations, showing where consideration of health and economic costs could improve regulations. Finally, we make policy recommendations for the development of methods to identify EDCs, prescribe specific steps to evaluate and restrict exposures, and call for a multifaceted and international programme to harmonise identification, characterisation, and regulation of EDCs in a global context.

Economic implications of EDC exposures

Estimates of the burden of disease and disability, and the costs of environmentally attributable disease, have proven extremely useful to translate findings and inform policy making. These costs are grounded in rigorous methodology first described by the US National Academy of Sciences[17] and leveraged to document the potential economic benefits of policy actions (eg, the phase-out of leaded gasoline, with annual benefits of US$110 billion to 319 billion in the USA[18] and $2·4 trillion globally[19]) when only increases in productivity are counted.

The Global Burden of Disease project uses an approach that calculates disability-adjusted life-year (DALY),[20] where valuations of $50 000 per DALY are used to calculate the costs[21] of clinically significant morbidities such as intellectual disability. DALY estimates currently generated by WHO[22] and Institute for Health Metrics and Evaluation[23] might not be sufficient to evaluate EDCs, which can adversely affect the intellectual capacity of individuals within the normal range of functioning; even decreases in intellectual quotient (IQ) within the normal range are associated with decreased lifetime economic productivity.[24] Economic evaluations relying solely on DALY estimates produce a 200-fold divergence from estimates taking IQ changes into account.[25]

Over the last several years, a series of economic evaluations estimated the burden and disease costs of EDCs on a range of outcomes including neurobehavioural deficits and diseases, male reproductive disorders, obesity and diabetes, and female reproductive disorders.[26–29] The economic burdens (€163 in the EU and $340 billion in the USA, annually) derived from these approaches are

	Representative EDCs
Pharmaceuticals	Trenbolone acetate, ethinylestradiol, dexamethasone, levonorgestrel, rosiglitazone
Cosmetics, personal care products	DBP, benzophenones, parabens, triclosan, DEET
Pesticides, herbicides, fungicides	Chlorpyrifos, glyphosate, pyraclostrobin, DDT, atrazine
Industrial chemicals	BPA, PCBs, triphenyl phosphate, PBDEs
Metals	Lead, cadmium, mercury, arsenic
Synthetic and naturally occurring hormones	Progesterone, testosterone, cortisol, oestrone

Representative EDCs from diverse functional use categories. EDC=endocrine-disrupting chemical. DBP=dibutyl phthalate. DEET=N,N-diethyl-m-toluamide. DDT=dichlorodiphenyltrichloroethane. BPA=bisphenol A. PCB=polychlorinated biphenyl. PBDE=polybrominated diphenyl ether.

Table 1: **List of representative EDCs in use**

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certain to be underestimates as they examined only a small subset of EDCs and health outcomes likely to be affected by EDC exposures.[30–32] These data demonstrate that improved regulations could improve citizens' health via reduction or elimination of exposures and result in huge economic benefits.

Current approaches to regulate EDCs

We review the approaches used for the regulation of EDCs in the EU and the USA, which have the most well developed and far-reaching regulations. We also identify regulatory approaches in other developed and industrialising nations and contrast approaches.

EU EDC regulations

EU regulations pertaining to chemical substances and environmental hazards are either usage-oriented (eg, biocidal products or cosmetics regulations) or medium-oriented (eg, air or water protection). European environmental policy[33] embraces the precautionary principle, which mandates that exposures should be limited when indications of potentially dangerous effects on the environment, human, animal, or planetary health exist, even in the absence of scientific certainty (table 2).[34,35] In 1999, the EU set in motion steps to prioritise substances for further evaluation as EDCs, monitor EDC exposures and effects, communicate information about EDCs to the public, and develop and validate new testing methods.[36] EU legislative instruments for consumer, health, and environmental protection were progressively amended to account for their EDC effects. In 2018, the EU reaffirmed its application of the precautionary principle and aim to minimise overall EDC exposures, with particular attention to critical windows of development.[37]

Plant protection products and biocides regulation

EDCs are banned from pesticides by the 2009 Plant Protection Products Regulation[38] and the 2012 Biocidal Products Regulation.[39] The hazard-based criteria for EDCs in pesticides are similar to the provisions regarding carcinogens, mutagens, and reproductive toxicants (CMRs).[38,39] Following scientific debate,[40,41] in 2018, the European Food Safety Authority and the European Chemicals Agency published a guidance document proposing how EDCs can be identified in pesticides, either individually or in mixtures, based on test results from the submitting company or the scientific literature.[42] To be considered an EDC, a chemical must produce an adverse effect, alter the functions of the endocrine system, and the adverse effect must be a biologically plausible consequence of the endocrine mode of action. Although these criteria are most aligned with a

