

## **PLASTICS, EDCs & HEALTH**

A GUIDE FOR PUBLIC INTEREST ORGANIZATIONS AND POLICY-MAKERS ON ENDOCRINE DISRUPTING CHEMICALS & PLASTICS



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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 EDC literature, and it represented the first public statement on the issue from a major mainstream international medical society.

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### FOREWORD

Chemical additives in plastic and the threat they pose to human health and the environment is an emerging issue of global concern that is garnering increasing attention as society is beginning to address the world-wide plastic pollution problem. The publication Plastics, EDCs and Health, produced by the Endocrine Society and authored by a leading international group of scientists and professors, is an authoritative and comprehensive resource. The report details the endocrine disrupting chemicals (EDCs) in plastics and the hazards that these chemicals pose to human health throughout the life-cycle of plastics.

Many plastic additives are known to interfere with hormone functioning and are, by definition, endocrine disrupting chemicals. This publication provides clear and extensive evidence of the human health impacts of many chemicals in common plastics. The health impacts of these widely used chemicals can be profound and life threatening. Cancers, diabetes, kidney, liver, and thyroid impacts, metabolic disorders, neurological impacts, inflammation, alterations to both male and female reproductive development, infertility, and impacts to future generations as a result of germ cell alterations are the consequence of many EDC exposures, EDCs that are integral to plastics.

Following the World Health Organization and UN Environment Programme report on the State of the Science of EDCs, the international community identified the need for action on EDCs. By 2015, more than 100 countries at the 4th International Conference on Chemicals Management (ICCM4) concurred that policy action on EDCs was called for. Since then, UNEP developed three overview reports on EDCs, and a list of EDCs recommended for regulatory control was recently published by European Union member states. In addition, in 2020, a UN Chemicals Conventions Expert Group, led by a Stockholm Convention Regional Center, released a report on Plastics' Toxic Additives and the Circular Economy that identified many common and widespread "substances of concern" in plastics, many of which are EDCs.

The Stockholm Convention on Persistent Organic Pollutants, has taken action to list several plastic chemical additives, including flame retardant substances, for global elimination as they pose unmanageable threats to human health and the environment. In May 2020, the Swiss Government submitted a proposal to the Stockholm Convention to list another plastic chemical additive, the first ultra-violet (UV) stabilizer, UV-328, to be proposed for listing under Annex A of the Convention. The Stockholm Convention is the definitive global instrument for assessing, identifying, and controlling some of the most hazardous chemical substances on the planet to protect human health and the environment. This publication provides insights to several UV stabilizers that are also EDCs and chemical additives to plastics.

The Swiss Government recognizes the threat from UV-328 to public health and the environment, noting it is a high production volume chemical used in transparent plastics, coatings, personal care products and single use plastics, including food contact materials. It has the defining characteristics of a Persistent Organic Pollutant: it is persistent (it does not readily break down), it is dispersive (it travels great distances and can be found in environments far removed from where products are made and used), it is bio-accumulative, and it is toxic, including to humans.

Plastics, EDCs and Health coalesces the science on EDCs and plastics. It is our collective responsibility to enact public policies to address this clear scientific evidence that EDCs in plastics are hazardous. It is our hope that the science will lead to global policy action to address the hazards that are widespread in plastics that threaten our environment, our health, and our future.

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Franz Xaver Perrez Ambassador for the Environment Government of Switzerland



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

Many potentially harmful chemicals are used during the production of plastics, either as building blocks of the plastic material itself or as additives to provide certain properties such as color or flexibility. These chemicals remain in the final product and therefore, plastics contain and leach many hazardous chemicals, including endocrine-disrupting chemicals (EDCs) that disturb the body's hormone systems. One well-known example is bisphenol A (BPA), which is used in polycarbonate plastics. Further, a wide range of other plastic additives, including phthalates, flame retardants, heavy metals are known EDCs. Pivotal research advances into EDCs, their prevalence, and their broad range of health effects have raised concerns about these chemicals and led a number of international scientific and health organizations to weigh in. Published statements, position papers, resolutions, and similar activities have successfully advanced global awareness and understanding of EDCs, and contributed to sciencebased action on EDCs by many stakeholders including some governments, retailers and manufacturers.

The Endocrine Society was the first scientific body to take a public stance on the state of EDC science with the 2009 publication of its Scientific Statement on EDCs [1]. At that time, the Society's membership asserted that there was sufficient evidence to conclude that EDCs pose a public health risk. In 2015, the Society issued a second statement [2], reiterating and updating the strength of evidence linking EDCs with human diseases and conditions including cancer, early puberty in young girls, obesity and diabetes, male and female reproductive disorders, and neurodevelopmental effects, among others. The second statement also highlighted key advancements in the understanding of how EDCs act, and the understanding of core concepts in EDC research, including effects at even very low exposures to EDCs, and the particular vulnerability of developing fetuses and infants, concepts that will be discussed in more detail below. These landmark publications were pivotal for synthesizing the science of EDCs and communicating the potential risks they pose to humans, the ecosystem, and even the economic well-being of a country.

The number of medical societies voicing concern over EDC exposure and EDCs in the context of the larger universe of toxic chemicals has since grown to include a diversity of voices. These include the American Medical Association (AMA), the largest organization of U.S. medical professionals that in 2009 and 2011 called for improved regulatory oversight of EDCs based on the body of scientific research (Policy D-135.982); The American Public Health Laboratories and The American Chemical Society that have recommended expanded education and research, updated

### TO ACCELERATE IDENTIFICATION OF EDCS FOR REGULATORY CONTROL IN THE EU, A LIST WAS RECENTLY PUBLISHED BY MEMBER STATES ABOUT THE CURRENT STATUS OF SUBSTANCES IDENTIFIED AS ENDOCRINE DISRUPTORS OR UNDER EVALUATION FOR ENDOCRINE DISRUPTING PROPERTIES.

testing protocols, and the development of safer alternatives to EDCs; the American College of Obstetrics and Gynecology and the American Society of Reproductive Medicine that in 2013 issued a joint committee opinion "calling for timely action to identify and reduce exposure to toxic environmental agents" [3]; The British Royal College of Obstetrics and Gynaecology, which 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." 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." In 2015, the International Federation of Gynecology and Obstetrics published an opinion on reproductive health impacts of exposure to toxic environmental chemicals [4].



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

Estimates of the health and other economic costs of EDC exposure are also emerging. In 2015, a study by Trasande *et al.* concluded that "EDC exposures in the EU are likely to contribute substantially to disease and dysfunction across the life course with costs in the hundreds of billions of Euros per year" [5]. In their landmark report 'Health costs that may be associated with Endocrine Disrupting Chemicals' the Institute for Risk Assessment Sciences at the University of Utrecht estimated the costs associated with five likely EDC-related health effects. They conclude that 'according to currently available literature, the socio-economic burden of EDC associated health effects for the EU may be substantial', ranging from EUR 46 billion to EUR 288 billion per year [6]. A similar 2016 study estimating the cost of EDC exposure in the United States concluded that "EDC exposure in the USA contributes to disease and dysfunction, with annual costs taking up more than 2% of the GDP"[7].

A number of international health organizations have taken up the call for improved EDC policies. One of the most influential is the 2012 joint World Health Organization (WHO) and United Nations Environment



Programme (UNEP) State of the Science of Endocrine Disrupting Chemicals Report [8]. The report outlines the current understanding of EDCs and their effects on human health. It also recommends improved testing and reduced exposures to EDCs.

The need for policy action has also been acknowledged by many governments. In 2015, a consensus agreement by more than 100 countries presented at the 4th International Conference on Chemicals Management (ICCM4) organized by UNEP affirmed in resolution IV/2 that the 2012 State of the Science Report is authoritative and should be utilized by governments.

Heeding the call, the Policy Department for Citizen's rights and Constitutional Affairs within the European Parliament commissioned its own study of EDCs. Released in January 2019, "Endocrine Disruptors: from Scientific Evidence to Human Health Protection" was written by two French EDC experts, both members of the Endocrine Society. It summarizes the state of the science surrounding EDCs including sources, effects, human exposure levels, and estimates of economic impacts. It also advocates for further research on EDC effects and the development of chemical alternatives to those with endocrine-disrupting activity. To accelerate identification of EDCs for regulatory control in the EU, a list was recently published by Member States about the current status of substances identified as endocrine disruptors or under evaluation for endocrine disrupting properties.

The repeated calls by the global scientific and medical community to enact public policies grounded in the latest available scientific evidence to protect against the harmful effects of EDCs are gaining traction, especially in the EU. In April 2019, the European Parliament issued a resolution on a comprehensive European Union framework on EDCs, which calls on the Commission to "swiftly take all necessary action to ensure a high level of protection of human health and the environment against EDCs by effectively minimizing overall exposure of humans and the environment to EDCs." This landmark resolution cited broader efforts to reduce pollution and improve sustainability, including the Sustainable Development Goals set forth by the United Nations, in its justification to "ensure that the Union framework on EDCs becomes an effective contribution to the Union strategy for a non-toxic environment, to be adopted as soon as possible." This follows the 2013 decision of the European Parliament and of the Council, which committed to a strategy that would limit exposures to EDCs. These types of national and international global efforts will be needed to reduce plastic pollution and, by extension, EDC exposures. Importantly, in early 2019, 170 countries agreed to "significantly reduce" the use of plastics by 2030 following talks at the UN Environment Assembly. Many countries, US states and municipalities, and some retailers are beginning to phase out single-use plastics.



# 2. INTRODUCTION TO THE HUMAN ENDOCRINE SYSTEM AND EDCs

#### BACKGROUND ON THE HUMAN ENDOCRINE SYSTEM

The endocrine system consists of a series of glands that are distributed throughout the body (*see "Visualizing the Endocrine System" on page 16*), each of which produces one or more hormones. These hormones are natural chemicals that are released into the bloodstream and circulate around the body. When they reach a target organ, they bind to specific receptors, triggering a response such as production of another hormone, a change in metabolism, a behavioral response, or others, depending upon the specific hormone and its target. A list of representative examples of endocrine glands, the hormones they produce, and their effects in the body, is provided in *"Table 1"*. Endocrine systems and their functions are complex and

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diverse, with each gland and hormone playing unique roles in health and well-being. Furthermore, the endocrine system is necessary for human health. Endocrine glands and the hormones they produce enable the body to adapt to environmental change; they allow metabolic adjustments to occur in response to different nutritional demands (e.g. hunger, starvation, obesity, etc.); they are critical to reproductive function; and they are essential to normal development of the body and brain through their effects on growth and maturation of organs. Thus, as a whole, the endocrine system is one of the body's major interfaces with the environment, allow-



**Visualizing the Endocrine System.** Shown are the major endocrine organs in the human body in a male (left) and female (right).

ing for the development and maintenance of bodily processes and health, and the procreation of the species through reproduction.

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. For example, diabetics have deficiencies in insulin release and/or action, and people with type I diabetes will die without insulin replacement. Often, under- or over-secretion of hormones such as thyroid hormone results in metabolic disturbances and many physical and neurobiological changes, due to thyroid hormone's key role in day-to-day cellular metabolism and brain function. Other hormonal dysfunctions include infertility, growth disturbances, sleep disorders, and many other chronic and acute diseases. Thus, endocrine hormones must be released at the appropriate amounts, and endocrine glands must be able to adjust hormone release in response to the changing environment, to enable a healthy life.

### **TABLE 1.** MAJOR ENDOCRINE GLANDS WITH EVIDENCE FOR ENDOCRINEDISRUPTION

Endocrine Gland	Location in the body	Major hormone(s) re- leased by the gland	General effect(s)
Pituitary	Just under the brain, and above the roof of the mouth	<ol> <li>Growth hormone</li> <li>Thyroid-stimulating hormone</li> <li>Adrenocorticotropic hormone</li> <li>Luteinizing hormone</li> <li>Follicle-stimulating hormone</li> <li>Prolactin</li> <li>Oxytocin</li> <li>Vasopressin</li> </ol>	<ol> <li>Growth</li> <li>Metabolism</li> <li>Stress and immune responses</li> <li>and 5. Reproduction in both males and females</li> <li>Milk production</li> <li>Milk release during nursing, and uterine contraction during delivery of a baby</li> <li>Electrolyte balance and blood pressure.</li> </ol>
Adipose Tissue	Distributed through the body	Leptin	Body weight regulation
Thyroid	Both sides of the lower throat	1. Thyroid hormones 2. Calcitonin	<ol> <li>Metabolism and neurodevelop- ment</li> <li>Calcium balance</li> </ol>
Hypothalamus	Part of the brain, located at its base	1. GHRH 2. TRH 3. CRH 4. GnRH 5. Dopamine	<ol> <li>Growth</li> <li>Metabolism</li> <li>Stress and immune responses</li> <li>Reproduction</li> <li>Lactation (dopamine is the prolactin-inhibiting hormone)</li> </ol>
Pancreas	Abdomen	1. Insulin 2. Glucagon	1 and 2. Blood sugar and other nutrient regulation.
Adrenal	Above the kidney	<ol> <li>Glucocorticoids (cor- tisol)</li> <li>Mineralocorticoids (aldosterone)</li> <li>Sex steroids (DHEA and others)</li> </ol>	<ol> <li>Stress and immune responses</li> <li>Blood pressure and water balance</li> <li>Growth of muscle and bone</li> </ol>
<b>Ovary</b> (female)	Abdomen	Sex steroids, especially estrogens and proges- terone	Reproduction in females
<b>Testis</b> (male)	Scrotum	Sex steroids, especially androgens (testoster- one)	Reproduction in males

Representative endocrine glands are shown, together with their location, the hormones they produce, and functions. When a gland produces more than one hormone, those hormones are numbered in the third column to correspond to the numbers in the fourth column describing their functions. Abbreviations: ACTH: adrenocorticotropic hormone; CRH: corticotropin-releasing hormone; DHEA: dehydroepiandrosterone; GHRH: growth hormone-releasing hormone; GnRH: gonadotropin-releasing hormone; TRH: thyrotropin-releasing hormone.



### WHAT ARE EDCs, HOW ARE THEY USED, AND WHERE ARE THEY FOUND?

EDCs were defined by the Endocrine Society (endocrine.org), the largest international group of scientists and physicians working and practicing in the field of endocrinology, as: "an exogenous [non-natural] chemical, or mixture of chemicals, that interferes with any aspect of hormone action" [9]. There is a vast amount of manufactured chemicals in use today. A recent study of chemical inventories from 19 countries and regions shows that the amount is far higher than previously thought, with over 350 000

chemicals and mixtures of chemicals registered for production and use. It should be noted that the study also found that the identities

### A CONSERVATIVE ESTIMATE IS THAT MORE THAN A THOUSAND OF THESE [350,000 CHEMICALS] MAY BE EDCs.

of many chemicals remain publicly unknown because they are claimed as confidential (over 50 000) or ambiguously described (up to 70 000) [10]. While most of these has not been assessed for endocrine disrupting properties, a conservative estimate is that more than a thousand of these may be EDCs. Although there are many types of EDCs, this guide will focus on EDCs in plastics, particularly bisphenols, phthalates, alkylphenol ethoxylates, nonylphenols, brominated flame retardants, perfluorinated substances, benzotriazole UV stabilizers, and toxic metals. Chemicals enter our body predominantly by the oral route (consuming food and water containing chemicals that have leached from the environment or from containers), contact with the skin (e.g., cosmetics, antibacterials, sunscreens), intravenous tubing, and inhalation (e.g., pesticide spraying, air pollution) (*see "Table 2"*) [11]. Chemicals in the body of a pregnant or lactating woman may also transfer to a fetus or infant via placental transfer or through breast milk. This latter concept is discussed in the next section.

Source		EDC example(s)
	Water	Perfluorinated compounds (PFAS)
	Food Contact Material	BPA Phthalates
	Furniture	Brominated Flame Retardants (BFRs)

#### TABLE 2. EXAMPLES OF WHERE YOU CAN FIND EDCs

Many EDCs interfere with the endocrine system because they can mimic or block natural hormones and their actions in the body. For example, in the case of EDCs in plastics, bisphenols and phthalates are best studied for mimicking or interfering with processes regulated by estrogens and androgens such as reproduction. These hormones are highly regulated; if disrupted by EDCs, reproductive dysfunctions can occur including reduced fertility, pregnancy loss, and infertility.

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### **3. IMPACTS OF EDCs**

#### HISTORICAL PERSPECTIVE ON EDCs

Since 1940, there has been an exponential increase in the number and abundance of manufactured chemicals, many of which have been released (intentionally or not) into the environment. This chemical revolution has irreversibly changed ecosystems with 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 the pesticide DDT, might be responsible for the reduced numbers of birds due to reproductive failure caused by this and other toxic chemi-

cals. Meanwhile, wild American alligators in Florida (USA) exposed to dicofol, a pesticide, exhibited genital and reproductive malformations. The discovery of deformed frogs in Minnesota (USA) by schoolchildren on a nature field trip further

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.

illuminated the problem of chronic pollution by agricultural runoff. These and many other examples of associations between these and other EDCs have since been confirmed in wildlife of every class [12,13] and were chronicled in the landmark 1996 book *Our Stolen Future* that warned that humans were similarly at risk [14].

In the case of humans, though, and with the exception of massive chemical spills or contamination, it has been difficult to prove with confidence whether a particular chemical exposure caused a specific toxic effect. As in wildlife, the most direct evidence for cause and effect unfortunately comes from large-scale disasters where humans were exposed to varying amounts of EDCs: high levels were acutely toxic, and lower levels were found to be associated with chronic, subtle, and long-lasting adverse health effects. One example is the explosion of a chemical manufacturing plant in Seveso, Italy, that exposed residents to high levels of dioxins. Two more tragic exposure examples are Yusho in Japan (PCBs), and Yucheng in Taiwan (polychlorinated dibenzofurans) in which contaminated cooking oil caused mass poisoning. Of recent concern is the poisoning of schoolchildren in India in July 2013 through oil contaminated with the organophosphate pesticide monocrotophos, which resulted in 23 deaths. The long-term endocrine-disrupting effects of monocrotophos in humans remain to be seen, although it interferes with estrogen and thyroid systems in studies on mice and fish [15-18].

### THE IMPORTANCE OF DEVELOPMENT AS A PERIOD OF VULNERABILITY TO EDCs

The developing fetus is uniquely vulnerable to EDCs. Although it is now well established that some chemicals and pharmaceuticals can cross the placenta, fifty years ago, it was thought that the placenta acted as a barrier, protecting the developing fetus from any drugs or chemicals in the mother. Two unfortunate clinical events transformed and ultimately negated this perspective. The first was the realization that pregnant women given thalidomide to alleviate nausea during the first trimester sometimes gave birth to infants with severe limb malformations. Clearly, the fetus was vulnerable to pharmaceuticals given to the mother. The second breakthrough discovery was in relation to diethylstilbestrol (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 had reproductive tract malformations and some developed rare reproductive cancers in adolescence that were normally only seen in postmenopausal women [19]. Because of the long latency between exposure (fetus) and disease (adolescence), the connection to DES was not initially obvious. However, experimental work in mice exposed to DES as fetuses also demonstrated reproductive disorders in the offspring as they matured to adulthood. This cause-and-effect relationship between fetal DES exposure, reproductive tract malformations, and cancer later in life in girls was tied together to experimental DES exposure effects in mice, and the field of endocrine disruption was born.

