nature reviews endocrinology

https://doi.org/10.1038/s41574-023-00872-x

Review article

Check for updates

# The regulation of endocrine-disrupting chemicals to minimize their impact on health

Carol Duh-Leong[1], Maricel V. Maffini[2], Christopher D. Kassotis[3], Laura N. Vandenberg[4] & Leonardo Trasande[1,5,6,7]

## Abstract

Endocrine-disrupting chemicals (EDCs) are substances generated by human industrial activities that are detrimental to human health through their effects on the endocrine system. The global societal and economic burden posed by EDCs is substantial. Poorly defined or unenforced policies can increase human exposure to EDCs, thereby contributing to human disease, disability and economic damage. Researchers have shown that policies and interventions implemented at both individual and government levels have the potential to reduce exposure to EDCs. This Review describes a set of evidence-based policy actions to manage, minimize or even eliminate the widespread use of these chemicals and better protect human health and society. A number of specific challenges exist: defining, identifying and prioritizing EDCs; considering the non-linear or non-monotonic properties of EDCs; accounting for EDC exposure effects that are latent and do not appear until later in life; and updating testing paradigms to reflect 'real-world' mixtures of chemicals and cumulative exposure. A sound strategy also requires partnering with health-care providers to integrate strategies to prevent EDC exposure in clinical care. Critical next steps include addressing EDCs within global policy frameworks by integrating EDC exposure prevention into emerging climate policy.

## Sections



[1]Department of Pediatrics, New York University Grossman School of Medicine, New York, NY, USA. [2]Independent Consultant, Frederick, MD, USA. [3]Institute of Environmental Health Sciences and Department of Pharmacology, Wayne State University, Detroit, MI, USA. [4]Department of Environmental Health Sciences, University of Massachusetts — Amherst, Amherst, MA, USA. [5]Department of Environmental Medicine, New York University Grossman School of Medicine, New York, NY, USA. [6]Department of Population Health, New York University Grossman School of Medicine, New York, NY, USA. [7]New York University Wagner Graduate School of Public Service, New York, NY, USA. e-mail: leonardo.trasande@nyulangone.org

## Key points

- Poorly defined or unenforced policies can increase global human exposure to endocrine-disrupting chemicals (EDCs), contributing to substantial human disease, disability and economic damage.
- Regulatory bodies have drawn from leading scientific and health organizations to define EDC properties but have not operationalized a consistent definition.
- Current risk-based paradigms do not consider the non-linear and/or non-monotonic properties of EDCs: default toxicology methods to measure minimum levels do not adequately protect from EDC exposure.
- Policies also need to account for latent EDC exposure effects that do not appear until later in life.
- EDC testing paradigms should reflect real-world mixtures and cumulative exposures.
- Many EDCs are manufactured from fossil fuels, linking their fate with our ability to develop sound policy to address the grand societal challenge of climate change.

## Introduction

Six decades ago, scientists uncovered the harmful consequences of the organochlorine pesticide dichlorodiphenyltrichloroethane[1] and the pharmaceutical diethylstilbestrol, a non-steroidal form of oestrogen[2], on the human endocrine system. Evidence has since rapidly accumulated to document the adverse effects and extensive costs of anthropogenic endocrine-disrupting chemicals (EDCs) on hormone action and, consequently, human health[3]. The 1991 Wingspread Conference specifically highlighted the disruptive consequences of EDCs on oestrogen receptors[4], but scientists have since revealed how EDCs can also affect androgen, thyroid, and other nuclear receptor and/or hormonal pathways and functions, subsequently altering health and development through multiple mechanisms (Table 1). In the past decade, numerous health, medical and scientific organizations, including the WHO and United Nations Environment Programme[5], the Endocrine Society[6,7], the American Academy of Pediatrics[8], and the International Federation of Gynecology and Obstetrics[9], have released statements that highlight convincing evidence of the harmful effects of EDCs.

The societal burden posed by EDCs is substantial, with attributable disease costs of US$ 340 billion per year in the USA (2.3% of GDP), € 163 billion per year in the European Union (EU) and CAD$ 24.6 billion per year in Canada, based on a 2010 population[3,10–16] (Table 2). These reports regarding EDC costs did not include estimates of the health effects of perfluoroalkyl substances (PFASs), which were assessed in 2018 and are anticipated to be at least US$ 5.5 billion annually, with possible projections of up to US$ 62.6 billion per year in the USA[17]. A 2022 publication documented ~90,000 deaths in the USA of individuals aged 55–64 years that were attributable to phthalate exposure, with lost productivity of US$ 39.9–47.1 billion per year[18]. Unsurprisingly, the disease burden and costs from EDCs fall unequally on people from minoritized racial or ethnic and socio-economic groups within countries[19] as well as unevenly between countries[20,21]. EDC-related consequences are disproportionately greater in low-income and middle-income countries, where increased human exposure to PFASs, for example, has contributed to over 400,000 babies being born with low birthweight over the past two decades[22].

While the public bears the health and economic costs of EDCs, current regulatory agencies and policies seldom hold manufacturers responsible for the consequences of these EDCs. Additionally, the regulation of EDCs varies across countries. For example, tributyltin (TBT)-based antifouling products, which improve paint durability by slowing the growth of marine organisms on boat surfaces, are associated with detrimental effects on the female reproductive axis[23]. The trade of TBT-based products has been banned by the Rotterdam Convention, but TBT-based antifouling paints continue to be manufactured in the USA and are thus persistently available and globally distributed[24].

Differences in policy between countries as well as poorly defined and unenforced policies can result in increased human exposure to EDCs, which contributes to human disease and disability, thereby harming the economy. As an example, in California, furniture manufacturers were required to add brominated flame retardants to their products until 2015, whereas the EU banned the use of these chemicals earlier. These differences in policy have contributed to greater neurocognitive disability in the USA than in the EU, resulting in tremendous societal and economic costs (US$ 4.5 trillion in the USA between 2001 and 2016 compared with <US$ 100 billion in the EU over the same period)[3]. Conversely, to account for the unique vulnerability of children to EDCs, the US Congress passed the Food Quality Protection Act in 1996, which established allowable levels for the use of pesticides in food crops. This legislation reduced exposure to organophosphate pesticides and, thus, the associated societal costs in the USA compared with the EU, which failed to implement similar legislation[25]. When communities bear the health costs of exposure, class action lawsuits can hold manufacturers accountable; for example, residents near Hoosick Falls in New York State successfully sued a corporation (Baker vs Saint-Gobain Performance Plastics Corp. et al., case no. 1:16-cv-0917) for contaminating their drinking water with perfluorooctanoic acid (PFOA)[26]. However, such examples are rare. Exposures often have multiple sources from multiple manufacturers, which stymies efforts to hold specific corporations responsible; instead, broad-scale regulatory actions are required.

Researchers have shown that policies and interventions — implemented on an individual basis and at government levels — have the potential to reduce exposure to EDCs. For example, an organic diet intervention decreased urinary levels of organophosphate pesticide metabolites in children[27], and strategies to decrease the use of personal care products containing parabens, phthalates and phenols lowered the levels of these chemicals in the urine of adolescent girls[28]. Dietary interventions (eating 'fresh foods' to limit food packaging) reduced exposure to bisphenol A (BPA) and di-2-ethylhexyl phthalate[29], and household renovation of spaces containing 'healthier' materials (furniture and carpets) contributed to reduced levels of brominated flame retardants, PFASs and organophosphate flame retardants in dust, a major pathway for human exposure, compared with spaces containing conventional materials[30]. Broad-scale regulatory actions, which are more far-reaching than individual or community-level interventions, have limited the use of BPA and certain phthalates, and these actions are likely to be responsible for decreases in the urinary levels of these chemicals seen in a study conducted in the USA between 2005 and 2016 (ref. 31). Regulatory-level strategies are known to produce successful and rapid reductions in exposure, and governments balance developing efficient regulation with adequate human protection from EDC

**Table 1 | Representative EDCs and their mechanisms of disruption**

| Source | EDC | Use | Mechanism of disruption | | | |
|---|---|---|---|---|---|---|
| | | | Oestrogen | Androgen | Thyroid | Other[a] |
| Cosmetics, personal care products | Dibutyl phthalate | Plasticizer (nail polish) | Yes | Yes | ND | Yes |
| | Benzophenones | Solvent (sunscreen) | Yes | ND | ND | Yes |
| | Paraben | Preservative (makeup, shampoo) | Yes | ND | ND | Yes |
| | Triclosan | Antimicrobial (soaps, detergents) | Yes | ND | ND | Yes |
| | *N*,*N*-diethyl-meta-toluamide | Insect repellent (personal spray) | Yes | ND | ND | Yes |
| Pesticides, herbicides, fungicides | Chlorpyrifos | Insecticide (organophosphate) | Yes | ND | ND | Yes |
| | Pyraclostrobin | Fungicide (quinone inhibitor) | ND | ND | Yes | Yes |
| | Dichlorodiphenyltrichloroethane | Insecticide (organochloride)[b] | Yes | Yes | ND | Yes |
| | Atrazine | Herbicide (corn crops, golf courses) | ND | Yes | Yes | Yes |
| Industrial chemicals | Bisphenols | Plastics (hard plastics), thermal paper receipts | Yes | Yes | ND | Yes |
| | Phthalates | Plastics (soft plastics), food packaging | Yes | Yes | ND | Yes |
| | Polychlorinated biphenyl | Plasticizer (paints, cements)[b] | ND | ND | Yes | Yes |
| | Triphenyl phosphates, organophosphates | Flame retardant (electronics, glues) | Yes | ND | Yes | Yes |
| | Polybrominated diphenyl ethers | Flame retardant (buildings, electronics) | Yes | Yes | Yes | Yes |
| Metals | Lead | Paint, water pipelines[b] | Yes | ND | ND | Yes |
| | Cadmium | Cigarette smoking, industrial emissions, fertilizer | Yes | ND | ND | Yes |
| | Mercury | Coal burning | Yes | ND | Yes | Yes |
| | Arsenic | Herbicides, fossil fuels | Yes | Yes | ND | Yes |

Table 1 is representative and is not a comprehensive table of endocrine-disrupting chemicals (EDCs) and their mechanisms of disruption[150,151]. ND, not determined. [a]'Other' encompasses nuclear receptors (for example, retinoid X receptors, peroxisome proliferator-activated receptors) and metabolic receptors. [b]Legacy chemicals: exposure to these chemicals is already highly regulated, but they are included in this table owing to their persistence and as historical examples.

exposure (Box 1). In this Review, we provide a set of science-based policy actions (Table 3) that can be taken to manage, minimize or eliminate the widespread use of these chemicals and better protect human health and society (Fig. 1).

## Meeting challenges with science-based policy solutions

### Challenge #1: defining, identifying and prioritizing EDCs

Although numerous regulatory bodies have drawn from scientific recommendations to define the properties of an EDC[32], they have been challenged by the task of operationalizing this definition to implement protective policies. The WHO definition of an EDC has two requirements: first, that a chemical must alter the function of the endocrine system; and, second, that a consequence of that alteration is an adverse effect observed in an intact animal, its progeny or a subpopulation of animals[33]. Historical applications of either component of the WHO definition have been inconsistent and problematic. For example, regulatory bodies will elude principles of endocrinology in their application of the first requirement ('a chemical must alter the function of the endocrine system') by limiting the function of the endocrine system to that of solely maintaining homeostasis in response to environmental stressors[32]. This interpretation allows agencies to construe that chemicals are natural physical stressors that the endocrine system can adapt to in the same manner as it does to temperature or water[32]. This narrow perspective, usually drawn from the exposure of adult individuals to chemicals, neglects the critical role of the endocrine system during human development, particularly in brain development or sexual differentiation, or in establishing stress responses or metabolism later in life (see the later discussion of latency).

