ENDOCRINE DISRUPTING CHEMICALS: THREATS TO HUMAN HEALTH

PESTICIDES, PLASTICS, FOREVER CHEMICALS, AND BEYOND

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ENDOCRINE SOCIETY
Hormone Science to Health

IPEN
for a toxics-free future

A JOINT ENDOCRINE SOCIETY & IPEN INITIATIVE TO RAISE GLOBAL AWARENESS ABOUT ENDOCRINE DISRUPTING CHEMICALS

Founded in 1916, the **Endocrine Society** is the world's oldest, largest, and most active organization devoted to research on hormones and the clinical practice of endocrinology. The Endocrine Society's membership consists of over 18,000 scientists, physicians, educators, nurses, and students in more than 100 countries. Society members represent all basic, applied and clinical interests in endocrinology. Included among the Society's members are the world's leading experts on the health effects of EDCs.

Endocrine Society members have been at the forefront of scientific advancements in the field of EDCs since it was first recognized that exogenous chemicals can have effects on endocrine systems. The Society held its first public meeting on EDCs in conjunction with its Annual Meeting in San Francisco in 2005. The Society's landmark 2009 Scientific Statement on EDCs was the first comprehensive review of the existing EDC literature, and it represented the first public statement on the issue from a major mainstream international medical society. This was followed by an updated Scientific Statement in 2015, EDC-2, reinforcing the scientific evidence that EDCs are a serious human health concern.

www.endocrine.org

Established in 1998, the **International Pollutants Elimination Network (IPEN)** is a leading global organization promoting policies to protect human health and environmental rights from the production, use, and disposal of toxic substances, especially in low- and middle-income countries. IPEN works to eliminate the world´s worst chemicals, including EDCs, and to prevent widespread harm from chemicals. Global controls on toxic chemicals have been a priority for IPEN for more than two decades.

IPEN's mission is a toxics-free future for all. Our global network, consisting of more than 600 participating organizations in more than 125 countries, collaborates to ensure that the voices of those most impacted by toxic pollution – communities in the developing world – are heard in international chemical policy decision-making bodies. With decades of experience in generating scientific data from the Global South, in areas that typically lack data, our support for our member groups' local work provides global data to move international policies, while international policies form the basis for local and national regulations.

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KEY TAKEAWAYS

- Our bodies' hormones (natural compounds produced by our endocrine glands) play many important biological and physiological functions – they are involved in development, adaptation, and health maintenance, and many are essential for survival.

- Endocrine disrupting chemicals are individual substances or mixtures that can interfere with our hormones' natural functioning, leading to disease or even death.

- The science on EDCs has been increasing rapidly, with mounting evidence showing global health threats posed by EDCs in the environment. Estimates suggest that more than 24% of human diseases and disorders globally are attributable to environmental factors, with such factors playing a role in 80% of the deadliest diseases, including cancer, heart disease, and others. EDCs in the environment may contribute to disorders with hormonal underpinnings such as diabetes, neurological disorders, reproductive disorders, inflammation, and compromised immune functioning.

- Numerous international scientific and health organizations have raised concerns about EDCs and many have called for stronger regulations, but there remain significant gaps between global and national chemical control policies and the latest science on EDCs.

- EDCs do not behave like other chemicals, and current regulatory practices do not account for the ways that EDCs can pose health threats. EDC exposures at even extremely low dosages can alter biological outcomes and the effects of low doses cannot be predicted by the effects observed at high doses. This means there may be no safe dose for exposure to EDCs.

- People may be exposed to EDCs by many different products and pathways. Products that may contain EDCs include furniture, toys and children's products, food packaging, electronics, building materials, cosmetics, and many others. People can also be exposed to EDCs from pesticides, air pollutants, industrial waste, and other pathways.

- EDC exposures can be harmful at any age, but they may be most harmful when people are exposed during sensitive developmental periods, such as during fetal development, infancy and childhood, adolescence, and pregnancy.

- While there are many ways that people are exposed to EDCs, our report reviews four areas as case studies:

  ◦ **Pesticides:** the report reviews three pesticides, including the world's most heavily applied herbicide, glyphosate. Glyphosate exposure is widespread and can occur from direct exposures and indirectly through air, water, dust, and food residues. A recent review found that glyphosate has properties of an EDC, with evidence to support impacts from glyphosate on eight of the ten EDC key characteristics. Studies have identified associations between glyphosate and adverse reproductive health outcomes.

  ◦ **Plastics and plasticizers:** the report reviews bisphenols and phthalates, two toxic plastic chemicals. Phthalates are found in many personal care products and other products. Some phthalates have been linked to effects on reproductive health and development and emerging evidence is revealing that phthalates may impair neurodevelopment resulting in impaired cognitive function, learning, attention, and impulsivity.

  ◦ **Chemicals in household and children's products:** the report reviews two heavy metals, arsenic and inorganic lead. Arsenic is a common toxic metalloid that has long been linked to cancer and other health conditions, and more recent evidence clearly shows that arsenic has the capacity to disrupt multiple endocrine systems. Arsenic exposure is associated with metabolic disorders such as diabetes, disruptions in reproductive function, and with cardiovascular and neurocognitive disorders.

  ◦ **Industrial chemicals:** the report reviews PFAS and brominated flame retardants. PFAS are a class of thousands of substances known as "forever chemicals." They are widely used in many consumer and industrial applications. People are exposed to PFAS from drinking water, food (often when PFAS in packaging contaminates food), and through occupational and environmental exposures. Evidence is emerging indicating that PFAS are EDCs, with some studies showing that some PFAS can disrupt hormones such as estrogen and testosterone, and some PFAS can impair thyroid hormone functions.

- The report also includes a review of potential EDC exposures across the life cycle of plastics, noting that plastics are made from fossil fuels and chemicals, including thousands of known toxic substances, some of which are known or suspected EDCs.

- Plastic poses risks of exposure to EDCs at every stage of the life cycle. People living near plastics production facilities or near waste disposal sites may face the greatest exposure risks, though consumers, including children, can also be exposed to EDCs when they use plastic products.

- The rapid increase in plastic production is accelerating problems of plastic waste disposal, and since plastic wastes are increasingly unequally exported from wealthier countries to low- and middle-income countries, people in the latter regions are disproportionately at risk from EDCs in plastics.

EXECUTIVE SUMMARY

EDCs are defined by the Endocrine Society as "an exogenous [non-natural] chemical, or mixture of chemicals, that interferes with any aspect of hormone action." Hormones are natural chemicals produced in cells within endocrine glands, which are located throughout the body. They allow for development, adaptation, and maintenance of bodily processes and health, play key roles in determining quality of life, and many are essential for survival.

Because of the endocrine system's critical role in so many important biological and physiological functions, impairments in any part of the endocrine system can lead to disease or even death. By interfering with the body's endocrine systems, EDC exposure can thus perturb many functions.

As we noted in our 2014 report, "Scientific knowledge about endocrine-disrupting chemicals (EDCs) has been increasing rapidly in recent years." This rapid advance has continued, with growing global attention to the health consequences from EDCs in the environment. EDCs remain a global problem, and the threat from these chemicals has only grown since our original publication.

NEW SCIENCE, MORE SOURCES OF EDC EXPOSURES

In addition to updated science on the endocrine disrupting properties of substances reviewed in our earlier report, this updated report reviews a few of the many known sources of EDC exposure that were not covered in the original, including:

- **Pesticides:** Exposures from the pesticide glyphosate, which recent evidence shows has endocrine disrupting properties.

- **Plastics:** Exposures to EDCs can occur throughout the plastics life cycle, including to production workers, fenceline communities, consumers, and waste workers.

- **PFAS:** Exposures to per-and polyfluoroalkyl substances (PFAS), a class of thousands of ubiquitous "forever chemicals" that are known or suspected to be EDCs.

- **Children's Products:** Exposures to arsenic, a toxic metalloid and known EDC, from children's products.

PESTICIDES: GLYPHOSATE

Glyphosate is the most widely used herbicide in the world. For many years it was the best-selling product of Monsanto (now Bayer), the company that patented the chemical and sold their glyphosate-based herbicides as Roundup™. With the introduction of Monsanto's Roundup Ready™ GMO crops in the late 1990s, which were developed to be used with repeated doses of the herbicide, the use of Roundup globally skyrocketed, and when Monsanto's glyphosate patent expired in the early 2000s, other companies developed glyphosate-based herbicides, leading to even greater use and the chemical's position as the planet's most widely applied herbicide today.

Glyphosate exposure is widespread and can occur from direct exposures to farm workers, to landscapers and homeowners who use the weed killer in gardening, and indirectly through air, water, dust, and food residues. In an analysis of samples collected in 2013-2014 from a representative U.S. population, 81.2% of participants had detectable levels of glyphosate in their urine. A recent review found that glyphosate has properties of an EDC, with evidence to support impacts from glyphosate on eight of the ten EDC key characteristics. Other studies have identified associations between glyphosate and adverse reproductive health outcomes.

PLASTICS

There is good reason to suspect that increasing chemical and plastic production and use are related to the growing incidence of endocrine-associated disorders over the past 20 years. Sales for the global chemical industry have sharply increased from USD$171 billion in 1970 to over USD$5 trillion in 2023 (with expected sales of over $6 trillion by 2027), and global production of plastics grew from 50 million tons in the mid-1970s to nearly 460 million tons today.

A wide range of chemicals are used to produce plastics, including many EDCs. In plastics production, toxic chemicals that are harmful to human health are released, with exposures to nearby communities and occupational risks for workers. Plastics from everyday products can leach chemicals, exposing consumers. For example, evidence indicates that people are exposed to EDCs including toxic flame retardants and bisphenols from plastic kitchen utensils. Plastic waste disposal is a global crisis, and with increasing production waste disposal problems will only worsen, with increasing exposure to toxic chemicals from plastics, including EDCs, for waste workers and communities near waste facilities.

PFAS – "FOREVER CHEMICALS"

PFAS are a class of thousands of substances known as "forever chemicals." Many are persistent organic pollutants (POPs) and some have been added to the list of highly toxic globally banned substances under the Stockholm

Convention. They are widely used in synthetic (plastic) materials and clothing, in non-stick and stain/water resistant products, and in many other consumer and industrial applications. People are exposed to PFAS from drinking water, food (often when PFAS in packaging contaminates food), and through occupational and environmental exposures, especially to fenceline communities near PFAS-polluting facilities.

Evidence is emerging indicating that PFAS are EDCs. Studies have shown that some PFAS can disrupt the production, transport, and break-down of hormones such as estrogen and testosterone, and some can impair thyroid hormone functions. Rodent studies have shown disruption to reproductive health effects with close links to endocrine function, including a study indicating that PFAS can reduce the production and transport of a key hormone involved in making milk. A study in mice showed effects on breast development across generations, with daughter and granddaughter mice of PFAS-exposed mice having delayed mammary gland development. Two human studies found that PFAS exposure was associated with a shorter duration of breast feeding.

CHILDREN'S PRODUCTS: ARSENIC

EDCs are found in many common household and personal products, and we can be exposed to these chemicals through skin contact, ingestion, and when they are released into our homes, schools, workplaces, and other environments. Children are especially at risk, due to their smaller body size, more common hand-to-mouth behaviors, and when they crawl on floors or otherwise encounter tainted household dust. Research by consumer advocacy groups has detected high levels of arsenic in a variety of foods, including baby foods.

Arsenic is a common toxic metalloid that has long been linked to cancer and other health conditions, and more recent evidence clearly shows that arsenic has the capacity to disrupt multiple endocrine systems. Arsenic exposure is associated with metabolic disorders such as diabetes, disruptions in reproductive function, and with metabolic, cardiovascular, and neurocognitive disorders.

REGULATORY GAPS

Although consensus is building on how exposures to EDCs pose risks to humans, there is still a gap between endocrine science and regulatory policy, particularly around the concept of low-dose exposures to EDCs. IPEN and the Endocrine Society call for chemical regulations based on the most modern scientific understanding of how hormones act and how EDCs can perturb these actions. We work to educate policy makers in global, regional, and national government assemblies and help ensure that regulations correlate with current scientific understanding.

1. MAJOR HEALTH AND SCIENCE INSTITUTIONS HIGHLIGHT CONCERNS ABOUT ENDOCRINE DISRUPTING CHEMICALS (EDCs)

Decades of research on endocrine disrupting chemicals (EDCs) and their health effects have elevated concerns about these chemicals among numerous international scientific and health organizations. In 2009, the Endocrine Society was the first major scientific society to take a public stance on the state of EDC science with the 2009 publication of its Scientific Statement on EDCs (9). At that time, the Society's membership asserted that there was sufficient evidence to conclude that EDCs pose a public health risk. Building on this statement, the Society further issued a 2012 Statement of Principles on EDCs and public health protection (10) and in 2015 developed a second scientific statement further demonstrating the links between EDCs and endocrine diseases (11).

Since the Endocrine Society's inaugural statement in 2009, the number of medical societies voicing concern over EDCs globally has grown in parallel with the body of literature revealing negative health effects of chemicals that interfere with hormone action. In the United States, the American Medical Association – the largest organization of U.S. medical professionals – adopted a policy in November 2009 (D-135.982, Regulation of Endocrine Disrupting Chemicals) calling for improved regulatory oversight of EDCs based on "comprehensive data covering both low-level and high-level exposures." In the same month, the American Public Health Association called for "a precautionary approach to reducing American exposure to endocrine disrupting chemicals." The American Chemical Society issued a public policy statement, updated in 2015, on testing for endocrine disruption, recommending expanded education and research, updated testing protocols, and the development of safer alternatives to EDCs.

International health organizations also have taken up the call for improved EDC policies. In February 2013, the World Health Organization and United Nations Environment Programme (UNEP) launched their joint report on the state of the science of EDCs (12). The report outlines

the current understanding of EDCs and their effects on human health; it also recommends improved testing and reduced exposures to EDCs. Also in 2013, the Collegium Ramazzini – an international academy of renowned occupational and environmental health experts – issued a statement on EDCs in the European Union, calling for the expansion of the scope of the REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) legislation and more inclusive assessment of the totality of scientific evidence in regulatory decision-making. Again in 2013, a large group of independent scientists issued the Berlaymont Declaration expressing concern over EDCs and calling on the European Commission to improve its regulatory regime governing these chemicals. The Declaration has been signed by nearly 100 scientists from 19 countries, including Chile, China, Mexico, South Africa, and several European Union member states.

The above examples are not an exhaustive list and do not even include statements by large medical associations that address EDCs in the context of the larger universe of toxic chemicals. In October 2013, the American College of Obstetrics and Gynecology and the American Society of Reproductive Medicine issued a joint committee opinion "calling for timely action to identify and reduce exposure to toxic environmental agents" and noting that many of the toxic agents impact endocrine pathways (13). The British Royal College of Obstetrics and Gynaecology issued a 2013 Scientific Impact Paper on chemical exposures during pregnancy "to inform women who are pregnant or breastfeeding of the sources and routes of chemical exposure in order for them to take positive action in regard to minimising harm to their unborn child." (14) Finally, the International Conference on Children's Health and Environment issued a 2013 Jerusalem Statement on its "commitment to protect children's health from environmental hazards."

SINCE THE ENDOCRINE SOCIETY'S INAUGURAL STATEMENT IN 2009, THE NUMBER OF MEDICAL SOCIETIES VOICING CONCERN OVER EDCS GLOBALLY HAS GROWN IN PARALLEL WITH THE BODY OF LITERATURE REVEALING NEGATIVE HEALTH EFFECTS OF CHEMICALS THAT INTERFERE WITH HORMONE ACTION.

2. REGULATORY POLICIES

With greater international attention to the public health effects of EDCs, many organizations have called for improved regulatory policies, grounded in the latest available scientific evidence, to protect the public from hazards associated with endocrine disruption. Although consensus is building on how exposures to EDCs are relevant to humans, there is still a gap between endocrine science and regulatory policy. One contentious issue in regulatory discussions is around the concept of low-dose exposures to EDCs and why these are biologically relevant. As scientists and clinicians with expertise in endocrinology have become increasingly involved in research and practice on EDCs, there is growing evidence that regulations need to address low-dose effects that do not conform to the general regulatory approach of "the dose makes the poison." It is important that decisions about regulation of chemicals be based on the most modern scientific understanding of how hormones act and how EDCs perturb these actions.

More than 100 countries acknowledged the need for policy action on EDCs at the 4th International Conference on Chemicals Management (ICCM4) organized by the UN Environmental Programme in 2015. Photo: Giulia Carlini

Global Policies

Recognizing the need to engage policymakers, the Endocrine Society developed its Position (10) and Scientific Statements (9, 11) on EDCs that aim to advance science-based policy on EDCs around the world. Drawing on these Statements, the Endocrine Society and partner organizations such as IPEN have successfully worked with national and international bodies to advance solutions to widespread exposure to EDCs. In 2012, the International Conference on Chemicals Management adopted a resolution on EDCs acknowledging the scientific consensus on harms to humans and wildlife and calling on further action on EDCs by all stakeholders.

The Plastics Treaty

In March 2022, 175 countries at the United Nations Environmental Assembly (UNEA) adopted a resolution calling for a global treaty to address the plastics crisis. While not specifically mentioned in the Treaty negotiation mandate, health threats from EDCs in plastics may

be considered in discussions around chemical exposures that can occur throughout the plastics life cycle. As noted in the section below reviewing some of the types of EDCs in plastics, people can be exposed to these chemicals when plastics are produced, transported, used, and disposed of. The Plastics Treaty may be a significant step toward global control of plastics and elimination of threats from exposures to EDCs in plastics.

EU Policies

In 2017 and 2018, the European Union adopted criteria for the identification of EDCs in biocides and pesticides laws, and in 2020 the European Commission acknowledged the need for attention to EDCs and called for several specific actions, including a ban on EDCs in consumer products, in the Commission's Chemicals Strategy for Sustainability. In 2022, the EU Commission proposed new hazard classes under its Regulation on classification, labelling, and packaging of chemicals (CLP), including endocrine disruption, to better protect people and the environment from hazardous chemicals.

US Policies

In the U.S., chemicals are regulated under the Toxic Substances Control Act (TSCA), but since this law's adoption in 1976, the U.S. EPA has regulated fewer than ten chemicals (of more than 62,000 chemicals in use). In 1998, following Congressional legislation the EPA established a program to assess pesticides used on food for endocrine disruption; however, to date the agency has tested very few pesticides and found none to be endocrine disruptors. The U.S. FDA is responsible for regulating food ingredients and food contact materials, but the agency has no requirements for EDC testing nor has taken any action following their identification, resulting in known EDCs such as BPA, triclosan, and several phthalates being used legally and intentionally in food contact materials (15, 16).

While significant progress has been made in recent years connecting scientific advances on EDCs with health-protective policies, additional education and awareness-raising among stakeholders remain necessary to achieve a safer and more sustainable environment that minimizes exposure to these harmful chemicals.