Vulnerability to EDC exposures continues into infancy and childhood, when the body and brain undergo rapid growth. Considerable research in laboratory animals shows that early life exposure affects all of the body's endocrine systems studied to date [20]. For the rest of the life cycle, both exposures and responses to EDCs can continue into adulthood and even aging. The body's endocrine systems are not static: throughout our lives, hormone release and levels go up and down in response to the needs of



A drill rig bores a well for a future natural gas fracking site very near homes and a school. Higher exposures occur in those living near agricultural pesticide use, heavy industry, mining, landfills, and fossil fuel extraction.

the body and to adapt to the environment. Any and all of these processes can be disrupted by EDCs.

### EDCs IN THE BODY

Every individual is exposed to a mixture of chemicals that is determined by the external environment, internal environment, and lifestyle. Higher exposure occurs in those living close to agriculture where pesticides are used, near heavy industry, mining, fossil fuel extraction (such as natural gas extraction/ fracking), or manufacturing, and in proximity to landfills. The indoor environment – e.g. use of household cleaning products, chemicals such as flame retardants released from furniture or biocides – further influences exposures. Finally, lifestyle plays a key role in chemical exposure. For example, an organic diet prevents exposure to many pesticides that are EDCs and eating fresh food avoids exposure to EDC contaminants in processed and canned foods.

It is well established that mixtures of chemicals can act together to generate combined effects, including mixtures of EDCs. In 2019, the EU-funded project EDC-MixRisk concluded, "Current regulations of man-made



chemicals systematically underestimate health risks associated with combined exposures to EDCs or potential EDCs" [21]. While not the topic of this report, it should be noted that the chemicals addressed do not occur in isolation, but as part of complex mixture exposure scenarios.

Animals and humans carry personal body burdens - the amount of chemicals contained in an individual's tissues - from direct exposures they experience throughout their lives. Some of these are EDCs and are persistent and bioaccumulative (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 all individuals worldwide. The exact number varies between populations. The 2012 WHO/UNEP State of the Science of Endocrine Disrupting Chemicals Report indicates, "close to 800 substances are known or suspected to be capable of interfering with hormone receptors, hormone synthesis, or hormone conversion." Three additional reports on EDCs were released by UNEP in 2017, covering initiatives to identify EDCs; current knowledge on a select group of them; and regulatory frameworks addressing EDCs. Fat is a particularly important reservoir for many EDCs, as their chemical compositions tend to make them fat-soluble. Measures of EDC body burdens reflect not only contemporary contact with EDCs, but they also include past exposures, sometimes decades ago, to persistent chemicals.

### MULTIGENERATIONAL EFFECTS OF EDCs

Environmental chemicals can have effects on future generations. When a person has a chemical body burden, his/her sperm or eggs may be exposed to those chemicals. Direct effects of EDCs have been shown on sperm number and quality, on chromosomal abnormalities in ova (eggs), and on biological processes involved in sperm and ova production [22-24] among others. A recent review of available studies of reduction in sperm count estimated a 50-60% decline in men from North America, Europe, Australia and New Zealand between 1973 and 2011 [25]. These processes are associated with poor reproductive outcomes such as subfertility or infertility, affecting viability and health of offspring.

EDCs can also induce effects on future generations through their actions on germ cells, which are the precursors to sperm and ova (*see "Early Exposure"*). When exposure occurs in a pregnant woman, her developing fetus is exposed (child), as are the germ cells within the fetus that become the grandchildren. Thus, three generations are exposed at the same time.

Why is this important? Germ cells contain the DNA that is transmitted from generation to generation. We know that mutations to DNA are heritable, and can result in inherited diseases, but this is not how the EDCs are acting. Rather, other types of heritable changes can be programmed into DNA: these are epigenetic changes, defined as modifications to DNA (but not mutations) that change how that DNA is regulated and turned into proteins [26]. That means that these changes can be inherited over one or more generations. EDCs have been shown to cause several types of epigenetic modifications in germ cells that, in the offspring (children) produced from the sperm or ova, result in increased propensity for endocrine and neurological



**Early Exposure.** Schematic of how EDC exposure can affect multiple generations: the mother, her children, and even her grandchildren, indicated by dots as the germ cells.

### SCIENTIFIC KNOWLEDGE OF ENDOCRINE DISRUPTING CHEMICALS

Following the 2015 ICCM4 decision, UNEP convened a multistakeholder EDC Advisory Group including Government, UN Agencies, Industry, Science and Public Interest institutions. This EDC Advisory Group produced the following UNEP EDC reports:

- **Overview Report I:** Worldwide initiatives to identify endocrine disrupting chemicals (EDCs) and potential EDCs
- Overview Report II: An overview of current scientific knowledge on the life cycles, environmental exposures, and environmental effects of select endocrine disrupting chemicals (EDCs) and potential EDCs
- Chemical Fact Sheets for Overview Report II
- Overview Report III: Existing national, regional, and global regulatory frameworks addressing Endocrine Disrupting Chemicals (EDCs)

These reports include the first UN international reference of a list of 45 substances named as EDCs and potential EDCs. Several of the EDCs listed are additives to plastic products.<sup>[283]</sup>

disorders in the next generation (grandchildren) [26]. Thus, preconceptional or early life exposures to EDCs influence multiple generations.

The cycle of exposure does not end with the grandchildren. Some epigenetic modifications to germ cells caused by EDCs are permanent and heritable to the great-grandchildren, great-great-grandchildren, and beyond. Indeed, this was shown first in a rat model using the EDC fungicide vinclozolin, in which transmission of disease propensity (reproductive and hormonal abnormalities) was seen up to 4 generations removed from the original exposure [27]. That study implicated an epigenetic mechanism for this disease transmission. Since then, numerous chemicals have been shown in animal studies to cause epigenetic effects across generations [28], including chemicals in plastics, and to be associated with reproductive and endocrine problems [29,30].

### EDCs AND ENDOCRINE DISEASE

It has been estimated that, globally, upwards of 23% of all deaths and 22% of human disability are attributable to environmental factors [16,31] and that the environment plays a role in 80% of the most deadly diseases, including cancer and respiratory and cardiovascular diseases [32]. The most susceptible individuals are children under 5 and adults over 50 years

of age [16]. Because disruptions to the endocrine system are fundamental to the most prevalent of these diseases, EDCs may be primary contributors. The incidence of endocrine-associated pedi-

#### GERM CELLS CONTAIN THE DNA THAT IS TRANSMITTED FROM GENERATION TO GENERATION.

atric 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% to 15% between 1997 and 2008 [33]. A significant increase was also found in 2014-2016, even when restrictive criteria for



Chemical industry sales are projected to rise with a complementary rise in plastics production. Derived from GRID-Arendal, Maphoto/Riccardo Pravettoni

what constitutes a developmental disability were used [34]. 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 [2].

The increased endocrine disease rates parallel increased production of manufactured chemicals, including chemicals added to plastics. Global production of plastics has grown exponentially from 50 million metric

EDCs ARE LINKED TO NEUROLOGICAL AND BEHAVIORAL DISORDERS, OBESITY AND METABOLIC DYSFUNCTION, REPRODUCTIVE DISORDERS, AND HORMONE-SENSITIVE CANCERS. tons in the mid-1970s to 360 million metric tons in 2018. 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 [35] to more than US\$5 trillion in 2019. By 2030, sales are expected to double [36]. A wide range of industrial and agricultur-

al chemicals such as PCBs, BPA, and phthalates, are detectable in human serum, fat, and umbilical cord blood [37-39] and recently per- and poly-fluoroalkyl substances (PFAS) have been detected in human fetuses [40].

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 have provided a wealth of evidence supporting direct cause-and-effect links. Proving 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 obviously be unethical and thus impossible for testing the impact of toxicants on humans. However, the capacity to infer risk from a mixture of scientific evidence is rapidly improving alongside the tools for generating critical data. High confidence conclusions about EDC-related health effects can be made using a combination of data from epidemiology studies, which can reveal associations, and experimental studies using animals or cell-based models. Thus, although finding a 'smoking gun' linking any specific EDC to any specific disease is difficult, it is possible to recognize when environmental



exposures are contributing to endocrine-related disorders. Despite the insistence by some groups – often those with financial interests – that the evidence is inconclusive, the body of data revealing EDC-related health effects is sufficient to warrant taking action to reduce exposure to EDCs and prevent their adverse impact on public health.

EDCs are linked to neurological and behavioral disorders, obesity and metabolic dysfunction, reproductive disorders, and hormone-sensitive cancers (*see "Table 3"*). Detailed evidence was provided in the 2014 IPEN-Endocrine Society *Introduction to Endocrine Disrupting Chemicals* [41]. It is important to note that these are all complex, multi-factorial diseases that occur due to a combination of genetic predisposition, lifestyle, and environment. Therefore, EDCs are one of the environmental factors that contribute to increased likelihood or severity of disease.

A new frontier in research is the immune and inflammatory effects of EDCs. Inflammation is associated with a wide range of chronic diseases including obesity, cognitive deficits, cardiovascular disease, respiratory disorders, cancer, diabetes, and even autism. The immune and endocrine systems often work hand-in-hand in responding to environmental threats, and the convergence of their signaling pathways may underlie some of the inflammatory effects of environmental chemicals. In addition to being carcinogenic, perfluorinated compounds have been shown to disrupt aspects of immune function including response to vaccines [42]. Work in animal models has demonstrated that BPA, PCBs, tributyltin, and other EDCs can heighten aspects of neuroinflammation [43-46].

Disease Class	Prevalence and demographics	Links to EDCs and the environment
Neurological and behavioral disorders	Increased prevalence of child- hood neuropsychiatric disor- ders such as autism spectrum disorders and attention deficit hyperactivity disorder	Associations between EDCs and impaired neurodevelopment, lower IQ, problems with attention, memory, and fine motor skills in humans, results supported by animal models
Obesity and metabolic dysfunction	Global increase in obesity and type 2 diabetes rates	Chemical "obesogens" enhance weight gain, stimulate fat cells, and predispose to metabolism-related disorders such as type 2 diabe- tes, cardiovascular disease, lipid metabolism disorders, and thyroid disorders
Reproductive disorders	Increased prevalence of infertil- ity or subfertility	Decreased sperm counts and se- men quality, genital malformations, abnormal timing of puberty, ovula- tory disorders in humans; corrobo- rated by animal models
Cancer	Most cancers are linked to the environment, with few cancers linked to a single gene	Associations between occupational exposure to chemicals and in- creased cancer risk; supported by animal models of breast, prostate, endometrial, and other reproduc- tive cancers

### SUMMARY OF MAJOR CONCEPTS ABOUT EDCS, AND THEIR IMPLICATIONS

There is widespread, conclusive agreement about the hazards posed by cigarette smoke, lead, radioactive materials, and many chemicals. In the case of chemical assessment and management, the ability to link an exposure to an adverse health outcome, or death directly, can be proven in cases of known exposures to high levels of a particular chemical, as discussed above for cases of contaminated cooking oil or industrial accidents. 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, especially during critical developmental periods, is much more difficult.

The basic principles necessary to understanding effects of EDC exposures and their long-term manifestations as impaired quality of life, chronic disease, and cancers are summarized in *"Table 4"*, and were discussed in detail in the 2014 IPEN-Endocrine Society *Introduction to Endocrine Disrupting Chemicals* [41]. These concepts are equally applicable to the EDCs in plastics.

Concept	Implication
EDC exposure and effects can occur at very low doses, below an established regulatory threshold	There is likely no 'safe' dose of an EDC
Effects of EDCs across a range of doses may not predict effects at higher or lower doses	EDCs (and hormones) have in many cases non- linear, non-monotonic dose-response curves
EDC exposures are lifelong	Acute EDC testing does not represent real- word exposures
Effects of EDC exposures vary depend- ing upon developmental age	Ages at the times of exposure and evaluation of outcomes need to be considered
We are exposed to multiple EDCs	Mixtures of EDCs need to be considered in research and regulation
There may be long latency between exposure and disease or dysfunction	Chronic endocrine and neurological diseases should consider EDCs as contributing to their etiology (cause)
EDC effects may be manifested across generations	Exposures to pregnant women also exposes their developing children (fetuses) and grand- children (germ cells within the fetuses)

#### TABLE 4. KEY CONCEPTS ABOUT EDCs



# 4. EDCs ADDED TO PLASTICS AND SYNTHETIC FIBERS

### TYPES OF PLASTICS

Most plastic materials today are manufactured from fossil fuel feedstock produced by the oil and gas industry. Petrochemicals, primarily ethylene and propylene, are processed to form long chains of polyethylene (PE) and polypropylene (PP) or used for producing other types of plastics such as polyvinyl chloride (PVC). Chemicals are then added to provide specific properties to the large and diverse group of polymeric materials called plastics. Plastics can be classified into different categories based on various sets of criteria and the most commonly used classification identifies seven groups based on their building blocks, the monomers. This was developed by the Society of the Plastics Industry to allow consumers and recyclers to identify different types of plastics (*see "Table 5"*). The category "other" includes plastics like acrylic, polycarbonate, and nylon. Fluoropolymers are another wide group of plastics based on fluorinated chemicals. Fluoropolymers such as PTFE can break down or leach perfluorinated chemicals such as PFOA.

Category	Type of plastic
	Polyethylene terephthalate (PET)
HDPE	High-density polyethylene (HDPE)
3 PVC	Polyvinyl chloride (PVC)
LDPE	Low-density Polyethylene (LDPE)
<b>5</b>	Polypropylene (PP)
6 PS	Polystyrene (PS)
273	Other

#### TABLE 5. CLASSIFICATION SYSTEM FOR PLASTICS

Another way to classify plastic materials is based on their properties: *thermoplastics* can be melted and reformed multiple times, whereas *thermosets* change chemical composition once they are prepared and permanently remain in the solid stage [47]. Common thermoplastics include polyethylene, PP, PVC, PET, PS, and polycarbonate. Thermosets include plastics like polyurethane, epoxy resins and silicone. Furthermore, plastics can be divided by their use into *commodity plastics* and *engineering plastics*. Commodity plastics are those used in applications where the demands for mechanical properties are low, the cost of production is therefore low, and production volumes consequently high. Examples of commodity plastic products include trash cans, clothing, packaging film, cups and trays. The most common types of commodity plastics are

### IT IS ESTIMATED THAT HALF OF ALL PLASTIC PRODUCED IS DESIGNED TO BE USED ONLY ONCE AND THEN THROWN AWAY.

polyethylene, PP, PVC, PS and PET. It is estimated that half of all plastic produced is designed to be used only once and then thrown away, so-called single use plastic. Engineering plastics are those that require higher mechanical or thermal performance.

These plastics are more costly to produce and are therefore used to smaller extent compared to commodity plastics. Examples of products with engineering plastics are Lego bricks, helmets, and skis, and common types of engineering plastics include acrylonitrile butadiene styrene (ABS) used e.g. in electronic casings, polycarbonates and polyamides. Plastics can also be seen from their life span point of view. Some products containing plastics have long service lives such as construction materials and cars, while plastic bags are single-use items.

#### MICROPLASTICS

Manufacture, use, and disposal of plastics leads to the release of microplastics into the environment. Microplastics is a general term for any plastic particle that is less than 5 mm in diameter. It should be recognized that this is only a size-based classification and that not all microplastics are the same; their properties depend on the type of plastic, their shape, and chemical additives [48].

Microplastics form because of degradation of plastic products or they are intentionally produced such as fibers in synthetic clothes that are released as microplastics e.g. during washing and microbeads in cosmetics. Microplastics can enter the environment from various sources, such as washing machine runoff, wearing off car tires, artificial lawns and building materi-



Nearly all plastics manufactured and used each year globally are thrown into landfills or end up in the environment, waterways, and oceans. (Jambeck 2015)

als, accidental spillage of plastic granules used in plastic manufacturing, and nets and fishing gear used by the fishing industry. Microplastics have mainly been studied in oceans and freshwater systems, but they can also be found in soil and even become airborne [48]. Microplastics are typically captured in the sludge of sewage treatment plants and transferred to the soil when this sludge is used as fertilizer, with the ability to alter the soil properties and affect performance of the plants grown there  $\lceil 49,50 \rceil$ . A common source of microplastics in soil is also various plastic materials used in agricultural practices. Microplastics have today spread to even the most remote environmental compartments, including the Arctic, the deepest trenches of the Pacific Ocean and remote mountain areas [51-53]. Several recent studies have also investigated food and beverages as important sources of exposure to microplastics. According to estimates, the world's oceans are polluted with over 5 trillion microplastic particles that sum up to 270,000 tons of plastic debris [54]. A recent report estimated that the amount is much higher, and that their result indicated that for buoyant microplastics (above 100 micrometer), the global plastic reservoir is in the order of 12.5–125 trillion particles [55].

### BIOPLASTICS

In an attempt to address some of the many problems of conventional plastics, the field of bioplastics has emerged. Bioplastics encompass bio-based plastics and biodegradable plastics [56]. In bio-based plastics, the non-renewable sources of plastic monomers have been replaced with renewable ones. For example, in bio-PE, the plastic monomer ethylene is produced from starch in sugar cane instead of petrochemicals. However, while the switch to plant-based sources has a positive impact by decreasing demand for petrochemicals, other problems arise such as deforestation, increased pesticide use, and the need for extensive chemical processing. Bio-based plastics do not differ in their properties from their conventional counterparts and they contain similar chemical additives as conventional plastics. In contrast to conventional plastics, biodegradable plastics can decompose to water, carbon dioxide and compost under certain circumstances in the environment by the action of microorganisms. There are no time limits set for plastic to be called biodegradable; the process may take months, and if the right circumstances are not met, biodegradable plastics will not degrade and end up contaminating landfills just like regular plastics. Biodegradable plastics can be prepared from non-renewable fossil sources or renewable resources such as wood, crops and food waste, and are typically used in short service life applications such as food packaging, disposable tableware and some agricultural applications. Altogether, the field of bioplastics reflects the need for a change in the plastics industry towards more environmentally sustainable solutions. However, much more development is required before we can fully address problems related to recyclability; land, biocide and water use in the production of starchcontaining plants for bio-based plastics; and toxic additives in plastics are solved.