	Approach in the EU	Approach in the USA	Argument for change
Overarching approach to chemical regulation	Largely a hazard-based approach—exposures should be limited when indications of potentially dangerous effects exist; no consideration of exposure	Entirely a risk-based approach—regulations must consider both hazards of a chemical and anticipated exposure to that chemical	Risk-based approach does not consider costs of EDCs to chronic disease burden; fails to appropriately capture exposure risks with long latency periods to health outcomes
Pesticides	EDCs banned from pesticides by the 2009 Plant Protection Products Regulation and 2012 Biocidal Products Regulation; EDCs not permitted as active ingredient unless human exposure is negligible; guidance document published on how to identify EDCs in pesticides	EPA mandated under Food Quality Protection Act (1996) to develop screening programme to identify oestrogenic EDCs in pesticide products; final committee report detailed two-tiered panel of assays for oestrogen, androgen, and thyroid-mediated effects; only ~50 pesticides have been screened through tier 1 assays and tier 2 is not yet validated	The approach to screening recommended by the Endocrine Disruptor Screening and Testing Committee was mired in regulatory hurdles and is too limited in testing only disruption of three receptors; need for screening systems that cover all endocrine modalities and that prevent authorisation if screening reveals EDCs
Cosmetics	Neither a general provision nor a definition regarding EDCs; EDCs handled on a case-by-case basis and can involve complete bans, or tolerable limits (eg, triclosan); animal testing is not allowed for substances used in cosmetics	Governed by the FDA Food, Drug, and Cosmetic Act; has no specific provisions to govern EDCs; fragrance loophole allows use of nondescript term fragrance to be used on labels to detail a mixture of chemicals and protect trade secrets	A definition and requirement to consider EDCs across all sectors will vastly simplify the regulatory landscape
Medical devices	EDCs are explicitly permitted above 0·1% in parts that come into contact with the body or bodily fluids only in certain conditions	Governed by the FDA Food, Drug, and Cosmetic Act; has no specific provisions to govern EDCs	A definition and requirement to consider EDCs across all sectors will vastly simplify the regulatory landscape
Drinking water	No specific requirements for testing of EDCs, but movement to add several EDCs to monitoring list	Safe Drinking Water Act explicitly covers oestrogenic EDCs and allows for submission to a screening programme if substantial populations might be exposed	A definition and requirement to consider EDCs across all sectors will vastly simplify the regulatory landscape; regulations must cover more than a single receptor and mode of action
Other sectors	Chemicals not explicitly covered in other specific regulations are covered under REACH; EDCs are regulated under REACH only if demonstrated to be of equivalent concern to CMR or PBT substances; authorisations and restrictions done under a risk-based approach	Chemicals not explicitly covered in other specific regulations are covered under TSCA. EDCs are not specified; authorisations and restrictions done under a risk-based approach	EDC-specific requirements under these overarching agreements would allow for more transparency about regulatory approach to these chemicals and consistent regulations across industries to reduce complexity and costs with standardisation

EDC regulations in the EU and the USA. Overarching approach to chemical regulation and sector or media-specific regulations and the discussion of potential avenues for improving these regulations. EPA=Environment Protection Agency. EDC=endocrine-disrupting chemical. FDA=Food and Drug Administration. REACH=Registration, Evaluation, Authorisation, and Restriction of Chemicals. CMR=carcinogenic, mutagenic, or toxic for reproduction. PBT=persistent, bioaccumulative, and toxic. TSCA=Toxic Substances Control Act.

Table 2: **Regulatory approach differences between the EU and the USA and proposed changes**

hazard-based approach, even when the criteria are met, permission to use the pesticide can still be granted if evidence exists that the adverse effect is irrelevant to humans (and other non-target organisms), or if exposure is negligible.

Registration, evaluation, authorisation, and restriction of chemicals (REACH)

REACH is a 2006 European programme that deals with the regulation of chemicals in the EU across multiple sectors, but excluding active substances of plant protection products, biocides, cosmetics, drugs, and chemicals used in medical devices. Annex XIV of REACH stipulates that chemicals that are CMRs, persistent, bioaccumulative, and toxic, and substances that are very persistent and very bioaccumulative, require approval by the European Chemicals Agency for use regardless of the level of human exposure. EDCs require approval by the European Chemicals Agency if demonstrated to be of equivalent concern to CMRs, which can only be achieved after rather lengthy procedures. For products regulated through REACH (including products with likely human exposure), hazards must be identified but authorisations and restrictions of use are decided after assessment of the risk resulting from exposure (ie, aligned with a risk-based rather than purely hazard-based management logic). As of February, 2020, 205 substances were included in the substances of very high concern (SVHC) list (16 for their endocrine-disrupting properties) and are subject to increased regulatory scrutiny and higher reporting standards. 43 substances were placed in annex XIV of REACH (two recognised as EDCs), marking the intent to ban their use once technically and economically suitable alternatives are available.

Compound-specific and country-specific regulations

Several EDCs have specific regulations that apply in all EU countries or in specific countries (table 3). A paramount case is that of bisphenol A (BPA), which in 2017 was listed as an SVHC by the EU due to its endocrine-disrupting properties. BPA was banned from baby bottles in 2011, and later from food containers for infants and young children; France has further banned BPA in all food containers and Sweden has banned its use in epoxies for household water pipes.

US EDC regulations

In the USA, the main chemical regulatory laws on food and food additives, drugs, and cosmetics are administered through the Food and Drug Administration (FDA) and those on pesticides and commercial chemicals not covered elsewhere through the Environmental Protection Agency (EPA).