IT IS IMPORTANT THAT DECISIONS ABOUT REGULATION OF CHEMICALS BE BASED ON THE MOST MODERN SCIENTIFIC UNDERSTANDING OF HOW HORMONES ACT, AND HOW EDCS PERTURB THESE ACTIONS.

Pineal
Hypothalamus
Pituitary

Thyroid
Parathyroid

Cardiovascular

Mammary

Liver
Adrenal
Kidney
Pancreas
Adipose Tissue
Ovary

Prostate
Testis

Bone
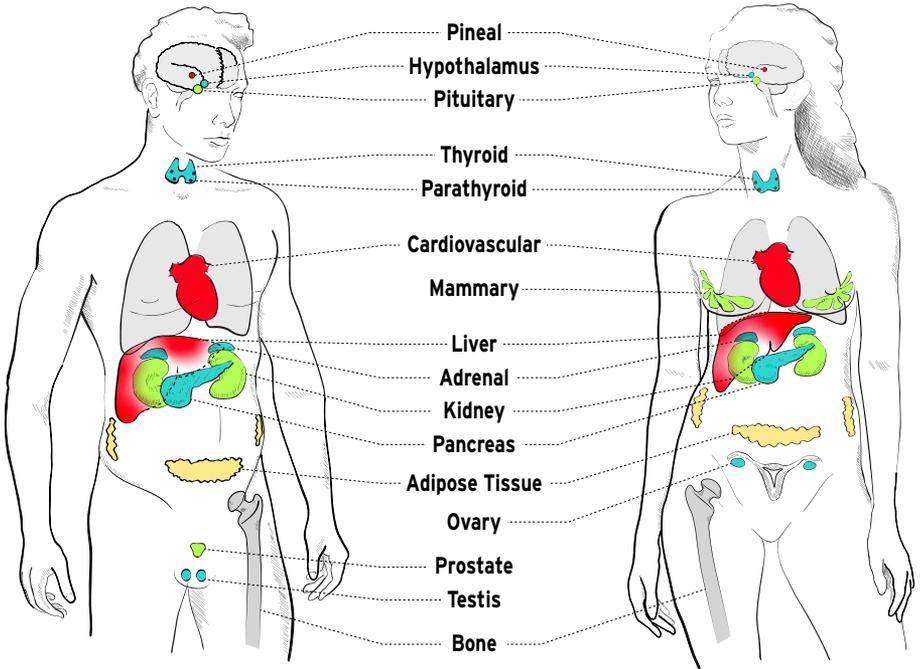
Figure 1. Diagram of major endocrine glands in the human body, shown in a female (right) and male (left). [From IPEN Plastics Guide, 2020].

3. INTRODUCTION TO THE HUMAN ENDOCRINE SYSTEM AND EDCs

3.1   BACKGROUND ON THE HUMAN ENDOCRINE SYSTEM

As their name implies, endocrine disrupting chemicals (EDCs) cause disturbances to the endocrine system. What is the endocrine system, and what are hormones? The endocrine system consists of a series of glands that are distributed throughout the body (**Figure 1**). Each gland produces one or more hormones. Hormones are natural substances that are produced in cells within a gland and released into the circulatory system, where they travel through the bloodstream until they reach a target tissue or organ. In other words, hormones are natural chemical messengers. In order to have an effect, each hormone binds to its specific receptors in a manner reminiscent of a key (hormone) opening a lock (receptor). At the target cell, a hormone triggers a very specific response such as production of another hormone, a change in metabolism, a behavioral response, or other physiological responses, depending upon the specific hormone and its target. Endocrine systems and functions are complex and diverse, with each gland and hormone playing unique roles in health and well-being (**Table 1**). Moreover, the endocrine system is one of the body's major interfaces with the environment, allowing for development, adaptation, and maintenance of bodily processes and health.

TABLE 1. ENDOCRINE SYSTEMS AND THEIR FUNCTIONS

Function	How it is regulated by hormones	Hormones	Example diseases and dysfunction
Growth	Hypothalamic-pituitary-liver system	The hypothalamus – a part of the brain - secretes hormones that regulate the release of growth hormone from the pituitary gland. Growth hormone, together with insulin-like growth factor from the liver, cause growth and have anabolic actions on muscle and fat.	Childhood growth disorders from deficiencies (dwarfism, gigantism) or adult acromegaly due to too little or too much growth hormone action.
Metabolism	Hypothalamic-pituitary-thyroid system	The thyroid gland releases thyroid hormones in response to hormones from the hypothalamus and pituitary gland.	Thyroid diseases (hypothyroidism: too little thyroid hormone; hyperthyroidism: too much thyroid hormone).
Stress regulation	Hypothalamic-pituitary-adrenal system	The adrenal gland releases cortisol in response to hormones from the hypothalamus and pituitary gland.	Cushing's Syndrome (too much cortisol action), Addison's disease (too little adrenal hormones).
Reproduction in females	Hypothalamic-pituitary-ovary system	The hypothalamus and pituitary secrete hormones that regulate ovarian production of sex hormones (mainly estrogens, progesterone) and control ovulation.	Infertility, precocious puberty and other reproductive disorders.
Reproduction in males	Hypothalamic-pituitary-testis system	The hypothalamus and pituitary secrete hormones that regulate testicular production of sex hormones (mainly testosterone) and control spermatogenesis.	Infertility and other reproductive disorders.
Lactation	Hypothalamic-pituitary system	The pituitary gland produces prolactin in response to hypothalamic hormone input. Prolactin stimulates milk synthesis in the breast.	Inappropriate or insufficient lactation.
Blood sugar and nutrient regulation	Pancreatic beta cells	A set of cells in the pancreas (beta cells) produce insulin in response to increased blood glucose after a meal.	Diabetes mellitus.

Function	How it is regulated by hormones	Hormones	Example diseases and dysfunction
Biological rhythms	Pineal gland	Melatonin release from the pineal gland increases prior to sleep.	Circadian (24-hour) rhythm and sleep disorders.
Calcium balance	Parathyroid gland	The parathyroid gland releases the parathyroid hormone when calcium gets too low.	Hypercalcemia (too much calcium) or hypocalcemia (too little calcium).
Blood pressure and water balance	Kidney-liver-adrenal system	The adrenal gland releases aldosterone in response to hormonal input from the kidney (renin) and liver (angiotensin).	Blood pressure disorders (hypotension, hypertension) and fluid/electrolyte imbalances.

Because of the endocrine system's critical role in so many important biological and physiological functions, impairments in any part of the endocrine system can lead to disease or even death. Thus, endocrine hormones must be released at the appropriate time and in the appropriate amounts to enable a healthy life.

The endocrine system and its hormones are key to homeostasis, the ability of the body to respond and adapt to challenges and regain equilibrium. This makes the endocrine system one of the body's major interfaces with the environment.

3.2 WHAT ARE EDCS, HOW ARE THEY USED, AND WHERE ARE THEY FOUND?

EDCs are defined by the Endocrine Society, the largest international group of scientists and physicians working and practicing in the field of endocrinology, as "an exogenous chemical [a chemical from outside the body] or mixture of chemicals that interferes with any aspect of hormone action" (10). There are over 350,000 manufactured chemicals, of which thousands may be EDCs (17). A short list of representative EDCs and common ways we are exposed to them is provided in Table 2. Beyond this table are dozens of other processes and products that include EDCs, too numerous to include.

TABLE 2. HOW WE ARE EXPOSED TO ENVIRONMENTAL CHEMICALS, AND THE POTENTIAL HEALTH EFFECTS

How our bodies are exposed to EDCs	Where EDCs come from	Examples of EDCs	Affected systems/ functions in the body
Oral consumption of contaminated food or water	Industrial waste or pesticides contaminating soil or groundwater	PCBs, dioxins, perfluorinated compounds, DDT, arsenic	Reproductive, neurological, metabolic, thyroid
	Food contact materials and cookware that leach into food and beverages	BPA, phthalates, PFAS	
	Pesticide residues in food or beverage	Chlorpyrifos, DDT	
Contact with skin and/or inhalation	Household furniture, textiles, clothing treated with flame retardants	Brominated flame retardants, PFAS	Reproductive, neurological, metabolic, thyroid
	Electronics and building materials	Brominated flame retardants, PCBs	
	Pesticides used in agriculture, homes, or for public disease vector control	DDT, chlorpyrifos, vinclozolin, pyrethroids	
	Air pollutants from industrial activity, traffic, forest fires, fossil fuel use, cooking	Chemicals in particulate matter, metals/metalloids	
Children's products	Mouthing or teething by infants and children	Lead, phthalates, cadmium	Neurological, metabolic, thyroid
Medical supplies and equipment	Intravenous tubing and solutions, blood product storage bags	Phthalates, bisphenols, parabens, PFAS, triclosan	Reproductive, neurological, metabolic, thyroid
Application to skin	Cosmetics, personal care products	Phthalates	Reproductive, neurological, metabolic, thyroid
	Anti-bacterials	Triclosan	

People and animals come into contact with EDCs by a variety of routes (**Table 2**), including consumption of food and water, through the skin, and by inhalation. In a pregnant or lactating woman, some chemicals may transfer from mother to fetus (across the placenta) or mother to infant (via lactation) if the woman has EDCs in her body.

To understand how EDCs perturb the endocrine system, it is necessary to have some basic understanding of how natural hormones work in the body. Each hormone has a unique composition and three-dimensional shape. Every hormone in turn has a corresponding receptor (or receptors) localized on the target cells (**Figure 2**). A receptor's shape is complementary to its hormone, as per a key and lock analogy. The response of a given tissue or organ to a hormone is determined by the presence of receptors on target cells and receptor activation by hormone binding. The ability of a hormone to activate its receptor depends upon several factors, including how much hormone is synthesized and released by the endocrine gland, how it is transported through the circulation, how much reaches the target organ, and how potently and for how long the hormone can activate its receptor. These properties are fundamental to normal hormonal signaling.
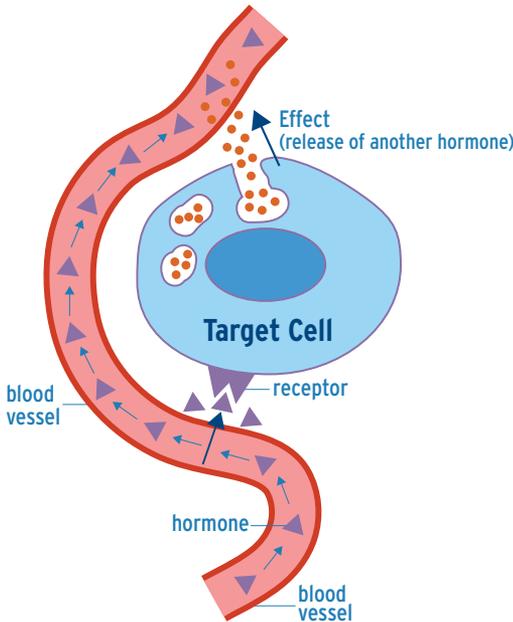
Figure 2. One hormone can influence the release of a another. As illustrated, the first hormone (purple triangles) has been released from its gland into the blood system, where it circulates through the body. When this hormone comes into contact with a target cell that expresses its receptor, the hormone binds to the receptor. When this happens, the cell is activated to release its own hormone (small red dots) that is released into the bloodstream.

EDCs can interfere with any – and all – of these steps. One of the best-known ways by which EDCs disrupt endocrine systems is by mimicking or blocking a natural hormone. In the case of hormone mimics, an EDC can "trick" that hormone's receptor into thinking that the EDC is the hormone, and this can inappropriately activate the receptor and trigger processes normally activated only by a natural hormone. In the case of hormone blockers, an EDC can bind to a hormone's receptor, but in this case, the receptor is blocked and cannot be activated, even if the natural hormone is present.

The best-known examples of hormone mimics are EDCs that act upon the body's estrogen receptors (ERs). Estrogens are a family of hormones that are produced in the gonads – the ovaries of females or the testes of males. Although we typically think of estrogens for their reproductive actions in females, they are also important for male reproduction, and they can act upon other tissues that express the estrogen receptors. Indeed, in both males and females, ERs are present in certain cells in the brain, in bone, and in vascular tissues, along with reproductive tissues and others. This explains why estrogens do more than control reproduction: they are also involved in neurobiological functions, bone growth and maintenance, cardiovascular functions, and others. Thus, EDCs that interfere with or mimic estrogren can have a wide array of actions.

Estrogen receptors are not the only receptors that are vulnerable in this manner by EDCs, although they are the best studied. Receptors for androgens (testosterone), progesterone, thyroid hormones, and many others are all potential targets of different EDCs. In addition, because EDCs are not natural hormones, a single EDC may be able to affect multiple hormonal signaling pathways. Thus, it is quite likely that a single EDC can disrupt two, three, or more endocrine functions, with widespread consequences on the biological processes that are controlled by those vulnerable endocrine glands.

4. IMPACTS OF EDCs

4.1   HISTORICAL PERSPECTIVE ON EDCS

Since the mid-20th century, the number and abundance of manufactured chemicals, some of which have been released (intentionally or not) into the environment, has increased exponentially. This modern "chemical revolution" has irreversibly changed ecosystems in a manner that has had severe impacts on wildlife and human health. Rachel Carson's book *Silent Spring*, published in 1962, was the first public warning that environmental contamination, in particular by the pesticide DDT, might be responsible for the reduced numbers of birds and other species due to reproductive failure caused by this and other toxic chemicals. Decades later, the Wingspread conference of 1991, a gathering of experts on environmental chemicals led by Dr. Theo Colborn, resulted in the publication of a consensus statement that was the first such articulation of links between man-made chemicals and adverse effects on the health of animals, including humans. Several books and thousands of publications later, it is widely accepted that at least 1,000 chemicals act as EDCs. This is however only the tip of the iceberg, as tens of thousands of chemicals have never been tested for any endocrine disrupting actions. With the new framework of using the key characteristics of EDCs (2) for hazard identification in place (**Figure 3**), this list will undoubtedly grow.

A cause-and-effect link between exposure to a putative EDC and a disease outcome is difficult to prove in humans. Nevertheless, it was known that incidents of major chemical spills and environmental contamination, discussed below, could cause toxicity in humans, raising the possibility that EDCs could affect human health. This was particularly important when considering a fetus or child, life stages at which even small amounts of natural hormones have large developmental effects. Moreover, although it is now well-accepted that some chemicals and pharmaceuticals can cross the placenta, this is a relatively recent departure from the once prevailing view that the placenta acted as a barrier protecting the developing fetus from environmental exposures.

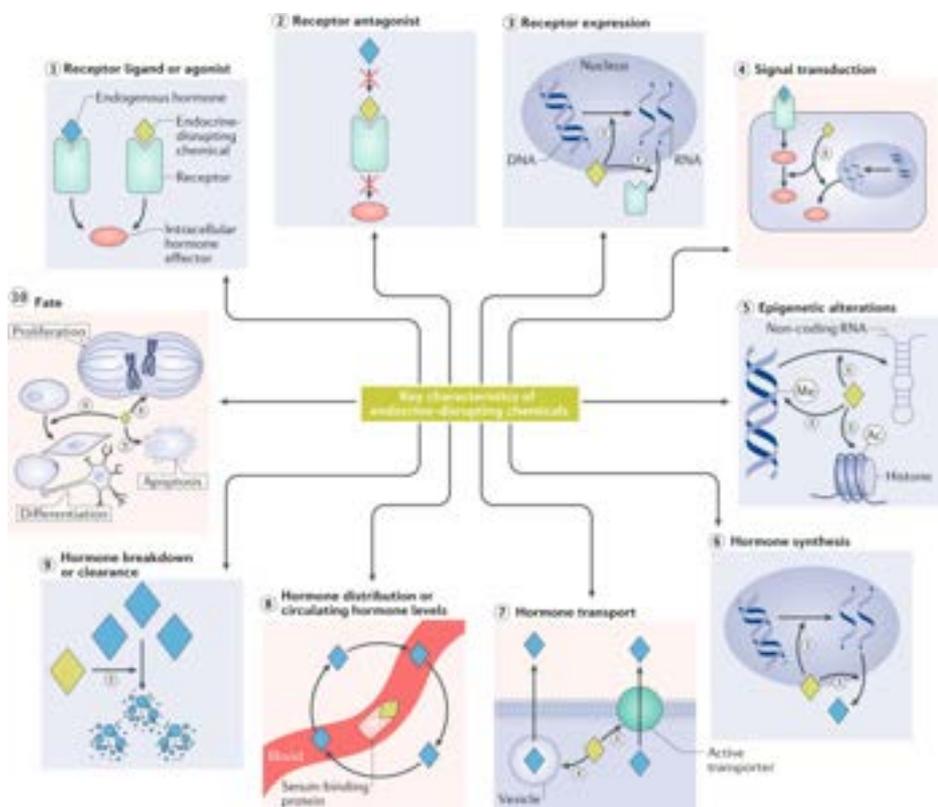**...IT IS WIDELY ACCEPTED THAT AT LEAST 1,000 CHEMICALS ACT AS EDCS.**

Figure 3. Ten key characteristics of EDCs are illustrated. If a chemical possesses at least one of these characteristics it is categorized as an EDC. From (2).

Two unfortunate events in the 1960s and 1970s transformed and ultimately negated this perspective that the fetus was protected from the environment. The first was the realization that pregnant women given the pharmaceutical thalidomide to alleviate nausea during the first trimester had a much greater risk of giving birth to infants with limb malformations. This proved that the fetus was vulnerable to pharmaceuticals given to the mother and that the placental barrier could be circumvented. The second breakthrough discovery was that of diesthylstilbestrol (DES) given to pregnant women to avert miscarriage. DES is similar in its properties to natural estrogen hormones. Girls who had been exposed to DES in the womb often developed reproductive tract malformations and some developed rare reproductive cancers in adolescence that were normally only seen in postmenopausal women (18). Because of the long latency between exposure (fetus) and disease (adolescence), the connection to the mother's use of DES was not initially obvious. However, experimental work in mice exposed to DES as fetuses identified reproductive disorders in the offspring of both sexes as they matured to adulthood. This cause-and-effect relationship between fetal DES, reproductive tract malformations, and reproductive tract cancer later in life seen both in humans and mice was compelling and the field of endocrine disruption was born.

Proving that chemical contamination of the environment adversely affects humans remains a scientific and public policy challenge. The most direct evidence for cause-and-effect between chemical exposures and toxicity came from several large-scale disasters in which humans were exposed to varying amounts of chemicals; high levels were acutely toxic, and lower levels were later found to have chronic, subtle, and long-lasting effects. One example is the 1976 explosion of a chemical manufacturing plant in Seveso, Italy, that exposed residents to high levels of dioxins. Two more tragic exposure examples occurred in 1968 in Yusho in Japan (PCBs), and in 1979 in Yucheng, Taiwan (polychlorinated dibenzofurans) in which contaminated cooking oil caused mass poisoning. Another common route of human exposure is in agriculture. An infamous act of agricultural contamination was the accidental poisoning of cattle in the US state of Michigan in the 1970s by feed containing the flame retardant polybrominated biphenyl (PBB), the human health outcomes of which remain poorly understood. Contamination also occurs by the routine seasonal spraying of crops with pesticides. This established practice can result in accumulation in body tissues of exposed workers, nearby residents, consumers of the food, and even future generations.