### WORLD PRODUCTION OF PLASTICS

The world production of plastics in 2017 was nearly 350 million tons with the majority being produced in Asia (50.1%), Europe (18.5%) and North America (Canada, Mexico and the United States) (17.7%) [47]. Bioplastics accounted only for approximately 1% of the total production volumes, 4.2 million tons in 2016, indicating the predominance of conventional plastics and petrochemical industry in the plastics industry. Approximately 6% of the world's oil and gas resources are used by the plastics industry [57]. The biggest sectors where plastics are used are the packaging industry, followed by the construction sector, automotive industry, electronics, textiles, and consumer products [47,57]. Bioplastics are mainly used in food packaging and textile industry [47]. The plastics industry in Europe encompasses 60,000 companies, and had a profit of 355 billion euros in 2018 [47]. The most common types of plastics in the EU are the typical
### Global Plastic Production Regional Production 2018



Includes thermoplastics, polyurethanes, thermosets, elastomers, adhesives, coatings and sealants, and PP-fibers. Not included: PET-fibers, PA-fibers, and polyacryl-fibers. Source: Plastics Europe Market Research Group and Conversio Market and Strategy GmbH

## 2018 Plastics Production by Type



commodity plastics: low- and high-density PE, PP, PVC, polyurethane, PS, and PET. The world production of plastics is expected to increase to 1.1 billion tons by 2050 [47], thus making this industry a significant source of chemical pollution to our water, soil, air, food chain and the wider environment. The health, environmental, and economic toll of exported plastic waste from industrialized countries to less wealthy countries in e.g. Asia and Africa is now gaining widespread attention.

Most plastic contamination in the environment begins on land via human actions. Land-based sources of plastic contamination come from plastic production, landfills, untreated sewage, and windblown debris [58]. In addition, plastic contamination exists in waterways. It is estimated that 70-80% of marine plastic pollution originates in rivers, mainly coming from manufacturing processes, agriculture, and wastewater treatment plants discharging their effluents into aquatic systems. Some marine sources of plastic contamination come from shipping, transport of plastic nurdles, oil and gas platforms, and discarded fishing nets [58,59]. The trade of plastic waste from developed to developing countries is one of the major contributors to the marine pollution, which lead to strong restrictions on plastics waste trade under the Basel Convention in 2019.

The majority of plastics produced have not been recycled. The Organisation for Economic Co-operation and Development (OECD) has estimated that around 6,300 million tons of plastics waste was generated between 1950 and 2015, but only 9% was recycled. In addition, 12% was incinerated and the rest (nearly 80%) was allowed to accumulate in landfills or the natural environment [60]. The World Economic Forum has estimated that 90% of all plastics are virgin plastics made from our finite gas and oil resources, and 8 million tons of plastics end up in the oceans annually [57].

### USES OF PLASTICS AND THEIR EDC ADDITIVES

The recent shale gas boom in the United States has made plastic feedstock very cheap, which means that plastics can be produced at a low cost today. Plastics also have sought-after properties such as being lightweight, waterresistant and non-corrosive. These circumstances have resulted in a rapid increase of a wide variety of uses such as packaging, construction, flooring, in the auto industry, food production and packaging and health care. Plastics are also used extensively in toys, leisure goods, home electronics, and they have made their way to clothing, furniture, textiles, cigarettes, medical equipment, and cosmetics.

Plastics are used in a wide range of applications with very different requirements and these requirements are met with the help of additives.



LANDFILL

Additives in plastics include chemicals shown to have hazardous effects on health, including disruption of endocrine systems. These chemicals persist through every part of the waste stream, including being recycled into new plastic products.

Different chemical additives are used as fillers, plasticizers, flame retardants, colorants, UV stabilizers, biocides, heat stabilizers, antioxidants, lubricants, foaming agents, and catalysts [61]. In addition to the additives that are intentionally put into plastics, unwanted side products can arise during the manufacturing process, get introduced as impurities associated with additives, or result from incomplete polymerization. For example, polystyrene plastics can contain residual styrene monomer, which is a carcinogen; plasticizers can contain polycyclic aromatic hydrocarbons as impurities; and brominated flame retardants may be contaminated with brominated dioxins and furans [61,62].

No systematic catalogues of chemicals used in the manufacture of plastics exist; however, the number ranges in the order of magnitude of thousands [61-63]. The most common additives include plasticizers such as bisphenols and phthalates, flame retardants, cadmium and lead compounds, alkyl phenols, curing agents like formaldehyde, biocides like arsenic compounds, organic tin compounds and triclosan, and colorants like azocolorants and cadmium compounds [61]. Many of these are EDCs. The amounts that are added to plastics vary. Plasticizers and flame retardants can comprise 70% and 25% of the final product by weight, respectively, whereas stabilizers, curing agents and colorants typically only constitute a small percentage of the product [61]. Some types of plastics are associated with higher use of additives than other plastics. PVC is the plastic that requires by far the highest use of additives: up to 80% of the final product may be added plasticizers such as phthalates. BPA is typically used in polycarbonate plastics. Many of the compounds used in plastics are known to be hazardous [63]. For example, the monomers used in synthesis of polyurethane, PVC, epoxy resins and styrenic polymers are CMR-classified, meaning that they are carcinogenic, mutagenic or toxic for reproduction [63].

A report from the Nordic Council of Ministers presents a list of 144 chemicals of chemical groups that are known to be hazardous and that are being actively used in plastics for functions varying from antimicrobial activity to colorants, flame retardants, solvents, and plasticizers [62]. For example, shower curtains, rainwear and diapers contain antimicrobial agents; plastic toys, car seats and clothes contain metal-based colorants and stabilizers; children's and worker's clothes contain perfluorinated compounds; and baby toys are contaminated with flame retardants and plasticizers such as short chain chlorinated paraffins that are known to be hazardous [62]. This includes use of industrial chemicals such as short chain chlorinated paraffins (SCCPs) that have been detected in toys and shown to have endocrine disrupting properties and adversely affect the kidney, liver, and thyroid. Likewise, Groh et al. identified over 100 hazardous chemicals used in plastics [63]. This is concerning as most additives are not bound into the plastic polymer structure and can migrate into the environment increasing the risk of exposure [61]. Exposure can take place during the entire life span of plastic products, from manufacturing process to consumer contact, recycling, waste management and disposal. Microplastics have been shown to absorb chemicals from water, functioning as carriers for toxic compounds in the environment. The concentration of absorbed hydrophobic pollutants in microplastics can be orders of magnitude higher than in the surrounding water [64].

When considering the chemical content of plastic products, the service age needs consideration. In long-lived products such as construction materials and electronic casings, chemicals that have been phased out can still be present [62]. In addition, different countries have regulation of varying restrictiveness. For example, PVC floors can contain toxic phthalates, brominated flame retardants, and toxic metals. Recycled plastics may also contain toxic chemicals if the plastic waste used for the manufacturing of the product was not efficiently processed or sorted to remove the hazards. Many types of consumer products made from recycled plastics have been shown to contain hazardous chemicals, including children's products and toys.

### HUMAN EXPOSURE TO PLASTICS AND EDC ADDITIVES

Human and environmental exposure to plastics is of concern. Large amounts of plastic waste enter the environment on a daily basis and many known EDCs leach out of the plastic and into the human body during use of various products. Known EDCs that leach from plastics include BPA, PBDE, TBBPA, and phthalates. For example, patients hospitalized in intensive care units are exposed to high doses of phthalates that leach from IV tubing and blood bags [65].

There are also concerns related to human exposure to microplastics. Not only do microplastics contain endogenous chemical additives, which are not bound to the microplastic and can leach out of the microplastic and expose the population, they can also bind and accumulate toxic chemicals from the surrounding environment such as sea water and sediment. Microplastics have a hydrophobic surface and thus, they readily concentrate hydrophobic organic contaminants such as polyaromatic hydrocarbons (PAHs), PCBs, and pesticides. They also accumulate toxic metals such as lead and cadmium. Different types of polymers appear to attract POPs from the environment differently. For example, adsorption occurs more readily onto LDPE and PP plastic debris than for PET and PVC fragments [66].

Shellfish consumption is a major source of exposure to microplastics. In China, nine of most commercially popular species of shellfish were contaminated with microplastics. In Canada and Belgium, wild and farmed mussels were contaminated by microplastics. It is likely that farmed mussels were contaminated with microplastics because they were cultured on polypropylene lines. As a result of the contamination of shellfish with microplastics, it is estimated that European shellfish consumer ingests up to 11,000 microplastic particles per year [67]. In addition, bottled water has been found to contain microplastics, and is estimated to contribute to daily human exposure by 40 mg/kg body weight [68].

Microplastics have been found in commercial (benthic and pelagic) fish species from the English Channel, the North Sea, the Baltic Sea, the Indo-Pacific Ocean, the Mediterranean Sea, the Adriatic Sea and the North Eastern Atlantic [26]. All samples of deep-sea fish from the South China Sea were contaminated by microplastics [134]. Fish from the Persian Gulf also had microplastics in their gastrointestinal tracts, skin, muscle, gills and liver while microplastics were found in the exoskeleton and importantly the muscle of tiger prawns from the Persian Gulf [192].

Humans can also inhale microplastics in the workplace and home. Occupational exposure can reach 0.5 particles/mL for PVC and



Microplastics have been found in commercial fish and shellfish in catches from around the world.

0.8 particles/mL for nylon [67]. People working in plastic manufacturing have higher levels of phthalate exposure than people working in occupations such as waste management [69]. One study shows 88-605 microplastic particles per 30 g of dry dust, ranging in size from 250-500 mm [70]. The study also estimates that street dust is an important source of microplastic contamination in urban environments and can result in 3223 microplastic particles being ingested by adults and 1063 microplastic particles being ingested by children each year.

Humans also have measurable levels of EDCs from plastics. For example, evidence indicates that people are exposed to 60 ng/day of flame retardants in plastic kitchen utensils [71]. Further, food contact items are thought to contribute to levels of unconjugated BPA in the urine, ranging from 2-4 ng/mL [72]. Food contact items also contribute to levels of phthalates in the body. The estimated daily intake of phthalates in women in the US is 41.7 mg/kg/day, a level that exceeds the tolerable daily intake level of 37 mg/kg/day [73]. Recent reports indicate that phthalate metabolites are present in nearly 100% of tested human urine samples [74-77]. The concentrations of DEHP in drinks such as bottled water, milk, and wine vary, with bottled water containing up to 13 mg/L, wine containing up to 242 mg/L, and raw milk containing up to 30 mg/L of DEHP [78]. Although DEHP is not used to make water bottles, it has been detected in many water samples from water bottles regardless of material, suggesting contamination from water sources and processing [78].

#### BISPHENOLS

Bisphenols such as bisphenol A (BPA) are used as chemical building blocks in polycarbonate plastics and epoxy resins, and can be found in reusable food and beverage containers, the linings of food cans, medical and sports equipment, eyeglass lenses, thermal paper receipts, and plastic water pipes (*see "Structures of known EDCs in plastics" on page 51*) [79]. Because of rising health concerns, use of BPA in some plastic containers, such as baby bottles, is banned in many countries and is being voluntarily reduced or phased out in others. As BPA-free products made from different materials become readily available, there are concerns that the replacement chemicals include many similar chemicals such as bisphenol analogues. In fact, evaluations of BPA-free thermal papers, plastics and canned foods have revealed the presence of bisphenol S (BPS), bisphenol F (BPF), and/or other compounds with similar chemical structures [80,81].

According to the US EPA, BPA is a high production volume chemical, with global estimates of more than 5 million metric tons produced annually and more than 450 metric tons released into the environment each year [82]. According to regulatory agencies around the world, most people are exposed to BPA through 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, and some evidence indicates that factors such as storage time and temperature can influence migration of BPA from can linings to food products [83,84]. Further, BPA is found in other consumer products including toys and sports equipment as well as textiles and infant clothing [85]. The presence of BPA in thermal paper used in receipts and various kinds of tickets may be an important source of human exposure [86]. Handling of thermal papers can transfer unbound BPA from the paper to human skin where it is easily absorbed, and this is made even more likely when people handle thermal paper in unpredictable ways [87]. Other possible, but not well-studied sources of exposure, include inhalation or ingestion of dust, as BPA has been documented in indoor and outdoor air samples [88].

Exposure to BPA is almost universal; measurements taken from around the world indicate that at any one time, 90-99% of individuals have BPA in their bodies [89]. BPA and its metabolites have been found in urine, blood, saliva, umbilical cord, placenta and amniotic fluid. Levels found

in infants and children are typically higher than in adolescents, with somewhat lower levels in adults. This is likely due to the increased food consumption per body weight in younger people, as well as increased use of plastic products and increased dust intake. Evidence also indicates that people who reduce consumption of canned foods and make other lifestyle changes to reduce contact with BPA-containing items have lower levels detected in their bodies [90-92]. BPA is rapidly metabolized, with about half of what is taken in by the body excreted within 6 hours. Because BPA does not accumulate in the body, decreased intake can have positive effects to reduce body burden [93]. However, even the best efforts to reduce exposures to BPA have not eliminated body burdens, suggesting that individuals are likely to be exposed from a range of unknown sources [94,95].

Even if BPA is phased out in specific jurisdictions, environmental exposures are likely to continue for decades or longer. In the US, the US EPA estimates that less than 10% of all plastics are recycled, with differences depending on the type of plastic and use [96]. The plastics that are not recycled often end up in landfills or aquatic systems. BPA and other bisphenol analogues have been detected in the leachates from landfills [97], waste water, freshwater, and ground water [98,99]. BPA, leaching from some of this waste, has been detected in seawater and marine species [100,101]. As plastic products containing BPA continue to break down over the period of centuries, exposures to humans and other species will likely continue to occur.

#### Evidence that BPA is an EDC

BPA is one of the most studied and well-known EDCs. It was first synthesized by chemists in 1891, and by the 1930s, BPA was identified as an estrogen mimic [102] and was considered for use as a pharmaceutical agent [103]. Cell and rodent assays have since revealed that BPA can mimic the effects of estrogens by binding to and stimulating estrogen receptors (ERs) both in the cell nucleus and on the surface of cells [104,105]. Although BPA was once considered a "weak" estrogen because it binds to the ERs more weakly than the natural estrogens, it can still exert actions on some tissues at the same low concentrations [106]. Furthermore, BPA binds other receptors in hormone-sensitive cells and can disrupt other natural hormones including testosterone and thyroid hormone [107].

The effects of BPA on hormone signaling extend beyond cell-based tests. Since 2017, BPA has been listed by the European Union as a "substance of very high concern" due to its toxic effects on reproduction, and since 2018, it has been acknowledged to be appropriate for this list because of its endocrine disrupting properties causing adverse effects to the environment



In response to rising health concerns, bisphenol-A (BPA) was banned or voluntarily removed from some products. However, even in those products where it has been removed, evaluations show it is often replaced with compounds, notably BPS and BPF, having similar health effects.

[108]. Hundreds of animal studies suggest that BPA disrupts reproductive functions, metabolism, immune responses, neurological features, and neurobehaviors [109]. Even low doses of BPA can disrupt the expression of hormone receptors like ER $\alpha$ , ER $\beta$  or progesterone receptor in specific regions of the brain [110], in the mammary gland [111], and in the uterus [112], among others. In several studies, it has been demonstrated that early life exposure to BPA increases the sensitivity of hormone-sensitive organs to later-life exposures to estrogens [113,114] or chemical carcinogens [115,116]. Evidence also indicates that BPA exposures can increase body weight, disrupt function of the pancreas, and induce non-alcoholic fatty liver disease in rodents, consistent with multiple aspects of metabolic syndrome [117].

More than 100 epidemiological studies have been published showing associations between BPA and human health effects [105,118]. These studies have examined human populations from many nations and have included people from many life stages. Several public health agencies have expressed concern regarding the impact of BPA on fetal brain development and behavior. In addition to many animal studies that have shown that exposures to BPA during early development can increase anxiety, aggression, and other behaviors, numerous studies from humans show similar effects in children exposed to higher levels of BPA [119]. Systematic reviews suggest that BPA exposures are associated with increased rates of anxiety, depression, hyperactivity, inattention, and conduct problems in children [120].

Studies also indicate that BPA exposure is linked to adverse reproductive outcomes. In females, BPA exposure adversely affects the onset of meiosis (cell division) in eggs, alters steroidogenesis (the process in which cholesterol is converted to biologically active steroid hormones), and reduces oocyte (egg cell) quality in women undergoing IVF [121].

BPA exposure is also associated with polycystic ovary syndrome (PCOS) in women. PCOS is a complex hormonal condition associated with irregular menstrual cycles, excessive facial and body hair growth, acne, obesity, reduced fertility and increased risk of diabetes. In males, BPA decreases sperm quality, motility, causes oxidative stress, and alters steroidogenesis. Further, BPA is associated with sexual dysfunction among men exposed to high occupational levels [121].

A large body of evidence also demonstrates associations between BPA exposures and several aspects of metabolic disease [105,117]. Human studies have shown associations between prenatal exposure to BPA and increased body fat or postnatal growth curves in children, outcomes that are relevant to early childhood obesity [122-124]. BPA exposures were also associated with altered  $\beta$ -cell function and increased insulin resistance in adults, consistent with health effects observed in type 2 diabetes [125]. Exposure to BPA was also associated with abnormal levels of liver enzymes, consistent with disrupted liver function and non-alcoholic fatty liver disease [126,127].

#### BPA replacements are also EDCs

As public health officials and consumers have raised concerns about BPA, it has been increasingly replaced with other compounds, including many bisphenol analogues such as BPS and BPF (*see "Structures of known EDCs in plastics" on page 51*). Concerns have been raised that these replacement chemicals are also EDCs [128]. Human exposures to these analogues are not as well documented in global populations, but studies suggest wide-spread exposures to both BPS and BPF [129,130]. Further evidence from the US Centers for Disease Control and Prevention (US CDC) indicate that exposures to these analogues are increasing in the US population [131].

Although BPA has been very well studied, other bisphenol analogues are relatively less well examined. Despite these limitations, studies utilizing cell-based tests have shown that many of these analogues have estrogenic properties [132,133]. Similar to what has been shown for BPA, BPS binds

#### LOW LEVELS OF EXPOSURE CAN HAVE TOXIC EFFECTS

Conventional understanding of toxicity holds that the greater the exposure, the greater the toxicity, with the corollary that low exposures – those less than acute toxicity – have no or negligible effect. However, non-monotonic response curves have been shown to mask toxic effects, especially at very low doses. And different dose-response relationships exist in different biological systems. So while a low dose might show no effect in one organ, toxic effects may occur in another.



Non-Monotonic Dose Response (NMDR) - Complex Biochemical Interactions



to ERs [134]. Several analogues including BPS, BPE, BPF and BPB bind to ERs and androgen receptors [133]. Studies in rodents have shown that exposures to low doses of BPS alter mammary gland development in both males and females, disrupt lactation, and induce mammary cancers [135-138]. BPS also alters maternal behaviors in female mice exposed during development as well as females exposed in adulthood during pregnancy [139]. BPF has only been studied at relatively high doses, but these exposures alter known hormonally-dependent outcomes including uterine weight, and weight of the male reproductive organs [140].