Toxic Substances Control Act (TSCA)

TSCA, as originally administered in 1976, was intended to regulate all commercial chemical uses not explicitly covered in other sectors. Despite a mandate to proactively assess chemical safety, the EPA reviewed less than 10% of the more than 35 000 chemicals proposed from 1979 to 2004[43] and actively regulated less than ten.[44,45] Approximately 62 000 current-use chemicals were assumed safe at implementation unless the EPA could provide substantial evidence of unreasonable risk to human or environmental health, or both.[43,45] Other reasons for the apparent failure of TSCA to successfully regulate[46,47] include an overly strict standard of judicial review,[46,48] insufficient toxicity information for most chemicals,[46] short timeframes for review, confidential business information provisions,[49] and vague or complicated definitions and exemptions.[50]

A growing appreciation of these limitations led to TSCA reform in 2016.[51] The updated legislation requires the

For **REACH** see https://echa.europa.eu/regulations/reach/understanding-reach

	Country	Approach taken
Pesticides in agriculture	EU and Brazil	Hazard-based exclusion; EU: unless the exclusion applies, unless adverse effect irrelevant to humans (and other non-target organisms), or exposure negligible
EDCs	Australia	Considers the European hazard-based criteria as an indicator, triggering further evaluation in risk assessment of a chemical for ongoing use in products
EDCs	South Korea and Canada	Risk assessment approach identical to other synthetic chemicals
EDCs	Japan	Led some of the earliest initiatives to identify EDCs beginning in 1998, relying heavily on aquatic toxicity tests
EDC pollution	China	Part of its 13th Five-Year Plan of national environmental protection, though the detailed approach to controlling pollution is not made explicit
DEHP, DBP, and BBP	USA, Canada, Israel, Brazil, Hong Kong, Australia, China	Banned or restricted in toys and products for children
BPA	EU, South Africa, India, Canada, Israel, Brazil, USA	Restrictions (EU) or bans (others) for infant baby bottles or food contact materials intended for infants; Brazil: also ban on importation; Sweden: ban on epoxies for household water pipes; USA: not explicit ban, but use in baby products no longer permitted (also further state-specific regulations)
Nonylphenol and ethoxylates	South Korea, Canada, EU	Canada: substantial limits on manufacturing, use, and imports; South Korea: similar, also limits on use of products containing these chemicals; EU: production and use restrictions, both commercial and domestic
Lindane	Banned in 50+ countries	International ban under Stockholm Convention, 2009 (USA not signatory); still permitted as second-line medical treatment in some countries (eg, USA)
Organohalogen flame retardants	USA	US Consumer Product Safety Commission proposed class ban of PBDEs and other groups of organohalogens for all uses in consumer products; PBDEs specifically also voluntarily phased out by manufacturers through negotiations with EPA; PBDEs now banned under Stockholm Convention (USA not signatory)
PFAS	USA, others	PFOS: international ban under Stockholm Convention, 2009 (USA not signatory); PFOA: recent addition with some exemptions; USA: no specific regulations, though a health advisory limit set for drinking water; individual states setting limits below these EPA-mandated levels

Selected endocrine-disrupting chemical regulations in the global context. Selected EDCs chosen to span several diverse chemical classes, and countries or regions participating in regulations for each should not be considered comprehensive. EDC=endocrine-disrupting chemical. DEHP=di(2-ethylhexyl) phthalate. DBP=dibutyl phthalate. BBP=butylbenzyl phthalate. PBDE=polybrominated diphenyl ethers. BPA=biosphenol A. EPA=Environmental Protection Agency. PFAS=perfluoroalkyl and polyfluoroalkyl substances. PFOS=perfluorooctanesulfonic acid. PFOA=perfluorooctanoic acid.

Table 3: **Selected chemical-specific approaches to addressing EDCs**

EPA to conduct a risk-based review of all chemicals in commerce, prioritise chemicals to facilitate risk-based review, consider vulnerable populations, and determine safety before allowing marketing. Although the new TSCA also provides authority for the EPA to regulate chemicals, request additional safety testing, and gather additional data as needed,[48,52] endocrine disruption testing is not mentioned. Even if such testing was required, resources and protocols are insufficient to prioritise, evaluate, and rigorously assess newly proposed chemicals or those already in use. Although the EPA states that it has completed approximately 2600 new chemical reviews (as of February, 2020) since enactment of the revised legislation, only eight chemicals were halted pending more information; none have been prohibited.[53] The long-standing gaps in toxicity testing for chemicals are unlikely to have been addressed in such a short period of time.

For **Strategic Alliance for International Chemicals Management** see http://www.saicm.org

Food, Drug, and Cosmetic Act (FDCA)

The FDCA of 1938 requires that manufacturers produce food products that are safe, pure, wholesome, and labelled without deception, giving the FDA broad regulatory authority over products that fail to meet the requirements of the Act.[54] The Food Additives Amendment of 1958 addressed concerns applicable to food additives, but also exempted food additives from regulation if they were generally recognised as safe (GRAS).[54,55] No requirements exist to submit information regarding GRAS determination to the FDA,[56,57] and a comprehensive review of GRAS substances initiated in the 1970s was never completed.[57] A 1997 amendment established the principle of food contact substances and set out regulatory guidance for these chemicals, exempting materials contributing to dietary concentrations below 0·5 µg/kg (with the exception of likely or known carcinogens).[58] These issues have contributed to the FDA failing to reconsider the status of any GRAS substance since 1982, and resulted in more than 10 000 GRAS substances allowable in US food products today.[56] Notably, the FDA has no specific requirements for EDC testing nor action following their identification.[59] As such, EDCs such as nonylphenol, BPA, tributyltin, triclosan, and several phthalates are legally and intentionally used in food contact materials. These materials also contain polymerisation byproducts, impurities, and breakdown compounds known as non-intentionally added substances, many of which migrate into food.[60]