4.2 EDC EXPOSURES TO THE INDIVIDUAL AND TO FUTURE GENERATIONS – EPIGENETIC MECHANISMS

Exposure to environmental chemicals is life-long and ubiquitous. Animals and humans living in contaminated environments carry personal body burdens – the amount of chemicals contained in an individual's tissues – from direct exposure accumulated throughout their lives (**Figure 4**). Some of these EDCs are persistent and bioaccumulate (i.e., build up over time in body tissues). When humans are tested for the presence of EDCs in their blood, fat, urine, and other tissues, the results consistently demonstrate a variety of EDCs in nearly all individuals worldwide (19-21). There are numerous studies documenting human body burdens, with the US National Health and Nutrition Examination Survey (NHANES) database containing 60 years of data on exposures, lifestyle, and health in humans. These measurements reflect contact with EDCs through food, water, skin absorption, the atmosphere, and other sources. Body fat is a particularly important reservoir for EDCs, as these chemicals' compositions tend to make them fat-soluble. In addition, measures of EDC body burdens reflect not only contemporary contact with EDCs; they also include past exposures, sometimes decades ago, to persistent chemicals such as PCBs and others that are not metabolized but instead

Figure 4. EDCs have effects on health across the entire life cycle, although early development has particular vulnerability.

accumulate in individuals throughout their lives. More detailed examples of endocrine and neurological disorders associated with direct exposures to individuals – especially when exposure occurs during development – are provided below.

Beyond an individual's own lifetime of exposures is the inheritance of exposures to EDCs from their ancestors. For example, during pregnancy, some of the chemicals stored in a woman's body or ingested through the diet may cross the placenta and affect her developing embryo. Some EDCs are detectable in breast milk and can be passed to the suckling infant (despite this risk experts agree that most women should breast feed). When a developing fetus or infant is exposed in this way, the cells that will become future gametes – sperm or egg cells – may also be exposed. These gametes are the progenitors of the next generation: the grandchildren. There is now considerable evidence that EDCs induce changes to these developing gametes that may be heritable, not due to mutations, but rather, due to a mechanism referred to as "epigenetics." Epigenetic modifications happen when a gene's likelihood of being expressed is altered by an addition or removal of factors in the nucleus that interact with DNA. These factors, as a population, play key roles in whether a cell produces a certain protein, how much, and when. Recent evidence shows that epigenetic "marks" to gametes induced by environmental factors such as EDCs are sometimes inherited. In other words, the exposures of ancestors to EDCs may be manifested across multiple generations. This is a key concept because it means that legacy chemicals from generations ago – even chemicals that are no longer manufactured – may have health consequences on the descendants today.

5. EDCS AND LINKS TO ENDOCRINE DISEASE

It has been estimated that, globally, upwards of 24% of human diseases and disorders are attributable to environmental factors (22) and that the environment plays a role in 80% of the most deadly diseases, including cancer and respiratory and cardiovascular diseases (23). EDCs may be primary contributors to those disorders with hormonal underpinnings. The incidence of endocrine-associated pediatric disorders, including male reproductive problems (cryptorchidism, hypospadias, testicular cancer), early female puberty, leukemia, brain cancer, and neurobehavioral disorders have all risen rapidly over the past 20 years. The prevalence of developmental disability in U.S. children increased from ~13% in 1997 (24) to 17% in 2022 (25). The preterm birth rate in the U.S., U.K., and Scandinavia has increased by more than 30% since 1981, an outcome associated with increased rates of neurological disorders, respiratory conditions, and childhood mortality, as well as obesity, type 2 diabetes, and cardiovascular disease in adulthood. Data from human, animal, and cell-based studies have generated considerable evidence linking EDC exposure to these and other human health disorders.

These increased rates of endocrine and neurological diseases have occurred in parallel with increased production of manufactured chemicals (1) (**Figure 5**). Global production of plastics grew from 50 million tons in the mid-1970s to nearly 460 million tons today. Similar trends hold for other chemical sources including pesticides, fire retardants, solvents, and surfactants. Sales for the global chemical industry have sharply increased from USD$171 billion in 1970 to over USD$5 trillion in 2023 (with expected sales of over $6 trillion by 2027).

While associations between increased human chemical exposures and increased disease rates are suggestive, they do not 'prove' that the two are linked. However, data from cell-based studies, animal studies, and other experimental systems over the past few decades provides a wealth of evidence supporting this direct link. Proving that a chemical contributes to a human disease would require exposing a group of humans and then observing the resulting disorder. Though this type of testing is done for pharmaceuticals, it would be unethical and impossible to test the impact of toxicants on humans in this way. Conclusions about EDC-related health

effects, therefore, must be made using data from epidemiology studies, which can only reveal associations, and by making inferences about human risk from experimental data obtained from animals or cell-based models. An additional challenge is that humans are exposed to a complex mixture of chemicals across the lifespan, making it difficult to establish if health effects result from exposure to a few problematic chemicals or a collective combination of chemicals. Thus, although environmental exposures are recognized to contribute to endocrine-related disorders, finding a 'smoking gun' linking any specific EDC to any specific disease is difficult.

In many ways, the present debate about EDCs parallels the long and contentious debate surrounding the risks of cigarette smoking. Tobacco smoke was first shown to cause lung cancer in 1950, but debate about this link and how to regulate tobacco raged for decades, with executives from the biggest tobacco companies famously falsely testifying before the US Congress in 1994 that the evidence showing cigarette smoking caused diseases such as cancer and heart disease was inconclusive. Today smoking remains the single biggest cause of cancer in the world, killing one person every 15 minutes (26). For EDCs the available data linking chemicals or a class of chemicals to chronic disease is, in some cases, comparable in strength and breadth to the evidence linking smoking with lung cancer. Thus, despite the insistence by some groups that the evidence is inconclusive, the body of data revealing EDC-related health effects is sufficient to warrant concern that EDCs adversely impact public health.
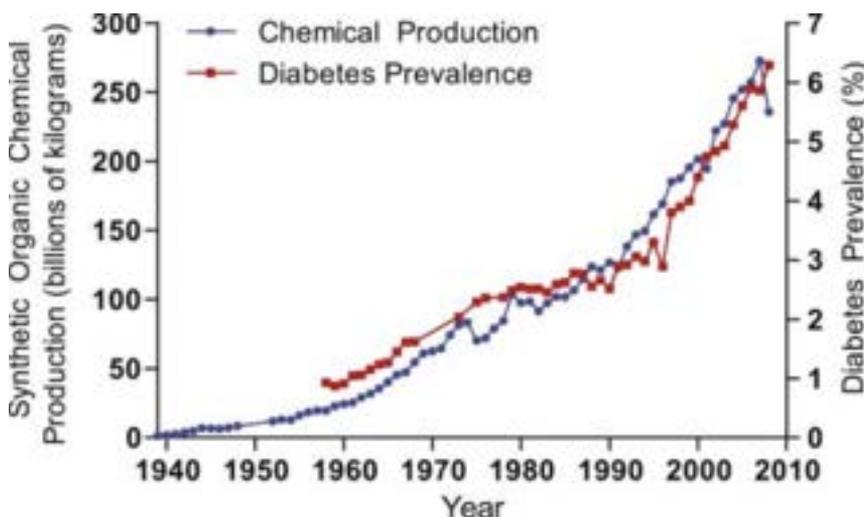
Figure 5. US synthetic chemical production and diabetes prevalence, illustrating similar increases over the decades. From (1)

5.1   NEUROLOGICAL AND BEHAVIORAL DISORDERS

Numerous public health agencies including the World Health Organization, the United Nations, and the National Toxicology Program in the U.S. have expressed concern about EDC effects on the brain and behavior (27, 28). Childhood neuropsychiatric disorders are increasing in prevalence with as many as 1 in 6 children in the USA now diagnosed with at least one such disorder (24). These disorders include attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD), as well as depression and other mood disorders, learning disabilities, executive function deficits, and conduct disorders. It is irrefutable that the environment is playing a role in the rising prevalence of these and other neurodevelopmental disorders (29, 30).

As a class, PCBs have the strongest and longest-known associations with neurological disorders. In humans, there is evidence for impaired neurodevelopment (31), lower IQ, and problems with attention, memory, and fine motor skills such as writing. Some of these studies were completed in communities living near the Arctic, a place long thought to be pristine but now known to bioconcentrate PCBs and other persistent pollutants to some of the highest levels on the planet (32). Some PCB metabolites alter thyroid activity, long recognized to elevate the risk of impaired neural development. Similarly, exposures to polybrominated diphenyl ethers (PBDEs), which were used as flame retardants, are associated with reduced IQ and other cognitive deficits (33). PBDEs affect thyroid activity, neurotransmitter activity, synaptic organization, and neuron viability suggesting that they impact not only brain development but also brain aging. The chemicals replacing PBDEs, including so-called "next generation" brominated flame retardants and organophosphate esters, also appear to be harmful to the developing brain (34). Brominated flame retardants, perfluorinated compounds, and pesticides (organophosphates such as chlorpyrifos, organochlorines such as DDT and its metabolites, and pyrethroids) (35, 36) are linked to ADHD, ASD, and related learning disabilities (37). Links have also been reported between pesticide exposures and neurodegenerative disorders such as Parkinson's Disease (38, 39) and with depressive behaviors (40). Experimental animal data show numerous neurobiological changes caused by all the chemicals listed here plus other EDCs. Effects on the developing brain include disruption to overall neuronal development, properties of synaptic organization, neurotransmitter synthesis and release, and sexual differentiation. These disruptions translate to cognitive, social, and other deficits. Emerging evidence is also revealing that EDC action at the level of the placenta can compromise neurodevelopment (41). In conjunction with a growing literature on behavioral effects of EDC exposures, especially during development, these studies underscore the brain as a vulnerable target of EDCs (42).

5.2 DIABETES, OBESITY, AND CARDIOVASCULAR DISORDERS

The prevalence of metabolic diseases is rising rapidly across the globe. While lifestyle factors such as diet and activity are clear contributors, accumulating evidence suggests that other factors, including chemical exposures, may also play a role. Chemicals that disrupt metabolism, referred to as metabolism disrupting chemicals (MDCs), are a subset of EDCs that are thought to promote metabolic dysfunction and increase the risk of common disorders such as obesity, diabetes, and non-alcoholic fatty liver disease (NAFLD) (43). Moreover, some MDCs are also linked to cardiovascular disease, a common clinical consequence of metabolic dysfunction. Indeed, recent data indicate that an expanding number of chemicals have the capacity to disrupt metabolic function and are associated with metabolic disorders in human cohorts.

Among the first MDCs described were the "obesogens," chemicals linked to the abnormal expansion of fat mass that enhance weight gain by altering or reprogramming key parts of the endocrine system governing metabolism, energy balance, and appetite, resulting in obesity and its related adverse health outcomes (43-46). Indeed, recent work has linked MDCs to diabetes, NAFLD, and cardiovascular disease, often with the same MDC linked to multiple metabolic disorders. Laboratory animal work shows that developmental exposure is particularly deleterious in predisposing an individual to weight gain and subsequent related adverse health outcomes including impaired insulin sensitivity, frank type 2 diabetes, cardiovascular disease, and altered lipid metabolism (47-49).

The best-studied obesogenic EDCs to date are tributyltin (TBT) and triphenyltin (TPT) (50), used as anti-foulants and anti-fungals. These and other chemicals act through hormone receptors such as PPARγ (49). Disruption of thyroid hormone function is another mechanism by which obesogenic chemicals can act, due to the thyroid gland's important role in the maintenance of normal metabolism and energy expenditure. Some effects of PCBs and PBDEs may be mediated via the thyroid axis (51, 52). A brominated flame retardant, Firemaster 550, was shown to alter thyroid hormone levels in pregnant rats and their offspring, with the pups growing up to develop obesity, cardiac disease, early puberty, and insulin resistance (53). Although that work needs to be repeated and extended, it is noteworthy that Firemaster 550 is now one of the most commonly used fire retardants in the U.S.; it is a ubiquitous contaminant of household dust, and biomonitoring studies have identified Firemaster 550 in human urine (54).

Maintenance of blood sugars in the normal range requires the tight coupling of insulin secretion from pancreatic β-cells with insulin action in insulin-responsive tissues such as muscle, liver, and adipose tissue. Failure to maintain this coupling results in elevated blood sugar levels and the clinical development of diabetes and its associated complications. Critically, global diabetes rates are increasing dramatically, with estimates that the number of adults afflicted will rise from 537 million in 2021 to 784 million by 2045. Multiple MDCs have been implicated in impaired insulin secretion, insulin resistance, or both, with evidence suggesting that developmental windows are periods of unique susceptibility to MDC-induced metabolic dysfunction (55). MDCs linked to disruptions in insulin secretion and action include a diversity of inorganic and organic compounds of both natural and synthetic origin, including arsenic, cadmium, bisphenol A, PBDEs, PCBs, phthalates, and DDT, among others (55-57). Of particular interest to public health is arsenic, a common toxicant to which 94 to 220 million individuals globally are exposed to via high levels in groundwater, with the vast majority living in Asia (58), where diabetes rates are increasing especially rapidly. Importantly, there is evidence that exposures to several MDCs linked to diabetes risk are higher among low-income communities and communities of color, suggesting that MDCs may contribute to clinically important diabetes disparities (59).

Although the field of environmental MDCs is relatively new, phthalates, perfluorinated compounds, BPA, dioxins, PCBs, metals, and some pesticides are emerging as potential MDCs, meriting additional study. Furthermore, the metabolic derangements associated with MDC exposure are expanding to include other disorders of increasing public health significance such as NAFLD (43). PCBs and PFAS are common environmental contaminants linked to NAFLD development through multiple mechanisms (60, 61). Moreover, metabolic abnormalities associated with MDC exposures are critical risk factors for cardiovascular disease, a leading global killer. Multiple MDCs have been linked to cardiovascular dysfunction, including metals, dioxins, and bisphenols among others (62, 63). More research examining the role of MDCs in the development and progression of cardiovascular disease, as well as other cardiovascular risk factors such as hypertension, are needed.

...RECENT DATA INDICATE THAT AN EXPANDING NUMBER OF CHEMICALS HAVE THE CAPACITY TO DISRUPT METABOLIC FUNCTION AND ARE ASSOCIATED WITH METABOLIC DISORDERS IN HUMAN COHORTS.

5.3   REPRODUCTIVE DISORDERS

Among the strongest associations between EDC exposures and adverse outcomes are those for reproductive development, physiology, and pathology. The increased prevalence over the past 50 years of hormone-sensitive cancers (e.g., breast and prostate), compromised fertility, early puberty, decreased sperm counts, genital malformations, and unbalanced sex ratios (64) are at least partially attributable to increased chemical abundance and exposures. The increase in early puberty in girls, while contributed to by many factors including nutrition, stress, and other social determinants, may in part be due to exposures to estrogenic EDCs (65, 66). Such estrogenic compounds are also associated with uterine fibroids, ovarian dysfunction, and subfertility in humans and in animal models (67-69). BPA is linked with reduced egg quality and other aspects of egg viability in patients seeking fertility treatment (70, 71) – effects which closely parallel those seen in animal models (72). Danish women under 40 working in the plastics industry were more likely to have sought fertility assistance than unexposed women of the same age (73). In men, sperm counts have declined as much as 50% over the last half century in certain regions (74). Several chemicals, most notably phthalates, are associated with a variety of adverse effects on the male urogenital tract, including cryptorchidism, hypospadias, prostate disease, and testicular cancer (75). Growing evidence suggests effects can be inter- and even trans-generational (76).

5.4   CANCERS

Like other complex diseases, most cancers result from the interplay of genetic predisposition and the environment encountered by the individual. Relatively few cancers are linked to a single gene, underscoring the key role played by the environment. In fact, 2 in 3 cancer cases are environmentally linked in some way, leading the American Cancer Society to conclude that most cancers are preventable with lifestyle changes such as improved diet, more exercise, and reduced smoking. Certain jobs are associated with an elevated risk of cancers, particularly those with high burdens of chemical exposure, including painting, firefighting, working in the coal, steel, or rubber industries, textile and paper manufacturing, and mining.

The International Agency for Research on Cancer (IARC), a part of the World Health Organization, is the international authority that determines what agents are carcinogenic (cause cancer) in humans. As per IARC (305), there are 122 agents that the experts assembled by IARC have deemed carcinogenic to humans and 93 agents that they have deemed probably carcinogenic to humans. Many of these agents are chemical

carcinogens and those that are carcinogenic to humans include metals (such as arsenic, cadmium, nickel, and chromium), vinyl chloride, benzidine (used in dyes), solvents such as benzene and trichloroethylene, polycyclic aromatic hydrocarbons (PAHs), dioxins, PCBs, fibers and dust (silica, asbestos, wood, etc.), some pesticides including those on the Stockholm Convention's list of Persistent Organic Pollutants, tobacco, betel quid, and numerous pharmaceuticals (**Box 1**).

There are additional known or suspected carcinogens that are EDCs. Considering how many cancers involve hormones, it is not surprising that hormone-active chemicals such as BPA, phthalates, and some pesticides, are known or thought to contribute to cancer risk (76, 77).

The questions of which EDCs have the greatest impact, and when in life (prenatal, childhood, adult) EDC exposure most significantly contributes to cancer risk, remain unresolved issues. Studies using cellular and animal models have revealed that early-life exposure to chemicals such as BPA, phthalates, perfluorinated compounds, PCBs, and malathion and DDT pesticides can heighten cancer risk later in life (77). Emerging epidemiological studies are beginning to establish correlative relationships for some of these chemicals in humans (78-80). Establishing such links in humans is difficult because it requires having information about exposures that may have occurred decades earlier. There is no question, however, that based on the critical and broad effects of the environment on cancer prevalence and manifestation, minimizing chemical exposures will have a tremendous positive impact on cancer risk and survival.

BOX 1. THE STOCKHOLM CONVENTION ON POPS

The Stockholm Convention on Persistent Organic Pollutants (POPs) is a global treaty to protect human health and the environment by eliminating or restricting the production and use of POPs. Annex A listing calls for elimination, Annex B listing calls for restricted use, and Annex C recognizes unintentional production. The Convention initially had 151 signatories in 2001 and went into effect in May 2004. Today the Convention has been ratified by 186 parties (185 states and the EU). The Convention requires a multi-step review process of nominated POPs by a committee of scientific experts who are nominated by parties from the five UN regional groups. This POPs Review Committee (POPRC) meets annually to assess whether nominated chemicals meet the Convention criteria of being persistent, bioaccumulative, can travel across boundaries, and lead to significant adverse impacts on human health and/or environmental. New chemicals were added to the Convention in 2001, 2009, 2015, 2017, 2019, 2022 and 2023.