With recent attention being given to bisphenol analogues, human studies are only just beginning to be conducted. One recent study conducted in

BPA Analogues show similar endocrine disrupting actions and merit closer study.



China found an association between BPS exposures and the duration of gestation in pregnant women, whereby those women with high concentrations of BPS in their urine were more likely to have longer pregnancies [141]. In contrast, a study in the US found an association between BPS exposure and preterm birth [142]. These differing results will need to be reconciled, and may reflect differences in exposures between these populations (e.g., BPS was only detected in the urine of 20% of samples from the US, but was present in 94% of urine samples from Chinese women). Another recent study using data from the US CDC's national biomonitoring study suggests associations between BPF and BPS exposures and obesity in children [143]. These studies, while limited in number and scope, provide initial evidence that bisphenol analogues may have adverse effects on exposed human populations.

#### ALKYLPHENOL ETHOXYLATES

Alkylphenol ethoxylates are surfactants<sup>1</sup> commonly used in latex paints, pesticides, industrial cleaners, detergents, personal care products, and many different kinds of plastics, e.g. as heat stabilizers in PVC. Examples include nonylphenol and octylphenol, which are used to stabilize, prevent

<sup>1</sup> Surfactants are chemicals added to products to reduce their surface tension, making it easier for them to spread. When surfactants are added to liquids like paint or dyes, it can allow them to spread evenly onto solid materials or fabrics. Surfactants are also commonly used in detergents to cause oils and greases to break up into smaller stains, where they can be suspended in water and removed. When surfactants are added to plastics, they can prevent static, act as lubricants, and control foaming.



#### **REGRETTABLE SUBSTITUTION:** SHIFTING TO BPA-FREE, BUT WITH BPF OR BPS



UV degradation, and improve surfactant properties of plastics to be used in contact with liquids (*see "Structures of known EDCs in plastics" on page 51*) [144]. Nonylphenol is also used as a catalyst in the manufacture of epoxy resins. Typically, in aquatic environments, alkylphenol ethoxylates break down into alkylphenols (e.g., nonylphenol ethoxylate becomes nonylphenol). Because these degradation products do not degrade in water systems, several alkylphenols have been banned in numerous jurisdictions including the European Union and Canada.



Some alkylphenols are approved for use as indirect food contact substances, and others are used as heat stabilizers for polyvinyl chloride (PVC), which is used in water pipes and flooring

Alkylphenols and alkylphenol ethoxylates are also produced in high volumes, and release into the environment, especially to aquatic environments, is widespread [145]. Nonylphenol ethoxylates were commonly used in household detergents, but this use has been phased out in many locations; their use in industrial cleaners and detergents continues, contributing to environmental contamination. Alkylphenols and alkylphenol ethoxylates are very effective surfactants, and are therefore used in numerous applications that contribute to human exposures including cleaners and degreasers, adhesives, emulsifiers, agrochemicals including indoor pesticides, cosmetics and personal care products, paints, and dust control agents [145]. Some alkylphenols are approved for use as indirect food contact substances, and others are used as heat stabilizers for PVC, which is used in water pipes and flooring [146]. Because of these varied applications, human exposures likely occur through oral routes (e.g., ingestion of contaminated products, food containers, and dust) and dermal routes (e.g., contact with personal care products, use of indoor pesticides) [147]. Inhalation may also occur, and because alkylphenols do not easily degrade in the environment, exposures from additional sources including water and soil are likely.

Human exposures to alkylphenols have been documented around the world. Urine samples evaluated by the US CDC, collected in 2003-2004, had detectable levels of 4-tertiary-octylphenol in 57% of individuals [148]. In samples collected in Korea in 2009, 83% of adults had detectable levels of 4-nonylphenol, and 92% had detectable levels of 4-tertiary-

#### Structures of known EDCs in plastics.



octylphenol [149]. Biomonitoring studies have also detected alkylphenols and alkylphenol ethoxylates in breast milk [150], suggesting that these compounds may bioaccumulate in fatty tissues. In fact, evaluations of adipose tissue collected from women in Spain revealed nonylphenol in all samples examined; octylphenol was also observed in some women [151].

In 2010, when the US EPA evaluated the risk for populations exposed to nonylphenol and nonylphenol ethoxylate, a number of factors were considered in the development of a risk management plan. First, the EPA noted that nonylphenol and short-chain ethoxylates can bioaccumulate in tissues and persist in the environment. Second, it was noted that ethoxylates are normally purchased and used as mixtures, complicating evaluations of these chemicals. Finally, the EPA estimated that the majority of releases to the environment come from the use of alkylphenol ethoxylates in industrial laundry operations.



Evidence for decreasing sperm counts over the past 50 years has been widely reported. Some chemicals used in plastics are known to cause lower sperm counts, and this may play a role in lower fertility rates in many countries. Source: Levine *et al.* 2017 [287]

#### Evidence that alkylphenols are EDCs

Alkylphenols and alkylphenol ethoxylates were some of the first compounds found to leach from plastics that were identified as EDCs. Studies from the early 1990s demonstrated that nonvlphenol released from plastic labware could induce cell proliferation in cells where proliferation is dependent on ER [152]. Additional studies have shown that alkylphenols and alkylphenol ethoxylates mimic the actions of estrogens in cells, aquatic animals, and rodents [153]. Several studies from rodents have shown that exposures to alkylphenol ethoxylates disrupt male reproductive functions including testis weight, organization of the cells and tissues in the testis, and sperm count [105]. A systematic literature review concluded that the effects of nonylphenol on sperm and other aspects of male reproductive health are consistent across studies of cells, rats, mice, sea urchins, boars, and fish [154]. Consistent with their ability to bind to ERs, alkylphenols can induce proliferation of human prostate epithelial cells [155]. Alkylphenols also disrupt prostate development, with changes to prostate weight after neonatal exposures [156].

In 2010, the US EPA considered the effects of nonylphenol and nonylphenol ethoxylates on aquatic organisms, laboratory animals, and humans [145]. At that time, the EPA indicated that it would be taking action to reduce the use of these alkylphenols, with the aim of reducing the release of these compounds to the environment. The EPA noted that there was relatively little human data available at that time, but that these chemicals should be regulated based on the effects of these chemicals on aquatic species because nonylphenol is highly toxic to fish and other aquatic animals, as well as aquatic plants.

Since then, a small number of epidemiology studies have shown associations between alkylphenol exposures and male reproductive outcomes, as well as cancers. In a case-control study examining men from China, urinary concentrations of 4-tert-octylphenol, 4-n-octylphenol and 4-nnonvlphenol were associated with idiopathic male infertility [157]. This study also revealed negative associations between exposure to two alkylphenols and sperm concentrations, where men with higher levels of 4-tert-octylphenol and 4-n-nonylphenol were more likely to have abnormally low sperm numbers per ejaculate. A few limited studies have examined associations between alkylphenols, alkylphenol ethoxylates, and cancer outcomes in human populations. Several of these studies have examined occupational exposures and found associations between alkylphenol exposures and cancers of the breast - in both males and females - and lymphoma [158-160]. Because alkylphenols have relatively short half-lives (i.e. the time it takes for substance concentration to be reduced to half) in mammals, these studies have significant limitations; there are

### 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

concerns over exposure misclassification (where measurements of exposure from a single point in time are not representative of exposures over longer periods of time). Yet, the study of occupational exposures, where exposure levels are high and are likely to be more consistent than in the general population, suggests that workers using alkylphenols may be at heightened risk.

#### Perfluorinated compounds

Per- and polyfluoroalkyl substances (PFAS) have been used since the 1940s in a wide variety of consumer products including water and stain resistant clothing, fast food wrappers, lubricants, carpet treatments, paints, cookware and firefighting foams (*see "Structures of Known EDCs in Plastics" on page 51*) [161,162]. PFAS have also been widely used in food-contact materials such as non-stick cooking surfaces and food-contact papers such as pizza boxes, microwave popcorn bags, baking papers, and other paper wraps; the use of PFAS in these materials is meant to prevent the transfer of food grease to other surfaces [163]. PFAS are also used in the production of polymers including fluoropolymers, like polytet-rafluoroethylene (PTFE). These are very stable and resistant to heat, light and other chemicals.

Due to their widespread and extensive use, as well as the manufacture of PFAS and the manufacture and disposal of products containing PFAS, PFAS are ubiquitous in surface water, deep-sea water, drinking water, waste-water treatment plants, leachates from landfills, sediment, ground-water, soil, the atmosphere, dust, as well as biota including wildlife and humans globally [164,165].

PFAS contaminate soil and groundwater due to use and disposal of firefighting foams, and they are prevalent in sediment and soil surrounding training centers and airfields in the US [166], Sweden [167], and other countries. Pervasive PFAS contamination of ground and drinking water continues at 172 PFAS-contaminated sites in 40 US states. Contamination has also been shown in over 90 sites in Australia from predominantly military defense sites. In Norway, 50 airports were investigated due to their extensive use of firefighting foams, and the majority were contaminated with PFAS. Water pollution with PFAS substances has been shown to be widespread throughout Asia [168].

Drinking water is acknowledged as an important source of human exposure to PFAS [167]. Consumption of fish and other aquatic creatures caught in waterways contaminated with PFAS also poses heightened risks due to bioaccumulation of persistent chemicals in these animals [169]; these risks may affect some populations more than others due to differing seafood consumption practices. As products containing PFAS are utilized, even when used according to the manufacturer's instructions, PFAS substances are leached into foods and beverages [170]. These chemicals are also detected in unpackaged foods due to bioaccumulation in meat and dairy products. PFAS are also regularly measured in household dust as they are shed and released from other consumer products and textiles [171].

The two most studied examples of PFAS are perfluorooctanesulfonate (PFOS) and perfluorooctanoic acid (PFOA), both of which are now listed under the Stockholm Convention on Persistent Organic Pollutants. Another PFAS, perfluorohexanesulfonic acid (PFHxS), has been recommended for inclusion in the treaty. PFOS and PFOA, together with a third PFAS, perfluorononanoic acid (PFNA), are proposed for regulation by one or more US state governments. The US EPA has a current health advisory for PFOS and PFOA in drinking water,  $0.07\mu$ g/L, which was established in 2016. Regulators from several states have proposed that regulatory action should be taken at a lower concentration in drinking water [172].

The Organisation for Economic Co-operation and Development (OECD) estimates that there are more than 4000 PFAS in commercial use [173]. As PFOS and PFOA have been regulated and removed from consumer products and firefighting foams, a large number of additional PFAS have been introduced including perfluorobutanesulfonic acid (PFBS), perfluorodecanoic acid (PFDA), perfluorohexanoic acid (PFHxA), perfluoroheptanoic acid (PFHpA), perfluorohexanesulfonic acid (PFHxS), perfluorodecanoic acid (PFDoA), perfluoroundecanoic acid (PFUnA), and perfluorotridecanoic acid (PFTrDA), among others.

Human exposures to PFAS, including PFOA and PFOS and their replacements [174] have been documented in urine, serum, plasma, placenta, umbilical cord, breast milk, and fetal tissues [40,175]. As several of these compounds such as PFOS and PFOA have been phased out of use or regulated by public health agencies, their concentrations reported in some human populations have begun to decline [176]. However, case studies continue to identify individuals and communities with higher exposures than the general population including fire fighters, workers in PFAS manufacturing plants and downstream product manufacturing, people living in communities affected by PFAS contamination from these manufacturing sites and/or firefighting training activities, and individuals exposed through other occupational sources including medical workers and fishery employees [177,178]. With so many PFAS not yet identified or adequately measured, information about human exposures to a larger number of these compounds is still urgently needed.



Studies of paper takeout containers, microwave packaging, deli papers, and other food wrapping have repeatedly shown elevated levels of fluorine, indicating they were likely treated with PFAS.

One reason why human exposures to PFAS have raised concerns is the relatively long half-lives of these compounds in the body. Evidence indicates that PFOA and PFOS never break down in the environment due to the extremely strong bond created between carbon and fluorine – the strongest carbon bond in existence. Further, PFOA and PFOS have half-lives of 3-5 years in the human body, and other PFAS may have half-lives that are even longer [175]. PFAS are acknowledged to bioaccumulate – building up in the body – and biomagnify – meaning that their concentrations are highest in the bodies of creatures at the top of the food chain, including humans.

#### Evidence that PFAS are EDCs

Several studies suggest that PFAS can mimic estrogen. In fish, exposure to PFHpA, PFOA, PFNA, PFDA or PFUnDA increases the expression of vitellogenin, a protein involved in the development of the egg [179]. In mice, exposures to PFOA increases the weight of the uterus, an effect that is also characteristic of estrogen exposures [180]. In another study utilizing human breast cancer cells, both PFOS and PFOA increase cell proliferation, consistent with estrogenic behavior [181]; yet, when these cells were stimulated with natural estrogens and also treated with PFOS or PFOA, the PFAS chemicals blocked cell proliferation. This study suggests that some PFAS may also have anti-estrogenic properties.

Evidence also indicates that several PFAS can bind to other receptors in cells including the receptor that regulates the metabolism of fats, peroxisome proliferator-activated receptor (PPAR)- $\alpha$  [182,183]. Consistent with this, a few studies have shown that low doses of PFOA induce obesity in exposed mice [184], increase insulin and leptin, the latter a hormone that regulates energy balance by inhibiting hunger, and altered glucose metabolism in mice [185]. These studies suggest that many PFAS are accurately described as metabolism disrupting chemicals.

Additional effects of PFAS on hormone-sensitive outcomes have been documented in exposed rodents [105]. For example, mice exposed to PFOA during pregnancy develop problems with milk production and their daughters, exposed during gestation, have stunted mammary gland development [186,187]. Mice and rats exposed to PFOA or PFOS during gestation are also typically smaller, with significantly reduced body weights observed at birth [188].

Considering the effects of PFAS on metabolic and immune outcomes in rodents, and concerns raised in occupationally exposed populations, a relatively large number of systematic reviews and meta-analyses have evaluated the effects of PFAS on humans. One systematic review found associations between PFAS and dyslipidemia – a liver dysfunction characterized by abnormal amounts of cholesterol and triglycerides in the blood [189]. Evidence from three separate studies indicates that serum PFAS concentrations were inversely associated with antibody response after some vaccinations – meaning that children with higher PFAS exposures were less able to mount an effective immune response after receiving vaccines [190].

A substantial body of literature has examined the effects of PFAS exposures on hormone-sensitive outcomes in different human populations. One systematic review found some evidence for an association between PFOS, PFNA, or PFHxS and thyroid hormone function in specific life stages (mothers or their sons evaluated prior to puberty) [191]. PFAS exposures were also associated with altered pubertal timing in children, measured by age at menarche in females and serum testosterone concentrations in males [192]. Although delayed puberty is generally considered to decrease risk of breast cancer, there is also some evidence that PFAS exposures are associated with increased risk of breast cancer [193] although this association may be stronger in ER-dependent cancers [194].



#### BFRs IN PLASTICS & E-WASTE RECYCLING IN AFRICA

A 2019 Study tracked E-waste from Europe to Ghana, where the e-waste was dismantled. The study also found the highest levels ever recorded of extremely toxic brominated dioxin in free range chicken eggs near the E-waste recycling community [285].



Studies also indicate strong associations between PFOA and specific cancers including kidney, testicular, prostate, ovarian and non-Hodgkin lymphoma [195]. Very large cohorts have been assembled, including individuals with occupational PFAS exposures as well as populations living in heavily contaminated areas [196]. These studies and others have led international experts to call for the phase-out of nonessential uses of PFAS, as well as increased awareness of the public and policymakers of the harms associated with PFAS exposures [197]. Regulators are now starting to call for action on PFAS chemicals as a group [198].

#### **BROMINATED FLAME RETARDANTS (BFRs)**

Brominated flame retardants (BFRs) are additives used in plastics and other polymer products to reduce flammability and to prevent the spread of fire. The BFRs are added to foam, polystyrene, ABS (Acrylonitrile butadiene styrene) and epoxy resins, which then are used to manufacture electrical and electronic equipment (including computers and televisions), textiles, furniture foam, foam insulation, and other building materials. Four major classes of BFRs are polybrominated biphenyls (PBBs), polybrominated diphenyl ethers (PBDEs), hexabromocyclododecanes (HBCDs), and tetrabromobisphenol A (TBBPA). Certain classes of PBDEs are banned in the EU or have been discontinued by the manufacturers. However, their use was replaced by HBCD, TBBPA and newly emerging BFRs. Hexabromobiphenyl (HBB), TetraBDE, pentaDBE, hexaBDE, heptaBDE, decaBDE, and HBCD have been added to Annex A of the Stockholm Convention on Persistent Organic Pollutants (POP) for global elimination in recognition of their adverse impact on health and the environment.

BFRs have been in use since the 1970s and are the most common flame retardants, leading to widespread exposure. BFRs are released into the environment by multiple routes including during their production and production of BFR containing products. Additionally, since BFRs are not chemically bound to products, they may leach from household goods or following disposal in landfills. Like other organohalogen compounds, BFRs are persistent in the environment [145] and bioaccumulate in the food chain [146]. BFRs may enter the human body via ingestion and inhalation of contaminated house dust and/or food. Children, on average, have three times higher concentrations of BFRs than adults in their bodies [153]. Exposures to infants occur from breast milk [199]. Children also have increased dust intake due to their hand to mouth behaviors and time spent crawling on the ground and furniture [154], leading to greater exposure to BFRs.

An additional source of BFR exposure is in the processing of 20 – 50 million tons of plastic waste. The listing of the commercial mixtures of PentaBDE and OctaBDE in the Stockholm Convention includes specific exemptions that allow for recycling and the use in articles of recycled materials containing these chemicals [200,201]. In contrast, in 2010, the Convention's expert committee, the POPs Review Committee recommended to "...eliminate brominated diphenyl ethers from the recycling streams as swiftly as possible" noting that, "Failure to do so will inevitably result in wider human and environmental contamination and the dispersal of brominated diphenyl ethers from which recovery is not technically or economically feasible and in the loss of the long-term credibility of recycling" [202].



# RECYCLED PLASTICS WITH BFRs & HUMAN EXPOSURE TO BROMINATED DIOXIN

Dioxin in new children's products made with recycled plastics: In 2020 Chemosphere published a study revealing that children mouthing toys made from this plastic are at risk of dangerous health effects from the toxic material. It is the first study to establish the toxic effects of plastic toys made of recycled plastics on human cells.