The second set of inconsistent applications involves debate and uncertainty over what constitutes an 'adverse effect' and whether such designations are reproducible from study to study or from regulator to regulator (for example, between agencies in the same country or even within the same agency)[32,34]. Current approaches to identifying adverse effects induced by EDCs are complicated by the extensive resources required for such a task, including time, cost and the use of laboratory animals[35]. In the USA, the Environmental Protection Agency (EPA) was mandated to develop a strong and sustainable programme, the Endocrine Disruptor Screening Program (EDSP), to prioritize and evaluate chemicals for their potential adverse endocrine-disrupting properties[35]. Conceived in 2012, the EDSP has received limited support from the EPA, with only 52 chemicals screened through its first tier of evaluative assays ('to identify chemicals with the potential to interact with oestrogen, androgen or thyroid receptors, or chemicals that alter steroidogenesis') and zero chemicals tested for endocrine disruption in its second tier of assays ('to evaluate endocrine-mediated adverse outcomes') over 25 years of the programme[35]. In 2023, the EPA proposed the replacement of several EDSP screening assays with high-throughput screening methods to rapidly screen a large number of diverse chemical samples to identify candidates and predict adverse health outcomes[36,37]. These high-throughput screening methods (for example, ToxCast and Tox21 (ref. 38)) have been developed by government agencies, such as

the EPA, NIH and FDA, to look for endocrine-active substances but have never been used to define a chemical as an EDC. Regulatory bodies are still unclear about which new methodologies can be used to fill in data gaps and to complement current resource-intensive approaches that are poorly designed and miss critical exposure windows and their associated longitudinal endpoints[39].

**Table 2 | Disease burden and economic cost of the outcomes associated with exposure to EDCs over the life course**

| EDC | Life stage of exposure | Outcome | USA | | Canada | | EU | |
|---|---|---|---|---|---|---|---|---|
| | | | Disease burden | Economic cost (US$) | Disease burden | Economic cost (US$) | Disease burden | Economic cost (US$) |
| PBDEs | Prenatal | Loss of IQ points and intellectual disability | 11 million IQ points lost; 43,000 intellectual disability cases | 266 billion | 374,395 IQ points lost; 1,610 intellectual disability cases | 11.4 billion | 873,000 IQ points lost; 3,290 intellectual disability cases | 12.6 billion |
| | | Cryptorchism | 4,300 cases | 35.7 million | 567 cases | 7.3 million | 4,615 cases | 172.6 million |
| Organophosphates | Prenatal | Loss of IQ points and intellectual disability | 1.8 million IQ points lost; 7,500 intellectual disability cases | 44.7 billion | 152,922 IQ points lost; 377 intellectual disability cases | 4.2 billion | 13 million IQ points lost; 59,300 intellectual disability cases | 194.0 billion |
| DDE | Prenatal | Childhood obesity | 857 cases | 29.6 million | 114 cases | 2.5 million | 1,555 cases | 32.7 million |
| | | Type 2 diabetes mellitus | 24,900 cases | 1.8 billion | 3,270 cases | 385.2 million | 28,200 cases | 1.1 billion |
| | Adulthood (female) | Fibroids | 37,000 cases | 259.0 million | 2,254 cases | 4.2 million | 56,700 cases | 216.8 million |
| DEHP | Adulthood | Obesity | 5,900 cases | 1.7 billion | 2,093 cases | 684.8 million | 53,900 cases | 20.8 billion |
| | | Type 2 diabetes mellitus | 1,300 cases | 91.4 million | 225 cases | 25.8 million | 20,500 cases | 807.2 million |
| | Adulthood (female) | Endometriosis | 86,000 cases | 47.0 billion | 10,151 cases | 5.7 billion | 145,000 cases | 1.7 billion |
| BPA | Prenatal | Childhood obesity | 33,000 cases | 2.4 billion | 1,023 cases | 59 million | 42,400 cases | 2.0 billion |
| Phthalates | Adulthood (male) | Male infertility | 240,100 cases | 2.5 billion | 1,395 cases | 17.0 million | 618,000 cases | 6.3 billion |
| | Adulthood | Cardiovascular mortality | 90,800 cases | 39.9 billion | ND | ND | ND | ND |
| PFASs | Prenatal | Low birthweight | 10,053 cases | 1.4 billion | ND | ND | ND | ND |
| | | Childhood obesity | 127,362 cases | 2.7 billion | ND | ND | ND | ND |
| | Childhood | Pneumonia | 447–6,759 cases | 1.5–22.5 million | ND | ND | ND | ND |
| | Pregnancy | Gestational diabetes | 6,061 cases | 414–852 million | ND | ND | ND | ND |
| | Adulthood | Obesity | 4,294,379 cases | 17 billion | ND | ND | ND | ND |
| | | Kidney cancer | 142 cases | 184 million | ND | ND | ND | ND |
| | | Couple infertility | 593–26,160 cases | 37.6 million to 1.7 billion | ND | ND | ND | ND |
| | Adulthood (female) | Hypothyroidism | 14,572 cases | 1.3–5.2 billion | ND | ND | ND | ND |
| | | Type 2 diabetes mellitus | 1,728 cases | 140 million | ND | ND | ND | ND |
| | | Endometriosis | 696–18,062 cases | 397 million to 10.2 billion | ND | ND | ND | ND |
| | | Polycystic ovary syndrome | 7,209–7,505 cases | 10.5–10.9 million | ND | ND | ND | ND |
| | | Breast cancer | 421–3,095 cases | 555 million to 4.1 billion | ND | ND | ND | ND |

All estimates are from 2010, except for perfluoroalkyl substances (PFASs), for which USA estimates are from 2018 (refs. 3,10,17,18). BPA, bisphenol A; DDE, dichlorodiphenyldichloroethylene; DEHP, di-2-ethylhexyl phthalate; EDCs, endocrine-disrupting chemicals; ND, not determined; PBDEs, polybrominated diphenyl ethers.

**Solutions to Challenge #1**

**Enforcing existing mandates to test chemicals for endocrine-disrupting properties.** First, and perhaps most important, is that several legal requirements already exist in the USA and EU to test chemicals for their endocrine-disrupting properties; therefore, an efficient policy solution would be for the regulatory bodies to enforce the legal mandates already in place. In the USA, the EPA is required to screen and test pesticides used in food crops for potential endocrine-disrupting properties[35]. However, as outlined above, the EDSP has failed to identify a single chemical as an EDC and, subsequently, no regulatory actions have been taken.

**Restricting the use of EDCs.** In the EU, the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulation of 2006 (ref. 40) determined that EDCs were considered substances of very high concern and their use must first be authorized (which involves demonstrating that any risks associated with their use are sufficiently controlled or that the socio-economic benefits of their use offset the risks) or, if the chemical is already in use, restricted (which could constitute a total ban or excluding its supply to the general public). Examples of restricted-use chemicals include known EDCs such as perchlorate, BPA and several phthalates. Because the REACH regulation applies to chemicals used in industrial processes and day-to-day products (for example, clothes, furniture, toys, appliances and building materials), these restrictions limit the use of BPA, several phthalates and perchlorate in paints, electronics, toys and paper goods. However, the scope of REACH does not include food or food contact materials, thus missing a key pathway of human exposure. REACH is an example of a regulation that can restrict the use and limit human exposure to EDCs but it is reliant on our ability to identify these chemicals (see the discussion below on screening substances with no endocrine testing data). Unfortunately, as of 2022, only 105 substances had been identified and regulated as EDCs using the REACH regulation[41]; therefore, this policy solution example remains 'in progress'.

**Screening substances that have no endocrine testing data.** Human industrial activities have generated over 350,000 estimated substances[42] used in products ranging from cosmetics to food packaging, electronics, furniture and building materials (Table 1). The chemical landscape continues to expand, with more than 42,000 active chemicals on the EPA Toxic Substance Control Act inventory of chemicals; more than 10,000 chemicals are allowed in food and food packaging[43], and more than 1,000 pesticide active ingredients are currently covered by the EDSP[39]. Hundreds of additional chemicals are introduced to the US market every year[44]. Given that the vast majority of new chemicals have not been evaluated for potential EDC effects (either individually or in combination)[45], they have incomplete or absent hazard assessment portfolios from which to inform regulation and restrictions.

Over the past decade, tens of millions of US dollars have been invested into high-throughput screening programmes such as ToxCast and Tox21, resulting in the generation of data for thousands of chemicals that have been tested across hundreds of assays and endpoints. Although these programmes have limitations (discussed elsewhere)[46,47], they do have strengths in the breadth of their potential chemical characterization. However, despite this potential, regulatory bodies, such as the EPA, lack a directed strategy to incorporate the use of these programmes into regulatory assessments of chemicals that currently have no EDC data or to recommend that the regulated industries implement them to restrict the use of harmful EDCs. Agencies like the EPA are currently in possession of data confirming EDC effects for numerous common-use chemicals without concrete plans to regulate them. For example, the EPA identified a correlation between maternal perchlorate exposure and thyroid dysfunction in mothers and neurological dysfunction in their children but did not regulate perchlorate as a drinking water contaminant (Natural Resources Defense Council vs Regan, No. 20–1335, Slip Opinion, D.C. Circuit May 9, 2023)[48].

A universally recognized approach is therefore needed to determine which, if any, high-throughput in vitro screening methods can be used to provide sufficient evidence that a chemical confers adverse effects. Many of these methods, such as ToxCast, have been used to develop robust models (>70% success) to predict diverse health endpoints, including metabolic health disruption and/or adipogenic effects[49], rat reproductive toxicity[50], prenatal developmental toxicity[51], and hepatotoxicity[52]. These models, which depend on accurate information on causal pathways underlying specific adverse health conditions, could be used to screen the tens of thousands of chemicals in commerce for more comprehensive evaluation. Particularly as the EPA moves towards reducing and eventually eliminating the use of vertebrate mammalian models from risk assessment testing, these alternative models could prove critical for helping to support the selection and prioritization of chemicals for potential regulation moving forward. However, despite these successes and potential applications, these predictive models have been less successful in other contexts; the main issues have primarily been the quality of the data input (later versions of ToxCast have better predictive utility than earlier versions[47]) and, as noted, the reliance of these efforts on a comprehensive understanding of the majority of causal pathways contributing to specific adverse health outcomes[53]. Without this mechanistic detail on human diseases, these predictive models will be less successful than

## Box 1

### The Goldilocks Principle applied to chemical regulation

Applying the Goldilocks Principle, or 'just the right amount', to chemical regulation means prioritizing policy that is not representative of either extreme approach (excessive or zero regulation) but, rather, adopting a balanced approach with a minimum set of standards and periodic re-evaluation. Examples include the following:

- Identifying a minimum amount of information to meet the regulatory safety standard before allowing chemicals to enter the market and setting up a periodic timeline for re-evaluation.
- Synthesizing existing knowledge, both mechanistic and animal based, about how diseases develop and progress rather than requiring years-long animal studies to conclude whether chemicals have endocrine-disrupting properties.
- Prioritizing the assessment of exposure to endocrine-disrupting chemicals from food and water instead of allowing multiple exposure pathways to paralyze the regulatory decision-making process.