5.5   INFLAMMATION AND IMMUNITY

Although the diseases and disorders associated with EDC exposures are diverse, many of them have in common increased inflammation and underlying immune system problems. Inflammation is at the heart of a wide range of chronic diseases including obesity, cognitive and behavioral deficits, cardiovascular disease, respiratory disorders, reproductive disorders, and cancers. The immune and endocrine systems often work together in responding to environmental challenges (80) and to protect against inflammation. Related to this is the potential of EDCs to affect the gut microbiome (81, 82), which comprises an ecosystem of microbes (bacteria, fungi, protozoans, archaea, and viruses) that colonize the digestive system and assist with protecting against pathogens (83). The microbiome is important for the body's immune function; when compromised, as can happen due to EDC exposures, inflammation and illness may ensue (84, 85).

THE INCREASED PREVALENCE OVER THE PAST 50 YEARS OF HORMONE-SENSITIVE CANCERS (E.G., BREAST AND PROSTATE), COMPROMISED FERTILITY, EARLY PUBERTY, DECREASED SPERM COUNTS, GENITAL MALFORMATIONS, AND UNBALANCED SEX RATIOS ARE AT LEAST PARTIALLY ATTRIBUTABLE TO INCREASED CHEMICAL ABUNDANCE AND EXPOSURES.

6. THE SCIENCE OF EDCs

There is widespread, conclusive agreement about the hazards posed by cigarette smoke, lead, radioactive materials, and many chemicals. Decades of laboratory research, together with clinical evidence in individuals and epidemiological data from human populations have provided conclusive evidence for cause-and-effect links between exposure and disease or death. In the case of chemical assessment and management, the ability to directly link an exposure to an adverse health outcome or death can be proven in cases of known exposures to high levels of a particular chemical. Thus, traditional toxicological testing has been very important in identifying and characterizing such chemicals that pose a threat to humans and wildlife. However, because most people are exposed to a variety of EDCs, usually at low doses, in mixtures, and at different life stages, the ability to directly relate a disease in adulthood – for example, type 2 diabetes – to exposures to EDCs during life, especially during critical developmental periods, is much more difficult. Furthermore, complex endocrine and neurological disorders are virtually never attributable to a single factor: they involve a combination of genetic predispositions, typically due to a suite of genes together with environmental challenges. Therefore, the current view is that EDCs are one class of contributing factors to the increasing prevalence of chronic disease.

6.1   KEY CHARACTERISTICS OF EDCs

Although there are tens of thousands of manufactured chemicals, as of the late 2010s there were still no agreed-upon features of a chemical that allowed it to be characterized as an EDC. Beginning in 2018, a group of experts developed a list of those key properties of chemicals that underlie a risk of endocrine disruption (2) (**Figure 3**). This framework allowed, for the first time, the transparent and reproducible organization of mechanistic data to identify the hazard of being an EDC and provided a basis for grouping chemicals as EDCs. These efforts, when data are deemed sufficient, provide a foundation for risk assessment or, when data are sparse, help identify data gaps and research priorities. Importantly, using the key characteristics does not require a complete understanding of how mechanistic properties of putative EDCs cause an endocrine disrupting effect(s). This is a notable contrast with other approaches, for example, mechanism of action and adverse outcome pathways, that require complete causal understanding because it allows for more rapid implementation of public health practices. A chemical need only have a single key characteristic to be considered an EDC; and some chemicals such as BPA have nine of ten of these key characteristics (**Figure 3**).

6.2   WHY UNDERSTANDING THE PROPERTIES OF HORMONES IS ESSENTIAL TO UNDERSTANDING HOW EDCs ACT

To properly understand effects of EDC exposures and their long-term consequences requires an understanding of hormones and their actions. When a new chemical is developed, traditional toxicity testing includes determining its effect on cell damage, whether it alters DNA or causes cancer, and/or causes birth defects. The majority of this testing is done at a range of high doses expected to rapidly reveal an adverse outcome. Little to none of this testing includes a hormonally relevant endpoint, which may be more subtle and which may require a long timeline for its effects to be observable. Thus, traditional toxicology testing is inadequate in determining whether a chemical is an endocrine disruptor (**Box 2**). The Endocrine Society has become a leader in EDC science and practice precisely because it is the leading international society focusing on the study of hormones, their physiological actions and the treatment of dysfunctions in pathophysiological endocrine conditions.

6.3 THERE MAY BE NO SAFE DOSE FOR CHEMICALS THAT DISRUPT THE ENDOCRINE SYSTEM

Regulatory toxicology operates under several flawed assumptions (**Box 2**). First is the assumption that each chemical has a safe or acceptable exposure level, with a threshold below which the chemical is safe. The 'old science' paradigm on which this conclusion is based uses as its endpoint some observable event such as a tumor or death that is caused by an exposure.

Second, regulators work under the assumption that chemicals act in a predictable linear manner. Based on the paradigm that 'the dose makes the poison,' testing begins with the identification of a toxic dose. To arrive at a 'safe' dose, lower and lower doses are tested in a linear manner – what is referred to as a monotonic or linear dose-response curve - until a dose is established with no obvious toxicity. This is then divided by an arbitrary 'safety factor,' usually 100. This is considered a safe dose that is allowable for use in the marketplace for the purposes of regulation.

Third, regulators test compounds one at a time. This ignores the reality that we are all exposed to dozens or hundreds of chemicals throughout our lives and that these chemicals may interact in complex manners (86).

These assumptions represent an outdated perspective that does not hold true for chemicals that affect the endocrine system. Endocrine disorders can take weeks, months, or years to manifest. This timeframe is far beyond the scope of regulatory studies. Furthermore, disruptions of hormone levels or actions may not be immediately observable in directly exposed individuals or may manifest in subsequent generations. The inability of toxicological testing to quantify such outcomes is a serious limitation of this approach to determining risk. Finally, "healthy" levels of hormones differ with sex and change with age thus creating vulnerable windows of exposure traditional toxicity testing does not account for.

Several additional concepts intrinsic to endocrinology are crucial to our understanding of how EDC exposures at even extremely low dosages can alter biological outcomes and importantly, and that the effects of low doses cannot be predicted by the effects observed at high doses (87).

Endocrinologists have long known that natural hormones often do not act with monotonic dose-response curves (88). The same has been shown again and again for EDCs, which at exceedingly low doses – often below the regulatory 'safe' level – can have adverse effects that are often not predicted by the chemical's effect at higher doses. In other words, there is no safe dose.

These principles of hormone and EDC actions have been incontrovertibly illustrated for BPA, which was extensively studied in a joint project called CLARITY-BPA funded by the NIEHS, National Toxicology Program, and the U.S. Food and Drug Administration (FDA). This study revealed that while there were few overt toxicity events, more careful analyses of endocrine glands and behavioral studies indicated effects on ovary, prostate, brain and behavior, heart, immune system, and testis (89). Most of the endpoints were affected in a manner not predicted by a linear dose-response curve, with lower doses often having greater effects.

7. REAL WORLD EXPOSURES TO EDCs

7.1 DEVELOPMENTAL EXPOSURE AND WINDOWS OF VULNERABILITY

Hormones coordinate the development of every individual, beginning with a single fertilized cell, up to the many millions of specialized cells that make up the blood, bones, brain, and other tissues. In a fetus, these natural chemicals come from the mother, the placenta, and from the developing fetus itself. At this time, hormones circulate in very low concentrations, typically in the part-per-trillion to part-per-billion range. As complexity builds, different endocrine organs can become activated. This is perfectly timed to ensure normal developmental processes; too little or too much leads to disease and pathology. More than a century of biological research has proven that the programming and regulation of life processes require hormones to be present in particular amounts at particular times and, further, that each organ's and tissue's needs change through the life cycle in response to demand. Hormones also establish and maintain critical sex differences in nearly every major organ system but especially the brain, reproductive system, liver, and heart.

Early life, especially the fetus and infant stages, is a period of vulnerability, when any disruption to natural processes may change, sometimes irreversibly, the structure and/or function of a physiological system. The timing of release, in addition to the amount of hormone, is absolutely crucial to normal development. It stands to reason, then, that because EDCs interfere with hormone actions, exposures during a sensitive developmental period can have both immediate and/or more latent consequences. The timing of exposure is key to understanding which organ or tissue may be affected, as the development of different parts of the body occurs at different rates. Thus, an organ that is developing during the time of the harmful exposure is more likely to be affected than an organ that has already completed development.

The outcomes of exposures during vulnerable periods may be physical malformations, functional defects, or both. Consider again the example of DES given to pregnant women, whose daughters (exposed in utero) often had structural malformations of the reproductive tract, together

with an increased propensity for rare vaginocervical carcinomas later in life. Another very real and complex aspect of the windows of vulnerability concept is that the same exposure can have different effects depending on when in development the exposure occurred. For instance, in rodents, first trimester exposure of a fetus to the pesticide chlorpyrifos, a known EDC, can alter thyroid structure and function in the offspring when they become adults, while second trimester exposure to chlorpyrifos can increase insulin levels in the adult offspring.

Some disturbances in hormone levels may not cause obvious structural changes, but may still lead to functional changes, disease, or dysfunction later in life. This concept of windows of vulnerability is referred to as the "Developmental origins of health and disease (DoHAD)" (**Box 3**). This field is well accepted by researchers who acknowledge that children are more vulnerable than adults to EDCs because their bodies are still developing. Children are also at greater risk of exposures than adults for a number of reasons including that: 1) they are exposed to many fat-soluble contaminants in breast milk or in formula; 2) they put their hands and objects in their mouth far more often than adults; 3) they live and play close to the ground; and 4) they have greater skin area relative to their body weight than adults allowing for more absorption of chemicals (90). The harm of exposures to children is thus due to differences in the ways they may be exposed, their developmental vulnerability, and a longer life expectancy with a much longer horizon for exposure to manifest as disease. Furthermore, they have limited understanding of danger and are politically powerless to avoid such exposures.

While this discussion has focused on the particular vulnerability of the embryo, fetus, infant, and child, every phase of the life cycle, from childhood to adolescence, adulthood, and aging, is sensitive to hormones and EDCs. Traditional toxicological testing invokes the concept that "the dose makes the poison." The new scientific insights into EDCs suggest instead that "the timing makes the poison" in considering the vulnerability of the developing organism.

EARLY LIFE, ESPECIALLY THE FETUS AND INFANT STAGES, IS A PERIOD OF VULNERABILITY, WHEN ANY DISRUPTION TO NATURAL PROCESSES MAY CHANGE, SOMETIMES IRREVERSIBLY, THE STRUCTURE AND/OR FUNCTION OF A PHYSIOLOGICAL SYSTEM.

7.2   MIXTURES

In a laboratory the emphasis is on rigorous control of the environment, so that a single change in condition can be compared to a control condition. For example, some work is conducted in homogeneous cultures of a cell line, grown under identical conditions from one culture plate to the next. Animal work is often conducted in a laboratory with row after row of cages of mice, each genetically identical to the others, with a very specific type of bedding, food, water, light cycle, and controlled temperature. The essence of traditional toxicological methods is the administration of a single, pure chemical in exact dosages, with all other conditions equal to allow comparison of the chemical to a control (placebo) group.

BOX 3. THE DEVELOPMENTAL ORIGINS OF HEALTH AND DISEASE (DOHAD) AND SEX DIFFERENCES

DOHaD, also referred to as the "Fetal basis of adult disease" (FeBAD), is based on scientific evidence that the roots of many diseases and dysfunctions occur very early in life, especially during the embryo, fetus, infant, and child stages. For example, under- or over-nutrition of a pregnant woman has an influence on the fetus's propensity to develop metabolic disorders including obesity, diabetes, and others later in life. This research has since been extended to environmental influences such as cigarette smoking, pollution, and environmental chemicals. Other evidence has shown that the developing germ cells – precursors to the sperm and egg cells of the fetus – are quite vulnerable to disruptions from even low doses of EDCs. More recently, the nervous system, the development of which begins in early gestation and continues well into childhood, has been found to be very sensitive to EDC exposures. These systems are often sexually dimorphic, particularly those governing reproduction and behavior, including socioemotional behaviors. Those sex differences are largely organized by hormones, arise during narrow critical periods during development, and result in sex-specific vulnerability to numerous neurodevelopmental and psychiatric disorders including autism, eating disorders, anxiety, and schizophrenia. Certain cancers, especially reproductive cancers, also seem to have their origins in early life. While the manifestation of disease or disorder may not be apparent at birth, following a latent period that could be years or even decades, the results of these exposures become evident, often in adolescence, adulthood, or aging. Thus, DOHaD is a key concept in understanding the influence of EDC exposures during these vulnerable periods.
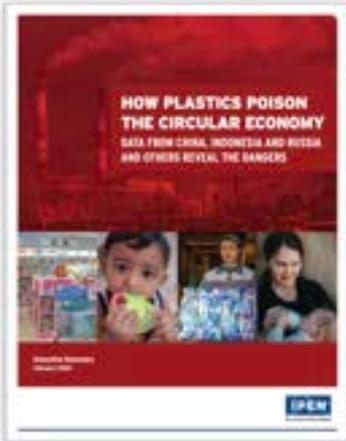
PLASTICS AND EDCs POISON THE CIRCULAR ECONOMY

IPEN studies looked at plastic production and waste management in China, Indonesia and Russia, finding all three countries struggled to safely manage massive volumes of plastic waste. We also tested plastic toys and consumer products, finding that highly toxic chemicals including BPA, BFRs, and other EDCs, were widely present, including in products for children.
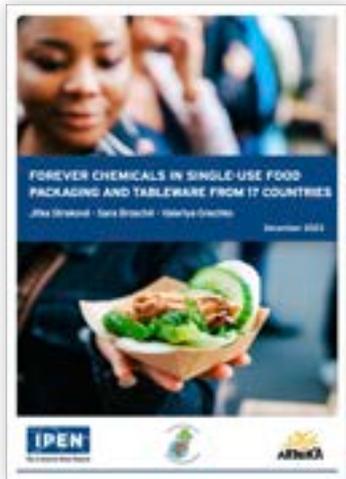
PFAS "FOREVER CHEMICALS" IN FOOD PACKAGING

A 2023 study by IPEN and 18 IPEN member groups found PFAS "forever chemicals," including substances known or suspected of being EDCs, were widespread in food packaging sampled from 17 countries. Of 119 samples tested, 57 contained PFAS at levels that exceed current or proposed EU safety levels.
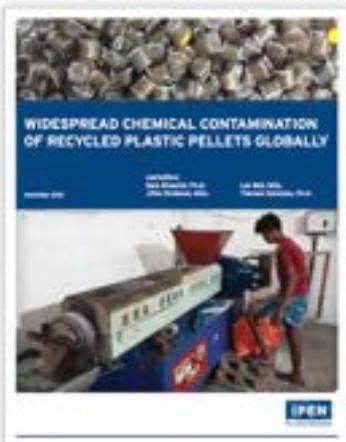
TOXIC CHEMICALS IN RECYCLED PLASTIC

For this IPEN study, we procured plastic pellets from 24 recycling facilities in 23 countries and tested them for three types of toxic chemicals, including known EDCs. All of the samples were contaminated with one or more of the chemical groups, and 21 of 24 samples contained one or more chemicals from all three groups of toxic substances. The study shows that recycling will not solve the plastic waste crisis because recycling disperses toxic chemicals through the market and the environment.

However, the world is not like a laboratory. Humans are genetically unique, they live in very different environments, they migrate, each person has their own dietary and nutritional exposures, and more. Moreover, each person is exposed to mixtures of EDCs throughout their lives – that is, each person has a unique "exposome," the sum of everything to which the individual is exposed. The 'new science' of EDCs recognizes these realities: that exposure in nature is lifelong; that EDCs are ubiquitous and global; and that there is bioaccumulation and biomagnification of EDCs up the food chain. Furthermore, with the exception of occupational exposures, it is rare that environmental exposure involves pure compounds. Instead, exposures involve mixtures of compounds, as well as degradation products of single compounds.

An achievement of the last decade has been progress in measuring mixtures of chemicals in humans, relating this to disease outcomes, and modeling this in animal studies (**Box 4**). For example, a mixture of chemicals commonly found in pregnant women in the EU was used to determine effects on thyroid hormone signaling in a frog embryo model (91). Results demonstrated that exposure to the mixture changed development and behavior and led to neurobehavioral and molecular changes in the brain. Similarly, a series of studies in the US using a mixture of phthalates determined to be environmentally relevant showed a number of adverse outcomes on reproductive functions in mice, including reproductive organ weight, disrupted reproductive cycles and diminished fertility (92). Another group exposed rats to a mixture of chemicals, each shown individually to have neurological effects, and reported changes to brain development and behavior (93).

BOX 4. RELEVANCE OF EDC MIXTURES

- Humans and wildlife are exposed to multiple chemicals throughout their lives and this may change due to migration or dietary changes.

- The chemical mixture that individuals are exposed to varies depending upon where someone live and works.

- Studies measuring chemicals and/or metabolites in human samples such as urine, blood, amniotic fluid, and umbilical cord blood reveal the presence of multiple chemicals.

- Chemicals tested at dosages that individually have no observable effect can cause endocrine disruption when combined.

7.3 EARLY LIFE EDC EXPOSURES CAN 'PRIME' RESPONSES TO SUBSEQUENT EXPOSURES OR OTHER EXPOSURES

Endocrine disrupting chemicals are just one of many factors that affect our health and well-being. The environment, writ large, includes both internal and external stimuli such as psychological and biological stressors; pollutants including but not limited to EDCs such as air pollutants, diesel exhaust, and cigarette smoke; nutrients in our diets; products in our homes and offices; personal care products; pathogens; substances of abuse; and many others.

Exposures to a single stressor such as an EDC can cause short- and long-term effects, particularly when exposure occurs during vulnerable life stages as per the DoHAD hypothesis. Such changes induced by early life EDCs can change the trajectory of health and disease later in life, and moreover, can affect how the individual responds to subsequent life challenges, whether EDCs or other insults. This concept is similar to the "two-hit" model of carcinogenesis (94) in which early life events may prime the organism to develop cancer in response to subsequent carcinogens.

For EDCs, this was modelled in a series of studies in which rats were exposed twice to a PCB mixture, once early in life and again in adolescence, a model often referred to as a "two-hit" model. Results of that two-hit work demonstrated that the effects of the second hit of PCB in adolescence was modified by the nature of the first hit, with differences in outcomes such as neurobehavior and gene expression in the brain (95, 96). Thus, a first exposure sets the stage for how the body might respond to a second exposure. In these models, it is believed that the initial "hit" causes some sort of programming change via epigenetic mechanisms that change how genes are expressed and translated to proteins. The consequence of this programming is a differential response to the second "hit."