State regulatory authority

Several US states have regulations relevant to specific EDCs (table 3). California passed Proposition 65 in 1986, requiring the state to maintain a list of chemicals known to cause cancer or reproductive toxicity. This regulation requires product documentation detailing a potential risk to consumers beyond the so-called safe levels, although it does not specifically require listing of EDCs. Despite this limitation, the Proposition has inspired new legislation for deliberation in New York, where, if passed, the Consumer Chemical Awareness Act would give consumers information about consumer and personal care products that contain a carcinogen, mutagen, EDC, or other chemical of concern.

EDC regulations beyond the USA and the EU

EDCs have been identified as an emerging policy issue by the UN Environment Programme (UNEP), which oversees global policy through Strategic Alliance for International Chemicals Management. In 2015, the alliance welcomed the 2012 WHO and UNEP State of the Science report on EDCs, noting scientific dissent only from the chemical and pesticide industries.[61] Although the report identified efforts by the USA, the EU, Japan, and the Organisation for Economic Cooperation and Development to develop testing guidelines for EDCs, these tests focus exclusively on the oestrogen, androgen, and thyroid pathways,[62] and ignore not only other receptors (48 known human nuclear receptors exist), but also many other potential mechanisms of action.[5]

A 2017 report commissioned by UNEP and authored by the International Panel on Chemical Pollution, identified 28 policy actions, by governments worldwide, that substantially vary in the scope of EDCs addressed and emphasise evaluation of industrial chemicals (select examples included in table 3). The highly variable approaches to address and limit hazardous EDCs are especially concerning as synthetic chemical manufacturing and use are increasing rapidly in developing countries and economies in transition.[63]

Model regulations and harmonisation across the globe would go far, especially in the context of limited regulatory resources for oversight. Current efforts largely focus on monitoring adherence to existing international conventions (Stockholm, Basel, Rotterdam, etc) which are notable because they limit a subset of persistent organic pollutants (many EDCs), through binding international agreements (table 3). However, the USA has not ratified these agreements and continues to produce and export certain chemicals (chlordane, several flame retardants, etc) that these conventions have banned.

Consideration of economic costs: current approaches to EDC regulations

Balanced analyses should evaluate the costs of regulations and compare them with the costs—health care, economic, and otherwise—of failing to regulate. The costs associated with regulating a chemical (or class) would include the actual burden of implementing new laws and policies, as well as possible lost economic activity. There could also be benefits for another industry making similar products posing lower environmental and human health risk. The costs associated with inaction would include the economic burden to health and the environment incurred by exposure to the

unregulated compounds. From a societal perspective, a proper approach would be to weigh the costs of developing safer alternatives (which are initially borne by producers but ultimately passed to the consumer) against the economic benefits of reduced disease and disability. The real costs of replacing EDCs are often lower than initial estimates as innovation and technological developments, as well as consumer demand, address the need to identify substitutes in products. Still agencies in the EU and the USA tasked with protecting public and environmental health fail to take these costs into account when making regulatory decisions. Two examples presented here illustrate how regulatory failures in the USA and the EU have allowed EDC exposures to continue, contributing to morbidity and serious economic burdens.

A neurotoxic EDC continues to escape regulation in the USA

Chlorpyrifos, an EDC known to disrupt thyroid hormone action,[26] represents a clear regulatory failure by the US EPA.[64] Chlorpyrifos was voluntarily withdrawn by manufacturers (under agreement with the EPA) in 2000 for indoor pesticide use (with some exceptions), following evidence of neurotoxic effects.[65–67] In 2015, the EPA proposed to revoke all permissible uses in food products in response to a petition;[64,68,69] however, the EPA administrator reversed this decision in 2017, suggesting that there was insufficient animal evidence of adverse health impacts and improper dependence on epidemiological data. Following extended court challenges, the revocation was fully reversed in July, 2019,[70] allowing this pesticide to continue to be used on food crops. In February, 2020, a major manufacturer, Corteva, announced its intention to cease production in the USA, due to decreasing demand from agricultural users.[71]

Allowing the continued use of chlorpyrifos does not consider the ensuing economic burden. Based on its well documented associations with reduced IQ, estimated annual costs of $44 billion are expected in the USA[64] if exposures continue at current levels. These estimates do not account for other potential health effect costs beyond IQ loss, nor do they account for potential damage to the environment, including possible effects on pollinator species.[72] Furthermore, the failure to regulate chlorpyrifos has negative economic consequences for industries marketing safer alternatives.

By contrast, the European Food Safety Authority released a human health assessment for the renewal of approval for chlorpyrifos, which expired in January 2020.[73] The authority determined that given neurodevelopmental effects at the lowest doses examined in toxicological studies, and support for these findings in the epidemiological literature, no safe exposure level could be set for chlorpyrifos, and thus a risk assessment for use could not be completed. Because the approval criteria could not be met, EU approval has not been renewed.