**Table 3 | Science-based policy actions for EDCs**

| Scientific consideration | Efforts | Current challenges | Policy or regulatory recommendations |
|---|---|---|---|
| Defining, identifying and prioritizing EDCs | Scientific organizations and regulatory agencies have defined the features of an EDC: (1) chemical must alter endocrine system function; (2) consequence is an adverse effect on an animal | (1) Inconsistent application of what it means to alter the endocrine system; (2) definition of adverse effect is unclear and untested; (3) incomplete and/or absent hazard assessments; (4) inconsistent regulation by agencies | (1) Enforce existing mandates to test for endocrine-disrupting properties; (2) restrict use of known EDCs; (3) screen substances added to food, food packaging or processing; (4) mandate screening new chemicals for endocrine disruption, focusing on chemicals in foods; (5) encourage coordination of governmental agencies within and between jurisdictions |
| Non-linear and/or non-monotonic properties of EDCs not considered | REACH and EU regulations use hazard-based approaches; EPA advises that there is no safe level of PFASs | Monotonicity (that is, the higher the dose, the worse the effect) is still the default dose–response assumption in toxicological science and regulatory toxicology; monotonicity does not reflect how EDCs operate | (1) Apply a no-threshold approach in regulations, meaning that a quantifiable safe dose does not exist; (2) agencies should use a hazard-based, and not risk-based, approach for EDCs |
| Effects of EDC exposure can be latent | Precautionary principles have been used (Bremen Declaration, 1984; London Declaration, 1987; Hague Declaration, 1990) | Current testing guidelines rely on short-latency effects, adult animal exposure and apical endpoints | (1) Require evidence of no harm to vulnerable populations prior to approval of new chemicals; (2) limit use of existing chemicals in the presence of partial but concerning information; (3) demand further studies |
| 'Real-world' mixtures and cumulative impacts not reflected by current testing paradigms | Mixtures | | Regulate and test chemicals as subclasses and classes |
| | CPSC, FDA, EFSA and ECHA have proposed guidelines that consider assessing mixtures; CPSC and FDA have begun regulating chemicals as classes and subclasses | (1) Agencies assess chemicals for risks one at a time; (2) heterogeneity of complex mixtures; (3) concerns about feasibility of regulating all possible mixture exposure scenarios; (4) vague, complicated definitions of chemical mixtures | |
| | Cumulative impacts | | |
| | Research indicates that (1) chemicals affecting the same health outcome act in an additive manner regardless of their molecular pathways; (2) structurally unrelated chemicals might cause cumulative health impacts | Agencies with authority to assess cumulative effects are either narrowly focused on shared molecular pathways to harm (for example, EPA organophosphate pesticides) or narrowly focused on related chemical structure (for example, EFSA phthalates) | |

CPSC, Consumer Product Safety Commission; ECHA, European Chemicals Agency; EDC, endocrine-disrupting chemical; EFSA, European Food Safety Authority; EPA, Environmental Protection Agency; PFASs, perfluoroalkyl substances; REACH, Registration, Evaluation, Authorisation and Restriction of Chemicals.

they could be as they are more likely to miss chemicals that influence these outcomes through less appreciated pathways. Nevertheless, these approaches can potentially be used to map novel pathways that might have contributory roles in specific health outcomes and could provide a new regulatory approach to chemical screening.

**Making screening for endocrine disruption mandatory for new chemicals.** Regulatory bodies need policies to protect the food supply by mandating screening for EDC properties in new chemicals that are due to be used as food ingredients or in food contact materials (Table 4). Unlike the EPA, the FDA has no mandate to identify and regulate EDCs. Generally, the FDA has yet to recommend standard screening tests for substances directly added to food or for chemicals used in food packaging or processing equipment that are transferred into foods. The FDA authorized the use of perchlorate in food packaging[54], has voiced concern about[55] the latest risk assessment by the European Food Safety Authority (EFSA)[56] recommending reductions in the safe levels of BPA by a factor of 20,000 (the tolerable daily intake was updated to 0.2 ng/kg per day from 4,000 ng/kg per day) owing to immunological and endocrine-related toxicity, and continues to allow phthalates in food packaging without migration limits (that is, limits on the amount of a particular substance that can 'migrate' from the packaging into the food). Additionally, the FDA has allowed ingredients such as soy isoflavone extracts[57] and resveratrol[58] to be added to foods without consideration of their EDC properties. Without its own standard screening procedures or coordination with international bodies that screen and test chemicals, the FDA is unable to ascertain EDC properties or their adverse effects on human health.

In the USA, at least, policies are needed to require the FDA to include in its guidance for industry a battery of in silico and in vitro screening tests looking at the potential effects of new chemicals on pathways involving oestrogen, androgen, thyroid, insulin, prolactin, glucocorticoids, leptin and others. Furthermore, endocrine disruption testing should be made mandatory for new food contact substances (such as those used in packaging or processing equipment) and new ingredients.

The FDA should follow its own safety regulation demanding that food chemicals affecting the same endocrine functions be assessed for their cumulative effects (see later discussion on cumulative effects). In 1959, the FDA established a framework on how to set acceptable daily intakes and/or safe doses of food chemicals and codified it as a rule in the Code of Federal Regulation at 21 CFR 170.18. In short, the rule states, first, that chemicals causing similar or related toxic effects will be treated as a class, having additive toxic effects, and will be considered related chemicals; and, second, that when two or more chemicals from the same class are present in food, the acceptable daily intake

and/or safe dose for the class will correspond to that of the chemical with the lowest safe dose. This rule applies to all chemicals, regardless of whether or not they are endocrine disruptors. Unfortunately, in a review of almost 900 chemical safety assessments carried out by the FDA, in only 1 assessment did a food manufacturer consider the cumulative effect legal requirement in a meaningful way[59].

**Coordination of government agencies.** Because chemicals are regulated by agencies on the basis of their use, a certain chemical can be restricted by one agency but allowed by another[60] and, thus, a chemical known to be hazardous in toys or personal care products might be used without restriction in food ingredients or food packaging. For example, in the USA, the Consumer Product Safety Improvement Act of 2013 excluded the use of five phthalates from toys due to concerns over health hazards associated with exposure to these chemicals, yet the use of several of these phthalates in contact with food has not yet been restricted by the FDA. As discussed earlier, this failure to harmonize decision-making across agencies is not unique to the USA: estimates show that there are almost 400 chemicals, including EDCs like BPA, that are considered substances of very high concern according to the EU REACH regulation but that are still authorized in the manufacture of food contact materials[61].

Although agencies tasked with regulating chemicals have specific mandates (for example, the EPA is tasked with environmental protection issues and does not regulate chemicals used in food), frameworks to facilitate harmonization between agencies within nations and internationally across nations should be essential. When one regulatory body evaluates the available scientific evidence and determines that a chemical is an EDC, this determination should be appropriately considered and accepted by all other regulatory agencies[62]. The exposure to a particular chemical, and therefore the associated health risk, might differ according to different agencies based on its use and, thus, on the corresponding pathways of exposure, yet the biological outcome — that is, endocrine disruption — does not change.

More than 10 years ago, experts advised that regulatory bodies should no longer require years-long animal studies to conclude that environmental chemicals are hazardous; rather, for many health outcomes, there is sufficient knowledge about how diseases develop and progress, and therefore effects occurring 'upstream' of the disease itself should be considered sufficient evidence for risk assessment and regulation[34]. Studies of EDCs, such as BPA, have highlighted how risk assessments conducted by human-run government agencies can review the same scientific data and yet draw very different conclusions about whether specific outcomes (for example, proliferation in the mammary gland, immune dysfunction and metabolic diseases) are indicative of harmful effects[63]. A harmonized approach would help to address the challenge of delineating and defining adverse outcomes.

## Challenge #2: considering the non-linear and non-monotonic properties of EDCs

The importance of the relationship between a quantitative measure of exposure to a toxicant and the resulting effect on a biological outcome, the so-called dose–response, has been recognized for several centuries. In fact, it is widely considered a principle of toxicology that 'the dose makes the poison': that is, the level of exposure is what predicts the extent of harm. This concept was first articulated by the sixteenth-century Swiss physician Paracelsus, but his actual words were, "Solely the dose determines that a thing is not a poison." Based on the words of Paracelsus, the adage that the dose is what determines the level of harm has been extrapolated to assume that harm will be seen at high doses but that there exist lower levels of exposure at which harm does not occur. This erroneous assumption has become the foundation of toxicological science and the default in regulatory toxicology.

Studies of EDCs have revealed the flaws in using this paradigm to frame regulation, with strong scientific evidence suggesting that non-linear and even non-monotonic responses (in which the responses at high doses are the opposite of what is expected from the responses observed at lower doses) occur in response to human exposure to

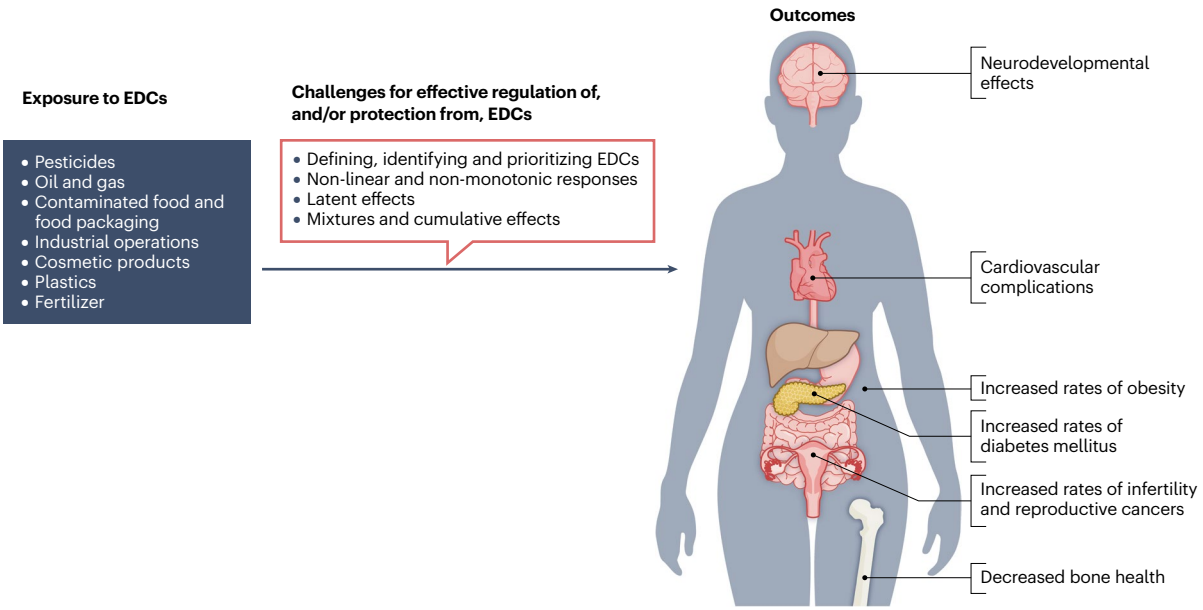


**Fig. 1 | Meeting policy challenges to protect the public from EDC exposure.** Endocrine-disrupting chemicals (EDCs) have harmful effects on human health through their effects on the endocrine system. EDC regulations face key challenges that require science-based policy solutions to protect the public from their harmful effects.

**Table 4 | Examples of EDCs commonly found in food**

| EDC[a] | Function and use | | | Exposure pathway |
|---|---|---|---|---|
| | Production | Packaging | Preservative | |
| Phthalates | Yes | Yes | Not commonly used | Migration into food during processing and storage (plastic tubing, conveyor belts, paper cardboard) |
| Bisphenols | Yes | Yes | Not commonly used | Migration into food from epoxy resin coating of canned foods, polycarbonate plastic |
| PFASs | Not commonly used | Yes | Not commonly used | Migration into food from grease-resistant paper, fluorinated plastics, contaminated fish or poultry |
| Nitrates | Not commonly used | Not commonly used | Yes | Added to meats as a preservative |

EDC, endocrine-disrupting chemical; PFASs, perfluoroalkyl substances. [a]Representative examples, see the Food Packaging Forum for a systematic database.

EDCs[64]. When non-monotonic dose responses are observed, the effects that occur at high doses cannot be extrapolated from the results of low-dose studies, and vice versa[65]. For example, pregnant mice showed increasing serum levels of testosterone when di-2-ethylhexyl phthalate was administered at increasing doses of 0.5, 1 or 5 µg/kg per day but not when administered at 500, 50,000 or 500,000 µg/kg per day, creating an inverted U-shaped relationship between dose and effect[66]. Similarly, epidemiology studies have evaluated the relationship between exposure to persistent organic pollutants and the risk of type 2 diabetes mellitus: individuals in sextiles 2 and 3 had higher odds of developing the disease compared with those in sextile 1, but the odds ratios in sextiles 4, 5 and 6 (corresponding to increasing exposure to persistent organic pollutants) were similar to the lowest exposed, again forming an inverted U-shaped relationship between exposure level and disease risk[67]. Similar non-monotonic dose–response relationships have been described for lead[68], methylmercury[69], organophosphate pesticides[70,71], PFASs[72] and polybrominated diphenyl ethers[73,74], among many others.