Researchers analyzed toys and toy components made from black plastic purchased in Argentina Germany the Czech Republic India Nigeria and Portugal. Black plastic often originates from highly toxic e-waste plastics containing toxic brominated flame-retardant chemicals. The researchers found perilously high levels of flame retardants and dioxin in the sampled toys in concentrations comparable to hazardous waste [284]. Recycling of electrical and electronic equipment, which occurs in Africa and Asia, leads to BFR exposures in workers during the recycling stage and in use of recycled products [147]. In fact, one study of recycled plastics in China found bromine, and predominately PBDEs, in 36.7% of consumer products, with electric appliances and toys the most likely objects (DOI: 10.1039/C8EM00483H). 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 plastic thermo cups and kitchen utensils on the European market [203]. A recent study by Arnika, HEAL, and IPEN also found that 29% of the 430 recycled plastic items tested contained bromine and when the subset was further tested for PBDEs and HBCD, 46% contained levels that would not meet the EU POPs regulation if the items were produced with new rather than recycled plastic [204].

Exposures to PBDEs in North America are 3-10 times higher than in Europe (https://www.cdc.gov/biomonitoring/PBDEs\_FactSheet.html). Residents of California historically have the world's highest non-occupational exposures to PentaBDE congeners because of the state's unique flammability standard for foam furniture [156]. Higher concentrations of PentaBDE congeners are also found among low-income communities [154] and those occupationally exposed to PBDEs [157]. Occupations with higher exposures include firefighters, manufacturers of flame retardant products, people involved in recycling flame retardant products, computer technicians, and carpet installers [157-160]. 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 [161].

In general, human exposure to HBCD is low. However, occupational exposure at an industrial plant was reported to result in a mean serum concentration of 190 ng/g lipids [205]. Highlighting that there may be regional differences, in China, children in residential areas had the highest HBCD exposure at 7.09 pg/kg/day [206].

For TBBPA, a study in Canada found 10-20 ng/kg bw/day intake for adults [207]. Lower intake is reported for Europe, where it is estimated that high fish consumers are exposed to 2.6 ng/kg/day. While these and other older studies concluded little to no health risk to humans occurs from TBBPA exposure, the International Agency for Research on Cancer (IARC) concluded in 2016 that "Tetrabromobisphenol A is probably carcinogenic to humans (Group 2A)" [208].

#### Evidence that BFRs are EDCs

Several studies have confirmed that the BFRs are indeed endocrine disruptors, with the potential to disrupt male and female reproductive development and adult reproductive function by having anti-androgenic actions (males) and by altering steroidogenic activities. This has been demonstrated in several in vivo studies using rodent models and by in vitro systems to determine effects on receptor binding (AR and PXR) and on steroidogenesis. In humans, developmental BFR exposure is linked to cryptorchidism and reduced anogenital distance in male offspring, suggesting disruption of androgen synthesis or action [196,209,210]. Additionally, increasing BFR exposure is also correlated with decreasing sperm concentration and motility [211].

Studies in animals and humans strongly suggest that BFRs alter thyroid hormone levels. It is especially concerning if exposure occurs during gestation and the first years of life as thyroid hormone is essential for neurodevelopment. Epidemiological studies have shown an association between developmental BFR exposure and subsequent deficits in children including psychomotor development index, attention-related behavior and IQ performance [212,213]. These effects may be mediated through thyroid hormone disruption or additional mechanisms of neurotoxicity. For example BFRs have been shown to bind to thyroid hormone receptor, preventing it's function, and reducing TSH levels [214]. These effects would lead to reduced thyroid hormone action.

There is also evidence to suggest BFRs can interfere with hormones important for the body's response to stress. Glucocorticoid receptor (GR) transcriptional activity and actions can be increased or decreased, depending on the BFR and the exposure parameters in *in vitro* studies [215,216]. There are limited data looking at human exposures and effects on the stress axis.

### PHTHALATES

Phthalates are widely used as plasticizers in the production of plastics. Plasticizers are added to synthetic resins to produce or promote flexibility and to reduce brittleness. Production of phthalates began in the 1920s and intensified in the 1950s when they were used to impart flexibility to PVC resins [217]. To date, phthalates are predominantly used as plasticizers in PVC consumer, medical, and building products, as matrices and solvents in personal care products, and as fillers in medications and dietary supplements [217,218]. As plasticizers, phthalates are present in commonly used items such as flooring, roofing, carpeting, shower curtains, packaging equipment, food and beverage packaging, automotive parts, and even in children's toys. Of concern, the phthalate known as di(2-ethylhexyl) phthalate (DEHP) is present in common medical devices containing PVC plastics such as tubing, blood and intravenous bags, dialysis equipment, and in the manufacturing of disposable and surgical gloves [219].

Humans are exposed to phthalates on a daily basis. This exposure is largely due to the widespread use of phthalates in plastics. The global production and use of plastics exceeds 150 million tons per year and the annual consumption of phthalates exceeds 6-8 million tons per year [220]. The production and consumption of phthalates leads to daily human exposure via oral ingestion, inhalation, and dermal contact. This is because phthalates are non-covalently bound to plastics, meaning they frequently leach from these items into the environment and into the products that humans use and consume. The most common routes of exposure are via oral ingestion from food packaging and use of cosmetic products, but high levels of phthalates are also present in household dust [221,222]. Based on large production volumes, widespread use, and environmental contamination, biomonitoring data suggest that nearly 100% of the US population is exposed to phthalates on a daily basis [75,76,223]. Further, phthalates can be extensively metabolized upon absorption in the body, creating potentially toxic metabolites. Studies show that DEHP and its metabolites are present in 90-100% of amniotic fluid samples from second trimester fetuses, cord blood samples from newborns, breast milk from nursing mothers, and even in human ovarian follicular fluid [74,75,77,224]. The levels of phthalate metabolites are highest in humans exposed to phthalates through their occupation or medical therapies that require use of IVs, blood bags, and oral medications containing phthalate coatings [225-227].

#### Evidence that phthalates are EDCs

The production and use of phthalates is a public health concern because several phthalates have been identified as EDCs [20,218]. Specifically,



DEHP, a pththalate, is present in common medical devices containing PVC plastics such as tubing, blood and intravenous bags, dialysis equipment, and is used in the manufacturing of disposable and surgical gloves.

phthalates have been shown to reduce both testosterone levels and estrogen levels and to block thyroid hormone action [218,228,229]. Further, phthalates have been identified as reproductive toxicants [20,218,230]. In the European Union, DEHP, DBP, DIBP, and BBP are classified as toxic to reproduction and substances of very high concern, and their use in products requires authorization.

In women, chronic phthalate exposure is associated with decreased pregnancy rates, high miscarriage rates, anemia, toxemia, preeclampsia, reduced follicle counts, early menopause, and abnormal sex steroid hormone levels (74,230-232). Further, phthalate exposure has been linked with pregnancy complications such as anemia, toxemia, and preeclampsia [233]. In addition, a study indicates an increased risk of infertility in women exposed in the plastic industry [54].

In men, phthalate exposure during fetal development has been associated with reduced sperm numbers, decreased sperm quality, and an increased risk of hypospadias/cryptorchidism, collectively called testicular dysgenesis syndrome [234]. A few studies show an association between phthalate metabolites levels in men working in the plastics industry and the disturbance of estrogen, testosterone levels, sperm motility and testicular cancer [51-53].

In female laboratory animals, phthalates reduce implantations, increase resorptions, decrease fetal weights of offspring, cause abnormal ovarian follicle growth, decrease follicle health, and decrease incidence of pregnancy [235,236]. Further, developmental exposure to phthalates reduces female fertility in a multi-generational and transgenerational manner. In male laboratory animals, phthalate exposure reduces sperm number, reduces testosterone levels, and increases the percentage of abnormal sperm [237].

Phthalates have also been identified as neurotoxicants [238]. Developmental exposure to phthalates affects the expression of genes and proteins in the hypothalamus and it changes expression of neurotransmitters in a sex-specific manner. Further, perinatal phthalate exposure affects social and sociosexual behaviors. Specifically, perinatal phthalate exposure causes male rats to spend less time in juvenile social play and increases time in passive contact and it causes females to spend more time alone. Similarly, phthalate exposure decreases social interactions in mice [239].

Phthalate exposure also has been associated with increased risk of insulin resistance and other cardiometabolic risk factors [240,241]. For example, phthalate exposure has been associated with elevated blood pressure, obesity, and elevated levels of triglycerides [241]. Further, exposure to phthalates has been persistently linked to diabetes [242].

### **UV STABILIZERS**

UV stabilizers are used to protect products such as building materials, automotive parts, waxes, and paints from harmful UV radiation. UV stabilizers absorb the full spectrum of UV light (UV-A and UV-B) from 280 to 400 nm. In addition to protecting some products from UV light, some UV stabilizers are used as corrosion inhibitors and to prevent fog. Further, some UV stabilizers are used as light stabilizers in plastics.

Some of the most common UV stabilizers include benzotriazole and its derivatives (UV-P, 1H-BT, UV-234, UV-326, UV-327, UV-328, UV-329, and UV-350). In 1999, the annual production of benzotriazole UV stabilizers was estimated to be 9000 tons per year [243,244]. In 2015, several benzotriazole UV stabilizers (UV-320, UV0327, UV-328, and UV-350) were placed on the Candidate List of Substances of Very High Concern by the European Chemicals Agency (ECHA) because of their persistent, bioaccumulative, and toxic nature (https://www.echa.europa.eu/candidate-list-table). In 2018, ECHA added UV-328, UV-320, UV-327, and



Several studies indicate that benzotriazole UV stabilizers – chemicals which absorb ultraviolet (UV) light – interfere with normal endocrine function, impeding normal development and inducing estrogenic effects.

UV-350 to the Authorisation List, which requires companies to apply for authorization from ECHA before continued use of the stabilizers (https:// www.echa.europa.eu/previous-recommendations). In Japan, UV-320 is regulated as a Class 1 Specified Chemical Substance under their Chemical Substances Control Law. In the USA, UV-320, UV-328, and UV-329 have been listed as chemicals under concern at the state level, but are not currently on the list of chemicals for review at the federal level.

#### Evidence that Benzotriazole UV Stabilizers are EDCs

Several studies indicate that benzotriazole stabilizers interfere with normal endocrine function. Specifically, UV-234, UV-236, UV-329, and UV-P have been shown to suppress thyroid function and decrease heart rate in zebrafish [245]. UV-P and 1HBT have antiandrogenic activity and UV-P and UV-326 induce the aryl hydrocarbon pathway in zebrafish, which is crucial for normal development. Interference can lead to chemicalinduced developmental toxicity [244]. Further, UV-P and UV-328 have antiandrogenic activity in metabolism bioassays [246]. In addition, benzotriazole induces estrogenic effects in male and female scallops [243].

# OTHER RELEVANT EDCS LINKED TO PLASTICS: TRICLOSAN SCCPs & DIOXIN

Other groups of EDC chemicals linked to plastics are also of concern.

#### Triclosan

Plastics can contain antimicrobial agents such as triclosan, which is used to inhibit material degradation, reduce odors and lessen discoloration. Antimicrobial chemicals were developed in the mid-1990s and since then, they have been incorporated into numerous consumer products, including plastics. In 2015, the estimated global production of triclosan was 10.5 million pounds [247]. Several studies indicate that triclosan is an EDC in fish, rodents, and humans. Further, triclosan exposure is associated with cancer development and decreased cardiovascular function in rodents [247]. It is also associated with increased risk of allergies and asthma as well reduced fecundity in women [247].

#### Short-chain chlorinated paraffins (SCCPs)

Plastics may also contain short-chain chlorinated paraffins (SCCPs). These chemicals are used as plasticizers in PVC and flame retardants. They have been banned from use by the European Parliament and Council Regulation (No 850/2004) because they do not degrade in the environment and are toxic to aquatic organisms. They are also listed under the Stockholm Convention on Persistent Organic Pollutants for global elimination [248]. However, a recent study indicates that some consumer products still contain SCCPs, likely due to contamination with the substance during manufacturing or delivery of the product. A study from April 2017 that examined consumer products for children [249]. Although few studies have focused on the health effects of SCCPs, they may cause endocrine disruption due to their structural similarity to other EDCs.

#### Dioxins

Plastics may also contain impurities or release toxic substances such as dioxins, which are highly toxic persistent organochlorine pollutants. A clear connection between the import and burning of plastic waste with dioxin contamination of the food chain was shown in a recent report from Indonesia, where the levels of dioxin detected rivaled those detected in some of the worst polluted areas in human history [250]. One of the most toxic members of the dioxin family is 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). TCDD is a persistent environmental contaminant inadvertently produced as a by-product of herbicide and pesticide manufacturing.



# DIOXINS, PFOS & OTHER BANNED CHEMICALS POISON FOOD CHAINS

Highly toxic chemicals, posing dire risks to human health, have been found in dangerous concentrations in free-range chicken eggs in Indonesian communities and other places where plastic waste accumulates and people burn plastics for fuel. The high dioxin concentrations

are similar to levels in eggs collected near the Agent Orange hotspot in Bien Hoa, Vietnam, considered one of the most dioxin-contaminated locations on earth.

Numerous studies have linked the chemicals found in eggs with a host of health impacts. Dioxin exposure is linked to a variety of serious illnesses in humans, including cardiovascular disease, cancer, diabetes, and endometriosis. Flame retardant chemicals, SCCPs and PBDEs disrupt endocrine function and negatively affect reproductive health. PFOS causes reproductive and immune system damage, and internal company documents indicate that manufacturers knew about its toxicity for decades, but continued manufacturing it.



E-waste, paper contaminated with plastics, and other wastes are largely imported from Australia, Canada, Ireland, Italy, New Zealand, UK, and the US. Waste that cannot be recycled is often reduced via open burning to toxic ash that contaminates agriculture and washes into rivers, lakes, and oceans [286].



Dioxins are created and released during burning of municipal solid waste, including plastics.

TCDD is also released during the bleaching process at tree pulp and paper mills, and during burning of municipal solid waste, including plastics. Dioxins, including TCDD, have a long environmental half-life, bioaccumulate in the food chain, and can be found in human fat tissue, blood serum, breast milk and ovarian follicular fluid. Studies of human populations accidentally exposed to high levels of TCDD, and controlled studies using various animal models exposed to TCDD, have shown that it is a potent EDC [251,252]. TCDD exposures have been linked to delayed puberty and early onset of menopause in women [253,254]. Similarly, TCDD exposures lead to early puberty, irregular estrous cycles, reduced or blocked ovulation, decreased circulating estradiol levels and early reproductive senescence in female rodents [251,252,255].

#### TOXIC METALS IN PLASTICS

#### Lead and cadmium

Lead and cadmium are metals with comparable atomic size and charge and thus, similar functions and biological effects. They are naturally occurring elements found in the Earth's crust, making them ubiquitous in nature. In plastics, lead, cadmium, and their compounds are used as pigments, stabilizers, and catalysts. Both lead and cadmium can be found in diverse plastic products including plastic shoes and bathroom products, floor mats, plastic and electronic toys, soft PVC packaging for toys, car seats and casings for consumer electronics like televisions and personal computers [62]. The widespread use of lead and cadmium in industrial applications has led to increased environmental pollution. Major sources of environmental contamination include mining, smelting, and battery manufacturing and recycling.

Only a small fraction of ingested dietary lead and cadmium is absorbed from the intestine, but uptake is significantly higher in children compared to adults [256,257]. Both metals have long half-lives that range from a few years in blood to decades in tissues, which means they are bioaccumulative. Once lead and cadmium enter the body, they are bound by metallothionein proteins and transported to tissues. Lead competes with calcium and accumulates in the bones, liver and kidneys, whereas cadmium accumulates mainly in the liver and kidneys. Both metals accumulate to other tissues too, and the levels differ with age. For example, cadmium accumulates in human ovaries [258]. Its uptake is also enhanced by mineral deficiencies, because cadmium and lead compete for the same metal transporter proteins such as iron. According to the World Health Organization (WHO), "iron deficiency is the most common and widespread nutritional disorder in the world," with an estimated 30% of the world population being anemic, and women of reproductive age particularly affected (www. who.int/nutrition/topics/ida/en/).

Lead and cadmium are toxic metals and ubiquitous contaminants of the environment. Lead exposure is strongly associated with developmental neurotoxicity. There is no known safe blood lead concentration for children or for renal dysfunction and cardiovascular effects in adults [257,259,260]. Adverse effects of cadmium exposure include nephrotoxicity and bone demineralization [256,260,261]. The European Food Safety Authority (EFSA) has carried out extensive risk assessment of lead and cadmium exposure, and concluded that adverse health effects may occur due to lead and cadmium exposure [256,257].

Exposure to lead and cadmium may also cause cancer. Based on human and animal studies, the International Agency for Cancer Research has classified inorganic lead compounds as *probably carcinogenic to humans* due to associations with an increased risk of cancers of the lung, stomach and brain (gliomas), and cadmium its compounds as *carcinogenic to humans* due to associations with an increased risk of cancers of the lung, prostate and kidney [259,261].

#### Evidence that lead and cadmium are EDCs

Although most knowledge on lead and cadmium focuses on their properties as toxic metals, lead and cadmium at low doses can also disrupt the endocrine system and are therefore EDCs [262]. In particular, low doses of cadmium can act as an estrogen mimic in rodents and cell lines [262]. The estrogenic effects of cadmium at the molecular level are likely to result from disruption of multiple hormonal signaling pathways, including sex steroids and the growth factor epidermal growth factor [262-264]. Compared to cadmium, EDC properties of lead have been less studied. However, lead also has been reported to be a weak estrogen [265].

In agreement with the reported disruption of hormone signaling, cadmium and lead are associated with abnormal hormone levels and reproductive development, and subfertility/infertility in humans. Both metals also are associated with increased risk of cancer in the breast and prostate, both of which are hormone-dependent [259,261,266]. Concentrations of lead in circulation are associated with delayed onset of puberty in girls [267,268] and even in boys in some studies [269]. Lead also is associated with earlier onset of menopause [270,271], suggesting that exposure to lead may shorten the reproductive life span of woman. In men, lead and cadmium levels in blood are significantly associated with poor semen guality [272]. In reproductive aged women, lead and cadmium are associated with significantly altered serum hormone profile during natural menstrual cycles [273]. Concentrations of lead and cadmium in blood are associated with longer time-to-pregnancy in couples actively trying to achieve pregnancy [274]. Effects of metals on fertility have also been studied with the help of infertile couples trying to conceive with the help of in vitro fertilization. Although the results are mixed, several studies suggest that higher lead in serum/blood or follicular fluid predicts lower chances of success in the treatments [275-278].

#### Tin and chromium

Tin, chromium, and their compounds are examples of other toxic metals that are used in the manufacture of plastics [279,280]. Tin and its compounds are used as heat stabilizers in particular in PVC, whereas chromium and its compounds are typically used as pigments and catalysts in PVC, PE, and PP. Both tin and chromium compounds are known hazardous substances and their use is problematic in the recycling phase of plastic life cycle, as they pose potential risks for human health and the environment.


Metals are used in plastics as stabilizers, catalyzers, or pigments. Many of these compounds are known to be harmful to health or to increase risk of disease.