An EDC is labelled an SVHC in the EU but given a clean bill of health in the USA

More than a hundred studies in humans suggest that exposures to BPA can contribute to endocrine diseases including obesity, diabetes, and neurodevelopmental disorders.[74] This literature is supported by more than 1000 studies from controlled laboratory experiments documenting the endocrine-disrupting properties of this chemical, and its effects on the health of rodents, aquatic animals, and non-human primates.[1,75,76] An extensive scientific literature on the associations between BPA and human diseases indicates that the procedures used to determine whether current human exposures are safe are insufficient and flawed.[77,78]

In response to concerns raised by health advocates and scientists, the National Institute of Environmental Health Sciences and National Toxicology Program developed a collaborative research study, CLARITY, to determine if the methods used for hazard assessments are sufficient for EDCs like BPA.[79,80] Exposures and standard toxicological endpoint examinations were done at the FDA, and masked organs, tissues, or animals were then transported to academic labs for additional mechanistic testing. Although the FDA continues to claim their results suggest BPA is safe at current levels of exposure, work from the academic partners shows that BPA affects the brain, prostate, ovary, and other organs at levels currently deemed safe.[81]

In the meantime, regulatory agencies in the EU have used these and other academic studies to conclude that BPA disrupts the mammary gland and cognitive function, and alters metabolism and reproduction.[82–84] The French environmental health agency, for example, has described in detail why BPA meets the legal criteria to be labelled an EDC. The substance was then recognised as an SVHC by the European Chemicals Agency.[85,86] Still, the agency concedes that this labelling is unlikely to sufficiently protect human health, noting that "authorisation is the most binding measure that can be associated with the SVHC status and it does not apply to monomers and intermediates. A significant amount of BPA is placed on the European market as a monomer and intermediate".[85]

Like chlorpyrifos, the failure to efficiently regulate BPA does not consider the economic costs of continued use of this chemical in consumer products. Estimates of BPA contributions to the costs associated with childhood obesity alone amount to $2 billion in the EU and $2·4 billion in the USA.[31] To date, there are no estimates of the economic contribution of BPA to other adverse health outcomes (eg, attention-deficit hyperactivity disorder, cancer, or infertility).

A path forward: policy recommendations

We next recommend actions centred on identification and mechanistic assessment of EDCs, strategies to monitor and reduce exposures, and regulatory actions that could better protect human and environmental health (table 4).

	Existing evidence	EDC change proposed	Argument for change
Consensus on EDC identification	Differing definitions of EDCs are currently used by nearly every agency and sector, no consensus; most require adverse effects in animal models	Legally valid definition of EDCs applicable in all sectors that does not require evidence of adverse effect in whole organism models	Different definitions are problematic for regulators and industry; requiring adverse effects as proof of harm necessitates a comprehensive understanding of all disease states and mechanisms of action
Consensus on methods to evaluate EDCs	Most US regulations require oestrogenic EDC testing only; most EU regulations for pesticides require oestrogen, androgen, and thyroid hormone axis	Two-tiered testing plan: tier 1 screening approach to evaluate all nuclear receptor-related and non-nuclear receptor mechanisms, some functional outcomes; tier 2 inclusive of diverse disease-state models in diverse species	Testing a single receptor for a single mechanism of action is insufficient; broad testing of known endocrine endpoints is needed to more thoroughly evaluate potential endocrine-mediated disruption and to prioritise for higher-order testing in animal models
Establishment of global biomonitoring programmes	Biomonitoring programmes are currently limited to very developed nations and monitor at most several hundred chemicals	Expansion of testing particularly to countries that do not have the resources to monitor these exposures is critical; expansion of testing to greater number of substances of high concern	A clear environmental justice issue; low-income and middle-income countries cannot afford a national biomonitoring programme and yet often are disproportionately exposed to products and waste deemed too contaminated from the wealthiest nations
Mandatory provision of chemical composition for marketed substances	Few requirements exist for provision of chemical compositions, often product suppliers do not appreciate chemical production chain for their own products; trade secret exemptions are considerable	Requirement for full disclosure of all chemical constituents and additives used in all consumer products; clear consequences for incorrect information	Far too much federal funding is going to simply identifying chemical constituents in consumer products rather than assessing potential health consequences from exposure; this expenditure is avoidable with regulations on industry disclosure and labelling
Inclusion of economic costs associated with EDC-related morbidities in cost	Economic costs related to EDC exposures are not included in relevant cost–benefit analyses	Requirement for regulations to consider the EDC-related morbidity costs and for WHO and Institute for Health Metrics and Evaluation to include these effects in estimates of the global burden of disease	Inclusion of these costs would have benefits on health outcomes, human suffering, health expenditures, and environmental justice concerns surrounding exposure inequalities; rapid increase in direct human evidence of adverse effects via EDCs
Hazard-based approach to regulation of EDCs	Used in part across EU regulations; USA uses a risk-based approach, using cost–benefit analyses	Shift to a hazard-based approach to regulating EDCs across all countries and sectors rather than using risk-based approaches	Delay to gather paramount human health studies, particularly with long latency disease outcomes; is not protective of human health; ignores potential impacts on health and biodiversity
Establishment of International Agency for Research on EDCs	Equivalent agency for the evaluation of chemical carcinogens has successfully operated for >50 years	An international agency under WHO to transparently evaluate potential EDCs	These consensus statements would be used by regulatory agencies around the world to limit exposures to EDCs and consolidate weight of evidence approaches

Key proposed policy changes needed to promote effective regulatory environment to protect human health from exposure to EDCs. EDC=endocrine-disrupting chemical.