8. EXPOSURE OF HUMANS TO EDCs

EDCs are a global and ubiquitous problem. Exposure occurs at home, in the office, on the farm, through the air we breathe, the food we eat, and the water we drink. Of the hundreds of thousands of manufactured chemicals that exist, it is estimated that about 1,000 to date have been shown to have endocrine-acting properties. Biomonitoring (measurement of chemicals in body fluids and tissues) shows that nearly 100% of humans have a chemical body burden. In addition to the known EDCs, there are countless suspected EDCs or chemicals that have never been tested.

Exposures to known EDCs are relatively high in contaminated environments in which industrial chemicals leach into soil and water, are taken up by microorganisms, algae, and plants, and move into the animal kingdom and up the food chain. Top predators, including humans, have among the highest concentrations of such environmental chemicals in their tissues. Of great concern is evidence that some chemicals are transported by air and water currents to other parts of the world that are quite distant from their original source. In fact, there are regions that never had any chemical industry, such as the polar regions, yet humans and animals who live in those regions have detectable levels of some EDCs in their bodies. Moreover, the persistence of some chemicals, especially those chemicals that are persistent organic pollutants (POPs), means that even some banned chemicals will persist in the environment for years still, if not decades. Some of these POPs, such as polychlorinated biphenyls (PCBs), perfluorinated chemicals (PFAS), dioxins, and DDT, are known endocrine disruptors.

Exposure to EDCs may also come in the form of pesticides, algicides, and other chemicals designed to kill unwanted organisms. Spraying of homes, agricultural crops, and ponds releases airborne and sedimented chemicals that are inhaled, get on skin, and are ingested from sprayed food. It is not surprising that some of these chemicals are EDCs. Many, especially those used for pest control (e.g., for extermination of insects or rodents), were specifically designed to be neurotoxicants or reproductive toxicants. The high sensitivity of reproductive and neural systems to natural hormones, and the similarity of these physiological processes in both invertebrates and vertebrates, means that chemicals designed to perturb these functions in one species will affect others as well – including humans. Herbicides in widespread use such as atrazine, 2,4-D, and glyphosate are considered

EDCs, and the fungicide vinclozolin is a known EDC. Further discussion of the pesticides DDT, chlorpyrifos, and glyphosate, of which the first is banned in many parts of the world but the other two are still registered in most countries, appears below.

Other routes of exposure to EDCs include food and water containers that are comprised of chemicals that may leach into foodstuffs and beverages. A well-known example of this is bisphenol A (BPA), and there is growing evidence that chemicals used as substitutes for BPA (in response to regulations banning BPA) are also EDCs. Intravenous and other medical tubing contain some classes of known EDCs such as phthalates, allowing direct contact between chemicals and the bloodstream.

The following sections include examples of commonly used EDCs from four categories:

- Pesticides (glyphosate, DDT, chlorpyrifos)
- Plastics and plasticizers (bisphenols, phthalates)
- Chemicals in household and children's products (arsenic, inorganic lead), and
- Industrial chemicals (PFAS, brominated flame retardants).

These are just a few of the many known sources of EDCs (see **Table 2**).

8.1 PESTICIDES

8.1.1 GLYPHOSATE

a. Where it is used

First synthesized in 1950, glyphosate is a wide-spectrum herbicide whose herbicidal properties were first identified in 1970, prompting its subsequent entry into commercial use in 1974 as Roundup™ (97). After progressive increases in use over the next two decades, glyphosate use entered a new phase of exponential growth starting in 1996 with the development and release of genetically-engineered "Roundup Ready" crops that are resistant to glyphosate, including corn (maize), soybeans, cotton, alfalfa, canola (rapeseed), and sugar beets (98). This genetic innovation extended the use of glyphosate to a post-emergence herbicide that could be used repeatedly over an extended duration of the growing season (98, 99). The development of GMO glyphosate-tolerant crops coupled with the expiration of the patent on glyphosate, which allowed widespread production of glyphosate-based herbicides by many companies, resulted in a dramatic growth in glyphosate sales, making it the dominant herbicide used globally today (100). Indeed, a 2015 analysis estimated that global glyphosate use increased nearly 15-fold since the introduction of glyphosate-resistant crops (98). In this analysis, 72% of all global glyphosate applied between 1974 and 2014 had been used in the last decade of the study period, with a total worldwide use in 2014 sufficient to apply 0.53 kg/ha on all global cropland.

Importantly, glyphosate is the active ingredient for a number of glyphosate-based herbicides (GBHs) that vary in their formulations (101). In these products, glyphosate can vary in the formulation of its chemical salt, while the products also vary in the adjuvants added to modulate glyphosate's herbicidal properties (102). GBHs are now used in approximately 140 countries (103).

b. Where people are exposed

Glyphosate exposure can occur through dermal contact, inhalation, and contaminated food and water. Exposure is not restricted to occupational settings: with its use in agriculture and in products available for use around the home, in addition to farmers and farm workers, homeowners, landscapers and others can be exposed through direct contact during application. Glyphosate is detected in air samples obtained in rural areas, soils, water, house dust, and a variety of foods, all of which reflect its widespread distribution in ecosystems (104). In an analysis of samples collected in 2013-2014 from a representative U.S. population, 81.2% of participants had detectable levels of glyphosate in their urine (104). Levels in this U.S. cohort were somewhat higher but of the same order of

magnitude as those obtained from a variety of non-occupationally exposed populations in Germany, Sweden, Spain, Ireland, Denmark, France, and Australia (104). In the U.S. study, school children had the highest average levels of glyphosate in their urine (104). Furthermore, urinary levels were lower among those with longer fasting times, suggesting diets as important contributors to glyphosate exposure.

c.   Science on why glyphosate is an EDC

A variety of approaches have been proposed for identifying agents with endocrine disrupting capacity, including the use of key characteristics. Recently, ten such key characteristics have been proposed to identify EDCs based upon their biochemical and physiological properties, as shown in **Figure 3** (2). Using this conceptual framework, an extensive review of glyphosate's endocrine disrupting properties was conducted (103). Based upon this analysis, the authors concluded that there was some evidence to support glyphosate or GBH impacts on eight of the ten EDC key characteristics, including: "interacts or activates hormone receptors"; "alters hormone level expression"; "alters signal transduction in hormone-responsive cells"; "induces epigenetic modifications in hormone-producing or hormone-responsive cells"; "alters hormone synthesis"; "alters hormone transport across cell membranes"; "alters hormone distribution or circulating levels of hormones"; and "alters the fate of hormone-producing or hormone-responsive cells" (103). The vast majority of this evidence focused on studies identifying the effects of glyphosate on sex steroid (estrogen, androgen, and progesterone) and thyroid biology. Similar conclusions have been made by others using the same or similar bodies of evidence (105, 106). Importantly, in some instances there have been discordant effects between glyphosate (the active ingredient in isolation) and GBHs on these endocrine parameters. More work is required to ascertain which endocrine disrupting effects are a result of glyphosate alone, which are adjuvant-enhanced glyphosate effects, and which are a direct consequence of the adjuvant in isolation. Furthermore, additional studies are required to understand how glyphosate and its formulations impact other endocrine and metabolic outcomes.

d.   Negative Endocrine Health Outcome: Reproductive Health

In addition to cell- and animal-based studies, some studies have investigated the associations between glyphosate exposure and health outcomes in human populations. While many of these studies have been controversial and have lacked direct measurement of glyphosate levels, some have identified associations between glyphosate and adverse health outcomes. In an exploratory analysis of the Ontario Farm Family Health Study, preconception exposure to glyphosate was associated with an

increased risk of late spontaneous abortion (107). In a study of pregnant women living in rural Indiana, higher glyphosate levels were associated with shorter durations of pregnancy (108). In another study, use of GBHs by pesticide applicators was associated with an increased risk of neurobehavioral deficits in their offspring (109). Additional work with robust measurements of glyphosate exposure (including specific GBH formulations) is needed to better define the impact of the widespread application of GBHs on female and male reproductive function as well as other health outcomes.

8.1.2   DDT

a.   Where it is used

DDT is an organochlorine insecticide that was used extensively worldwide in the 1940s, 1950s and 1960s. Its use included insect control in the commercial and private production of crops and livestock, and in homes, gardens, public places, and institutions. Due to DDT's toxicity to wildlife and its persistence, numerous countries banned DDT production in the 1970s, and the pesticide was among the initial 12 "dirty dozen" chemicals banned globally under the Stockholm Convention in 2004. Despite this, DDT is still used extensively for vector control, to control insects that transmit human diseases such as malaria, leishmaniasis, dengue and Chagas disease. It seems that all DDT is currently produced in India. Moreover, while the Stockholm Convention only allows the use of DDT for vector control (110), monitoring reports suggest illegal agricultural use may still be occurring in some countries such as India, Ethiopia, and Ghana (111-114).

b.   Where people are exposed

People in areas where DDT is manufactured or being used to control malaria are exposed to DDT and its metabolite DDE (groups of DDT related chemicals are referred to as DDX) in their homes and workplaces (115). For instance, South African adults living in homes sprayed with DDT have an average blood DDT concentration about 10 times higher than that of people living nearby without DDT spraying and several hundred times that of people living in countries with long time DDT bans. Further, studies of immigrants from India who have lived in the United Kingdom and the U.S. for decades reveal persistently high DDX exposure levels. Hence, while monitoring studies have established that banning DDT succeeds in lowering human exposure, levels of DDX can be exceptionally high in some immigrant populations. Countries that do not use DDT should recognize the possibility of higher exposures to DDX within their population, such as in migrants and in people living in communities that are near sites of previous DDT production.

The persistence of DDX in our food supply from prior DDT use, coupled with global migration patterns of humans, both contribute to levels of DDX in people even in countries with long-time bans of DDT. The majority of people worldwide are still exposed to DDX through their food supply, where DDX are most abundantly stored in animal fats. Due to the longer half-life of DDE than DDT, there may be detectable DDE even if the shorter half-life DDT is no longer detectable among people living where DDT is not used or produced (118).

c.   Science on why DDT is an EDC

Laboratory animal studies and human observations consistently show associations between DDX and negative endocrine health consequences, making DDX one of the most widely recognized EDCs. In animals and cell lines, DDX modify the thyroid, estrogen, androgen, renin-angiotensin, insulin, and neuroendocrine systems. These hormone systems are involved in the normal functioning of reproductive, cardiovascular, and metabolic processes, among others. Some effects of DDX are as estrogen mimics, and DDX also interfere with androgen (testosterone) pathways in the body (119).

Like most EDCs, the health consequences of DDX exposures are most pronounced when exposure occurs in developing fetuses and children. Several human studies indicate that DDT increases the risk of urogenital birth defects such as cryptorchidism (failure of the testes to descend), and one rat study also showed that fetal DDT exposure caused male reproductive abnormalities (118). Numerous studies indicate that high exposure to DDX reduces male, and possibly female, fertility, including in humans (118). IARC determined that DDX are probable human carcinogens, with evidence of increased risk of germ cell testicular cancer in studies from North America and Europe and strong evidence of key characteristics of carcinogens that operate in humans (120).

d.   Negative Endocrine Health Outcome: Adverse Metabolic Outcomes

Numerous epidemiological studies have demonstrated a strong positive association between the DDT metabolite DDE and risk of both obesity and type 2 diabetes (T2D) (121, 122). Grandmaternal exposure to DDT was associated with increased obesity in adult daughters and granddaughters. These studies came from countries that have banned DDT use for decades, and also from areas contaminated with higher levels of DDX. These documented human associations are corroborated by studies in rodents demonstrating that exposure to DDX caused obesity and the reduction of insulin production and action that is a hallmark of type 2 diabetes (123-125). Under normal circumstances, increased glucose levels cause the beta cells of the pancreas to produce insulin, but beta cell numbers and their secretion of insulin in response to glucose was reduced (126). Another study of rats showed that high doses of DDT to grandparent rats increased obesity of their rat grandchildren (127). DDX was also associated with increased risk of cardiac hypertrophy in mice and humans and this relationship was mediated by obesity among humans (128).

8.1.3   CHLORPYRIFOS

a.   Where it is used

Organophosphorus pesticides (OPs) are some of the most commonly used insecticides worldwide, and chlorpyrifos is a typical OP that for decades was one of the most widely used agricultural insecticides worldwide (129). It is used to control household pests such as cockroaches, flies, termites, fire ants, mosquitoes, and lice. Chlorpyrifos is used agriculturally to combat pests on cotton, grain, seed, nut, fruit, wine, and vegetable crops. It is also used in forestry, nurseries, food processing plants, on golf courses, and in water supplies to combat larvae, especially mosquitoes. It has numerous other uses, such as in impregnated bags to cover ripening bananas in plantations, in cattle ear tags, and in paint. Chlorpyrifos was banned in the European Union in 2020 due to concern about genotoxicity and developmental neurotoxicity (130).

b.   Where people are exposed

Relative to organochlorine pesticides, OPs including chlorpyrifos degrade more rapidly in the environment. However, chlorpyrifos can still be persistent, meeting the Stockholm Convention criteria for persistence under some circumstances (**Box 1**) [e.g., (131-135)]. Its regular use in agriculture and home gardens can cause its accumulation in soil, water, food, and air (136). It can persist in soil for up to four years (137).

Dietary chlorpyrifos exposure is the principal source of non-occupational exposure to humans (137). There is some evidence that chlorpyrifos can accumulate up the food chain in certain species, and it has been measured in fish in the Arctic as a result of global transport (131, 138-140). Chlorpyrifos residues are commonly found in vegetables, fruit, rice, and cereal products in many countries. Pakistan, Turkey, Thailand, Iran, Senegal, and Chile had noteworthy high levels of residues in vegetables across 43 countries surveyed (141). Residues are also found in fish, dairy products, drinking water, and even soft drinks in some countries. A survey of chlorpyrifos in pasteurized milk from Mexico found that 8% of milk sampled exceeded the regulatory threshold, a sizable proportion when considering how common milk consumption is among households with children (142).

Chlorpyrifos can also enter humans through their skin and lungs (137). After residential applications, chlorpyrifos is detected in flooring, furniture, toys, dust, and air (143). In a study of urban apartments, chlorpyrifos lingered on absorbent and soft surfaces for as long as two weeks after application, including areas not directly sprayed (143). Furthermore, all indoor air and dust samples collected in a study of homes

and childcare centers in the United States had chlorpyrifos present, even though the majority had not used pesticides for at least a week (144). In one study, chlorpyrifos was still measured in the air inside houses eight years after it had been applied for termite control (145).

Chlorpyrifos is relatively short-lived in people (half is removed from the blood and fat in about 24 and 60 hours, respectively). Instead of accumulating in the body, chlorpyrifos transforms to metabolites that can also cause harm. Chlorpyrifos and its metabolites have been found in urine, maternal and cord blood, the meconium (first feces) of newborn infants, breast milk, in cervical fluid, semen, and infants' hair (146-151).

Exposure to chlorpyrifos occurs from agricultural and household use, use on livestock and pets, and through residues in food and water. It can result from spray drift, and inhalation of air and dust in vehicles, homes, and childcare centers and other buildings in which it is used. A survey of schoolchildren in Chile found that 80% of them had metabolites of chlorpyrifos in their urine, and this was associated with eating fruits and vegetables (152).

OPs are detectable in nearly all agricultural workers who have been examined, including those from countries where the use of OPs is declining (153). A biomonitoring study conducted in Egypt among agricultural workers who primarily work with chlorpyrifos found that their OP exposure levels varied according to the extent of OP contact within their job duties (153). Elevated levels of chlorpyrifos metabolites have been found in the urine of both adults and children involved in banana plantation work and small-scale farming in Nicaragua (154).

The primary route of chlorpyrifos exposure is thought to be through the skin for most occupational chlorpyrifos exposures. However, measurements of chlorpyrifos levels in ambient air breathed by farmers in Tambon Bang Rieng, Thailand, found that farmers were inhaling concentrations up to 0.61 mg/m³, more than twice the acceptable daily intake for all routes of exposure (155).

Residential use of chlorpyrifos can be a major source of exposure to non-agricultural workers and to children. One study of cities in the United States estimated that 140 µg of daily chlorpyrifos exposure comes from food, while daily chlorpyrifos exposure from air was 27 times that amount (143). Children are at further risk of chlorpyrifos exposure through air because after chlorpyrifos treatment, its concentrations are greater closer to the floor in the low areas where children breathe compared to the areas where adults breathe (136). Indeed, infants in United States homes treated with chlorpyrifos absorbed approximately 2.7 mg/kg (136), and the urinary metabolites of chlorpyrifos were about 120 ng metabolite/kg body weight per day in children (144). This is appreciably higher than the levels of urinary metabolites of chlorpyrifos found in pregnant women in both the United States and Mexico (average 1.4-1.8 ng/ml, respectively (156)).

c.   Science on why chlorpyrifos is an EDC

Chlorpyrifos is acutely toxic to some species that are beneficial to agriculture, such as earthworms and honeybees, in addition to humans in the form of acute myocardial infarction (heart attack) (157). Developmental neurotoxicity is the primary adverse chronic health outcome observed in experimental and human observational studies of chlorpyrifos, and these effects are at least partially caused through disruptions of cholinesterase- and endocannabinoid-signaling (158). The neurotransmitter acetylcholine is involved in signaling of nerve cells in the brain, and it is metabolized by the enzyme cholinesterase. The endocannabinoid pathways of the brain are also important for neural functions. This is why chlorpyrifos's most potent effects are on the brain. Developmental exposures to chlorpyrifos at levels typically observed in people caused hyperactivity and reduced learning in rodents, the latter associated with changes in thyroid hormone (159, 160). Additional endocrine disruption by chlorpyrifos is suggested by changes in the endocrine adrenal gland weight and structure, reduced sperm count, and hormone levels such as estrogen and testosterone in rodent experiments (137).

Cholinergic symptoms, e.g., salivation, urination, defecation, gastrointestinal distress, and vomiting that are caused by nervous system damage are present in acute chlorpyrifos poisonings of adult humans, and nerve damage was observed weeks later. Adult agricultural workers use OP pesticides as mixtures, and workers with moderate OP exposure inclusive of

chlorpyrifos, also exhibit signs of neurotoxicity, such as impaired peripheral nervous system function (161). Two studies of US residents exposed to mixtures of pesticides found that chlorpyrifos was associated with Parkinson's disease (162, 163). Although it is difficult to find human studies that have examined the neurotoxicity effects of chlorpyrifos in isolation from other pesticides, a study of chlorpyrifos applicators found they did not perform as well on neurological tests compared to people with much lower chlorpyrifos exposure (164). They also reported memory problems, fatigue, and loss of muscle strength (164).