### Solutions to Challenge #2

**Applying a no-threshold approach in regulations and enforcement.** Regulatory bodies routinely evaluate the available scientific evidence to apply two approaches to determine 'safe' levels of human exposure to chemicals: the first approach involves identifying a dose at which no adverse effects are observed, whereas the second uses a no-threshold model.

In the first approach, which is most frequently used for toxic chemicals, a dose is identified at which no adverse effects are observed in animals exposed to the chemical. This so-called no-observed-adverse-effect level (NOAEL) is then typically adjusted to account for uncertainties and variability in response to environmental exposures (for example, extrapolations from rodents to humans, increased susceptibility during specific stages of life, exposure to non-chemical stressors, and so on)[75]. Once the NOAEL considers these factors, the 'safe' dose is thus determined (often referred to as the Tolerable Daily Intake, Acceptable Daily Intake or Reference Dose, depending on the regulatory agency). Using this approach, the NOAEL is assumed to represent a true 'threshold' – that is, an empirically identified dose at (or below) which no adverse effects truly exist. However, as noted by endocrinology experts, there is no evidence that EDCs have a threshold and, thus, the methods necessary to demonstrate a true threshold are not applicable[76]. Rather, because EDCs act on a 'biologically active background', where hormones are naturally already having an effect, a quantifiable threshold is not likely to exist for EDCs. For this reason, regulatory agencies should adopt the second approach, which assumes that no such threshold exists, and instead use calculations similar to the 'linear no-threshold' model used to evaluate the carcinogenic risk associated with increasing doses of ionizing radiation. This approach takes into account that there is no safe level of exposure because even minute quantities of EDCs might disrupt endocrine processes.

Through these approaches to determine safe levels of human exposures, regulatory bodies can generate health advisories or technical guidance on how a pollutant can be measured and provide information about technologies available to remediate contamination. Currently, unless a chemical is specifically regulated as a contaminant, health advisories are considered non-enforceable and non-regulatory. There are several examples where government agencies have determined that environmental chemicals pose a significant health risk to the public at any exposure level given their non-linear or non-monotonic properties but these advisories remain non-enforceable and non-regulatory. For example, in 2022, the EPA updated its health advisory levels for several PFASs in drinking water, including PFOA (lowered from 70 parts per thousand (ppt) to 0.004 ppt) and PFOS (lowered from 70 ppt to 0.020 ppt), and acknowledged at the time that these advisories set the 'safe' levels in drinking water below its ability to measure them. Yet, without additional regulations, these health advisories lack substance, so even communities with serious PFAS contamination in their drinking water have limited recourse to pursue clean-up efforts.

**Using hazard-based instead of risk-based approaches for EDCs.** When using risk-based approaches, chemicals are first evaluated to determine what kind of hazard they pose (for example, is the chemical a carcinogen, does it have toxic effects on the reproductive or metabolic system, or does it have adverse neurodevelopmental effects?) and at which doses those hazards are observed. The doses at which harm occurs are then compared to the (known or estimated) human exposures and, if a sufficient margin exists between these doses, no risk management steps need to be taken. If, instead, the doses at which harm occurs overlap with, or are higher than, the anticipated exposure levels, steps are required to take control of human exposure and reduce risks.

However, in some circumstances, identifying a chemical as posing a legally unacceptable hazard is sufficient to invoke restrictions on its use. For example, under the EU REACH regulation, chemicals in the EU that are identified as carcinogenic, mutagenic or toxic to reproduction (also called CMR chemicals) are restricted in use; similarly, EU Regulation 1223/2009 restricts the use of CMR chemicals in cosmetics and EU regulation 1107/2009 restricts the use of CMR chemicals in plant protection products; EU regulation 528/2012 calls for the substitution of chemicals in biocides if they have 'certain intrinsic hazardous properties'. As discussed above, REACH requires that EDCs be targeted for replacement with safer alternatives. Similarly, associations between

EDCs such as PFASs and metabolic derangement, such as insulin resistance, have triggered regulations by the EPA stating that there is no safe level of PFAS exposure[77]. This regulation is a hazard-based rather than a risk-based approach, occurring regardless of exposure estimates or use of the chemicals.

### Challenge #3: EDC exposure and latent effects

A key function of the endocrine system is to regulate human development, and exposure to EDCs during susceptible periods of human development can therefore result in serious consequences later on in life. These 'critical windows of exposure' are periods of time that are exquisitely sensitive to developmental disruption by environmental toxicants[6,7]. The periods of embryonic, fetal and perinatal development are well described; developmental disruption by environmental contaminants is most likely during these windows and particularly well characterized for diverse health outcomes. In one well-documented example, studies of children who were born during the Dutch Hunger Winter of 1944–1945 demonstrated adverse long-term metabolic health outcomes following gestational exposure to famine; individuals who were exposed early in gestation were disproportionately more likely than those exposed in late gestation to be affected by increased adiposity, diabetes mellitus and other metabolic diseases[78–80]. Studies applying a life-course approach have shown that exposure to EDCs during pregnancy is associated with future metabolic, reproductive or neurodevelopmental impairment[81] (Table 2). Adverse metabolic health outcomes following developmental exposure during embryonic, fetal and perinatal windows have since been robustly demonstrated for diverse environmental contaminants and mixtures[82–89], providing support for the idea that humans are highly susceptible to exposure to environmental contaminants during these windows. Studies of other outcomes, such as breast development, indicate that additional periods of development, including puberty and pregnancy and/or lactation, are also sensitive to environmental disruption; exposure to EDCs during these periods can have effects that manifest years or decades later such as an increased risk of breast disease[90].

### Solutions to Challenge #3

**Requirement for evidence of safety in vulnerable stages of development prior to the use of new chemicals.** The disastrous consequences of the use of diethylstilbestrol and brominated flame retardants serve as a crucial reminder of the need for premarket testing to protect vulnerable subpopulations. To assess these periods of extreme sensitivity, testing guidelines must incorporate exposure occurring during critical windows[91] (for example, gestation, early neonatal life, pubertal development, and so on) to provide confidence that adverse effects on human health will not be observed for the most vulnerable populations. On assessing chemicals that are directly added to food, researchers have found that only ~1 in 5 has evidence estimating safe levels of exposure and fewer than 1 in 10 has reproductive or developmental toxicity data reported in the FDA database[45]. Premarket testing should evaluate not only the effects of prenatal and infant exposure on child health but also on the potential consequences of diseases that manifest in adulthood, including ageing. Testing guidelines that rely on short-latency effects for decision-making do not reflect the well-established developmental origins of the health and disease paradigm.

**Limiting the use of existing chemicals in the presence of partial but concerning information.** The precautionary principle is an approach that emphasizes caution and prudence when extensive scientific knowledge is still in development. This approach is consistently accepted in environmental policy, adopted at the Bremen Declaration in 1984, the London Declaration in 1987 and the Hague Declaration in 1990 (ref. 92). It is further articulated in the Wingspread statement[4] but often misconstrued with the converse logic to argue that action should be taken in the absence of any identified hazard. Frequently, the argument is made that products cannot be constructed without a particular chemical of concern owing to the lack of safer alternatives. The social costs of safer alternatives are also inflated in these scenarios because the need for safer alternatives creates a market for innovation in the development of lower-cost and safer materials. The benefits of proactive protection are often minimized or discounted because the consequences might be delayed, sometimes far into the future. The reality is that proactive prevention of lead (in the form of its phasing out) from gasoline and paint continues to produce an estimated 4% increase (US$ 2.4 trillion) in GDP annually[93], exemplifying the large societal benefits of this approach. Regulatory 'issues' (for example, when regulation transpires not to be needed in the light of subsequent information that suggests the safety of a chemical) can also be reversed, whereas the consequences of inaction upon health cannot.

### Challenge #4: current testing paradigms do not reflect 'real-world' exposure

**Mixtures.** The disease burden and high costs (Tables 1 and 2) associated with individual EDCs represent only a narrow subset of the broader implications of EDCs for human health. Chemical mixtures, or compounds made up of two or more chemical components that are not necessarily chemically linked, can produce cumulative effects greater than those predicted by their individual constituent chemicals alone in both in vitro and in vivo models[94–98]. Combinations of chemicals at doses or concentrations that alone have low or no activity, for example, can produce additive or synergistic effects and/or can modulate the effects of background hormone activity[94,95]. Increasing research has also begun to evaluate the effects of chemical mixtures, and the adverse effects of more complex mixtures are being detected[99,100], but >80% of mixture studies still currently focus on small, technically simple mixtures of two or three similar components[101]. Although these early studies involving chemical mixtures are informative, the mixtures studied lack environmental relevance, especially as biomonitoring studies continue to report routine human exposure to hundreds or thousands of chemicals[102,103], thus highlighting the need to design studies that examine the effects of realistic chemical mixture exposures. The EFSA has described a risk assessment framework to approach chemical mixtures as well as their individual components, demonstrating how approaches to assess the risk of chemical mixtures could be harmonized[104].

For the most part, agencies continue to develop regulatory and policy activities on a chemical-by-chemical basis[60]. This approach is not only inefficient but likely to underestimate the risk to human health. In addition to the critical data gaps concerning mixtures relative to individual chemicals, several other issues exist. Individual chemicals or mixtures at varying concentrations can directly disrupt multiple hormone receptors to induce observable clinical outcomes. However, interactions that occur between chemicals and other receptors might subsequently influence the levels of the chemical: for example, the interaction of an EDC with the aryl hydrocarbon receptor can activate cytochrome P450 enzymes, triggering changes in the metabolism of the EDC and subsequent exposure levels[105–107]. Furthermore, similar

indirect interactions might be responsible for generating certain metabolites from EDCs, causing mixtures of inactive chemicals to become active in response to co-exposure to other chemicals: for example, the induction of cytochrome P450 by the polychlorinated biphenyl 126 activates polychlorinated biphenyls 105 and/or 118 to form a compound that functions as an agonist of thyroid hormone receptor[108]. In addition, a systematic review of mixture studies reported that potential additivity of mixture components was more common with more complex mixtures than with less complex mixtures[101], which is mirrored by numerous studies that have reported additivity or synergism across diverse in vitro and in vivo study designs[109–112] and also across epidemiology studies[113–120]. Heterogeneity is also a major challenge as each mixture is likely to be unique, with every individual being exposed to a distinct assortment of macroenvironments and microenvironments (distinct sets of consumer products in their home environment) throughout their lifetime.

There have been few attempts to regulate chemical mixtures to limit human exposure. In 2018, the EFSA and European Chemicals Agency (ECHA) published guidelines proposing steps for identifying EDCs in pesticides[121,122], either individually or in a mixture[123], although little has been accomplished with regard to mixtures. Since then, the European Commission has dampened its resolve to regulate mixtures by asserting that it is 'not realistic nor economically feasible to specifically assess and regulate an almost infinite number of possible combinations of chemicals'[124]. In the USA, vague or complicated definitions and exemptions have hindered the evaluation of mixtures through the Toxic Substance Control Act[125]. Despite these difficulties, however, there are a few prime examples of regulatory decisions on groups of chemicals both in the USA by the EPA[126], Consumer Product Safety Commission and FDA, and in the EU by the EFSA and ECHA, as discussed later.