Table 4: **Proposed policy changes to EDC regulations**

Testing and identifying EDCs

Our first recommendation centres on the identification of EDCs, as effective screening programmes are essential to subsequent actions. Unfortunately, the currently available or validated tests used to determine if a chemical is an EDC do not cover all endocrine modes of action. In the USA, regulations require testing for oestrogen agonist activity only for pesticides and drinking water contaminants, while the recommendations from the Endocrine Disruptor Screening and Testing Advisory Committee[87] promote evaluation of oestrogen, androgen, and thyroid receptor disruption. In the EU, the European Chemicals Agency and the European Food Safety Authority guidance document on the identification of EDCs in pesticides also recommends gathering information on oestrogenic, androgenic, thyroidal, and steroidogenic modalities.[88] Of these, disruption of the thyroid axis has particularly poor coverage, and other pathways (eg, metabolic, glucocorticoid, etc) are not covered at all. Further still, for the better covered modalities (eg, oestrogen and androgen signalling), the validated tests appear too insensitive for some EDCs, working best for endogenous hormones. For example, the uterotrophic assay measures oestrogen-dependent changes in uterine weight, though relatively high concentrations of oestrogenic EDCs must be administered to alter uterine weight,[89] and disruption of oestrogen signalling can occur without organ weight effects.[90] Sensitive assays exist to test a broader number of nuclear receptors, and other receptor types, and to assess some of the more diverse mechanisms of action for EDCs.[5] Assays to examine these mechanisms, such as receptor expression, hormone transport, hormone synthesis, and epigenetic alterations, should soon be validated for inclusion in regulatory requirements. In contrast, the Organisation for Economic Cooperation and Development guidance provides comprehensive documents pertaining to the development and validation of test guidelines for a variety of endocrine activities, including standardised protocols, mechanistic insights, and evaluation of new assays for potential inclusion, covering more diverse pathways than those formally required under US or EU regulations.

We propose that a two-tiered system be employed to identify suspected EDCs and known EDCs, similar to what others have suggested previously.[91] In the first tier, high-throughput screening methods are used to evaluate

substances for a wide range of endocrine modalities.[92,93] These assays should assess both agonist and antagonist activities of a broad range of receptors (not limited to nuclear types), and receptor-independent mechanisms, for comprehensive coverage across endpoints.[5] Work is needed to ensure appropriate validation and rigour in testing (including positive and negative controls, technical and biological replicates, quality assurance and control), to determine how results will be interpreted, how conflicting results from different screening assays targeting the same endpoint will be reconciled,[94] and how chemicals will be prioritised for additional higher-order testing. This high-throughput approach can support the testing of all receptor systems conducive to in-vitro screens, rather than focusing on a select few. Efforts to address this through high-throughput testing of diverse chemicals in diverse mechanism assays are underway through the ToxCast and Tox21 programmes,[95,96] though questions remain as to interpretation and quality control of these efforts.[94,97,98] These first-order tests should be coupled with more functional in-vitro assays to assess outcomes such as adipocyte development, steroidogenesis, and spermatogenesis, among others, to cover a broader biological base of potential EDC-induced disruption.

In the second tier, testing using more sensitive assays should be conducted, with a focus on endpoints relevant to human diseases, and targeting relevant critical windows to identify likely adverse impacts.[91] Because current regulations require that a chemical induces adverse effects to be recognised as an EDC, and adverse effects can only be observed in vivo, second tier assays will need to use vertebrate animals or epidemiological evidence until the regulatory definition of an EDC is significantly altered. The EPA has proposed restrictions and plans to eventually ban the use of mammals for regulatory testing, though there are no guidelines yet in place for how in-vitro assays will be used to fill this gap. EU authorities, in contrast, have legislation in place proposing the replacement, reduction, and refinement of vertebrate animal testing, like the Organisation for Economic Cooperation and Development guidelines. Until the EDC definition is updated and guidelines are available to use in-vitro data for regulatory purposes, in-vivo assays must continue to provide crucial toxicological data. Non-mammalian vertebrate models such as fish (zebrafish, medaka) and amphibians (*Xenopus*)—particularly larval stages that would obviate the EU restrictions—and invertebrate models have great potential to also fill this research gap. Hormone receptors are highly conserved across vertebrates,[99] the ease of breeding and short developmental timing allow for comprehensive mixture testing, and functional conservation in areas such as adipose biology, lipid metabolism, and glucose signalling provides robust utility in modelling human disease states.[100] These and more typical mammalian models (eg, rodents) should be used to help ensure rigorous validation of in-vitro assays and to examine more complex organismal responses. Where possible, linkages should be assessed between first-order mechanistic testing and higher-order in-vivo outcomes to elucidate potential pathways underlying effects; importantly, however, adverse endocrine outcomes should not be discounted for lacking this mechanistic information. A determination of adverse effect should be sufficient for identification as an EDC and subsequent regulation.