Developmental susceptibility appears to be an important risk factor for human neurotoxicity associated with exposure to chlorpyrifos. Indeed, the majority of scientific experts on a scientific panel on chlorpyrifos toxicity agreed that chlorpyrifos should be banned from home use due to resulting neurodevelopment defects (136). For example, prenatal and childhood chlorpyrifos exposures are linked to attention deficit hyperactivity disorder, and impaired mental- and motor-skill development in young children (136, 165). Extensive animal studies also support a strong role of chlorpyrifos in causing neurotoxicity during development (166).

Emerging experimental evidence indicates that developmental exposure to chlorpyrifos also alters the regulation of lipid and glucose metabolism. Developing rats exposed to doses comparable to levels typical in people had elevated cholesterol, triglycerides, and insulin in adulthood (167). These findings raise the possibility that people exposed to chlorpyrifos would have increased risk of developing type 2 diabetes and cardiovascular disease. To date, this prediction has not yet been evaluated in well-designed human studies.

d.   Negative Endocrine Health Outcome: Thyroid Disruption

Most studies of chlorpyrifos focus on its nervous system toxicity but reports on its effects on the thyroid hormone system are emerging and suggest that chlorpyrifos may be a risk factor for thyroid disease. A chlorpyrifos metabolite was associated with decreased thyroid stimulating hormone and increased T4 in men in one study (165), and had the opposite association with these thyroid hormones of men in another study (156). Experimental studies in animals also indicate that developmental chlorpyrifos exposure alters the thyroid hormone system (168). Very low prenatal chlorpyrifos exposure, below the level that produces any cholinergic toxicity or behavioral changes, reduced brain thyroxine levels from early life into adulthood in rats (168). This is consistent with several studies in mice and sheep demonstrating that developmental chlorpyrifos exposure also decreased circulating thyroid hormones (169, 170). Other actions of chlorpyrifos, including neuroendocrine, estrogenic, and androgenic effects, have been reported.

8.2   PLASTICS AND PLASTICIZERS

People are exposed to chemicals in plastics, including EDCs, throughout the plastics life cycle. For more on EDC exposures from plastic production, transport, use, recycling, and disposal, see the special feature: "EDCs Throughout the Plastics Life Cycle" on page 60.

8.2.1   BISPHENOLS

a.   Where it is used

The best-known bisphenol is bisphenol A (BPA) but there are many others with endocrine disrupting properties, including bisphenol A, F, AF, and S. Bisphenols are found in a wide variety of products, most notably hard, rigid plastic food containers including some water bottles, and the epoxy-based linings of canned foods. Because of rising health concerns, use of BPA in some plastic containers, such as baby bottles, is now banned in many countries and voluntarily reduced or phased out in others. Although these products are now available in "BPA-free" versions, some of these contain other bisphenols, especially BPS. BPA and BPS remain a common component of the epoxy resins that line the interior of canned foods such as soup, canned vegetables, and beans. This liner is important because it helps protect the contents from contamination by pathogens, which can cause serious food-borne illnesses such as botulism. There are alternatives to bisphenols that can serve this purpose, and not all can linings contain bisphenols, but it is impossible for the consumer to know which do and which do not. Bisphenols can leach from these linings into the food, thereby exposing consumers. Other common household products containing bisphenols include polycarbonate eyeglasses, thermal paper receipts, electronics, plastic water pipes and tanks, industrial flooring, adhesives, grouts, paints and lacquers, and some medical devices including oral prosthetics. Polycarbonate and epoxy resins account for more than 70% of the global BPA market. Tetrabromobisphenol A (TBBPA) is a common flame retardant, particularly in electronics.

b.   Where people are exposed

BPA is a high-volume production chemical and global production exceeded 5.5 million tonnes in 2021 and is projected to exceed 8.0 million tonnes by 2032. Production of BPA replacements, including BPS, F and AF, is also abundant and growing. Exposure appears to be universal (**Box 5**); the U.S. Centers for Disease Control have estimated that greater than 96% of all Americans have BPA in their bodies (171). BPA has been found in urine, blood, umbilical cord blood, and amniotic fluid. Because children are more likely to eat and drink from plastics, spend so much time on the floor, and put so many items in their mouths, exposure levels are typically higher in children than adults. Conversely, people who use fewer plastics,

personal care products, and make other lifestyle changes that reduce contact with BPA-containing items have lower body burdens (172, 173).

BOX 5. WIDESPREAD DETECTION OF BPA IN CHILDREN'S PRODUCTS

In 2020, IPEN and NGO partners purchased hard and transparent plastic bottles and cups for children from local markets in 8 countries (Bangladesh, Bhutan, China, Indonesia, Malaysia, Russia, Sri Lanka and Tanzania) and analyzed 98 of them for leachable BPA content. BPA was detected in the leachate from 76 (78%) of them. Out of the 23 products labelled "BPA-free" or "0% BPA", 14 contained BPA. The study concludes that children in Bangladesh, Bhutan, China, Indonesia, Malaysia, Russia, Sri Lanka and Tanzania are likely exposed to the endocrine disrupting chemical Bisphenol A (BPA) from widely used products, and that consumers in Malaysia, Bhutan, Indonesia and Sri Lanka are deceived by misleading "BPA-free" or "0% BPA" labelling of baby products. While China, India, Indonesia and Malaysia already have prohibitions or migratory limits for BPA, the study recommends all governments to take immediate steps to restrict manufacture, sale, and distribution of all bisphenols as a class. See the IPEN report "A Call to Action" for more details.

Most people are exposed by consuming food and beverages into which bisphenols have leached from the container. Leaching is enhanced by environmental factors such as heat, sunlight, and acidity, so acidic foods such as tomatoes are more likely to absorb leached BPA from can linings. Common activities such as reheating food in or on plasticware in the microwave and storing water bottles in a hot car are known to enhance the transfer of BPA and other bisphenols from plastics. Other possible but not well-studied routes of exposure include inhalation or ingestion of contaminated house dust and dermal exposure from handling BPA-containing thermal paper receipts.

Bisphenols are used in so many products that exposure is thought to be ubiquitous and nearly continual. Unlike DDT and some other EDCs, bisphenols are rapidly metabolized and do not bioaccumulate in the body, so reducing exposure can rapidly reduce body burden. Several studies have shown that basic lifestyle changes, such as minimizing the use of canned foods and plastic containers, can rapidly reduce BPA levels in urine and other body fluids (172, 173). Increasing availability of BPA-free plastics and can linings will likely reduce BPA but not overall bisphenol exposure, which is concerning because some of these other bisphenols are now also recognized to be endocrine disrupting (174, 175, 176).

PLASTIC BABY BOTTLES AND EDCs

A 2022 IPEN study found BPA, a known EDC, in 78% of baby bottles sampled from 7 countries. The study showed that BPA was present and leached from the tested products. Though 23 baby bottles were labeled "BPA-free," testing showed that 14 of these (61%) contained BPA.

Although the introduction of BPA-free food containers to global markets is clearly an advantageous step for reducing human exposure, BPA and other bisphenols remain high-volume production chemicals, so exposure from compounding sources remains a significant concern. Environmental contamination is also a widespread problem and BPA has been detected in all environmental compartments, including air, soil and water. Although data are lacking for many low- and middle-income countries, BPA has been detected for example in surface water, groundwater, freshwater sediment, and air in Asia, Africa, North and South America, and Europe (177, 306-308). Sources of BPA release into the environment include wastewater treatment effluent and sludge, leachate from landfills, recycling facilities, and open burning of waste (178, 308, 309). BPA and other bisphenols leaching from trash have been detected in seawater and marine species meaning that it will continue to remain a significant environmental contaminant as it will take centuries for all this plastic trash to weather and degrade.[1]

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1   While countries including Austria, Chile, India and Kenya are aggressively phasing out single use plastics, unfortunately, per capita plastic waste in the USA has grown from 60 pounds per year in 1980 to 218 pounds in 2018 - a 263% total increase. Less than 5% of plastic waste is recycled in the USA, so much of it ends up in landfills or aquatic systems. In 2000, BPA was detected in 41% of 139 U.S. streams in 30 states and this trash ultimately ends up in the ocean. Greater than 90% of all ocean trash is plastic, and it can linger there for decades or longer. See (310, 311).

c.   Science on why BPA and some other bisphenols are EDCs

BPA is one of the most extensively studied and well-known EDCs. First synthesized in 1891, BPA was identified as an estrogen mimic in the early 1930s so its endocrine disrupting properties have been recognized for decades. BPA can interfere with estrogen signaling via several different mechanisms. It can bind to and stimulate estrogen receptors (ERs), albeit more weakly compared to natural estrogens (179, 180). BPA exposure, even low levels, can alter the density of estrogen receptors in tissues such as the brain (181), an effect that consequently alters the sensitivity of that tissue to natural estrogens. Because estrogen plays a critical role in the development and sexual differentiation of numerous tissues, including the brain, mammary gland, and even the testis, interference with estrogen activity during development can result in permanent changes that affect reproductive functions later in life. One of the most comprehensive toxicity studies on BPA to date found a higher risk of breast cancer, ovarian dysfunction, and disrupted brain sexual differentiation (182, 183). This is one of many examples of the effects of BPA on tissues that are sensitive to estrogens. While less studied, other bisphenols including F and AF appear to have similar effects (175, 176). Considering that males and females both produce and respond to natural estrogens, but that there are considerable sex differences in these processes, it is not surprising that bisphenol actions are not identical between the sexes.

A biological mechanism by which bisphenols act is through DNA methylation. Every human has a unique set of genes. Within our bodies, expression of those genes – that is, whether they are activated and lead to expression of a protein within a cell – differs considerably. For example, the genetic material (DNA) is identical between a skin cell and a nerve cell, but the proteins that are produced in these very different tissues are unique for each cell type. It is the *expression* of genes that determines these differences. DNA methylation is the addition of a small chemical group, called a methyl group, to DNA. The amount and location of these methyl groups determines whether and how much a gene is expressed. Several EDCs, among which there is the most information for BPA, induce such changes in genes. BPA causes DNA methylation changes in neuroendocrine pathways fundamental to reproductive health, energy balance, and behavior, including estrogen-sensitive pathways (72, 184-186). Altered patterns of DNA methylation in key genes related to cell growth may be a potential mechanism explaining why developmental exposure to human-relevant, low levels of BPA heighten the risk of uterine and prostate cancer in animal models (187-189). Similar disruptions have also been identified in the liver, brain, and ovary.

Bisphenols have several modes of action. For example, BPA was shown, using a variety of cell-based models, to disrupt the action of other steroid

hormones including testosterone and thyroid hormone. In monkeys, BPA blocks the androgen-dependent enhancement of dendritic spines in the hippocampus, an effect which suggests BPA may interfere with neural plasticity (190). Human studies have shown associations between elevated androgen levels with BPA levels in men, women, and infants, an effect which remains poorly explained but may result from altered androgen metabolism, disruption of feedback loops regulating androgen production, or enhanced androgen production by the ovary (191). It has also been observed in vitro that BPA may be 80 times more potent on estrogen-related receptor gamma (ERRγ) than classical estrogen receptors (192). Little is known about the functional role of ERRγ but it is highly expressed in fetal brain and placenta, a distribution that supports the concern that the fetus is particularly sensitive to BPA.

d. Negative Endocrine Health Outcome: Behavior and Reproductive Health

As of 2023, nearly 500 epidemiological studies have been published associating BPA with human health effects, most notably disorders of reproduction, behavior, and energy balance (191) (193-196). Most support the prevailing concern that developmental exposure has the most profound effects. BPA has been linked with reduced oocyte quality in women undergoing fertility assistance, including in vitro fertilization (70, 71), effects which are consistent with ovarian effects observed in animal models (197) (182). Evidence from animal models, including non-human primates whose reproductive biology is virtually identical to that of humans, has also shown that developmental BPA exposure compromises ovarian development, uterine structure, and embryo implantation (198-200). Similarly, in men, BPA has been linked to reduced sperm quality and sexual function following exposure in an occupational setting but there is not sufficient evidence to establish if BPA has similar effects at the doses to which the general public is exposed. Compelling but comparatively limited evidence links BPA to higher risk of premature female puberty, low birth weight, preeclampsia, polycystic ovarian syndrome (PCOS), reduced semen quality, and breast cancer (196).

Several agencies including the WHO and the US National Toxicology Program have expressed concern regarding the impact of BPA on fetal brain development and behavior. Evidence from numerous animal models have shown that developmental BPA exposure elevates anxiety, aggression, and other behaviors (201), effects which have now been reported in children (202-204). This has led some to hypothesize that BPA may contribute to behavioral disorders such as ADHD and ASD (37, 193, 205, 206). Impacts on brain sexual differentiation and synaptic plasticity have also been observed in animals.

Linkages between BPA and cardiovascular disease and hypertension are fairly robust, documented in numerous epidemiological studies, and are supported by mechanistic studies in animals (191, 196, 207). Importantly, this is an endpoint for which there is strong evidence associating adult (rather than developmental) BPA exposure with disease. Significant correlations have been reported in a range of populations and are consistent across study cohorts, an observation that strengthens confidence in the relationship. Because associations with obesity are tenuous, cardiovascular effects appear to be direct rather than a secondary outcome of increased body weight.

8.2.2 PHTHALATES

a.   Where are they used

Phthalates (also referred to as ortho-phthalates) are a class of high-volume production plasticizers used to soften polyvinyl chloride (PVCs), add fragrance to a product, or enhance pliability in plastics and other materials. They are found in a huge diversity of products including a multitude of personal care products and cosmetics, child and pet toys, food contact materials, scented products such as candles, detergent, and air fresheners (including the "new car" smell in automobiles), medical equipment such as tubing and blood bags, textiles including recreational gear and mattresses, vinyl flooring, wall paper and other building materials, adhesives, the enteric coatings of pharmaceuticals, and art supplies such as paint, clay, wax, and ink. This has prompted some to call them "the everywhere chemical." Globally, phthalate production exceeds 4.9 million metric tons. The highest-production phthalates are di-2-ethylhexyl phthalate (DEHP), diisononyl phthalate (DiNP), butylbenzyl phthalate (BBzP), di-butyl phthalates (DBPs), and diethyl phthalate (DEP) (208).

The phthalates comprise a great number of compounds, not all of which are EDCs. To simplify, phthalates are classified as low molecular weight (3-6 carbon backbone) and high molecular weight (>6 carbon backbone), with the low molecular weight classes thought to pose the most significant health risks.

b.   Where people are exposed

Because they are so ubiquitously used, combined exposures are typical, particularly for children (209, 210). Consequently, phthalates have been found in urine, blood, umbilical cord blood, and amniotic fluid, with levels higher in children, particularly those in the NICU where plastics abound. Like BPA and many other EDCs, they cross the placenta. Exposure occurs via food intake, inhalation, dermal contact, and intravenously from medical equipment. For the dialkyl phthalates such as DEHP, the body metabolizes them to monoesters (e.g. MEHP) that are generally more bioactive. Because some countries and companies have begun to phase some phthalates out of use, the human exposure landscape has evolved in the last decade. Exposures to di-n-butyl phthalate (DnBP), DEHP, and BBzP have decreased, while exposures to replacement phthalates such as DiNP and diisobutyl phthalate (DiBP) have increased. Interestingly, women have higher exposures than men, likely because women use more personal care products (211).

Phthalates were first recognized to act as EDCs by interfering with fetal androgen (testosterone) production and insulin-like hormone 3 (insl3) expression which is critical for testis descent (212). DEHP and DBP are particularly well established to have this mode of action. Because androgens are critical to male development, including genital development, and brain masculinization, boys are thought to be most vulnerable to exposure. However, androgens also play important roles in females, making phthalate exposure potentially harmful to both sexes.

Because development is such a vulnerable exposure period, reducing phthalate exposure to fetuses and young children is a priority globally. Consequently, use of some phthalates has been restricted from toys and products for young children since 1999 in the EU and 2008 in the U.S. Some countries have also restricted use in food contact materials. In 2022 the US FDA deauthorized use of 23 phthalates from food packaging citing that they were no longer used for that purpose, but nine others remain in use despite repeated petitions to deauthorize them. These include DEHP, DINP, DCHP, and DIDP. A 2014 report by the Chronic Hazard Advisory Panel (CHAP) to the Consumer Products Safety Commission (CPSC) together with the CPSC staff assessed phthalates in 261 food items and concluded that food, beverages, and drugs via direct ingestion constituted the highest phthalate-exposure sources, including for pregnant women.

Notably, phthalates are highly prevalent in U.S. fast food likely because they leach from food processing and contact materials. The well-studied and health-concerning phthalates DnBP and DEHP were detected in 81% and 70% of sampled foods, respectively. DEHT, a chemical used as a phthalate replacement and not yet well-studied for adverse health effects in humans, was detected in 86% of sampled foods. Generally, items containing meats, such as chicken burritos and hamburgers, had higher concentrations of phthalates. Thus, like BPA, phthalates are used in so many products that exposure is thought to be ubiquitous and nearly continual (213). The specific cocktail of common phthalate exposures, however, differs geographically.

c. Science on why phthalates are EDCs

Phthalates interfere with testicular androgen production, with the fetal testis more sensitive than the adult testis. Disruption of testicular growth factors and other hormones has also been observed along with toxicity to fetal Leydig and Sertoli cells. At higher doses phthalates can also have more overt toxic effects. Phthalates also disrupt hormone production and function in the developing and mature ovary resulting in increased oxidative stress, disrupted estrogen signaling, dysregulated follicle development, and oocyte death. Emerging evidence suggests ovarian effects can persist across the lifetime and possibly transgenerationally (214). In the brain, there is limited evidence of altered ion homeostasis including calcium signaling, disrupted thyroid hormone signaling, activation of peroxisome proliferator-activated receptors, and altered lipid metabolism, particularly in the hippocampus which is a critical mediator of memory and emotional-learning. The neural actions of phthalates are far less studied than their reproductive actions.

Phthalate exposure has been linked to genital abnormalities in boys, reduced sperm counts, and behavioral changes. Accumulating epidemiology data also suggest that developmental phthalate exposure impacts neurodevelopment impacting cognitive function and socioemotional behaviors (215-217). Exposure has also been associated with higher risk of endometriosis and aspects of metabolic disruption, including obesity. In particular, DEHP, DBP, DIBP, and BBP have been classified under REACH as toxic for reproduction and identified by ECHA as contributing to male infertility and asthma. DEHP (and its primary metabolite MEHP) has been classified by the US Department of Health and Human Services, the US EPA, and IARC as a likely human carcinogen.

d.   Negative Endocrine Health Outcomes: Reproductive Health and Brain Development

Because they can interfere with fetal testosterone production, DEHP, DBP, and similar phthalates have been linked to decreased testis weight, impaired spermatogenesis, and external genital malformations including hypospadias and cryptorchidism (218). This constellation of effects is famously labeled "Testicular Dysgenesis Syndrome" and linked with higher risk of testicular cancer (219). In adult men, numerous phthalates including MiBP, MEHP, MnBP, and monobenzyl phthalates have been associated with poor semen quality including low motility, decreased sperm concentration, spermatic DNA damage, and immature sperm (220). Similar outcomes have been observed in rat studies dating back decades. Phthalate exposure may also interfere with timing of male puberty, with some differences observed between ethnic groups. A heightened risk of prostate and testicular cancer has also been suggested but direct evidence remains lacking.