**Cumulative effects.** Ongoing exposure to the same chemical or several different chemicals might result in the accumulation of toxic effects in the same organ, thereby increasing functional damage to the organ and resulting in its eventual failure. For example, perchlorate and nitrate are EDCs that disrupt the function of the thyroid gland and share the same mechanism of toxicity: inhibition of the iodine–sodium symporter[54]. Both chemicals are commonly found in foods and drinking water, thus providing ample opportunity for human exposure. Other EDCs known to interfere with thyroid function include thiocyanate, a food additive also present in cigarette smoke, BPA and some phthalates, with multiple exposure pathways (Table 1). Current regulations in both the USA and EU have taken into account safe levels of exposure for specific endpoints of concern such as neurotoxicity. However, the cumulative effect of EDCs through various exposure pathways on the thyroid is unknown[127].

Regulatory bodies face similar challenges in trying to adequately protect the public from exposure to the cumulative effects of EDCs as they do for mixtures of chemicals. However, regulatory bodies have information available to them that would enable chemicals to be grouped according to their similar effects on health to enable efficient regulation. Regulatory bodies with current mandates to assess the cumulative effects of EDCs have taken different approaches to group chemicals. For instance, the EPA mandate to address cumulative effects has been narrowly defined in the law; the agency is able to group pesticides that share the same molecular toxicity pathway (for example, organophosphate pesticides), and therefore regulation can be efficiently applied to EDCs with similar toxicity. Other agencies, including the EFSA and the Consumer Product Safety Commission (CPSC), have instead focused on a common health outcome (such as phthalates and male developmental toxicity) or a common target organ or system (such as pesticides and the nervous system or thyroid gland). Although there are numerous reasonable methods to group chemicals to assess their cumulative effects, regulatory bodies have a responsibility to utilize all the available information to avoid putting public health at unnecessary risk.

### Solutions to Challenge #4

**Regulating chemicals as a class.** Class regulation, or regulating chemicals by group, has multiple benefits, which are likely to lead to improvements in environmental and human health. First, by reducing the high use of financial and human resources needed to regulate chemicals on a one-by-one basis, efficiency is increased. Second, health protection is enhanced by reducing opportunities to assume that chemicals with no data pose no risk. Third, the real-life risk can be estimated by considering the cumulative health impacts of multiple chemicals and mixtures. Fourth, the risk of introducing regrettable substitutions (Box 2) by extrapolating information from data-rich to data-poor chemicals is reduced if the chemicals are in the same class. Finally, the monitoring of environmental and human exposures is facilitated.

In the USA, the FDA has a legal obligation[128] to consider chemicals as a class when they trigger similar or related toxic effects, and to assume that chemicals have additive effects unless there is evidence to the contrary. The regulation of PFASs as a class represents one of the few but promising examples of effective class regulation and can

## Box 2

## Regrettable substitutes

Regrettable substitutes are chemicals that can perform a similar function but that have not been adequately assessed for their endocrine-disrupting properties. They tend to emerge when chemicals are not regulated as classes. Important examples include:

- Bisphenol S replacing bisphenol A in plastic products[152–157]
- Diisononylphthalate, diisodecyl phthalate and 1,2-cyclohexane dicarboxylic acid diisononyl ester replacing di-2-ethylhexyl phthalate in food packaging[158]
- Short-chain perfluoroalkyl substances replacing their long-chain counterparts in food packaging[159]

Regrettable substitutes have hindered several attempts to improve public health by allowing chemicals that are equally problematic, and for which we have less understanding of their toxicity than their original counterparts, to enter the market. Furthermore, regrettable substitutes trigger additional mixture concerns as problematic chemicals are slowly being phased out while problematic alternatives are introduced, resulting in co-exposure. Implementing replacements should require testing to assess whether the replacement chemical has a favourable toxicological profile relative to the one it is replacing, particularly when the substituted chemicals are minor variations of the chemical being replaced.

serve as a model for other mixtures and cumulative exposure. In 2016, the FDA banned three types of complex long-chain PFAS because they were unsafe for human exposure. In its assessment, the FDA defined the long-chain class[129] as chemical perfluorinated alkyl chains with at least eight carbons and assumed that members of the class without data would show the same toxicity as those with data, namely PFOA. In another example of class regulation, in 2019, the FDA defined short-chain PFASs[130] as chemicals with seven or fewer carbons in an alkyl chain (n-1 carbons are perfluorinated); in an agreement with three chemical manufacturers, the FDA secured the phase-out of a subset of short-chain PFASs, namely 6:2 fluorotelomer alcohols[131]. In 2023, the ECHA published its PFASs restriction proposal, which evaluates PFASs as a group of chemicals to incorporate the evaluation of exposure to mixtures, rather than individual compounds, into the risk analysis[132].

The EPA is also mandated to carry out a cumulative risk assessment for pesticides grouped by shared molecular mechanisms of toxicity but has set this definition so narrowly that only a few groups of chemicals or pesticides have been assessed[126]. In the Consumer Product Safety Improvement Act of 2008, Congress asked the CPSC to review the safety of phthalates[133]. The CPSC performed a cumulative risk assessment for phthalates based on toxicity to male development, a common health outcome; consequently, to date, eight anti-androgenic phthalates that are likely to be toxic to male development have been excluded from the manufacture of toys and other articles[133].

In 2017, a petition from consumer groups requested the CPSC to apply class regulation to group and ban organohalogen flame retardants as a class of toxic chemicals. The Commission sought expert advice from the National Academies of Sciences, Engineering, and Medicine, which determined that the CPSC could not regulate these chemicals as a single class but, rather, that it should regulate them as several subclasses based on scientific evidence, outlining 14 subclasses according to chemical structure, physicochemical properties and anticipated biological activity[134]. A subsequent 2020 CPSC report detailed the next steps in addressing the diversity of organohalogen flame retardants: the establishment of procedures for class-based risk assessment; refinement of the chemicals and analogues for subclasses; identification of data sources; and determination of the available toxicity, chemical use and exposure information[135]. This process is ongoing and will inform future efforts for class and subclass regulation[136].

**Testing and biomonitoring.** Given the increased reliance on, and deep investment in, high-throughput in vitro screening programmes, these mechanistic assays are likely to be the best starting point for the evaluation of mixture effects for regulatory purposes. Testing programmes overall should include mixtures of chemicals with similar mechanisms of action to identify potential additive and/or synergistic effects, as well as complex mixtures extracted from materials (food packaging, electronics), household products (carpets, furniture) and other commercial products such as pesticides (currently, 'active' ingredients are examined in isolation, whereas the chemical mixtures that users are actually exposed to are never directly examined). If chemicals have been demonstrated to display additive and/or synergistic effects, this finding should trigger requirements for the consideration of co-exposure in the risk assessments for any chemical use. Finally, to adequately protect humans from harmful EDC exposure, health assessments should account for real-world mixture and cumulative exposures, particularly for exposure to chemicals acting through similar mechanisms of action[94,95,137].

Biomonitoring in wildlife and in humans not only reveals real-life exposures to mixtures but can also help us to predict potential complications and consequences[44]. For example, although polybrominated diphenyl ethers, previously used as flame retardants in furniture, electronics and textiles, have been phased out worldwide and banned in the EU, biomonitoring studies have been able to show that these EDCs are still present not only in wildlife but also in human blood and breastmilk[44,138].

## The need for partners in policy interventions

### Integrating EDC exposure prevention into clinical care

A comprehensive approach to minimizing or preventing EDC exposure would be incomplete in the absence of engagement with health practitioners and clinicians. The health-care system is a platform with ripe opportunities to implement clinical screening for EDCs as well as to mitigate exposure to EDCs unintentionally delivered during the course of medical care.

Screening programmes for lead have demonstrated how it is possible to abate environmental hazard exposure in millions of homes, decrease lead levels and subsequently reduce adverse health effects on a population level[139]. The National Academies of Sciences, Engineering, and Medicine released a report in 2022 recommending that clinicians offer screening for PFAS exposure to individuals who are likely to have been exposed to elevated levels through their occupation or from living in communities with documented or likely contamination[140]. Citing evidence of adverse immunological, metabolic, developmental and renal effects in response to PFAS exposure, this report aims to shape Centers for Disease Control and Prevention clinical guidelines and support clinicians with strategies for the interpretation of screening results in special populations (for example, pregnant people), decreasing current exposures and screening for relevant health sequelae[140].

Common medical supplies, equipment and devices, such as syringes, blood tubes, venous catheters and intravenous fluid, represent potential exposure sources to multiple classes of EDCs[141]. Given that substances in the USA and, until a few years ago, in the EU were not regulated based on their EDC potential, the medical system and community do not have access to transparent information about substances present in medications and medical equipment[142]. Decreasing the medical sources of EDCs is contingent upon policy regulation and education efforts with health practitioners who advocate for accessible information about the full chemical content of medications and medical equipment.

### Addressing EDCs in global policy and climate policy frameworks

Many EDCs are manufactured from fossil fuels, linking their fates with global climate considerations. Natural gas is a major source of ethane and propane, which can be cracked to make monomers and then polymerized into plastics and other substances with EDC properties[143]. If we avoid addressing climate change by persisting in our use of fossil fuel-derived chemicals, scientific reports hint that cases of disease and disability owing to EDCs will increase. Scientists have already documented examples of how climate change has induced biological changes through endocrine disruption, affecting sex determination and population decline in wildlife[144,145].

EDCs also contribute to two substantial societal challenges, both of which intersect with climate change: plastic pollution and biodiversity loss[143]. The United Nations is actively leading negotiations to address both challenges. However, we have witnessed efforts to limit

the scope of these discussions only to the environmental effects that are immediately visible, such as ocean plastic, despite the substantial health effects associated with both challenges. As the planet warms, environmental disasters are becoming more common than they previously were, water insecurity is increasing and infectious conditions such as Dengue are spreading to new territories[146]. Phthalates, bisphenols and PFASs are widely detectible in low-income and high-income countries at levels known to contribute to disease. Pesticides reduce biodiversity, which is crucial to the food supply[143].

Of the current UN processes proposed to address these challenges, climate change negotiations are the most evolved and advanced but are a case study of the failure of voluntary commitments. The global addiction to petrochemical production and consumption has prevented governments from meeting targets set with much fanfare and produced a scenario in which global warming exceeding a threshold of 1.5 °C is inevitable[147]. Global plastics treaty negotiations at their early stages are following a similar pattern, in which the High Ambition Coalition is focused on circular economy approaches that emphasize recycling. The fatal flaw in this approach is that technologies and systems are maladapted to recycle plastic even in high-income countries, with cumulative plastic recycling rates remaining below 10%[148]. However, and perhaps even more important for human health, recycled plastics have been shown to have greater metal and organic chemical contamination than virgin materials[149]. Nevertheless, some governments publicly denied the health effects of chemicals used in plastics at the first meeting of the Intergovernmental Negotiation Committee on Plastic Pollution in Uruguay.

The financial disincentives to follow the science and prevent disease resulting from toxic chemicals have long been powerful. Manufactured doubt is real and has delayed progress to prevent lead exposure, reduce cigarette smoking and combat climate change. We have witnessed industry-affiliated scientists on a WHO panel shape a report on the health effects of PFASs that is antiquated at best in comparison to USA and European regulatory reviews. Peer review of science has been compromised with the emergence of industry-funded journals and a lack of intention to report conflicts of interest. An intergovernmental agency that addresses the effects of EDCs on human health modelled on the WHO International Agency for Research in Cancer has been called for[150]. To complement this approach as a longer-term solution, the Basel, Rotterdam and Stockholm conventions could include a broader array of EDCs. Of note, the treaties are only as strong as the countries that ratify them (for example, the USA has not ratified these agreements). The inclusion of PFOA (in the Stockholm convention) is a small step forward, but sufficient toxicology evidence has accumulated to include PFASs as a class. Similarly, the inclusion of non-persistent compounds, such as phthalates and bisphenols, can support implementation of the global plastics treaty.