As chemicals are identified as EDCs and regulated based on these tests, care must also be taken to limit regrettable substitutions. Polybrominated diphenyl ethers were replaced with organophosphate ester flame retardants that have their own health concerns,[101] and BPA has been replaced in some products with other bisphenols that have similar or worse effects for particular endpoints.[102,103] Regulations that support development of safer alternatives and require testing before allowing alternatives onto the market should help prevent regrettable substitutions. These pre-market tests should encompass the defined in-vitro and in-vivo endpoints we have discussed; chemicals intended for commerce should receive the same attention given to chemicals already present on the market.

Evaluating exposures to EDCs

Our second recommendation encompasses evaluating exposures to EDCs. In a hazard-based regulatory environment, chemicals identified as EDCs would simply be removed from use, at least for products entailing possible human exposure. A risk-based regulatory approach currently prevails in which the effects are evaluated on the basis of degree of exposure. It is therefore essential that decision makers know how chemicals are being used, can access robust biomonitoring data so that exposures can be characterised, and can implement exposure mitigation programmes as needed. Although some developed nations have highly informative biomonitoring programmes, more of such efforts must be developed worldwide (eg, to capture the dynamic complexity of exposures). Human exposure data should be accessible to researchers and organisations to foster analyses of global trends and factors influencing exposures. These factors can also power global and local educational campaigns to inform the broader public about safe and simple steps to reduce EDC exposures, accompanied by regulations that make it compulsory to provide information on the chemical composition of marketed products and their hazards. A type of measure that has long proven to have a high impact in decreasing human exposure to EDCs is to withdraw from the market a product or set of consumer products causing such exposure.

Limiting exposures to EDCs through regulations

Our third major recommendation centres on improving regulations governing EDCs. We suggest three main avenues to bolster regulatory approaches to these chemicals: a legally valid definition of EDCs applicable in all sectors of the economy and jurisdictions of the world,

inclusion of economic costs of EDC-related health effects in global disease estimates, and a hazard-based approach to EDC regulation, at least when human exposures occur. The Endocrine Society has defined an EDC as "any chemical or mixture of chemicals that interferes with any aspect of hormone action" whereas other definitions, such as that from WHO, specifically require that an adverse effect is documented.[1,104,105] Requiring an adverse effect to define an EDC is problematic because regulatory agencies often disagree on which outcomes are adverse.[106] This notion is especially true in the context of in-vitro high-throughput assays that have been proposed for use in regulations; these assays would determine activity based on receptor binding, reporter gene activation or inhibition, or functional outcomes such as altered steroidogenesis or differentiation. As such, moving away from definitions that require the observation of adverse effects in vivo, and adopting the Endocrine Society definition, provides a relevant path forward, especially in the context of the limitation of animal testing. Such an approach should be adopted across all sectors to ensure consistent treatment of EDCs regardless of product source.

Our second proposed strategy to bolster the regulatory approach to EDCs is to include EDCs in estimates of the global burden of disease, particularly important considering the substantial human and economic costs due to EDC-related morbidities.[107] The European Commission considers the aim of minimising human and environmental exposure to EDCs as scientifically justified. In parallel, in countries and sectors where risk-based approaches remain the paradigm, reductions in EDC exposures are warranted based on direct human evidence of adverse effects, as described in paper 1 of this Series. Where implemented, such policies will have positive impacts not only on health outcomes, but also on health expenditures and other indirect costs. In the USA, EDC exposures are often higher in ethnic minorities[108] and contribute to inequalities in diseases and disability, including neurocognitive outcomes.[29] EDC policies are justified on economic grounds and to further environmental justice.

Our third proposed strategy is to focus on a hazard-based approach to the regulation of EDCs. With risk-based approaches, a regulatory response is only triggered if exposure levels reach some critical level (eg, a reference level or value assumed to trigger a response of a given amplitude, or an insufficient margin between exposures and doses that are anticipated to cause hazards).[109] In contrast, a hazard-based approach finds the hazardous properties of a chemical as sufficient for regulation and marketing prohibition, independent of exposure risks and cost–benefit analyses. For many EDCs, data are lacking to support using risk-based approaches, hampering other regulatory actions.[110] The lag from identifying new exposures to completing human studies of effects, especially for disease outcomes with longer latencies such as diabetes or cancers, is the most serious and intrinsic flaw of the risk-based regulatory paradigm. To delay regulating chemical hazards until sufficient data are available to inform risk assessment is costly in human health as well as economic terms. A shift in the paradigm towards hazard-based regulation, as has been embraced by the EU pesticides regulation, is thus warranted.

We argue that such hazard-based regulations should be used for regulating EDCs across all sectors (or at least for those with potential human or ecological exposures) in all countries. Because non-monotonic exposure–response relationships exist for many synthetic chemicals including EDCs,[5,111] doses that cause harm cannot be used to extrapolate to lower doses that are safe.[112] Although some risk-based approaches attempt to account for age-related vulnerability, they falsely presume that the population sensitivity can be quantified a priori. As such, we suggest the inclusion of EDCs as a specific hazard category for regulatory purposes across countries, of similar concern to other hazards such as carcinogens. A first step would be for endocrine disruption to be part of the international Globally Harmonised System of classification and labelling of chemicals and of the area-specific corresponding regulations such as the EU 2008 regulation on the classification, labelling and packaging of substances and mixtures.[113] We propose a defined testing paradigm to evaluate all chemicals in commerce, hazard-based approaches to regulation, and clear timelines and actions required following EDC identification.