Organotins are tin compounds that have up to four organic groups attached to a tin atom. Organotins in plastics typically contain one or two groups, referred to as mono- or diorganic tin compounds, respectively. The toxicity of mono- and diorganic tin compounds depends on their composition of organic groups. For example, dibutyltin is more toxic than dioctyltin, but both may adversely affect the immune system. Further, dibutyltin is corrosive, mutagenic and toxic for reproduction [281,282]. Organotin compounds accumulate in marine sediments, biomagnify in the food chain, and therefore are considered as environmentally hazardous.

Plastic pollution washed up on shore in Conakry, Guinea. Photo Ibrahima Sory Sylla, Carbone Guinée

## **5. SUMMARY**

The world production of plastics in 2017 was nearly 350 million metric tons and is expected to increase to 1.1 billion tons by 2050. Many potentially harmful chemicals are used during the production of plastics, either as building blocks of the plastic material itself or as additives to provide certain properties such as color or flexibility. Hazardous chemicals may also be present in plastics from contamination during production, such as styrene monomers, or formed during recycling, such as dioxins. These chemicals can leach into food, water, and the environment. Microplastics are widespread contaminants of the environment today that both contain hazardous chemicals as part of the material but that can also adsorb, magnify, and spread environmental contaminants such as PCBs. Hazardous chemicals in plastics are a source of concern because many of the chemicals that leach from plastics are EDCs. These EDCs include bisphenols, alkylphenol ethoxylates, perfluorinated compounds, brominated flame retardants, phthalates, UV stabilizer, and metals. The leaching of these EDCs from plastics is of concern because they have been shown to cause abnormal reproductive, metabolic, thyroid, immune, and neurological function. This has led to numerous international scientific societies such as the Endocrine Society and health organizations to weigh in and it has contributed to science-based action on EDCs by many stakeholders including some governments, retailers, and manufacturers. However, more efforts are needed to protect people and the environment from potentially harmful EDCs in plastics. Not all countries screen and regulate many known or potential EDCs and numerous compounds have yet to be tested for EDC activity and their impact on health.

## REFERENCES

- Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, Hauser R, Prins GS, Soto AM, Zoeller RT, Gore AC. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. *Endocr Rev.* 2009;30(4):293-342.
- Gore AC, Chappell VA, Fenton SE, Flaws JA, Nadal A, Prins GS, Toppari J, Zoeller RT. EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals. *Endocrine Reviews*. 2015;36(6):E1-E150.
- 3. Exposure to Toxic Environmental Agents. American College of Obstetricians and Gynecologists Committee on Health Care for Underserved Women; American Society for Reproductive Medicine Practice Committee; The University of California, San Francisco Program on Reproductive Health and the Environment; 2012
- 4. Di Renzo GC, Conry JA, Blake J, DeFrancesco MS, DeNicola N, Martin JN, Jr., McCue KA, Richmond D, Shah A, Sutton P, Woodruff TJ, van der Poel SZ, Giudice LC. International Federation of Gynecology and Obstetrics opinion on reproductive health impacts of exposure to toxic environmental chemicals. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics*. 2015;131(3):219-225.
- Trasande L, Zoeller RT, Hass U, Kortenkamp A, Grandjean P, Myers JP, DiGangi J, Bellanger M, Hauser R, Legler J, Skakkebaek NE, Heindel JJ. Estimating burden and disease costs of exposure to endocrine-disrupting chemicals in the European union. *The Journal of clinical endocrinology and metabolism*. 2015;100(4):1245-1255.
- Rijk I, van Duursen M, van den Berg M. Health cost that may be associated with Endocrine Disrupting Chemical. Universiteit Utrecht Institute for Risk Assessment Sciences (IRAS), Toxicology Division; 2016.
- Attina TM, Hauser R, Sathyanarayana S, Hunt PA, Bourguignon JP, Myers JP, DiGangi J, Zoeller RT, Trasande L. Exposure to endocrine-disrupting chemicals in the USA: a population-based disease burden and cost analysis. *Lancet Diabetes & Endocrinology*. 2016;4(12):996-1003.
- 8. World Health Organization. State of the Science of Endocrine Disrupting Chemicals. Geneva: International Programme on Chemical Safety.; 2012.
- Zoeller RT, Brown TR, Doan LL, Gore AC, Skakkebaek NE, Soto AM, Woodruff TJ, Vom Saal FS. Endocrine-Disrupting Chemicals and Public Health Protection: A Statement of Principles from The Endocrine Society. *Endocrinology*. 2012;153:4097-4110.
- Wang ZY, Walker GW, Muir DCG, Nagatani-Yoshida K. Toward a Global Understanding of Chemical Pollution: A First Comprehensive Analysis of National and Regional Chemical Inventories. *Environ Sci Technol.* 2020;54(5):2575-2584.
- Frye CA, Bo E, Calamandrei G, Calza L, Dessi-Fulgheri F, Fernandez M, Fusani L, Kah O, Kajta M, Le Page Y, Patisaul HB, Venerosi A, Wojtowicz AK, Panzica GC. Endocrine disrupters: a review of some sources, effects, and mechanisms of actions on behaviour and neuroendocrine systems. J Neuroendocrinol. 2012;24(1):144-159.
- 12. McLachlan JA. Environmental signaling: what embryos and evolution teach us about endocrine disrupting chemicals. *Endocrine Reviews*. 2001;22:319-341.
- Godfray HCJ, Stephens AEA, Jepson PD, Jobling S, Johnson AC, Matthiessen P, Sumpter JP, Tyler CR, McLean AR. A restatement of the natural science evidence base on the effects of endocrine disrupting chemicals on wildlife. *Proc Biol Sci.* 2019;286(1897):20182416.
- 14. Colborn T, Dumanoski D, Myers JP. Our stolen future : are we threatening our fertility, intelligence, and survival? : a scientific detective story. New York: Dutton.

- Zhang X, Liu W, Wang J, Tian H, Wang W, Ru S. Quantitative analysis of in-vivo responses of reproductive and thyroid endpoints in male goldfish exposed to monocrotophos pesticide. *Comp Biochem Physiol C Toxicol Pharmacol.* 2018;211:41-47.
- Zhang X, Tian H, Wang W, Ru S. Exposure to monocrotophos pesticide causes disruption of the hypothalamic-pituitary-thyroid axis in adult male goldfish (Carassius auratus). *Gen Comp Endocrinol.* 2013;193:158-166.
- 17. Rao RP, Kaliwal BB. Monocrotophos induced dysfunction on estrous cycle and follicular development in mice. *Ind Health*. 2002;40(3):237-244.
- Tian YH, Baek JH, Lee SY, Jang CG. Prenatal and postnatal exposure to bisphenol a induces anxiolytic behaviors and cognitive deficits in mice. *Synapse*. 2010;64(6):432-439.
- Herbst AL, Ulfelder H, Poskanzer DC. Adenocarcinoma of the vagina. Association of maternal stilbestrol therapy with tumor appearance in young women. N Engl J Med. 1971;284:878-881.
- Gore AC, Chappell VA, Fenton SE, Flaws JA, Nadal A, Prins GS, Toppari J, Zoeller RT. EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals. *Endocrine reviews*. 2015;36(6):E1-e150.
- 21. Bergman Å, Rüegg J, Drakvik E, Consortium EDCM. Report: Final Technical Report of EDC-MixRisk.18.
- Hunt PA, Koehler KE, Susiarjo M, Hodges CA, Ilagan A, Voigt RC, Thomas S, Thomas BF, Hassold TJ. Bisphenol a exposure causes meiotic aneuploidy in the female mouse. *Current biology : CB*. 2003;13(7):546-553.
- Skakkebaek NE. Endocrine disrupters and testicular dysgenesis syndrome. Horm Res. 2002;57 Suppl 2:43.
- Campion S, Catlin N, Heger N, McDonnell EV, Pacheco SE, Saffarini C, Sandrof MA, Boekelheide K. Male reprotoxicity and endocrine disruption. *Exp Suppl.* 2012;101:315-360.
- Levine H, Jorgensen N, Martino-Andrade A, Mendiola J, Weksler-Derri D, Mindlis I, Pinotti R, Swan SH. Temporal trends in sperm count: a systematic review and meta-regression analysis. *Human Reproduction Update*. 2017;23(6):646-659.
- Walker DM, Gore AC. Epigenetic impacts of endocrine disruptors in the brain. Front Neuroendocrinol. 2017;44:1-26.
- 27. Anway MD, Cupp AS, Uzumcu M, Skinner MK. Epigenetic transgenerational actions of endocrine disruptors and male fertility. *Science (New York, NY)*. 2005;308(5727):1466-1469.
- Walker DM, Gore AC. Transgenerational neuroendocrine disruption of reproduction. *Nature reviews Endocrinology*, 2011;7(4):197-207.
- Manikkam M, Tracey R, Guerrero-Bosagna C, Skinner MK. Plastics derived endocrine disruptors (BPA, DEHP and DBP) induce epigenetic transgenerational inheritance of obesity, reproductive disease and sperm epimutations. *PloS one*. 2013;8(1):e55387.
- Rattan S, Brehm E, Gao L, Flaws JA. Di(2-ethylhexyl) phthalate exposure during prenatal development causes adverse transgenerational effects on female fertility in mice. *Toxicological sciences : an official journal of the Society of Toxicology*. 2018.
- Fingerhut M, Nelson DI, Driscoll T, Concha-Barrientos M, Steenland K, Punnett L, Pruss-Ustun A, Leigh J, Corvalan C, Eijkemans G, Takala J. The contribution of occupational risks to the global burden of disease: summary and next steps. *Med Lav.* 2006;97(2):313-321.
- 32. World Health Organization. Preventing disease through healthy environments towards an estimate of the environmental burden of disease. Geneva: World Health Organization.; 2006.
- Boyle CA, Boulet S, Schieve LA, Cohen RA, Blumberg SJ, Yeargin-Allsopp M, Visser S, Kogan MD. Trends in the prevalence of developmental disabilities in US children, 1997-2008. *Pediatrics*. 2011;127(6):1034-1042.
- 34. Zablotsky B. Estimated Prevalence of Children With Diagnosed Developmental Disabilities in the United States, 2014–2016. 2017(291):8.

- 35. Global chemicals outlook: Towards the sound management of chemicals. Geneva, Switzerland: United Nations Environment Programme and the World Health Organization; 2013.
- 36. Global chemicals outlook: Towards the sound management of chemicals. Geneva, Switzerland: United Nations Environment Programme and the World Health Organization.
- 37. Buck Louis GM, Sundaram R, Sweeney AM, Schisterman EF, Maisog J, Kannan K. Urinary bisphenol A, phthalates, and couple fecundity: the Longitudinal Investigation of Fertility and the Environment (LIFE) Study. *Fertil Steril.* 2014;In Press.
- Gerona RR, Woodruff TJ, Dickenson CA, Pan J, Schwartz JM, Sen S, Friesen MW, Fujimoto VY, Hunt PA. Bisphenol-A (BPA), BPA glucuronide, and BPA sulfate in midgestation umbilical cord serum in a northern and central California population. *Environ Sci Technol*. 2013;47(21):12477-12485.
- 39. Skakkebaek NE, Toppari J, Soder O, Gordon CM, Divall S, Draznin M. The exposure of fetuses and children to endocrine disrupting chemicals: a European Society for Paediatric Endocrinology (ESPE) and Pediatric Endocrine Society (PES) call to action statement. *The Journal of clinical endocrinology and metabolism*. 2011;96(10):3056-3058.
- 40. Mamsen LS, Bjorvang RD, Mucs D, Vinnars MT, Papadogiannakis N, Lindh CH, Andersen CY, Damdimopoulou P. Concentrations of perfluoroalkyl substances (PFASs) in human embryonic and fetal organs from first, second, and third trimester pregnancies. *Environment international*. 2019;124:482-492.
- 41. Gore AC, Crews D, Doan LL, Merrill ML, Patisaul H, Zota A. Introduction To Endocrine Disrupting Chemicals (EDCs).76.
- 42. DeWitt JC, Germolec DR, Luebke RW, Johnson VJ. Associating Changes in the Immune System with Clinical Diseases for Interpretation in Risk Assessment. *Curr Protoc Toxicol.* 2016;67:18 11 11-18 11 22.
- Rebuli ME, Gibson P, Rhodes CL, Cushing BS, Patisaul HB. Sex differences in microglial colonization and vulnerabilities to endocrine disruption in the social brain. *Gen Comp Endocrinol.* 2016;238:39-46.
- Ferraz da Silva I, Freitas-Lima LC, Graceli JB, Rodrigues LCM. Organotins in Neuronal Damage, Brain Function, and Behavior: A Short Review. Front Endocrinol (Lausanne). 2017;8:366.
- Bell MR, Dryden A, Will R, Gore AC. Sex differences in effects of gestational polychlorinated biphenyl exposure on hypothalamic neuroimmune and neuromodulator systems in neonatal rats. *Toxicol Appl Pharmacol.* 2018;353:55-66.
- 46. Bilbo SD, Block CL, Bolton JL, Hanamsagar R, Tran PK. Beyond infection Maternal immune activation by environmental factors, microglial development, and relevance for autism spectrum disorders. *Experimental neurology*. 2018;299(Pt A):241-251.
- PlasticsEurope, EPRO. Plastics the facts 2018. An analysis of European plastics production, demand and waste data. 2018.
- 48. Rochman CM, Brookson C, Bikker J, Djuric N, Earn A, Bucci K, Athey S, Huntington A, McIlwraith H, Munno K, De Frond H, Kolomijeca A, Erdle L, Grbic J, Bayoumi M, Borrelle SB, Wu T, Santoro S, Werbowski LM, Zhu X, Giles RK, Hamilton BM, Thaysen C, Kaura A, Klasios N, Ead L, Kim J, Sherlock C, Ho A, Hung C. Rethinking microplastics as a diverse contaminant suite. *Environ Toxicol Chem.* 2019;38(4):703-711.
- Corradini F, Meza P, Eguiluz R, Casado F, Huerta-Lwanga E, Geissen V. Evidence of microplastic accumulation in agricultural soils from sewage sludge disposal. *The Science of the total environment*. 2019;671:411-420.
- de Souza Machado AA, Lau CW, Kloas W, Bergmann J, Bachelier JB, Faltin E, Becker R, Gorlich AS, Rillig MC. Microplastics Can Change Soil Properties and Affect Plant Performance. *Environ Sci Technol.* 2019;53(10):6044-6052.
- 51. Kanhai DK, Gardfeldt K, Lyashevska O, Hassellov M, Thompson RC, O'Connor I. Microplastics in sub-surface waters of the Arctic Central Basin. *Marine pollution bulletin.* 2018;130:8-18.

- Ambrosini R, Azzoni RS, Pittino F, Diolaiuti G, Franzetti A, Parolini M. First evidence of microplastic contamination in the supraglacial debris of an alpine glacier. *Environmental pollution (Barking, Essex : 1987).* 2019;253:297-301.
- Peng G, Bellerby R, Zhang F, Sun X, Li D. The ocean's ultimate trashcan: Hadal trenches as major depositories for plastic pollution. *Water research*. 2020;168:115121.
- Eriksen M, Lebreton LC, Carson HS, Thiel M, Moore CJ, Borerro JC, Galgani F, Ryan PG, Reisser J. Plastic Pollution in the World's Oceans: More than 5 Trillion Plastic Pieces Weighing over 250,000 Tons Afloat at Sea. *PloS one*. 2014;9(12):e111913.
- 55. Lindeque PK, Cole M, Coppock RL, Lewis CN, Miller RZ, Watts AJR, Wilson-McNeal A, Wright SL, Galloway TS. Are we underestimating microplastic abundance in the marine environment? A comparison of microplastic capture with nets of different mesh-size. *Environmental Pollution*. 2020:114721.
- 56. PlasticsEurope. Bio-based and biodegradable plastics. In: PlasticsEurope, ed2018.
- 57. Forum WE. The new plastics economy -rethinking the future of plastics. 2016.
- Karlsson TM, Arneborg L, Brostrom G, Almroth BC, Gipperth L, Hassellov M. The unaccountability case of plastic pellet pollution. *Marine pollution bulletin*. 2018;129(1):52-60.
- 59. Waring RH, Harris RM, Mitchell SC. Plastic contamination of the food chain: A threat to human health? *Maturitas*. 2018;115:64-68.
- 60. Improving Plastics Management: Trends, policy responses, and the role of international co-operation and trade. 2018.
- Hahladakis JN, Velis CA, Weber R, Iacovidou E, Purnell P. An overview of chemical additives present in plastics: Migration, release, fate and environmental impact during their use, disposal and recycling. J Hazard Mater. 2018;344:179-199.
- Stenmarck Å, Belleza EL, Fråne A, Busch N, Larsen Å, Wahlström M. Hazardous substances in plastics -ways to increase recycling. In: Ministers NCo, ed. *TemaNord*2017.
- 63. Groh KJ, Backhaus T, Carney-Almroth B, Geueke B, Inostroza PA, Lennquist A, Leslie HA, Maffini M, Slunge D, Trasande L, Warhurst AM, Muncke J. Overview of known plastic packaging-associated chemicals and their hazards. *The Science of the total environment*. 2019;651(Pt 2):3253-3268.
- Ziccardi LM, Edgington A, Hentz K, Kulacki KJ, Kane Driscoll S. Microplastics as vectors for bioaccumulation of hydrophobic organic chemicals in the marine environment: A state-of-the-science review. *Environ Toxicol Chem.* 2016;35(7):1667-1676.
- Koch HM, Preuss R, Angerer J. Di(2-ethylhexyl)phthalate (DEHP): human metabolism and internal exposure-- an update and latest results. *International journal of andrology*. 2006;29(1):155-165; discussion 181-155.
- 66. Rochman CM, Hoh E, Kurobe T, Teh SJ. Ingested plastic transfers hazardous chemicals to fish and induces hepatic stress. *Scientific Reports.* 2013;3.
- Wright SL, Kelly FJ. Plastic and Human Health: A Micro Issue? *Environ Sci Technol.* 2017;51(12):6634-6647.
- Zuccarello P, Ferrante M, Cristaldi A, Copat C, Grasso A, Sangregorio D, Fiore M, Oliveri Conti G. Exposure to microplastics (<10mum) associated to plastic bottles mineral water consumption: The first quantitative study. *Water research*. 2019;157:365-371.
- 69. Petrovicova I, Kolena B, Sidlovska M, Pilka T, Wimmerova S, Trnovec T. Occupational exposure to phthalates in relation to gender, consumer practices and body composition. *Environmental science and pollution research international*. 2016;23(23):24125-24134.
- Dehghani S, Moore F, Akhbarizadeh R. Microplastic pollution in deposited urban dust, Tehran metropolis, Iran. *Environmental science and pollution research international*. 2017;24(25):20360-20371.