## Conclusions

In this Review, we have outlined the public health and economic costs of anthropogenic EDCs to provide context for a set of science-based policy actions to manage, minimize or eliminate the widespread use of EDCs. The examples given focus almost exclusively on the USA and EU, whose governments have had the most experience in developing regulations to address EDCs. Poorly defined or unenforced policies increase global human exposure to EDCs; consequently, regulatory bodies are encouraged to operationalize a consistent definition. The non-linear and/or non-monotonic properties of EDCs challenge current risk-based paradigms, which do not currently consider these properties. To account for real-world exposures and effects, policies should also consider mixtures and cumulative exposures as well as latent exposure effects on the human life course. Given that many EDCs are manufactured from fossil fuels, future research and policy directions are likely to link the use of EDCs to our understanding of climate change, the grand societal challenge of this generation.

Published online: 8 August 2023

## References


1. Carson R., Lear L., Wilson E. O. *Silent Spring* Anniversary edition (Houghton Mifflin, 2002).
2. Herbst, A. L., Ulfelder, H. & Poskanzer, D. C. Adenocarcinoma of the vagina. Association of maternal stilbestrol therapy with tumor appearance in young women. *N. Engl. J. Med.* **284**, 878–881 (1971).
3. Attina, T. M. et al. Exposure to endocrine-disrupting chemicals in the USA: a population-based disease burden and cost analysis. *Lancet Diabetes Endocrinol.* **4**, 996–1003 (2016).
4. Hotchkiss, A. K. et al. Fifteen years after "Wingspread" — environmental endocrine disrupters and human and wildlife health: where we are today and where we need to go. *Toxicol. Sci.* **105**, 235–259 (2008).
5. World Health Organization. *State of the Science of Endocrine Disrupting Chemicals. Inter-Organization Programme for the Sound Management of Chemicals* https://apps.who.int/iris/handle/10665/78101 (2013).
6. Diamanti-Kandarakis, E. et al. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. *Endocr. Rev.* **30**, 293–342 (2009).
7. Gore, A. C. et al. EDC-2: The Endocrine Society's second scientific statement on endocrine-disrupting chemicals. *Endocr. Rev.* **36**, E1–E150 (2015).
**This manuscript remains the most authoritative review and analysis of the effects of EDCs on health outcomes.**
8. Trasande, L., Shaffer, R. M. & Sathyanarayana, S. Food additives and child health. *Pediatrics* **142**, e20181410 (2018).
9. Di Renzo, G. C. et al. International Federation of Gynecology and Obstetrics opinion on reproductive health impacts of exposure to toxic environmental chemicals. *Int. J. Gynaecol. Obstet.* **131**, 219–225 (2015).
10. Malits, J., Naidu, M. & Trasande, L. Exposure to endocrine disrupting chemicals in Canada: population-based estimates of disease burden and economic costs. *Toxics* **10**, 146 (2022).
11. Bellanger, M., Demeneix, B., Grandjean, P., Zoeller, R. T. & Trasande, L. Neurobehavioral deficits, diseases, and associated costs of exposure to endocrine-disrupting chemicals in the European Union. *J. Clin. Endocrinol. Metab.* **100**, 1256–1266 (2015).
12. Hauser, R. et al. Male reproductive disorders, diseases, and costs of exposure to endocrine-disrupting chemicals in the European Union. *J. Clin. Endocrinol. Metab.* **100**, 1267–1277 (2015).
13. Hunt, P. A., Sathyanarayana, S., Fowler, P. A. & Trasande, L. Female reproductive disorders, diseases, and costs of exposure to endocrine disrupting chemicals in the European Union. *J. Clin. Endocrinol. Metab.* **101**, 1562–1570 (2016).
14. Legler, J. et al. Trasande L. Obesity, diabetes, and associated costs of exposure to endocrine-disrupting chemicals in the European Union. *J. Clin. Endocrinol. Metab.* **100**, 1278–1288 (2015).
15. Trasande, L. et al. Estimating burden and disease costs of exposure to endocrine-disrupting chemicals in the European union. *J. Clin. Endocrinol. Metab.* **100**, 1245–1255 (2015).
**The first assessment demonstrating that EDC exposures were contributing to significant cost burdens.**
16. Trasande, L. et al. Burden of disease and costs of exposure to endocrine disrupting chemicals in the European Union: an updated analysis. *Andrology* **4**, 565–572 (2016).
17. Obsekov, V., Kahn, L. G. & Trasande, L. Leveraging systematic reviews to explore disease burden and costs of per- and polyfluoroalkyl substance exposures in the United States. *Expo. Health* **15**, 373–394 (2023).
18. Trasande, L., Liu, B. & Bao, W. Phthalates and attributable mortality: a population-based longitudinal cohort study and cost analysis. *Environ. Pollut.* **292**, 118021 (2022).
19. Ruiz, D., Becerra, M., Jagai, J. S., Ard, K. & Sargis, R. M. Disparities in environmental exposures to endocrine-disrupting chemicals and diabetes risk in vulnerable populations. *Diabetes Care* **41**, 193–205 (2018).
20. Abellan, A. et al. In utero exposure to bisphenols and asthma, wheeze, and lung function in school-age children: a prospective meta-analysis of 8 European birth cohorts. *Environ. Int.* **162**, 107178 (2022).
21. Lam, J. et al. The navigation guide — evidence-based medicine meets environmental health: integration of animal and human evidence for PFOA effects on fetal growth. *Environ. Health Perspect.* **122**, 1040–1051 (2014).
22. Fan, X. et al. Global exposure to per- and polyfluoroalkyl substances and associated burden of low birthweight. *Environ. Sci. Technol.* **56**, 4282–4294 (2022).
23. Barbosa, K. L. et al. Tributyltin and the female hypothalamic-pituitary-gonadal disruption. *Toxicol. Sci.* **186**, 179–189 (2022).
24. Uc-Peraza, R. G., Castro, Í. B. & Fillmann, G. An absurd scenario in 2021: banned TBT-based antifouling products still available on the market. *Sci. Total Environ.* **805**, 150377 (2022).
25. Trasande, L. When enough data are not enough to enact policy: the failure to ban chlorpyrifos. *PLoS Biol.* **15**, e2003671 (2017).