Effects on female reproductive health have also been reported, most notably on ovarian development and function. In mice, a phthalate mixture modeled after a real-world exposure altered follicular development resulting in impaired folliculogenesis and fertility (214). Evidence of disrupted oocyte growth and DNA damage has also been reported in zebra fish, *C. elegans*, and other model organisms. In humans there is some evidence linking phthalate exposure to premature ovarian failure and disrupted timing of female pubertal onset (220, 221). Exposure has also been linked to increased adiposity, which is also known to shift the timing of pubertal onset (222).

Rapidly emerging evidence, particularly from human epidemiological studies, is revealing that phthalates, particularly DEHP, DBP, and their metabolites, impair neurodevelopment resulting in impaired cognitive function, learning, attention, and impulsivity (208). Multiple longitudinal birth cohort studies have linked prenatal exposure to ADHD and lower IQ. Unsurprisingly, given their activity on androgen production, boys appear to be more vulnerable to exposure.

BECAUSE DEVELOPMENT IS SUCH A VULNERABLE EXPOSURE PERIOD, REDUCING PHTHALATE EXPOSURE TO FETUSES AND YOUNG CHILDREN IS A PRIORITY GLOBALLY.

SPECIAL FEATURE:

EDCs THROUGHOUT THE PLASTICS LIFE CYCLE

To better understand the health threats posed by EDCs in plastics, it is important to follow the life cycle of plastics and the potential for human exposures to toxic chemicals when plastics are produced, transported, used, and disposed of. Plastic poses risks of exposure to EDCs at every stage of its life cycle, and most people worldwide are exposed at multiple stages. People living near plastics production facilities and people living near waste disposal sites may face the greatest exposure risks. Since plastic wastes are increasingly unequally exported from wealthier countries to low- and middle-income countries, people in the latter regions are disproportionately at risk from EDCs in plastics.

EXPOSURE FROM FOSSIL FUELS EXTRACTION AND PLASTICS PRODUCTION

Plastics are made from fossil fuels and chemicals. While a full review of EDCs from oil and gas operations is beyond the scope of this report, studies have shown that dozens of EDCs are used by the industry and have found groundwater contamination from EDCs near oil and gas operations (312). The recent increase in fracking for natural gas has raised concerns about chemical exposures from these operations, including exposures to chemicals linked to neuro-, reproductive-, and developmental toxicity (313). Chemical exposures related to petrochemical production tend to disproportionally impact low-income communities of color in the U.S. and low- and middle-income countries in the Global South.

A wide range of chemicals are used to produce plastics, including many EDCs. In plastics production toxic chemicals that are harmful to human health are released, with exposures to nearby communities and occupational risks imposed upon workers. One study found that people working in plastic manufacturing have higher levels of phthalate exposure than people working in other occupations (314). A study of women workers in the plastics industry noted that these workers can be exposed to numerous EDCs, including phthalates, BPA, flame retardants, heavy metals, and others. The publication also reviewed previous

biomonitoring studies of plastic plant workers, finding that they have chemical body burdens significantly higher than unexposed workers or the general population, including of phthalates and BPA (315). In a 12-month period from 2019-2020, plastics plants in the U.S received 527 citations for worker safety violations and were fined $2.3 million. Worker safety complaints increased even though on-site inspections were down by 50% due to COVID restrictions.

Air pollution around plastic plants is also a health hazard to nearby communities: more than 100 concerning chemicals in air pollution from plastic manufacture have been identified, including cancer-causing chemicals such as benzene, toluene, ethylbenzene, and xylene. Plastic production also poses significant water pollution threats. Manufacturing of plastics creates plastic pellets (also called nurdles), lentil-sized plastic discs that are shipped for further production into products. Spilled plastic pellets are routinely found around plastic plants and throughout transportation routes. Plastic pellets have been found in surface water samples and on beaches all over the world, including in areas without any petrochemical or polymer industries (316). When pellets are made with EDCs, these spills and transport losses spread the toxic chemicals globally.

One study estimated that 230,000 tons of plastic pellets per year enter the environment, but since industry is not held accountable for documenting releases, estimates vary widely. One study, for example, estimated that there are between 5 and 53 billion pellets released annually from the UK alone (317). A 2018 study assessed plastic released from a Swedish plastic facility, finding that the total annual release of plastics could be between 300 and 3000 kg annually (this from a company that four years earlier had announced its goal "to not lose a single pellet." (317)).

In the U.S., plastic production plants have faced significant fines for air and water pollution that violates safety standards. One Texas plastic producer was fined $13.9 million for numerous air and water safety violations between 1999-2009, and the company later agreed to a $50 million legal settlement with local residents after a judge found it had illegally dumped billions of plastic pellets into waterways. A Delaware plastic plant owned by the same company has been repeatedly fined for air and water pollution violations as well as worker safety violations. In 2018, the U.S. EPA fined two California plastics companies for releasing pellets and plastic flakes into waterways.

Microplastics have been identified as a source of global dispersal of toxic chemicals in plastics, and according to one researcher, pellets are the second most common type of microplastics found in their environmental surveys.

EXPOSURE FROM PLASTICS TRANSPORT

As noted above, spills during transport are a significant source of potential exposure to chemicals in plastics. A Scottish environmental group documented plastic pellet pollution in 28 of the 32 countries they surveyed, from Ecuador to South Africa. Unfortunately, most spills tend to go undocumented. One report calculated that between October 2020 and January 2021, 3,000 containers were lost in the Pacific and according to the World Shipping Council the annual average is 1,382 lost containers.

Pellets can spill from rail, sea, and other transportation routes. Reviews of plastic spill incidents have found dozens of cargo ship, trucking, and rail spills, including, among others:

- A 2012 spill south of Hong Kong that released 150 tons of pellets into the sea. Six years later piles of pellets were still washing up on nearby beaches.

- In 2017 a collision of shipping vessels off the coast of South Africa released 49 tons of pellets. As much as 2,000 km of coastline were polluted with pellets from the spill.

- In 2020, a cargo ship spilled more than 13 tons of pellets into the North Sea, polluting the coastlines of Denmark, Sweden, and Norway.

- In 2020, an estimated 743 million plastic pellets spilled from a container ship into the Mississippi River (USA). Six months later pellets were still seen washing up on nearby beaches.

- A 2008 train derailment in Ontario, Canada, dumped four rail cars of pellets into Lake Superior. For more than a decade, pellets from the spill washed up on Canadian and U.S. beaches.

- A 2022 train derailment outside of Pittsburgh resulted in potentially millions of pellets released into waterways. One report of U.S. rail-related plastic pellet spills found more than 80 such incidents in at least two dozen states since 2010.

A 2022 IPEN report with the Sri Lankan Centre for Environmental Justice (CEJ) documented the impacts of one major plastic pellet spill resulting from the X-Press Pearl cargo ship disaster. In May 2021 the ship caught fire off the coast of Sri Lanka, releasing as much as 84 billion plastic pellets (1,680 tonnes), as well as toxic chemicals and other wastes. In nearby areas plastic pellets accumulated to reported levels of two meters and the geographic extent of the plastic spill has been reported to be the largest on record.

CHEMICALS THROUGHOUT THE PLASTIC LIFE CYCLE

IPEN's Introduction to Plastics and Toxic Chemicals provides a comprehensive look at the science behind threats posed by EDCs and other toxic substances in plastics. The report reviews how harmful chemicals are released at every phase of the plastics life cycle – from oil extraction to plastics production, transport, use, and disposal, with solutions to the plastics crisis including through a strong, global Plastics Treaty.

As noted in the IPEN report, toxic chemicals, including EDCs, in plastic pellets can leach into animals that feed on the pellets, onto the beach, and into the water. In addition to pellets, burned plastic debris posed additional chemical contamination threats. The ship also carried several types of plastic resins, including epoxy resins that are made from bisphenols, such as bisphenol A.

To assess the impacts from the spill, IPEN and CEJ collected plastic pellet samples and burnt lumps from beaches in three areas near the spill and analyzed them for bisphenols, PFAS, heavy metals, and other chemicals. BPA was found in all burnt plastic samples and one pellet sample. The pellets also contained a variety of metals as well as UV stabilizers. Polyaromatic hydrocarbons (PAHs), chemicals that some studies have found to be EDCs (318), were the most frequently detected chemicals.

Another IPEN study with International Pellet Watch (IPW) tested plastic pellets collected from beaches in 23 countries for PCBs and UV-stabilizers, chemicals known or suspected of being EDCs. Samples from all locations contained the toxic chemicals, with samples from African countries showing the highest concentrations.

EXPOSURES FROM PLASTICS IN CONSUMER PRODUCTS

Exposures from using plastics

Plastics from everyday products can leach chemicals, exposing people who use these products. For example, evidence indicates that people are exposed to 60 ng/day of toxic flame retardants in plastic kitchen utensils (319). Further, food contact items are thought to contribute to levels of BPA in urine, ranging from 2-4 ng/mL (320). Food contact items also contribute to levels of phthalates in the body.

Bisphenols including bisphenol A (BPA) can be found in reusable plastic food and beverage containers, the plastic linings of food cans, and plastic water pipes. Most people are exposed to BPA through plastic food contact materials by consuming food and beverages into which BPA has leached from the container. BPA concentrations have been measured in a wide variety of canned foods, showing that the chemical leaches from plastic liners into food. Because of rising health concerns, use of BPA in some products, especially products for young children, is banned in many countries, but the chemical is often replaced by other closely related bisphenols such as BPS, BPF, and others. Concerns have been raised that these replacement chemicals are also EDCs (321). Studies have shown that many of these related chemicals have estrogenic properties (323, 323). One study has suggested associations between BPF and BPS exposures and obesity in children (324).

Exposure from using products made from recycled plastics

Plastic recycling is often posed as a solution to the plastics crisis, but since plastics are made from toxic chemicals, when plastics are recycled these chemicals are passed along to the new products, creating new exposure threats to consumers. As a 2021 IPEN report with IPW noted, there are some materials we should not recycle, including highly toxic materials. This is recognized in the Stockholm Convention and its general prohibition on recycling POPs waste.

A 2021 IPEN study found that recycled plastic pellets contain toxic chemicals, including EDCs. Recycled plastic pellets were purchased from 24 recycling facilities in 23 countries across Africa, Latin America, Asia, and Europe and were tested for BPA, toxic flame retardants, and UV-stabilizers. The findings showed that all samples contained one or more toxic chemicals, with 88% containing at least one substance from all three chemical groups tested for. BPA was found in 92% of the plastic samples.

Recycled plastics often include plastics from e-waste and automobiles; to promote fire resistance, plastics in these products are typically made with high levels of toxic flame-retardant chemicals. Polybrominated diphenyl ethers (PBDEs) are persistent organic pollutants (POPs) that have widely been used as flame retardants. An IPEN study of more than 100 children's toys made from recycled plastics and purchased in 26 countries found toxic PBDEs in 90% of the tested products, including three chemicals listed in the Stockholm Convention for global elimination. In some cases, the new toys could be classified as hazardous waste, given the high levels of the toxic flame retardants that they contained.

Another study by IPEN and partners tested 430 plastic products purchased from across Europe. After screening the products for likely recycled plastic content, 109 samples were tested for flame retardant chemicals. One hundred seven out of the 109 items (98%) contained PBDEs. Fifty of the products had levels of flame retardants that exceeded the EU safety levels for products made from new plastics.

A 2022 IPEN study tested 83 plastic toys, kitchen utensils, and other products purchased from eleven African and Arabic countries, finding 80 of the samples contained one or more PBDEs, including three chemicals listed in the Stockholm Convention for global elimination.

THE TOXIC PLASTIC RECYCLING STREAM:

TOXIC EXPOSURES WHEN PLASTIC WASTE IS COLLECTED AND SORTED
Plastics are made with over 3,200 chemicals known to be hazardous or of potential concern.

TOXIC EXPOSURES WHEN EXPORTED PLASTICS ARE DUMPED
22 million tonnes of plastics (and chemicals from these plastics) are released into the environment every year.

TOXIC EXPOSURES WHEN PLASTIC IS PROCESSED FOR RECYCLING
Chemical recycling can generate as much as 80% hazardous waste.

TOXIC EXPOSURES WHEN WE USE RECYCLED PLASTIC PRODUCTS
Globally banned chemicals have been found in products made from recycled plastics.

RECYCLING PLASTICS IS RECYCLING TOXIC CHEMICALS
PLASTICS POISON RECYCLING - WE SHOULD NOT RECYCLE TOXIC CHEMICALS WE NEED TOXICS-FREE MATERIALS FOR A TRULY SAFE, CIRCULAR ECONOMY

IPEN

EXPOSURE FROM PLASTIC WASTE DISPOSAL

Plastic waste disposal has created a global crisis, and if the current trend of increasing plastics production continues, 108 million tonnes of plastic waste will be landfilled, dumped, or openly burned in 2050, mainly in low-income countries. The result will be increasing exposure to toxic chemicals from plastics, including EDCs.

Plastic pollution is found in every marine habitat and is one of the most serious threats to ocean ecosystems. Plastics break down into (or are released as) microplastics, which further concentrate and spread toxic chemicals. Some chemicals that are not normally considered persistent, such as phthalates, may remain in plastics in marine environments and travel globally. Chemicals from plastics in marine environments can contaminate food chains, resulting in human exposure through seafood consumption. A recent IPEN "Ocean Pollutants Guide" reviewed evidence suggesting that exposure to EDCs plays a significant role in the worldwide threats to species, including freshwater and marine fish and invertebrates, and could pose food-chain risks.

Plastic waste disposal also poses threats to food chains in areas where plastics are dumped or burned. A 2019 IPEN study looked at two sites in Indonesia where plastic waste is dumped and used for fuel or burned, sampling free-range chicken eggs from the area. The study found the eggs contained PCBs, PBDEs, and PFAS, among other chemicals.

The sampling also found very high levels of dioxins in the eggs; an adult eating just one egg from the vicinity of one site would exceed the EU safety level for daily dioxin intake by 70 times. The eggs contained levels of dioxins 2,000 times higher than the background levels found in supermarket eggs in the area. Dioxins are EDCs and cancer-causing chemicals that are produced when plastics are burned. They are among the most toxic chemicals known and were among the original "dirty dozen" chemicals banned under the Stockholm Convention.

Some eggs also contained high levels of PFAS, including PFOS, one of the three PFAS banned globally under the Stockholm Convention. An adult eating just one egg per week from one site would exceed proposed EU safety levels for a weekly intake of PFOS.

Another IPEN study with the Basel Action Network (BAN) looked at egg samples from an area of Ghana where e-waste is burned, finding high levels of dioxins, brominated dioxins, PCBs, PBDE, and other chemicals. E-waste typically contains about 20% plastic. An adult eating just one egg from the area would consume dioxin at 220 times the EU daily safety levels. Tracking by BAN showed that e-waste was exported from Europe to Ghana, Nigeria, and Tanzania, likely in violation of the Basel Convention as the e-waste qualifies as hazardous material.

8.3 CHEMICALS IN HOUSEHOLD AND CHILDREN'S PRODUCTS

EDCs are found in many common-use, household, and personal products that come into contact with the body or are around us in our home and work environments. For example, children's products, electronics, food contact materials, personal care products, textiles/clothing, and building products are regular parts of daily life around the world (www.ipen.org/site/toxics-products-overview).

Consumers have little to no choice in whether or not they are exposed to chemicals in these products because there is generally not full disclosure about these items' chemical constituents. Some of these chemicals are released into the air and remain in the indoor environment, particularly in poorly ventilated buildings. From the air, some chemicals can settle out into carpets and dust. This is of great concern for infants and children who often pick up and put items from the floor into their mouths or eat food that has fallen on the floor. Personal care products are applied to skin, and there are also chemicals in toothpastes and antimicrobial soaps that are absorbed or even ingested in small amounts. Both lead and arsenic can be EDCs; below is the evidence for arsenic, with brief coverage of inorganic lead, the latter is discussed in depth in the original Guide (**Box 6**).

8.3.1 ARSENIC

a. Where it is encountered

Arsenic is a naturally occurring, complex metalloid that exists in multiple oxidation states and in both inorganic and organified forms. It is widely distributed in the Earth's crust, which contributes to its widespread global distribution in groundwater. High levels of arsenic in groundwater have been detected across the globe, including in Argentina, Bangladesh, Cambodia, China, India, Mexico, Pakistan, the United States, and Vietnam. Indeed, recent global analyses estimate that 94-220 million people are potentially exposed to groundwater with high arsenic concentrations (58). In this analysis, regions with high levels of predicted arsenic contamination of groundwater occurred on all continents, with most located in Asia, Africa, and the Americas. The vast majority (~94%) of individuals likely impacted by elevated groundwater arsenic reside in Asia. In addition to natural contamination, arsenic-containing compounds have been used in pig and poultry husbandry as well as historically as pesticides in agriculture (223-225). Moreover, Agent Blue, a mixture of arsenic-containing pesticides, was sprayed during the Vietnam War, potentially contributing to high levels of arsenic observed in the country (226). Finally, arsenic-based drugs have a unique role in the treatment of acute promyelocytic leukemia, a rare type of blood cancer (227).

b.   Where people are exposed

The primary source of exposure to arsenic is through consumption of contaminated water. While this contamination largely results from leaching of arsenic from natural geological formations, anthropogenic factors can exacerbate arsenic exposure. For example, hydraulic fracturing, a newer approach used for fossil fuel extraction, increases arsenic leaching into groundwater (228). Coal ash is a waste product of coal combustion that is high in toxic metals including arsenic. Combustion of coal releases arsenic into the atmosphere while breaches in ash containment facilities can increase arsenic contamination of local water sources (229). Natural disasters and extreme weather events may increase arsenic release into the environment through disruptions in coal ash containment or via ash from forest fires. Human contact with arsenic can also occur via other routes as well. An important source of arsenic exposure is food, particularly rice, which has a unique capacity to absorb toxic metals and metalloids when grown in contaminated soil and water. Research by consumer advocacy groups have detected higher than acceptable levels of arsenic in a variety of foods, including those intended for infants. Seafood also contains arsenic; however, this is generally in organified forms that are currently thought to be less toxic and not of significant public health concern. Finally, occupational arsenic exposure may occur through industrial activities.

c.   Science on why arsenic is an EDC

While traditionally associated with an increased risk of skin disorders and cancer, evidence clearly shows that arsenic has the capacity to disrupt multiple endocrine systems. Arsenic exposure is associated with metabolic disorders such as diabetes, with robust evidence linking arsenic to impairments in insulin secretion from pancreatic β-cells as well as alterations in insulin action and other metabolic derangements. In addition, arsenic has been associated with disruptions in reproductive function, including reduced testosterone levels and erectile dysfunction (230, 231) as well as adverse pregnancy outcomes and infant mortality (232, 233). Arsenic has also been shown to alter the hypothalamic-pituitary-adrenal axis and glucocorticoid receptor signaling as well as the hypothalamic-pituitary-thyroid axis, thyroid hormone levels, and thyroid hormone biology (234, 235). Importantly, there is strong evidence from animal models that exposure to arsenic during sensitive windows of development in early life can adversely affect outcomes in offspring. Indeed, some evidence indicates that preconceptual arsenic exposure may be sufficient to modulate endocrine outcomes in the offspring (236).