- Kuang J, Abdallah MA, Harrad S. Brominated flame retardants in black plastic kitchen utensils: Concentrations and human exposure implications. *The Science of the total environment*. 2018;610-611:1138-1146.
- Vandenberg LN, Hauser R, Marcus M, Olea N, Welshons WV. Human exposure to bisphenol A (BPA). Reproductive toxicology (Elmsford, NY). 2007;24(2):139-177.
- 73. Koo HJ, Lee BM. Human monitoring of phthalates and risk assessment. *Journal of toxicology and environmental health Part A.* 2005;68(16):1379-1392.
- Heudorf U, Mersch-Sundermann V, Angerer J. Phthalates: toxicology and exposure. International journal of hygiene and environmental health. 2007;210(5):623-634.
- Silva MJ, Barr DB, Reidy JA, Malek NA, Hodge CC, Caudill SP, Brock JW, Needham LL, Calafat AM. Urinary levels of seven phthalate metabolites in the U.S. population from the National Health and Nutrition Examination Survey (NHANES) 1999-2000. *Environmental health perspectives*. 2004;112(3):331-338.
- Hogberg J, Hanberg A, Berglund M, Skerfving S, Remberger M, Calafat AM, Filipsson AF, Jansson B, Johansson N, Appelgren M, Hakansson H. Phthalate diesters and their metabolites in human breast milk, blood or serum, and urine as biomarkers of exposure in vulnerable populations. *Environmental health perspectives*. 2008;116(3):334-339.
- Marsee K, Woodruff TJ, Axelrad DA, Calafat AM, Swan SH. Estimated daily phthalate exposures in a population of mothers of male infants exhibiting reduced anogenital distance. *Environmental health perspectives*. 2006;114(6):805-809.
- Erythropel HC, Maric M, Nicell JA, Leask RL, Yargeau V. Leaching of the plasticizer di(2-ethylhexyl)phthalate (DEHP) from plastic containers and the question of human exposure. *Applied microbiology and biotechnology*. 2014;98(24):9967-9981.
- Onundi Y, Drake BA, Malecky RT, DeNardo MA, Mills MR, Kundu S, Ryabov AD, Beach ES, Horwitz CP, Simonich MT, Truong L, Tanguay RL, Wright LJ, Singhal N, Collins TJ. A multidisciplinary investigation of the technical and environmental performances of TAML/peroxide elimination of Bisphenol A compounds from water. *Green Chemistry*. 2017.
- 80. Liao C, Liu F, Kannan K. Bisphenol s, a new bisphenol analogue, in paper products and currency bills and its association with bisphenol a residues. *Environ Sci Technol.* 2012;46(12):6515-6522.
- Liao C, Kannan K. Concentrations and profiles of bisphenol a and other bisphenol analogues in foodstuffs from the United States and their implications for human exposure. *J Agric Food Chem.* 2013;61(19):4655-4662.
- US EPA. Risk management for bisphenol A (BPA). Assessing and managing chemicals under TSCA. https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/risk-management-bisphenolbpa2019.
- Vandenberg LN, Hauser R, Marcus M, Olea N, Welshons WV. Human exposure to bisphenol A (BPA). Reproductive Toxicology. 2007;24:139 - 177.
- Schecter A, Malik N, Haffner D, Smith S, Harris TR, Paepke O, Birnbaum L. Bisphenol A (BPA) in U.S. food. *Environ Sci Technol.* 2010;44(24):9425-9430.
- Xue J, Liu W, Kannan K. Bisphenols, Benzophenones, and Bisphenol A Diglycidyl Ethers in Textiles and Infant Clothing. *Environ Sci Technol.* 2017;51(9):5279-5286.
- Hormann AM, Vom Saal FS, Nagel SC, Stahlhut RW, Moyer CL, Ellersieck MR, Welshons WV, Toutain PL, Taylor JA. Holding thermal receipt paper and eating food after using hand sanitizer results in high serum bioactive and urine total levels of bisphenol A (BPA). *PloS one*. 2014;9(10):e110509.
- 87. Bernier MR, Vandenberg LN. Handling of thermal paper: Implications for dermal exposure to bisphenol A and its alternatives. *PloS one*. 2017;12(6):e0178449.
- Liao C, Liu F, Guo Y, Moon HB, Nakata H, Wu Q, Kannan K. Occurrence of eight bisphenol analogues in indoor dust from the United States and several Asian countries: implications for human exposure. *Environ Sci Technol.* 2012;46(16):9138-9145.

- Vandenberg LN. Exposure to bisphenol A in Canada: invoking the precautionary principle. CMAJ. 2011;online Feb 22:doi:10.1503/cmaj.101408.
- Sathyanarayana S, Alcedo G, Saelens BE, Zhou C, Dills RL, Yu J, Lanphear B. Unexpected results in a randomized dietary trial to reduce phthalate and bisphenol A exposures. *J Expo Sci Environ Epidemiol.* 2013.
- 91. Carwile JL, Ye X, Zhou X, Calafat AM, Michels KB. Canned soup consumption and urinary bisphenol A: a randomized crossover trial. *JAMA*. 2011;306(20):2218-2220.
- Carwile JL, Luu HT, Bassett LS, Driscoll DA, Yuan C, Chang JY, Ye X, Calafat AM, Michels KB. Polycarbonate bottle use and urinary bisphenol A concentrations. *Environmental health perspectives*. 2009;117(9):1368-1372.
- Vandenberg LN, Hunt PA, Myers JP, Vom Saal FS. Human exposures to bisphenol A: mismatches between data and assumptions. *Rev Environ Health*. 2013;28(1):37-58.
- Rudel RA, Gray JM, Engel CL, Rawsthorne TW, Dodson RE, Ackerman JM, Rizzo J, Nudelman JL, Brody JG. Food packaging and bisphenol A and bis(2-ethylhexyl) phthalate exposure: findings from a dietary intervention. *Environmental health perspectives*. 2011;119(7):914-920.
- Stahlhut RW, Welshons WV, Swan SH. Bisphenol A data in NHANES suggest longer than expected half-life, substantial nonfood exposure, or both. *Environmental health perspectives*. 2009;117(5):784-789.
- Staub C. EPA: US plastics recycling rate declines. *Plastics Recycling Update: A Resource Recycling, Inc. Publication.* https://resource-recycling.com/plastics/2018/08/01/epa-u-s-plastics-recyclingrate-declines/2018.
- 97. Masoner JR, Kolpin DW, Furlong ET, Cozzarelli IM, Gray JL. Landfill leachate as a mirror of today's disposable society: Pharmaceuticals and other contaminants of emerging concern in final leachate from landfills in the conterminous United States. *Environ Toxicol Chem.* 2016;35(4):906-918.
- Bexfield LM, Toccalino PL, Belitz K, Foreman WT, Furlong ET. Hormones and Pharmaceuticals in Groundwater Used As a Source of Drinking Water Across the United States. *Environ Sci Technol.* 2019;53(6):2950-2960.
- 99. Petrie B, Lopardo L, Proctor K, Youdan J, Barden R, Kasprzyk-Hordern B. Assessment of bisphenol-A in the urban water cycle. *The Science of the total environment*. 2019;650(Pt 1):900-907.
- 100. Chiu JMY, Po BHK, Degger N, Tse A, Liu W, Zheng G, Zhao DM, Xu D, Richardson B, Wu RSS. Contamination and risk implications of endocrine disrupting chemicals along the coastline of China: A systematic study using mussels and semipermeable membrane devices. *The Science of the total environment*. 2018;624:1298-1307.
- 101. Salgueiro-Gonzalez N, Campillo JA, Vinas L, Beiras R, Lopez-Mahia P, Muniategui-Lorenzo S. Occurrence of selected endocrine disrupting compounds in Iberian coastal areas and assessment of the environmental risk. *Environmental pollution (Barking, Essex : 1987)*. 2019;249:767-775.
- Dodds EC, Lawson W. Synthetic estrogenic agents without the phenanthrene nucleus. Nature. 1936;137:996.
- 103. Krimsky S. Hormonal chaos: the scientific and social origins of the environmental endocrine hypothesis. Baltimore, MD: Johns Hopkins University Press.
- 104. Nadal A, Fuentes E, Ripoll C, Villar-Pazos S, Castellano-Munoz M, Soriano S, Martinez-Pinna J, Quesada I, Alonso-Magdalena P. Extranuclear-initiated estrogenic actions of endocrine disrupting chemicals: Is there toxicology beyond paracelsus? *The Journal of steroid biochemistry and molecular biology*. 2018;176:16-22.
- 105. Gore AC, Chappell VA, Fenton SE, Flaws JA, Nadal A, Prins GS, Toppari J, Zoeller RT. EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals. *Endocr Rev.* 2015;36(6):E1-150.
- 106. Soriano S, Alonso-Magdalena P, Garcia-Arevalo M, Novials A, Muhammed SJ, Salehi A, Gustafsson JA, Quesada I, Nadal A. Rapid insulinotropic action of low doses of bisphenol-A on mouse and human islets of Langerhans: role of estrogen receptor beta. *PloS one*. 2012;7(2):e31109.

- Vandenberg LN, Maffini MV, Sonnenschein C, Rubin BS, Soto AM. Bisphenol-A and the great divide: a review of controversies in the field of endocrine disruption. *Endocrine Reviews*. 2009;30(1):75-95.
- European Chemicals Agency (ECHA). Hot topics: Bisphenol A. Vol Accessed 19 June 2019. https:// echa.europa.eu/hot-topics/bisphenol-a2018.
- 109. Vandenberg LN, Ehrlich S, Belcher SM, Ben-Jonathan N, Dolinoy DC, Hugo ER, Hunt PA, Newbold RR, Rubin BS, Salli KS, Soto AM, Wang H-S, vom Saal FS. Low dose effects of Bisphenol A: An integrated review of in vitro, laboratory animal and epidemiology studies. *Endocrine Disruptors*. 2013;1:e26490.
- 110. Cao J, Rebuli ME, Rogers J, Todd KL, Leyrer SM, Ferguson SA, Patisaul HB. Prenatal bisphenol a exposure alters sex-specific estrogen receptor expression in the neonatal rat hypothalamus and amygdala. *Toxicological sciences : an official journal of the Society of Toxicology*. 2013;133(1):157-173.
- Munoz-de-Toro M, Markey CM, Wadia PR, Luque EH, Rubin BS, Sonnenschein C, Soto AM. Perinatal exposure to bisphenol-A alters peripubertal mammary gland development in mice. *Endocri*nology. 2005;146(9):4138-4147.
- 112. Markey CM, Wadia PR, Rubin BS, Sonnenschein C, Soto AM. Long-term effects of fetal exposure to low doses of the xenoestrogen bisphenol-A in the female mouse genital tract. *Biology of Reproduction*. 2005;72(6):1344-1351.
- 113. Wadia PR, Vandenberg LN, Schaeberle CM, Rubin BS, Sonnenschein C, Soto AM. Perinatal bisphenol A exposure increases estrogen sensitivity of the mammary gland in diverse mouse strains. *Environmental health perspectives*. 2007;115(4):592-598.
- Ho SM, Tang WY, Belmonte de Frausto J, Prins GS. Developmental exposure to estradiol and bisphenol A increases susceptibility to prostate carcinogenesis and epigenetically regulates phosphodiesterase type 4 variant 4. *Cancer Research*. 2006;66(11):5624-5632.
- Lamartiniere CA, Jenkins S, Betancourt AM, Wang J, Russo J. Exposure to the Endocrine Disruptor Bisphenol A Alters Susceptibility for Mammary Cancer. *Horm Mol Biol Clin Investig.* 2011;5(2):45-52.
- Jenkins S, Raghuraman N, Eltoum I, Carpenter M, Russo J, Lamartiniere CA. Oral exposure to bisphenol A increases dimethylbenzanthracene-induced mammary cancer in rats. *Environmental health perspectives*. 2009;117(6):910-915.
- 117. Heindel JJ, Blumberg B, Cave M, Machtinger R, Mantovani A, Mendez MA, Nadal A, Palanza P, Panzica G, Sargis R, Vandenberg LN, Vom Saal F. Metabolism disrupting chemicals and metabolic disorders. *Reproductive toxicology (Elmsford, NY)*. 2017;68:3-33.
- Rochester JR. Bisphenol A and human health: a review of the literature. *Reproductive toxicology* (*Elmsford, NY*). 2013;42:132-155.
- Braun JM. Early-life exposure to EDCs: role in childhood obesity and neurodevelopment. Nature reviews Endocrinology. 2017;13(3):161-173.
- Ejaredar M, Lee Y, Roberts DJ, Sauve R, Dewey D. Bisphenol A exposure and children's behavior: A systematic review. J Expo Sci Environ Epidemiol. 2017;27(2):175-183.
- 121. Peretz J, Vrooman L, Ricke WA, Hunt PA, Ehrlich S, Hauser R, Padmanabhan V, Taylor HS, Swan SH, VandeVoort CA, Flaws JA. Bisphenol A and Reproductive Health: Update of Experimental and Human Evidence, 2007-2013. *Environmental health perspectives*. 2014.
- 122. Hoepner LA, Whyatt RM, Widen EM, Hassoun A, Oberfield SE, Mueller NT, Diaz D, Calafat AM, Perera FP, Rundle AG. Bisphenol A and Adiposity in an Inner-City Birth Cohort. *Environmental health perspectives.* 2016.
- 123. Valvi D, Casas M, Mendez MA, Ballesteros-Gomez A, Luque N, Rubio S, Sunyer J, Vrijheid M. Prenatal bisphenol a urine concentrations and early rapid growth and overweight risk in the offspring. *Epidemiology*. 2013;24(6):791-799.

- 124. Braun JM, Lanphear BP, Calafat AM, Deria S, Khoury J, Howe CJ, Venners SA. Early-life bisphenol a exposure and child body mass index: a prospective cohort study. *Environmental health perspectives*. 2014;122(11):1239-1245.
- Beydoun HA, Khanal S, Zonderman AB, Beydoun MA. Sex differences in the association of urinary bisphenol-A concentration with selected indices of glucose homeostasis among U.S. adults. *Annals* of epidemiology. 2014;24(2):90-97.
- 126. Lee MR, Park H, Bae S, Lim YH, Kim JH, Cho SH, Hong YC. Urinary bisphenol A concentrations are associated with abnormal liver function in the elderly: a repeated panel study. *Journal of epidemiology and community health*. 2014;68(4):312-317.
- 127. Lang IA, Galloway TS, Scarlett A, Henley WE, Depledge M, Wallace RB, Melzer D. Association of urinary bisphenol A concentration with medical disorders and laboratory abnormalities in adults. *JAMA*. 2008;300(11):1303-1310.
- Vandenberg LN, Luthi D, Quinerly D. Plastic bodies in a plastic world: multi-disciplinary approaches to study endocrine disrupting chemicals. J Cleaner Production. 2017;140(1):373-385.
- 129. Liao C, Liu F, Alomirah H, Loi VD, Mohd MA, Moon HB, Nakata H, Kannan K. Bisphenol S in urine from the United States and seven Asian countries: occurrence and human exposures. *Environ Sci Technol.* 2012;46(12):6860-6866.
- Lehmler HJ, Liu B, Gadogbe M, Bao W. Exposure to Bisphenol A, Bisphenol F, and Bisphenol S in U.S. Adults and Children: The National Health and Nutrition Examination Survey 2013-2014. ACS omega. 2018;3(6):6523-6532.
- 131. Ye X, Wong LY, Kramer J, Zhou X, Jia T, Calafat AM. Urinary Concentrations of Bisphenol A and Three Other Bisphenols in Convenience Samples of U.S. Adults during 2000-2014. *Environ Sci Technol.* 2015;49(19):11834-11839.
- 132. Molina-Molina JM, Amaya E, Grimaldi M, Saenz JM, Real M, Fernandez MF, Balaguer P, Olea N. In vitro study on the agonistic and antagonistic activities of bisphenol-S and other bisphenol-A congeners and derivatives via nuclear receptors. *Toxicol Appl Pharmacol.* 2013.
- 133. Rosenmai AK, Dybdahl M, Pedersen M, Alice van Vugt-Lussenburg BM, Wedebye EB, Taxvig C, Vinggaard AM. Are structural analogues to bisphenol a safe alternatives? *Toxicological sciences : an* official journal of the Society of Toxicology. 2014;139(1):35-47.
- 134. Vinas P, Watson CS. Bisphenol S disrupts estradiol-induced nongenomic signaling in a rat pituitary cell line: effects on cell functions. *Environmental health perspectives*. 2013;121(3):352-358.
- Kolla S, Morcos M, Martin B, Vandenberg LN. Low dose bisphenol S or ethinyl estradiol exposures during the perinatal period alter female mouse mammary gland development. *Reproductive Toxicol*ogy. 2018;78:50-59.
- LaPlante CD, Catanese MC, Bansal R, Vandenberg LN. Bisphenol S Alters the Lactating Mammary Gland and Nursing Behaviors in Mice Exposed During Pregnancy and Lactation. *Endocrinology*. 2017;158(10):3448-3461.
- 137. Tucker DK, Hayes Bouknight S, Brar SS, Kissling GE, Fenton SE. Evaluation of Prenatal Exposure to Bisphenol Analogues on Development and Long-Term Health of the Mammary Gland in Female Mice. *Environmental health perspectives*. 2018;126(8):087003.
- Kolla S, McSweeney DB, Pokharel A, Vandenberg LN. Bisphenol S alters development of the male mouse mammary gland and sensitizes it to a peripubertal estrogen challenge. *Toxicology*. 2019.
- Catanese MC, Vandenberg LN. Bisphenol S (BPS) alters maternal behavior and brain in mice exposed during pregnancy/lactation and their daughters. *Endocrinology*. 2017;158(3):516-530.
- 140. Rochester JR, Bolden AL. Bisphenol S and F: A Systematic Review and Comparison of the Hormonal Activity of Bisphenol A Substitutes. *Environmental health perspectives*. 2015;123(7):643-650.
- 141. Wan Y, Huo W, Xu S, Zheng T, Zhang B, Li Y, Zhou A, Zhang Y, Hu J, Zhu Y, Chen Z, Lu S, Wu C, Jiang M, Jiang Y, Liu H, Yang X, Xia W. Relationship between maternal exposure to bisphenol S and pregnancy duration. *Environmental pollution (Barking, Essex : 1987)*. 2018;238:717-724.