26. Malo, S. 3M, others reach $65 mln deal with NY town over PFOA in drinking water. *Reuters* https://www.reuters.com/legal/litigation/3m-others-reach-65-mln-deal-with-ny-town-over-pfoa-drinking-water-2021-07-22/ (2021).
27. Bradman, A. et al. Effect of organic diet intervention on pesticide exposures in young children living in low-income urban and agricultural communities. *Environ. Health Perspect.* **123**, 1086–1093 (2015).
**An outstanding intervention study showing that lifestyle changes can impact exposures to EDCs.**
28. Harley, K. G. et al. Reducing phthalate, paraben, and phenol exposure from personal care products in adolescent girls: findings from the HERMOSA intervention study. *Environ. Health Perspect.* **124**, 1600–1607 (2016).
29. Rudel, R. A. et al. Food packaging and bisphenol A and bis(2-ethyhexyl) phthalate exposure: findings from a dietary intervention. *Environ. Health Perspect.* **119**, 914–920 (2011).
30. Young, A. S. et al. Impact of "healthier" materials interventions on dust concentrations of per- and polyfluoroalkyl substances, polybrominated diphenyl ethers, and organophosphate esters. *Environ. Int.* **150**, 106151 (2021).
31. Li, R. et al. Temporal trends in risk of bisphenol A, benzophenone-3 and triclosan exposure among U.S. children and adolescents aged 6-19 years: findings from the National Health and Nutrition Examination Survey 2005-2016. *Environ. Res.* **216**, 114474 (2023).
32. Zoeller, R. T. et al. A path forward in the debate over health impacts of endocrine disrupting chemicals. *Environ. Health* **13**, 118 (2014).
33. International Programme on Chemical Safety. Global Assessment of the State of the Science of Endocrine Disruptors. *World Health Organization* https://apps.who.int/iris/handle/10665/67357 (2002).
34. Woodruff, T. J. et al. Meeting report: moving upstream-evaluating adverse upstream end points for improved risk assessment and decision-making. *Environ. Health Perspect.* **116**, 1568–1575 (2008).
35. Maffini, M. V. & Vandenberg, L. N. Failure to launch: the endocrine disruptor screening program at the U.S. Environmental Protection Agency. *Front. Toxicol.* **4**, 908439 (2022).
**A new analysis demonstrating how and why the EPA screening programme for EDCs has failed to protect the public from chemicals with endocrine-disrupting properties.**
36. Knudsen, T. B. et al. FutureTox II: in vitro data and in silico models for predictive toxicology. *Toxicol. Sci.* **143**, 256–267 (2015).
37. Malo, N., Hanley, J. A., Cerquozzi, S., Pelletier, J. & Nadon, R. Statistical practice in high-throughput screening data analysis. *Nat. Biotechnol.* **24**, 167–175 (2006).
38. Richard, A. M. et al. ToxCast chemical landscape: paving the road to 21st century toxicology. *Chem. Res. Toxicol.* **29**, 1225–1251 (2016).
39. Environmental Protection Agency. *Availability of New Approach Methodologies (NAMs) in the Endocrine Disruptor Screening Program (EDSP)* https://www.regulations.gov/document/EPA-HQ-OPP-2021-0756-0002 (2023).
40. European Agency for Safety and Health at Work. Regulation (EC) No 1907/2006 — Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). *Safety and Health at Work EU-OSHA* https://osha.europa.eu/en/legislation/directives/regulation-ec-no-1907-2006-of-the-european-parliament-and-of-the-council (2021).
41. Endocrine Disruptor Lists. *Substances Identified as Endocrine Disruptors at EU Level* https://edlists.org/the-ed-lists/list-i-substances-identified-as-endocrine-disruptors-by-the-eu (2022).
42. Wang, Z., Walker, G. W., Muir, D. C. G. & Nagatani-Yoshida, K. Toward a global understanding of chemical pollution: a first comprehensive analysis of national and regional chemical inventories. *Environ. Sci. Technol.* **54**, 2575–2584 (2020).
43. Neltner, T. G. et al. Navigating the U.S. Food Additive Regulatory Program. *Compr. Rev. Food Sci. Food Saf.* **10**, 342–368 (2011).
44. Encarnação, T., Pais, A. A., Campos, M. G. & Burrows, H. D. Endocrine disrupting chemicals: Impact on human health, wildlife and the environment. *Sci. Prog.* **102**, 3–42 (2019).
45. Neltner, T. G., Alger, H. M., Leonard, J. E. & Maffini, M. V. Data gaps in toxicity testing of chemicals allowed in food in the United States. *Reprod. Toxicol.* **42**, 85–94 (2013).
46. Janesick, A. S. et al. On the utility of ToxCast™ and ToxPi as methods for identifying new obesogens. *Environ. Health Perspect.* **124**, 1214–1226 (2016).
47. Filer, D., Patisaul, H. B., Schug, T., Reif, D. & Thayer, K. Test driving ToxCast: endocrine profiling for 1858 chemicals included in phase II. *Curr. Opin. Pharmacol.* **19**, 145–152 (2014).
48. NRDC. *Court Rules EPA Must Regulate Perchlorate* https://www.nrdc.org/press-releases/court-rules-epa-must-regulate-perchlorate (2023).
49. Filer, D. L., Hoffman, K., Sargis, R. M., Trasande, L. & Kassotis, C. D. On the utility of ToxCast-based predictive models to evaluate potential metabolic disruption by environmental chemicals. *Env. Health Perspect.* **130**, 57005 (2022).
50. Martin, M. T. et al. Predictive model of rat reproductive toxicity from ToxCast high throughput screening. *Biol. Reprod.* **85**, 327–339 (2011).
51. Sipes, N. S. et al. Predictive models of prenatal developmental toxicity from ToxCast high-throughput screening data. *Toxicol. Sci.* **124**, 109–127 (2011).
52. Liu, J. et al. Predicting hepatotoxicity using ToxCast in vitro bioactivity and chemical structure. *Chem. Res. Toxicol.* **28**, 738–751 (2015).
53. Schwarzman, M. R. et al. Screening for chemical contributions to breast cancer risk: a case study for chemical safety evaluation. *Environ. Health Perspect.* **123**, 1255–1264 (2015).
54. Maffini, M. V., Trasande, L. & Neltner, T. G. Perchlorate and diet: human exposures, risks, and mitigation strategies. *Curr. Environ. Health Rep.* **3**, 107–117 (2016).
55. EFSA. *Public Consultation: Re-evaluation of the Risks to Public Health Related to the Presence of Bisphenol A (BPA) in Foodstuffs* https://connect.efsa.europa.eu/RM/s/publicconsultation2/a0l1v00000E8BRD/pc0109 (2022).
56. EFSA Panel on Food Contact Materials, Enzymes and Processing Aids (CEP) et al. Re-evaluation of the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs.*EFSA J.* **21**, e06857 (2023).
57. FDA. *GRAS Notices: Soy Isoflavone Extract* https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&id=1 (1998).
58. FDA. *GRAS Notices: trans-Resveratrol* https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&id=224 (2007).
59. Maffini, M. V. & Neltner, T. G. How the FDA Ignores the Law When Approving New Chemical Additives to Food. *Environmental Health News* https://www.ehn.org/health-issues-associated-with-food-additives-2649620272.html (2020).
60. Maffini, M. V. et al. Advancing the science on chemical classes. *Environ. Health* **21**, 120 (2023).
**A new policy analysis that reviews the approaches that are available to regulate environmental chemicals in classes rather than as individual chemicals.**
61. Zimmermann, L. et al. Implementing the EU chemicals strategy for sustainability: the case of food contact chemicals of concern. *J. Hazard. Mater.* **437**, 129167 (2022).
62. Solecki, R. et al. Scientific principles for the identification of endocrine-disrupting chemicals: a consensus statement. *Arch. Toxicol.* **91**, 1001–1006 (2017).
63. ANSES's Working Group on Endocrine Disruptors et al. Concerns related to ED-mediated effects of Bisphenol A and their regulatory consideration. *Mol. Cell Endocrinol.* **475**, 92–106 (2018).
64. Vandenberg, L. N. et al. Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses. *Endocr. Rev.* **33**, 378–455 (2012).
65. Hill, C. E., Myers, J. P. & Vandenberg, L. N. Nonmonotonic dose–response curves occur in dose ranges that are relevant to regulatory decision-making. *Dose Response* **16**, 1559325818798282 (2018).
66. Do, R. P., Stahlhut, R. W., Ponzi, D., Vom Saal, F. S. & Taylor, J. A. Non-monotonic dose effects of in utero exposure to di(2-ethylhexyl) phthalate (DEHP) on testicular and serum testosterone and anogenital distance in male mouse fetuses. *Reprod. Toxicol.* **34**, 614–621 (2012).
67. Lee, D. H. et al. Low dose of some persistent organic pollutants predicts type 2 diabetes: a nested case–control study. *Environ. Health Perspect.* **118**, 1235–1242 (2010).
68. Lanphear, B. P. et al. Low-level environmental lead exposure and children's intellectual function: an international pooled analysis. *Environ. Health Perspect.* **113**, 894–899 (2005).
69. Grandjean, P. et al. Methylmercury exposure biomarkers as indicators of neurotoxicity in children aged 7 years. *Am. J. Epidemiol.* **150**, 301–305 (1999).
70. Bouchard, M. F. et al. Prenatal exposure to organophosphate pesticides and IQ in 7-year-old children. *Environ. Health Perspect.* **119**, 1189–1195 (2011).
71. Rauh, V. A. et al. Impact of prenatal chlorpyrifos exposure on neurodevelopment in the first 3 years of life among inner-city children. *Pediatrics* **118**, e1845–e1859 (2006).
72. Mancini, F. R. et al. Nonlinear associations between dietary exposures to perfluorooctanoic acid (PFOA) or perfluorooctane sulfonate (PFOS) and type 2 diabetes risk in women: findings from the E3N cohort study. *Int. J. Hyg. Environ. Health* **221**, 1054–1060 (2018).
73. Chen, A. et al. Prenatal polybrominated diphenyl ether exposures and neurodevelopment in U.S. children through 5 years of age: the HOME study. *Environ. Health Perspect.* **122**, 856–862 (2014).
74. Herbstman, J. B. et al. Prenatal exposure to PBDEs and neurodevelopment. *Environ. Health Perspect.* **118**, 712–719 (2010).
75. Varshavsky, J. R. et al. Current practice and recommendations for advancing how human variability and susceptibility are considered in chemical risk assessment. *Environ. Health* **21**, 133 (2023).
**A new policy analysis that illustrates best practices for using measures of variability and susceptibility in models for risk assessment.**
76. Demeneix, B., Vandenberg, L. N., Ivell, R. & Zoeller, R. T. Thresholds and endocrine disruptors: an endocrine society policy perspective. *J. Endocr. Soc.* **4**, bvaa085 (2020).
77. Hall, A. M. & Braun, J. M. Per- and polyfluoroalkyl substances and outcomes related to metabolic syndrome: a review of the literature and current recommendations for clinicians. *Am. J. Lifestyle Med.* https://doi.org/10.1177/15598276231162802 (2023).
78. Jackson, A. A., Langley-Evans, S. C. & McCarthy, H. D. Nutritional influences in early life upon obesity and body proportions. *CIBA Found. Symp.* **201**, 118–129 (1996).
79. Kahn, H. S., Graff, M., Stein, A. D. & Lumey, L. H. A fingerprint marker from early gestation associated with diabetes in middle age: the Dutch Hunger Winter Families Study. *Int. J. Epidemiol.* **38**, 101–109 (2009).
80. Schulz, L. C. The Dutch Hunger Winter and the developmental origins of health and disease. *Proc. Natl Acad. Sci. USA* **107**, 16757–16758 (2010).
81. Ghassabian, A., Vandenberg, L., Kannan, K. & Trasande, L. Endocrine-disrupting chemicals and child health. *Annu. Rev. Pharmacol. Toxicol.* **62**, 573–594 (2022).
82. Newbold, R. R., Padilla-Banks, E., Snyder, R. J. & Jefferson, W. N. Perinatal exposure to environmental estrogens and the development of obesity. *Mol. Nutr. Food Res.* **51**, 912–917 (2007).
83. Somm, E. et al. Perinatal exposure to bisphenol a alters early adipogenesis in the rat. *Environ. Health Perspect.* **117**, 1549–1555 (2009).
84. Hao, C. J., Cheng, X. J., Xia, H. F. & Ma, X. The endocrine disruptor 4-nonylphenol promotes adipocyte differentiation and induces obesity in mice. *Cell Physiol. Biochem.* **30**, 382–394 (2012).