Importantly, the various endocrine systems influenced by arsenic exposure exhibit significant cross-talk with each other, collectively influencing the development of function of many tissues throughout the body. As such, it is not surprising that arsenic exposure has been associated with various adverse health effects, including reproductive, metabolic, cardiovascular, and neurocognitive disorders.

d.   Negative Endocrine Health Outcome: Type 2 Diabetes (T2D)

Diabetes mellitus is a common metabolic disorder projected to afflict 785 million adults globally by the year 2045. Diabetes is defined by elevations in blood sugar levels that arise from impairments in the secretion or action of the hormone insulin as well as associated metabolic derangements. The consequences of developing diabetes are grave as it is a leading cause of kidney failure, blindness, and non-traumatic amputations as well as a potent contributor to cardiovascular disease. While excess energy intake and reduced physical activity are undoubted drivers of diabetes development, recent evidence suggests that exposure to environmental toxicants likely also contributes to disease development (43, 55). Among these diabetes-associated toxicants is arsenic (237, 238). In addition to studies in human populations, a recent "state-of-the-science" review of the basic science literature affirmed the capacity of arsenic to disrupt various aspects of blood sugar control through a variety of mechanisms, including impaired insulin secretion and action (239). Moreover, studies of developmental arsenic exposure are suggestive of a link to diabetes risk, however, more studies of human cohorts are needed (240). Importantly, the complexity of arsenic chemistry means that individuals are exposed to a variety of arsenic species; moreover, individuals metabolize inorganic arsenic by adding two methyl groups to it. The efficiency of this methylation is influenced by an individual's genetics. Data indicate that both the form of arsenic and its methylation status alter the associations between arsenic and various adverse health outcomes, including diabetes, where more efficient methylation is associated with a higher risk of disease (241). Given the morbidity and mortality associated with diabetes as well as its significant disease-associated healthcare costs, comprehensive efforts to address this highly prevalent metabolic disease should include environmental policies to reduce exposures to diabetes-promoting chemicals, including arsenic (242).

...ARSENIC EXPOSURE HAS BEEN ASSOCIATED WITH VARIOUS ADVERSE HEALTH EFFECTS, INCLUDING REPRODUCTIVE, METABOLIC, CARDIOVASCULAR, AND NEUROCOGNITIVE DISORDERS.

BOX 6. LEAD IN COMMON PRODUCTS

Lead is a naturally occurring element found in the Earth's crust with its widespread occurrence in the environment largely the result of human activity. The distribution of lead worldwide, however, is greatest in developing regions, particularly within those countries that still use leaded petrol. Additional subpopulations that may face elevated risks include children of lower-income families living in degraded housing, communities living in 'hotspots' of industrial activity, and occupational groups. Those most at risk from lead exposure are pregnant women and young children. Lead exposure is associated with a variety of adverse health effects, including neurocognitive, cardiovascular, hematological, and gastrointestinal disorders. Indeed, lead exposure is estimated to account for 0.6% of the global burden of disease. Endocrine manifestations of lead exposure include delayed onset of puberty as well as early menopause. Collectively, evidence of delayed puberty coupled with earlier menopause suggests that lead exposure may shorten women's reproductive lifespan.

Sources and Uses of Lead
- Mining, smelting, refining, and recycling of lead
- Leaded petrol (gasoline)
- Production and use of lead-acid batteries and paints
- Jewelry making, soldering, ceramics, and leaded glass manufacture in informal and cottage industries
- Electronic waste
- Use in water pipes and solder

Exposures to Lead
- Ingestion of contaminated food, water, and house dust
- Inhalation of lead-contaminated air
- Smoking tobacco
- Use of lead-glazed pottery
- Consumption of some traditional medicines
- Use of cosmetics (e.g., kohl)

Abnormalities associated with lead exposure include:
- Neurocognitive disorders (e.g., cognitive impairment)
- Cardiovascular disorders (e.g., hypertension)
- Hematological disorders (e.g., anemia)
- Gastrointestinal disorders
- Reproductive abnormalities (e.g., altered reproductive hormones, delayed puberty, early menopause)

8.4   INDUSTRIAL CHEMICALS

8.4.1   PFAS

a.   Where they are used and produced

PFAS, often referred to as 'forever chemicals,' have been in military use since the World Wars with consumer use growing since the mid-20th century. PFAS are used in most industrial branches, including the production of fire-fighting foams, food packaging, textiles, and building materials (243). Over 5,000 PFAS have been identified. Historically, PFOS and PFOA appeared to be most abundantly used though they are increasingly replaced by other PFAS, among which GenX is prominent. PFASs are persistent organic pollutants (POPs), and as such, some have been added to Annex A (Elimination of PFOA, PFHxS, their salts and related compounds) and B (Restricted use of PFOS, its salts and PFOSF) of the Stockholm Convention for global elimination (**Box 1**).

b.   Where people are exposed

PFAS are ubiquitous water contaminants and people are exposed to PFAS through their drinking water. Private and public drinking water sources are often contaminated with PFAS. Similarly, fresh water (e.g., rivers, lakes, and streams) and oceanic water are contaminated with PFAS. Sites of and near PFAS manufacturing and military use have elevated PFAS levels in their water. People with occupations that involve the manufacturing or utilization of PFAS can have PFAS exposures above general populations. People residing near these sites with a heavy PFAS presence also have elevated PFAS levels. For example, PFAS levels were about 10% lower in women who drank bottled water compared to tap-water drinkers among residents of Shanghai (244), a region of China highly polluted with PFAS.

People are exposed to PFAS through the food supply both because of the PFAS in food packaging and the PFAS in water used to produce food. PFAS are used to make grease-resistant food packaging and various PFAS have been detected in fast food wrappers, pizza, French fry/chips/fried potato wrappers, sandwich boxes, ice cream cups, packaging for cupcakes and muffins, microwave popcorn bags, baking paper, and non-stick pots and pans. PFAS can migrate from these food contact materials into the food (245). Shellfish in Europe frequently contain PFAS hence the European Food Safety Authority considers this an important source of direct consumption of PFAS (245). Shellfish and especially freshwater fish consumption was an important determinant of PFAS levels in women residing in Shanghai (244). Rice is also an important source of PFAS due to the amount of water used to produce rice (246). For example, higher levels of PFAS in food such as rice is attributed to higher levels in people

PRODUCTS THAT MAY CONTAIN PFAS

COSMETICS

BAKING PAPER

CANDY WRAPPERS

POPCORN BAGS

NO-STAINS CLOTHES

NONSTICK PANS

DENTAL FLOSS

PIZZA BOXES

WATERPROOFING

PAINT & SEALANTS

FOOD CONTAINERS

CLEANING PRODUCTS

in Taiwan compared to people in Western countries (246). Elsewhere in households, PFAS are found in consumer products (e.g., waterproof clothing), building materials (e.g., carpets), and dust. Air inhalation, dust ingestion, and absorption from direct skin contact bring PFAS from these household substances into the human body (247).

c.   Science on why PFASs are EDCs

Evidence continues to emerge that indicates PFAS are EDCs. For example, computer models have predicted some PFAS can bind the androgen receptor, the estrogen receptors, and the vitamin D (a hormone) receptor (248, 249). Some of this mechanistic computer evidence has been confirmed experimentally (250, 251). Some PFAS can also disrupt the production, transport, and break-down of hormones such as estrogen and testosterone (252). Some PFAS can impair thyroid hormone functions in experiments (252). In adolescents, adults, and pregnant women in numerous studies, elevated levels of several PFAS are associated with elevated levels of the thyroid hormone T4 (252). Because there are thousands of PFAS, this evidence that highlights half of the key characteristics of EDCs is of concern to public health.

The state of California (USA) determined by expert committee in 2021 and 2022 that PFOS, PFOA, and their salts and transformation and degradation precursors cause cancer. Although they do not name specific types of cancer caused by these PFAS, the number of human and experimental studies evaluating breast cancer was noteworthy. IARC intends to review PFOS and PFOA to decide the carcinogen status of these PFAS in late 2023.

d.   Negative Endocrine Health Outcome: Adverse Reproductive and Developmental Outcomes

Experimental studies of PFAS in rodents reveal disruption of reproductive health with close links to endocrine function. The effects of PFOS and PFOA on the mammary gland and breast have been extensively studied compared to other endocrine-dependent health outcomes. PFOA and PFOS delay the normal development of mammary glands in rodents (253). In one study, exposure of pregnant mice to PFOA at levels typically found in US drinking water caused the daughter and granddaughter mice to have delayed mammary gland development (254). Although a relationship of PFAS to human breast development has not yet been evaluated, exposure to PFAS in the womb or near puberty has been associated with delayed menarche in girls (255).

In addition to the structural effects of PFAS on rodent mammary glands, PFAS can impact mammary gland function. Rodent studies indicate that PFAS can reduce the production and transport of a key hormone involved

in making milk called prolactin (252). As less prolactin would be expected to generate less milk, the two human studies finding that PFAS exposure was associated with a shorter duration of breast feeding is consistent with rodent mammary gland dysfunction caused by PFAS (252).

8.4.2 BROMINATED FLAME RETARDANTS

a. Where they are used

Polybrominated diphenyl ethers (PBDEs) are persistent organic pollutants (POPs) that have widely been used as flame retardants in consumer products since the 1970s, including in computers, electronics and electrical equipment, textiles, foam furniture, insulating foams, and other building materials (256). Historically, three different mixtures known as PentaBDE, OctaBDE, and DecaBDE have been commercially available. The predominant use of PentaBDE has been in polyurethane foam in furniture, while OctaBDE and DecaBDE have been used in electronics and other plastic products where fire resistance is desired. In many countries PentaBDE, OctaBDE, and DecaBDE have been phased out and replaced by other brominated flame retardants, including "next generation" BFRs, a variety of organophosphate esters (OPFRs), tetrabromobisphenol A (TBBPA), and hexabromocyclododecane (HBCD) (54, 257). Some of these replacements are now also thought to be EDCs and developmentally neurotoxic (34). Due to their persistent and bioaccumulative properties, and their ability to be transported long distances, PentaBDE, Octa BDE, DecaBDE, and HBCD have been added to Annex A of the Stockholm Convention for global elimination (258).

HAZARDOUS CHEMICALS FOUND IN PLASTIC PRODUCTS IN AFRICA

BROMINATED FLAME RETARDANTS IN CONSUMER PRODUCTS MADE OF RECYCLED PLASTIC FROM SEVEN AFRICAN COUNTRIES

June 2021

ARNIKA   IPEN

TOXIC CHEMICALS IN PLASTIC TOYS

For this 2021 study, IPEN sampled toys and other consumer products made from recycled e-waste plastic, finding that toxic flame retardant chemicals (BFRs) were widely present in consumer goods sold in 7 African countries. Several samples contained globally banned BFRs, and 16% of the products tested had such high levels of BFRs that under global rules they would be considered hazardous waste.

b.   Where people are exposed

BFRs and other chemical flame retardants are not chemically bound to products and are therefore released into the environment where they may enter the human body via ingestion and inhalation of contaminated house dust and/or food. Even though PBDE exposures in Europe and the US have consistently declined since the phase-out (259), they remain a public health concern because PBDEs have long elimination half lives in the body (260, 261), may persist in the indoor environment (262), and can biomagnify in the food web (263). An additional source of PBDE exposure in developing countries is the processing of 20–50 million tons of e-waste annually, primarily in Africa and Asia.

The listing of PBDEs in the Stockholm Convention includes specific exemptions that allow for recycling and the use in articles of recycled materials containing these chemicals (258). Recycling of electrical and electronic equipment, which primarily occurs in Africa and Asia, leads to BFR exposures in workers, communities, and consumers during the recycling stream and in use of recycled products (264). For example, one study of recycled plastics in India found concentrations of Deca-PBDE in 50% of samples examined (265). The contamination of recycled plastic products with BFRs also occurs in Europe. For example, a recent study found DecaBDE, TBBPA, and a variety of other flame-retardant chemicals in recycled black thermo cups and kitchen utensils on the European market (266). In 2020, the European Union announced that they are withdrawing from that exemption.

Sources and routes of exposure can vary by life stage and by individual PBDEs (261, 267). For example, serum concentrations of BDE-47, -99, and -100 (characteristic of PentaBDE)(268) are highly correlated with dust exposures (257, 269). In contrast, BDE-153 [a minor component of PentaBDE and OctaBDE (268)] shows strong correlations with dietary exposures (including breast milk) and less consistent relationships with dust exposures. Children, on average, have three times higher concentrations than adults (270); this is likely due to exposures from breast milk and increased dust intake due to their hand-to-mouth behaviors and close time on the ground (271). Interestingly, placental PBDE levels are higher in placental tissues from male infants compared to female infants, suggesting boys may have higher fetal exposures than girls (272) and are at greater risk for thyroid hormone disruption and, consequently, compromised brain development.

Exposures in North America are an order of magnitude higher than in Europe and Asia (273). Residents of California historically have the world's highest non-occupational exposures to PentaBDE congeners because of the state's unique flammability standard that encouraged the use of flame retardants in foam furniture for decades (274). This standard has now been revised and, consequently, exposures have declined. Higher concentrations of PentaBDE congeners are also found among low-income communities (271) and those occupationally exposed (275). Occupations with higher exposures include firefighting, manufacturers of flame-retardant products, people involved in recycling flame retardant products, computer technicians, and carpet installers (275-278). Mean PBDE body burdens among child waste recyclers in Nicaragua were between 500 – 600 ng/g lipid, about 10-fold higher than US children and among some of the highest recorded to date (279).

c.   Science on why BFRs are EDCs

BFRs are potential EDCs because both the original compounds as well as their breakdown metabolites may interfere with the thyroid system. Thyroid hormones (TH) play a critical role in fetal and childhood development (280). In animal studies, PentaBDE mixtures as well as their components reduce thyroid hormones in developing and adult rodents, possibly by activating liver enzymes that increase TH clearance from serum (281-283). Metabolites of PBDEs called hydroxylated PBDEs [OH-PBDEs (284)] have more potent actions on the thyroid system, and structural similarities between PBDEs and thyroid hormones enable the chemicals to interact with thyroid hormone-binding proteins (285). In addition, some OH-PBDEs can bind to thyroid and estrogen hormone receptors (286, 287).

Several epidemiological studies find that PBDE exposures during early life are associated with thyroid hormone disruption and that the developing fetus is particularly vulnerable (288-291). Pregnancy represents a period of increased demand on the thyroid gland. Serum TH levels increase by almost 50 percent during the first trimester (292). TH insufficiency during pregnancy can impair the health of mother and offspring (293). Even modest reductions in maternal thyroid hormone during early pregnancy are associated with long lasting developmental deficits in their children, including reduced IQ (294). Thus, PBDE exposure may impair the function of the thyroid gland of pregnant women, something that could have lifelong effects on the neurobiological health of their offspring.

d.   Negative Endocrine Health Outcome: Adverse Neurodevelopmental Outcomes

One of the greatest public health concerns of PBDEs is neurodevelopmental toxicity. Experimental, animal, and human studies find that PBDEs can cause neurodevelopmental toxicity both by altering brain development directly and by interfering with thyroid hormone regulation (33). In human studies, prenatal and/or early postnatal exposures to PBDEs are associated with neurodevelopmental harm in children including deficits in concentration, fine motor coordination, and cognition (295-297). For example, in the largest study to date, Eskenazi et al. (296) examined associations between prenatal and childhood PBDE exposures and neurobehavioral development at 5 and 7 years of age among a California migrant farmworker community in the US. They found that a ten-fold increase in both prenatal and childhood PBDE exposures was associated with an average reduction in five IQ points among seven-year-old children. These neurodevelopmental effects are similar in magnitude to those observed due to exposure to lead and polychlorinated biphenyl ethers (PCBs) during early development. Unfortunately, some of the compounds replacing PBDEs, most notably the OPFRs, are also likely to be developmental neurotoxicants with similar and/or other mechanisms including disruption of neurotransmitter signaling (298).

9. FUTURE CONCERNS: EDCs AND CLIMATE CHANGE

Several aspects of climate change predictions indicate that exposure to EDCs will increase over the next decades. First, there is elevated exposure to POPs in circumpolar countries because these chemicals rise into the air in temperate regions and travel via wind to deposit at the earth's surface in colder regions. For example, intake of DDX by Inuit people is comparable to that of people living in regions using DDT to control malaria (299). Climate change is expected to increase the deposition of POPs in the circumpolar regions. Furthermore, POPs deposited into glaciers will be released by melting glaciers, sea ice, and permafrost where POPs will magnify up aquatic food webs (300, 301).

Next, extreme temperatures and precipitation (flood and drought) associated with climate change will make agriculture more difficult. To feed a growing population under less favorable conditions for agriculture, a greater reliance on and persistence of endocrine disrupting pesticides will likely result (302, 303). Pesticide use is likely to expand to control disease vectors moving into new geographic areas due to climate change. For example, climate change is expected to increase the incidence of malaria, potentially leading to increased demand for and use of DDT (304). Furthermore, flooding from extreme weather events is likely to release EDCs into the environment by breaching containment measures.

Lastly, the destruction of property due to climate change will increase exposure to EDCs in several ways. Manufacturing, military, and hazardous waste sites contain relatively high levels of EDCs. Because they are often sited in flood-prone areas, climate change-related flooding of these sites is expected to contaminate communities with these EDCs. Resilience to climate disasters requires the use of building materials including many that contain fire retardants and plastics which may be EDCs. The increased risk of fire associated with climate change could result in public health practices that increase the use of fire-retarding and firefighting materials that contain BFRs and PFAS, respectively, while fires in forests and populated areas are likely to liberate EDCs into the environment. Consequently, it is important to consider EDC-free materials in property protection and replacement.

In a rapidly changing world transformed by climate change, it is especially urgent to address the simultaneous threat of chemical pollution and its adverse impact on endocrine health in order to protect human health in a manner that is both equitable and just.

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