An International Agency for Research on EDCs (IARE)

To foster the development of some of these recommendations, we suggest the establishment of a new international agency, or a broadening of the International Agency for Research on Cancer (IARC)'s scientific charge, to include endocrine disruption. When the IARC was established in 1965, it was tasked with evaluating the evidence of carcinogenesis due to environmental hazards.[114] Since that time, the IARC has evaluated hundreds of environmental chemicals and agents in a transparent and reproducible manner.[115] We propose that an IARE should be created within WHO and funded in a similar manner to protect against undue influence from industry or other stakeholders, and managed with a parallel structure to allow expert working groups to evaluate chemicals that are suspected to be EDCs, adapting the approach applied by the IARC.[116,117] Such an independent body will promote more efficient procedures for identifying EDCs globally. Like the operation of the IARC, monographs published as a result of the efforts from IARE working groups would describe the state of the evidence using three streams of evidence (eg, mechanistic, animal, and epidemiological studies) and principles similar to those used in systematic reviews.[118] One of the key reasons cited for the success of the IARC is that it explicitly does not make policy recommendations; thus, the body of work that would be created by the IARE would be used by regulatory agencies

Search strategy and selection criteria

This Series paper relied on the collective expertise and experience of the authors; thus, a comprehensive literature search was not done before initiating the study. Authors have previously published extensively on the economic costs of various environmental contaminants including endocrine-disrupting chemicals. Regulatory context was examined via direct evaluation of legislation and through targeted evaluation of regulatory critiques published previously to compare and contrast hazard and risk-based regulations globally, though focusing on the EU and the USA.

around the world to limit, or hopefully eliminate, EDC exposures, with the IARE staying expressly apolitical.[117] A January, 2020, consensus on the key characteristics of EDCs, provides a framework, with ten mechanisms of action and assays that are available to probe some of these, that could be used to identify EDCs.[5] This approach follows a similar framework describing key characteristics of carcinogens that has been used by IARC expert panels.[119] We propose that an autonomous body that can bring together diverse experts for international collaborative reports on EDCs would foster global movement on regulations.[115,116] As noted with the creation of the IARC, an international organisation is likely to be freer of non-scientific constraints in suggesting regulatory actions than national organisations,[117] a point that is easily demonstrated by the recent US and EU regulatory failures discussed in preceding sections.

Conclusions

In the past decades, regulatory efforts and policies to decrease human exposure to EDCs have been insufficient to minimise exposure to the vast majority of EDCs.[120,121] Given the overwhelming scientific evidence of EDCs as a human health hazard and the economic costs of inaction, it is clear that improved regulations are needed. As we have described, the current approach to limiting exposure to EDCs in humans is dangerously slow and insufficient. Simply too few chemicals used in commerce have been thoroughly tested for endocrine-disrupting properties, with an ever-expanding list of chemicals requiring evaluation; other serious weaknesses persist in testing approaches. Although the EU has taken positive steps toward regulating EDCs, the approach taken in the USA (and other countries) is limited or altogether absent. Regulatory bodies that have applied risk-based evaluations of regulatory options have failed to consider the full cost of EDC-related health impacts to adequately protect health. To this end, we suggest expanded and comprehensive testing strategies to conclusively identify EDCs, and a shift from a flawed, risk-based paradigm to one that proactively excludes chemicals with some evidence of hazardous properties until further detailed reassuring testing data become available. An international initiative on EDCs, which would be supported by UN, could address the weaknesses related to hazard identification and provide much-needed guidance for policies globally.

Contributors

LT conceptualised the Series paper, and contributed equally to the US policy section with CDK and LNV. RS, BAD, and MP equally contributed to the EU policy section, relying on a published report prepared by BAD and RS for the EU Parliament, while LNV and CDK developed the proposal for the International Agency for Research on Endocrine Disruption with LT and RS. LT had final editorial oversight.

Declaration of interests

LNV reports grants from National Institutes of Environmental Health Sciences, funding from the Cornell Douglas Foundation and Great Neck Breast Cancer Coalition, and a grant from Paul G Allen Family Foundation; she has received reimbursement for travel, or in-kind donation of travel accommodations, from Food Packaging Forum, World Federation of Scientists, European Association for Veterinary Pharmacology & Toxicology, Stowe Cancer Survivors Group, Society of Toxicology, and Endocrine Society. BAD has a patent Transgenic clawed frog embryos and use thereof as detectors of endocrine disrupters in the environment. A French patent application filed in 2002 (FR0206669), was extended through a Patent Cooperation Treaty application filled in 2003. Applicants: Centre National de la Recherche Scientifique and Muséum National d'Histoire Naturelle. Inventors: B Demeneix and N Turque. The patent has been extended worldwide: France (2007), Japan (2011), USA (2013), Canada (2013), and Europe (2015) with royalties paid to Watchfrog. BAD and RS report reimbursement for travels from the Endocrine Society. LT reports personal fees from Houghton Mifflin Harcourt and Audible. All other authors declare no competing interests.

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