85. Patisaul, H. B. et al. Accumulation and endocrine disrupting effects of the flame retardant mixture Firemaster® 550 in rats: an exploratory assessment. *J. Biochem. Mol. Toxicol.* **27**, 124–136 (2013).
86. Kassotis, C. D. et al. Endocrine-disrupting activity of hydraulic fracturing chemicals and adverse health outcomes after prenatal exposure in male mice. *Endocrinology* **156**, 4458–4473 (2015).
87. Kassotis, C. D. et al. Adverse reproductive and developmental health outcomes following prenatal exposure to a hydraulic fracturing chemical mixture in female C57Bl/6 mice. *Endocrinology* **157**, 3469–3481 (2016).
88. Balise, V. D. et al. Preconceptional, gestational, and lactational exposure to an unconventional oil and gas chemical mixture alters energy expenditure in adult female mice. *Front. Endocrinol.* **10**, 323 (2019).
89. Balise, V. D. et al. Developmental exposure to a mixture of unconventional oil and gas chemicals increased risk-taking behavior, activity and Energy expenditure in aged female mice after a metabolic challenge. *Front. Endocrinol.* **10**, 460 (2019).
90. Vandenberg, L. N. Endocrine disrupting chemicals and the mammary gland. *Adv. Pharmacol.* **92**, 237–277 (2021).
91. Neal-Kluever, A. et al. Infant toxicology: State of the science and considerations in evaluation of safety. *Food Chem. Toxicol.* **70**, 68–83 (2014).
92. Cameron, J., & Abouchar, J. *The precautionary principle: a fundamental principle of law and policy for the protection of the global environment*. 14 BC Int'l & Comp. L. Rev. 1 (1991).
93. Tsai, P. L. & Hatfield, T. H. Global benefits from the phaseout of leaded fuel. *J. Environ. Health* **74**, 8–15 (2011).
94. Silva, E., Rajapakse, N. & Kortenkamp, A. Something from "nothing"-eight weak estrogenic chemicals combined at concentrations below NOECs produce significant mixture effects. *Environ. Sci. Technol.* **36**, 1751–1756 (2002).
95. Rajapakse, N., Silva, E. & Kortenkamp, A. Combining xenoestrogens at levels below individual no-observed-effect concentrations dramatically enhances steroid hormone action. *Environ. Health Perspect.* **110**, 917–921 (2002).
96. Christiansen, S. et al. Combined exposure to anti-androgens causes markedly increased frequencies of hypospadias in the rat. *Int. J. Androl.* **31**, 241–248 (2008).
97. Orton, F., Rosivatz, E., Scholze, M. & Kortenkamp, A. Competitive androgen receptor antagonism as a factor determining the predictability of cumulative antiandrogenic effects of widely used pesticides. *Environ. Health Perspect.* **120**, 1578–1584 (2012).
98. Thrupp, T. J. et al. The consequences of exposure to mixtures of chemicals: something from 'nothing' and 'a lot from a little' when fish are exposed to steroid hormones. *Sci. Total Environ.* **619–620**, 1482–1492 (2018).
99. Yang, M., Park, M. S. & Lee, H. S. Endocrine disrupting chemicals: human exposure and health risks. *J. Environ. Sci. Health C. Environ. Carcinog. Ecotoxicol. Rev.* **24**, 183–224 (2006).
100. Conley, J. M. et al. A mixture of 15 phthalates and pesticides below individual chemical no observed adverse effect levels (NOAELs) produces reproductive tract malformations in the male rat. *Environ. Int.* **156**, 106615 (2021).
**An important study of chemical mixtures, highlighting that chemicals at doses that individually have no adverse effects can produce serious adverse effects when combined.**
101. Martin, O. et al. Ten years of research on synergisms and antagonisms in chemical mixtures: a systematic review and quantitative reappraisal of mixture studies. *Environ. Int.* **146**, 106206 (2021).
102. Centers for Disease Control and Prevention. *National Report on Human Exposure to Environmental Chemicals* https://www.cdc.gov/exposurereport/index.html (2015).
103. Houlihan, J. Body Burden: The Pollution in Newborns. *Environmental Working Group* https://www.ewg.org/research/body-burden-pollution-newborns (2005).
104. EFSA Scientific Committee et al. Guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals. *EFSA J.* **17**, e05634 (2019).
105. Anzenbacher, P. & Anzenbacherová, E. Cytochromes P450 and metabolism of xenobiotics. *Cell Mol. Life Sci.* **58**, 737–747 (2001).
106. Markowitz, J. S. et al. Effect of St John's wort on drug metabolism by induction of cytochrome P450 3A4 enzyme. *J. Am. Med. Assoc.* **290**, 1500–1504 (2003).
107. Kassotis, C. D., Tillitt, D. E., Lin, C. H., McElroy, J. A. & Nagel, S. C. Endocrine-disrupting chemicals and oil and natural gas operations: potential environmental contamination and recommendations to assess complex environmental mixtures. *Environ. Health Perspect.* **124**, 256–264 (2016).
108. Gauger, K. J. et al. Polychlorinated biphenyls 105 and 118 form thyroid hormone receptor agonists after cytochrome P4501A1 activation in rat pituitary GH3 cells. *Environ. Health Perspect.* **115**, 1623–1630 (2007).
109. Hoover, G., Kar, S., Guffey, S., Leszczynski, J. & Sepúlveda, M. S. In vitro and in silico modeling of perfluoroalkyl substances mixture toxicity in an amphibian fibroblast cell line. *Chemosphere* **233**, 25–33 (2019).
110. Ojo, A. F., Peng, C. & Ng, J. C. Combined effects and toxicological interactions of perfluoroalkyl and polyfluoroalkyl substances mixtures in human liver cells (HepG2). *Environ. Pollut.* **263**, 114182 (2020).
111. Ding, G. et al. Combined effects of PFOS and PFOA on zebrafish (*Danio rerio*) embryos. *Arch. Environ. Contam. Toxicol.* **64**, 668–675 (2013).
112. Marques, E. S. et al. The role of maternal high fat diet on mouse pup metabolic endpoints following perinatal PFAS and PFAS mixture exposure. *Toxicology* **462**, 152921 (2021).
113. Liew, Z. et al. Maternal plasma perfluoroalkyl substances and miscarriage: a nested case-control study in the Danish National Birth Cohort. *Environ. Health Perspect.* **128**, 47007 (2020).
114. Shih, Y. H., Blomberg, A. J., Jørgensen, L. H., Weihe, P. & Grandjean, P. Early-life exposure to perfluoroalkyl substances in relation to serum adipokines in a longitudinal birth cohort. *Environ. Res* **204**, 111905 (2022).
115. Guo, J. et al. Umbilical cord serum perfluoroalkyl substance mixtures in relation to thyroid function of newborns: findings from Sheyang Mini Birth Cohort Study. *Chemosphere* **273**, 129664 (2021).
116. Zhuang L. H. et al. Effects of gestational exposures to chemical mixtures on birth weight using Bayesian factor analysis in the Health Outcome and Measures of Environment (HOME) Study. Environ Epidemiol. 2021;5:e159.
117. Preston, E. V. et al. Prenatal exposure to per- and polyfluoroalkyl substances and maternal and neonatal thyroid function in the Project Viva Cohort: a mixtures approach. *Environ. Int.* **139**, 105728 (2020).
118. Luo, D. et al. Associations of prenatal exposure to per- and polyfluoroalkyl substances with the neonatal birth size and hormones in the growth hormone/insulin-like growth factor axis. *Environ. Sci. Technol.* **55**, 11859–11873 (2021).
119. Woods, M. M., Lanphear, B. P., Braun, J. M. & McCandless, L. C. Gestational exposure to endocrine disrupting chemicals in relation to infant birth weight: a Bayesian analysis of the HOME Study. *Environ. Health* **16**, 115 (2017).
120. Liang, H. et al. Prenatal exposure to perfluoroalkyl substances and thyroid hormone concentrations in cord plasma in a Chinese birth cohort. *Environ. Health* **19**, 127 (2020).
121. Slama, R. et al. Scientific issues relevant to setting regulatory criteria to identify endocrine-disrupting substances in the European Union. *Environ. Health Perspect.* **124**, 1497–1503 (2016).
122. Bourguignon, J. P. et al. Science-based regulation of endocrine disrupting chemicals in Europe: which approach? *Lancet Diabetes Endocrinol.* **4**, 643–646 (2016).
123. European Chemical Agency (ECHA) and European Food Safety Authority (EFSA) with the technical support of the Joint Research Centre (JRC) et al. Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009. *EFSA J.* **16**, e05311 (2018).
124. European Commission. *Chemicals Strategy for Sustainability Towards a Toxic-Free Environment* https://environment.ec.europa.eu/strategy/chemicals-strategy_en (2020).
125. O'Reilly, J. T. What REACH can teach us about TSCA: retrospectives of America's failed Toxics Statute. *Eur. J. Risk Regul.* **1**, 40–50 (2010).
126. Environmental Protection Agency. *Cumulative Assessment of Risk from Pesticides* https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/cumulative-assessment-risk-pesticides (2015).
127. Maffini, M. V. & Neltner, T. G. Brain drain: the cost of neglected responsibilities in evaluating cumulative effects of environmental chemicals.*J. Epidemiol. Community Health* **69**, 496–499 (2015).
128. US Food and Drug Administration. *CFR — Code of Federal Regulations Title 21* https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=170.18 (2022).
129. Federal Register. *Indirect Food Additives: Paper and Paperboard Components* https://www.federalregister.gov/documents/2016/01/04/2015-33026/indirect-food-additives-paper-and-paperboard-components (2016).
130. Keefe D. M. RE: Pre-Notification Consultation (PNC) 2422. *US Food and Drug Administration* https://blogs.edf.org/health/files/2021/04/Daikin-PNC-2422-PFAS_Daikin-Final-10-1-2019-and-response-combined.pdf (2019).
131. Brennan, N. M., Evans, A. T., Fritz, M. K., Peak, S. A. & von Holst, H. E. Trends in the regulation of Per- and polyfluoroalkyl substances (PFAS): a scoping review. *Int. J. Environ. Res. Public Health* **18**, 10900 (2021).
132. ECHA. ECHA Publishes PFAS Restriction Proposal. *ECHA All News*. https://echa.europa.eu/-/echa-publishes-pfas-restriction-proposal (2023).
133. US Consumer Product Safety Commission. *The Consumer Product Safety Improvement Act of 2008* https://www.cpsc.gov/s3fs-public/pdfs/blk_pdf_cpsia.pdf (2008).
134. National Academies of Sciences, Engineering, and Medicine. A Class Approach to Hazard Assessment of Organohalogen Flame Retardants. *National Academies Press* http://www.ncbi.nlm.nih.gov/books/NBK545458/ (2019).
135. Babich M. A. Commission Briefing Package: Project Plan: Organohalogen Flame Retardant Chemicals Assessment. *US Consumer Product Safety Commission* https://www.cpsc.gov/content/Commission-Briefing-Package-Project-Plan-Organohalogen-Flame-Retardant-Chemicals-Assessment (2020).
136. Bevington, C. et al. Development of a flame retardant and an organohalogen flame retardant chemical inventory. *Sci. Data* **9**, 295 (2022).
137. Payne, J., Rajapakse, N., Wilkins, M. & Kortenkamp, A. Prediction and assessment of the effects of mixtures of four xenoestrogens. *Env. Health Perspect.* **108**, 983–987 (2000).
138. Miller, M. F., Chernyak, S. M., Batterman, S. & Loch-Caruso, R. Polybrominated diphenyl ethers in human gestational membranes from women in Southeast Michigan (USA). *Environ. Sci. Technol.* **43**, 3042–3046 (2009).
139. Jacobs, D. E. Lead screening update from the US Preventive Services Task Force. *J. Pediatr.* **212**, 243 (2019).
140. National Academies of Sciences, Engineering, and Medicine. *Guidance on PFAS Exposure, Testing, and Clinical Follow-Up* https://nap.nationalacademies.org/catalog/26156/guidance-on-pfas-exposure-testing-and-clinical-follow-up (2022).
141. Gosetti, F. et al. Study of endocrine disrupting compound release from different medical devices through an on-line SPE UHPLC-MS/MS method. *Analytica Chim. Acta* **1042**, 141–154 (2018).

142. Genco, M., Anderson-Shaw, L. & Sargis, R. M. Unwitting accomplices: endocrine disruptors confounding clinical care. *J. Clin. Endocrinol. Metab.* **105**, e3822–e3827 (2020). **Essential reading for the clinician who is concerned about exposures to EDCs in the medical setting, and how these exposures might be affecting the health of patients.**
143. Demeneix, B. A. How fossil fuel-derived pesticides and plastics harm health, biodiversity, and the climate. *Lancet Diabetes Endocrinol.* **8**, 462–464 (2020).
144. DeCourten, B. M. & Brander, S. M. Combined effects of increased temperature and endocrine disrupting pollutants on sex determination, survival, and development across generations. *Sci. Rep.* **7**, 9310 (2017).
145. Brown, A. R. et al. Climate change and pollution speed declines in zebrafish populations. *Proc. Natl Acad. Sci.* **112**, E1237–E1246 (2015).
146. Kulkarni, M. A., Duguay, C. & Ost, K. Charting the evidence for climate change impacts on the global spread of malaria and dengue and adaptive responses: a scoping review of reviews. *Globalization Health* **18**, 1 (2022).
147. IPCC. Masson-Delmotte, V. et al. *Special Report: Global Warming of 1.5°C. Summary for Policymakers* 3-24 (Cambridge University Press, 2018). https://www.ipcc.ch/sr15/chapter/spm/.
148. d'Ambrières, W. Plastics recycling worldwide: current overview and desirable changes. *Field Actions Sci. Rep.* **19**, 12–21 (2019).
149. Turner, A. & Filella, M. Hazardous metal additives in plastics and their environmental impacts. *Environ. Int.* **156**, 106622 (2021).
150. Kassotis, C. D. et al. Endocrine-disrupting chemicals: economic, regulatory, and policy implications. *Lancet Diabetes Endocrinol.* **8**, 719–730 (2020). **An important contribution showing how EDC policies and regulations are handled in different jurisdictions.**
151. Kahn, L. G., Philippat, C., Nakayama, S. F., Slama, R. & Trasande, L. Endocrine-disrupting chemicals: implications for human health.*Lancet Diabetes Endocrinol.* **8**, 703–718 (2020).
152. Kuruto-Niwa, R., Nozawa, R., Miyakoshi, T., Shiozawa, T. & Terao, Y. Estrogenic activity of alkylphenols, bisphenol S, and their chlorinated derivatives using a GFP expression system. *Environ. Toxicol. Pharmacol.* **19**, 121–130 (2005).
153. Chen, M. Y., Ike, M. & Fujita, M. Acute toxicity, mutagenicity, and estrogenicity of bisphenol-A and other bisphenols. *Environ. Toxicol.* **17**, 80–86 (2002).
154. Yoshihara, S. et al. Potent estrogenic metabolites of bisphenol A and bisphenol B formed by rat liver S9 fraction: their structures and estrogenic potency. *Toxicol. Sci.* **78**, 50–59 (2004).
155. Okuda, K., Fukuuchi, T., Takiguchi, M. & Yoshihara, S. Novel pathway of metabolic activation of bisphenol A-related compounds for estrogenic activity. *Drug Metab. Dispos.* **39**, 1696–1703 (2011).
156. Audebert, M., Dolo, L., Perdu, E., Cravedi, J. P. & Zalko, D. Use of the γH2AX assay for assessing the genotoxicity of bisphenol A and bisphenol F in human cell lines. *Arch. Toxicol.* **85**, 1463–1473 (2011).
157. Viñas, R. & Watson, C. S. Bisphenol S disrupts estradiol-induced nongenomic signaling in a rat pituitary cell line: effects on cell functions. *Environ. Health Perspect.* **121**, 352–358 (2013).
158. Kunikane, H. et al. Double-blind randomized control trial of the effect of recombinant human erythropoietin on chemotherapy-induced anemia in patients with non-small cell lung cancer. *Int. J. Clin. Oncol.* **6**, 296–301 (2001).
159. Brendel, S., Fetter, É., Staude, C., Vierke, L. & Biegel-Engler, A. Short-chain perfluoroalkyl acids: environmental concerns and a regulatory strategy under REACH. *Environ. Sci. Eur.* **30**, 9 (2018).



## Acknowledgements
The authors would like to share their appreciation for their support networks during the writing of this manuscript.


## Author contributions
C.D.-L. and M.V.M. researched data for the article and wrote the article. L.T. wrote the article and reviewed and/or edited the manuscript before submission. C.D.K. contributed substantially to the discussion of content and wrote the article. L.N.V. researched data for the article, contributed substantially to the discussion of content, and reviewed and/or edited the manuscript before submission.

## Competing interests
The authors declare no competing interests.

## Additional information
**Peer review information** *Nature Reviews Endocrinology* thanks Mariana Fátima Fernández and Jones Bernardes Graceli for their contribution to the peer review of this work.

**Publisher's note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.



## Related links
**Food Packaging Forum:** https://www.foodpackagingforum.org/fcch-project