- 142. Aung MT, Ferguson KK, Cantonwine DE, McElrath TF, Meeker JD. Preterm birth in relation to the bisphenol A replacement, bisphenol S, and other phenols and parabens. *Environmental research*. 2019;169:131-138.
- 143. Liu B, Lehmler HJ, Sun Y, Xu G, Sun Q, Snetselaar LG, Wallace RB, Bao W. Association of Bisphenol A and Its Substitutes, Bisphenol F and Bisphenol S, with Obesity in United States Children and Adolescents. *Diabetes & metabolism journal*. 2019;43(1):59-75.
- 144. Acir IH, Guenther K. Endocrine-disrupting metabolites of alkylphenol ethoxylates A critical review of analytical methods, environmental occurrences, toxicity, and regulation. *The Science of the total environment*. 2018;635:1530-1546.
- US EPA. Nonylphenol (NP) and Nonylphenol ethoxylates (NPE) action plan. https://www. epa.gov/sites/production/files/2015-09/documents/rin2070-za09\_np-npes\_action\_plan\_final\_2010-08-09.pdf2010.
- 146. Vazquez-Duhalt R, Marquez-Rocha F, Ponce E, Licea A, Viana MT. Nonylphenol, an integrated vision of a pollutant. *Applied Ecology and Environmental Research*. 2005;4(1):1-25.
- 147. Guenther K, Heinke V, Thiele B, Kleist E, Prast H, Raecker T. Endocrine disrupting nonylphenols are ubiquitous in food. *Environ Sci Technol.* 2002;36(8):1676-1680.
- Calafat AM, Ye X, Wong LY, Reidy JA, Needham LL. Exposure of the U.S. population to bisphenol A and 4-tertiary-octylphenol: 2003-2004. *Environmental health perspectives*. 2008;116(1):39-44.
- 149. Park H, Kim K. Urinary Levels of 4-Nonylphenol and 4-t-Octylphenol in a Representative Sample of the Korean Adult Population. *International journal of environmental research and public health*. 2017;14(8).
- 150. Ademollo N, Ferrara F, Delise M, Fabietti F, Funari E. Nonylphenol and octylphenol in human breast milk. *Environment international*. 2008;34(7):984-987.
- Lopez-Espinosa M, Freire C, Arrebola J, Navea N, Taoufiki J, Fernandez M, Ballesteros O, Prada R, Olea N. Nonylphenol and octylphenol in adipose tissue of women in Southern Spain. *Chemosphere*. 2009;76(6):847-852.
- 152. Soto AM, Justicia H, Wray JW, Sonnenschein C. p-Nonyl-phenol: an estrogenic xenobiotic released from "modified" polystyrene. *Environmental health perspectives*. 1991;92:167-173.
- White R, Jobling S, Hoare SA, Sumpter JP, Parker MG. Environmentally persistent alkylphenolic compounds are estrogenic. *Endocrinology*. 1994;135(1):175-182.
- 154. Noorimotlagh Z, Haghighi NJ, Ahmadimoghadam M, Rahim F. An updated systematic review on the possible effect of nonylphenol on male fertility. *Environmental science and pollution research international.* 2017;24(4):3298-3314.
- Forte M, Di Lorenzo M, Carrizzo A, Valiante S, Vecchione C, Laforgia V, De Falco M. Nonylphenol effects on human prostate non tumorigenic cells. *Toxicology*. 2016;357-358:21-32.
- Lee PC. Disruption of male reproductive tract development by administration of the xenoestrogen, nonylphenol, to male newborn rats. *Endocrine*. 1998;9(1):105-111.
- 157. Chen M, Tang R, Fu G, Xu B, Zhu P, Qiao S, Chen X, Xu B, Qin Y, Lu C. Association of exposure to phenols and idiopathic male infertility. *Journal of hazardous materials*. 2013;250:115-121.
- 158. Peremiquel-Trillas P, Benavente Y, Martín-Bustamante M, Casabonne D, Pérez-Gómez B, Gómez-Acebo I, Oliete-Canela A, Diéguez-Rodríguez M, Tusquets I, Amiano P, Mengual L, Ardanaz E, Capelo R, Molina de la Torre AJ, Salas Trejo D, Fernández-Tardón G, Lope V, Jimenez-Moleon JJ, Marcos-Gragera R, Dierssen-Sotos T, Azpiri M, Muñoz M, Guevara M, Fernández-Villa T, Molina-Barceló A, Aragonés N, Pollán M, Castaño-Vinyals G, Alguacil J, Kogevinas M, de Sanjosé S, Costas L. Alkylphenolic compounds and risk of breast and prostate cancer in the MCC-Spain study. *Environment international.* 2019;122:389-399.
- 159. Costas L, Infante-Rivard C, Zock J, Van Tongeren M, Boffetta P, Cusson A, Robles C, Casabonne D, Benavente Y, Becker N. Occupational exposure to endocrine disruptors and lymphoma risk in a multi-centric European study. *British journal of cancer*. 2015;112(7):1251.

- 160. Villeneuve S, Cyr D, Lynge E, Orsi L, Sabroe S, Merletti F, Gorini G, Morales-Suarez-Varela M, Ahrens W, Baumgardt-Elms C. Occupation and occupational exposure to endocrine disrupting chemicals in male breast cancer: a case–control study in Europe. *Occupational and environmental medicine*. 2010;67(12):837-844.
- 161. Wu XM, Bennett DH, Calafat AM, Kato K, Strynar M, Andersen E, Moran RE, Tancredi DJ, Tulve NS, Hertz-Picciotto I. Serum concentrations of perfluorinated compounds (PFC) among selected populations of children and adults in California. *Environmental research*. 2015;136:264-273.
- US EPA. Basic Information on PFAS. PFOA, PFOS and other PFASs. Vol Accessed 19 June 2019. https://www.epa.gov/pfas/basic-information-pfas2019.
- 163. Surma M, Wiczkowski W, Zieliński H, Cieślik E. Determination of Selected Perfluorinated Acids (PFCAs) and Perfluorinated Sulfonates (PFASs) in Food Contact Materials Using LC-MS/MS. Packaging Technology and Science. 2015;28(9):789-799.
- 164. Ahrens L, Bundschuh M. Fate and effects of poly- and perfluoroalkyl substances in the aquatic environment: A review. *Environmental toxicology and chemistry*. 2014;33(9):1921-1929.
- 165. Ross I, McDonough J, Miles J, Storch P, Thelakkat Kochunarayanan P, Kalve E, Hurst J, S. Dasgupta S, Burdick J. A review of emerging technologies for remediation of PFASs. *Remediation Journal*. 2018;28(2):101-126.
- 166. Ahrens L, Norstrom K, Viktor T, Cousins AP, Josefsson S. Stockholm Arlanda Airport as a source of per- and polyfluoroalkyl substances to water, sediment and fish. *Chemosphere*. 2015;129:33-38.
- 167. Banzhaf S, Filipovic M, Lewis J, Sparrenbom CJ, Barthel R. A review of contamination of surface-, ground-, and drinking water in Sweden by perfluoroalkyl and polyfluoroalkyl substances (PFASs). *Ambio.* 2017;46(3):335-346.
- IPEN. PFAS pollution across the Middle East and Asia. https://ipen.org/sites/default/files/documents/pfas\_pollution\_across\_the\_middle\_east\_and\_asia.pdf2019.
- 169. Ye X, Strynar MJ, Nakayama SF, Varns J, Helfant L, Lazorchak J, Lindstrom AB. Perfluorinated compounds in whole fish homogenates from the Ohio, Missouri, and Upper Mississippi Rivers, USA. Environmental pollution (Barking, Essex : 1987). 2008;156(3):1227-1232.
- 170. Jian J-M, Guo Y, Zeng L, Liang-Ying L, Lu X, Wang F, Zeng EY. Global distribution of perfluorochemicals (PFCs) in potential human exposure source-a review. *Environment international*. 2017;108:51-62.
- Eriksson U, Kärrman A. World-wide indoor exposure to polyfluoroalkyl phosphate esters (PAPs) and other PFASs in household dust. *Environ Sci Technol.* 2015;49(24):14503-14511.
- 172. Post GB, Louis JB, Cooper KR, Boros-Russo BJ, Lippincott RL. Occurrence and potential significance of perfluorooctanoic acid (PFOA) detected in New Jersey public drinking water systems. *Environ Sci Technol.* 2009;43(12):4547-4554.
- 173. OECD. Toward a new comprehensive global database of per- and polyfluoroalkyl substances (PFASs): Summary report on updating the OECD 2007 list of per- and polyfluoroalkyl substances (PFASs). In: Environment Directorate, ed. Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology. http://www.oecd.org/officialdocuments/publi cdisplaydocumentpdf/?cote=ENV-JM-MONO(2018)7&doclanguage=en2018.
- 174. Olsen GW, Mair DC, Lange CC, Harrington LM, Church TR, Goldberg CL, Herron RM, Hanna H, Nobiletti JB, Rios JA. Per-and polyfluoroalkyl substances (PFAS) in American Red Cross adult blood donors, 2000–2015. *Environmental research*. 2017;157:87-95.
- 175. Jian J-M, Chen D, Han F-J, Guo Y, Zeng L, Lu X, Wang F. A short review on human exposure to and tissue distribution of per-and polyfluoroalkyl substances (PFASs). *Science of The Total Environment*. 2018;636:1058-1069.
- 176. Sagiv SK, Rifas-Shiman SL, Webster TF, Mora AM, Harris MH, Calafat AM, Ye X, Gillman MW, Oken E. Sociodemographic and perinatal predictors of early pregnancy per-and polyfluoroalkyl substance (PFAS) concentrations. *Environ Sci Technol.* 2015;49(19):11849-11858.
- 177. Olsen GW. PFAS biomonitoring in higher exposed populations. Toxicological Effects of Perfluoroalkyl and Polyfluoroalkyl Substances: Springer; 2015:77-125.

- 178. Zhou Z, Shi Y, Vestergren R, Wang T, Liang Y, Cai Y. Highly elevated serum concentrations of perfluoroalkyl substances in fishery employees from Tangxun lake, china. *Environ Sci Technol.* 2014;48(7):3864-3874.
- 179. Benninghoff AD, Bisson WH, Koch DC, Ehresman DJ, Kolluri SK, Williams DE. Estrogen-like activity of perfluoroalkyl acids in vivo and interaction with human and rainbow trout estrogen receptors in vitro. *Toxicological sciences : an official journal of the Society of Toxicology.* 2011;120(1):42-58.
- 180. Dixon D, Reed CE, Moore AB, Gibbs-Flournoy EA, Hines EP, Wallace EA, Stanko JP, Lu Y, Jefferson WN, Newbold RR, Fenton SE. Histopathologic changes in the uterus, cervix and vagina of immature CD-1 mice exposed to low doses of perfluorooctanoic acid (PFOA) in a uterotrophic assay. *Reproductive Toxicology*. 2012;33(4):506-512.
- Henry ND, Fair PA. Comparison of in vitro cytotoxicity, estrogenicity and anti-estrogenicity of triclosan, perfluorooctane sulfonate and perfluorooctanoic acid. *Journal of Applied Toxicology*. 2013;33(4):265-272.
- 182. Takacs ML, Abbott BD. Activation of mouse and human peroxisome proliferator-activated receptors (alpha, beta/delta, gamma) by perfluorooctanoic acid and perfluorooctane sulfonate. *Toxicological sciences : an official journal of the Society of Toxicology.* 2007;95(1):108-117.
- 183. Wolf CJ, Takacs ML, Schmid JE, Lau C, Abbott BD. Activation of mouse and human peroxisome proliferator-activated receptor alpha by perfluoroalkyl acids of different functional groups and chain lengths. *Toxicological sciences : an official journal of the Society of Toxicology*. 2008;106(1):162-171.
- 184. Hines EP, White SS, Stanko JP, Gibbs-Flournoy EA, Lau C, Fenton SE. Phenotypic dichotomy following developmental exposure to perfluorooctanoic acid (PFOA) in female CD-1 mice: Low doses induce elevated serum leptin and insulin, and overweight in mid-life. *Molecular and cellular endocrinology*. 2009;304(1-2):97-105.
- Wan HT, Zhao YG, Leung PY, Wong CK. Perinatal exposure to perfluorooctane sulfonate affects glucose metabolism in adult offspring. *PloS one*. 2014;9(1):e87137.
- 186. White SS, Calafat AM, Kuklenyik Z, Villanueva L, Zehr RD, Helfant L, Strynar MJ, Lindstrom AB, Thibodeaux JR, Wood C, Fenton SE. Gestational PFOA exposure of mice is associated with altered mammary gland development in dams and female offspring. *Toxicological sciences : an official journal of the Society of Toxicology.* 2007;96(1):133-144.
- 187. White SS, Stanko JP, Kato K, Calafat AM, Hines EP, Fenton SE. Gestational and chronic low-dose PFOA exposures and mammary gland growth and differentiation in three generations of CD-1 mice. *Environmental health perspectives*. 2011;119(8):1070-1076.
- 188. Negri E, Metruccio F, Guercio V, Tosti L, Benfenati E, Bonzi R, La Vecchia C, Moretto A. Exposure to PFOA and PFOS and fetal growth: a critical merging of toxicological and epidemiological data. *Critical reviews in toxicology.* 2017;47(6):482-508.
- 189. Rappazzo KM, Coffman E, Hines EP. Exposure to Perfluorinated Alkyl Substances and Health Outcomes in Children: A Systematic Review of the Epidemiologic Literature. *International journal* of environmental research and public health. 2017;14(7).
- 190. Grandjean P, Heilmann C, Weihe P, Nielsen F, Mogensen UB, Timmermann A, Budtz-Jørgensen E. Estimated exposures to perfluorinated compounds in infancy predict attenuated vaccine antibody concentrations at age 5-years. *J Immunotoxicol.* 2017;14(1):188-195.
- 191. Ballesteros V, Costa O, Iniguez C, Fletcher T, Ballester F, Lopez-Espinosa MJ. Exposure to perfluoroalkyl substances and thyroid function in pregnant women and children: A systematic review of epidemiologic studies. *Environment international*. 2017;99:15-28.
- 192. Lopez-Espinosa MJ, Fletcher T, Armstrong B, Genser B, Dhatariya K, Mondal D, Ducatman A, Leonardi G. Association of Perfluorooctanoic Acid (PFOA) and Perfluorooctane Sulfonate (PFOS) with age of puberty among children living near a chemical plant. *Environ Sci Technol.* 2011;45(19):8160-8166.
- 193. Bonefeld-Jorgensen EC, Long M, Bossi R, Ayotte P, Asmund G, Kruger T, Ghisari M, Mulvad G, Kern P, Nzulumiki P, Dewailly E. Perfluorinated compounds are related to breast cancer risk

in Greenlandic Inuit: a case control study. *Environmental health : a global access science source*. 2011;10:88.

- 194. Mancini FR, Cano-Sancho G, Gambaretti J, Marchand P, Boutron-Ruault MC, Severi G, Arveux P, Antignac JP, Kvaskoff M. Perfluorinated alkylated substances serum concentration and breast cancer risk: Evidence from a nested case-control study in the French E3N cohort. *International journal* of cancer. 2019.
- 195. Vieira VM, Hoffman K, Shin HM, Weinberg JM, Webster TF, Fletcher T. Perfluorooctanoic acid exposure and cancer outcomes in a contaminated community: a geographic analysis. *Environmen*tal health perspectives. 2013;121(3):318-323.
- Lyche JL, Rosseland C, Berge G, Polder A. Human health risk associated with brominated flameretardants (BFRs). *Environment international*. 2015;74:170-180.
- 197. Ritscher A, Wang Z, Scheringer M, Boucher JM, Ahrens L, Berger U, Bintein S, Bopp SK, Borg D, Buser AM, Cousins I, DeWitt J, Fletcher T, Green C, Herzke D, Higgins C, Huang J, Hung H, Knepper T, Lau CS, Leinala E, Lindstrom AB, Liu J, Miller M, Ohno K, Perkola N, Shi Y, Smastuen Haug L, Trier X, Valsecchi S, van der Jagt K, Vierke L. Zurich Statement on Future Actions on Per- and Polyfluoroalkyl Substances (PFASs). *Environmental health perspectives*. 2018;126(8):84502.
- 198. Ivarsson J. Elements for an EU-strategy for PFASs. 2019:21.
- Domingo JL, Rovira J, Nadal M, Schuhmacher M. High cancer risks by exposure to PCDD/Fs in the neighborhood of an Integrated Waste Management Facility. *The Science of the total environment*. 2017;607-608:63-68.
- 200. Programme UE. UNEP-POPS-COP.4-SC-4-14. 2009.
- 201. Programme UE. UNEP-POPS-COP.4-SC-4-18. 2009.
- 202. Programme UE. UNEP/POPs/COP.5/15. 2011.
- 203. Samsonek J, Puype F. Occurrence of brominated flame retardants in black thermo cups and selected kitchen utensils purchased on the European market. *Food additives & contaminants Part A, Chemistry, analysis, control, exposure & risk assessment.* 2013;30(11):1976-1986.
- Strakova J, DiGangi J, Jensen GK. Toxic Loophole: recycling hazardous waste into new products. 2018.
- Okonski K, Melymuk L, Kohoutek J, Klanova J. Hexabromocyclododecane: concentrations and isomer profiles from sources to environmental sinks. *Environmental science and pollution research international*. 2018;25(36):36624-36635.
- 206. Gao CJ, Xia LL, Wu CC, Wong CS, Guo Y. The effects of prosperity indices and land use indicators of an urban conurbation on the occurrence of hexabromocyclododecanes and tetrabromobisphenol A in surface soil in South China. *Environmental pollution (Barking, Essex : 1987)*. 2019;252(Pt B):1810-1818.
- Scientific Opinion on Tetrabromobisphenol A (TBBPA) and its derivatives in food. EFSA Journal. 2011;9(12):2477.
- 208. Some Industrial Chemicals. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* Vol 1152018.
- 209. Kim YR, Harden FA, Toms LM, Norman RE. Health consequences of exposure to brominated flame retardants: a systematic review. *Chemosphere*. 2014;106:1-19.
- 210. Garcia-Villarino M, Riano-Galan I, Rodriguez-Dehli AC, Vizcaino E, Grimalt JO, Tardon A, Fernandez-Somoano A. Prenatal Exposure to Persistent Organic Pollutants and Anogenital Distance in Children at 18 Months. *Hormone research in paediatrics*. 2018;90(2):116-122.
- 211. Albert O, Huang JY, Aleksa K, Hales BF, Goodyer CG, Robaire B, Chevrier J, Chan P. Exposure to polybrominated diphenyl ethers and phthalates in healthy men living in the greater Montreal area: A study of hormonal balance and semen quality. *Environment international*. 2018;116:165-175.

- 212. Gibson EA, Siegel EL, Eniola F, Herbstman JB, Factor-Litvak P. Effects of Polybrominated Diphenyl Ethers on Child Cognitive, Behavioral, and Motor Development. *International journal of environmental research and public health*. 2018;15(8).
- 213. Lam J, Lanphear BP, Bellinger D, Axelrad DA, McPartland J, Sutton P, Davidson L, Daniels N, Sen S, Woodruff TJ. Developmental PBDE Exposure and IQ/ADHD in Childhood: A Systematic Review and Meta-analysis. *Environmental health perspectives*. 2017;125(8):086001.
- Marchesini GR, Meimaridou A, Haasnoot W, Meulenberg E, Albertus F, Mizuguchi M, Takeuchi M, Irth H, Murk AJ. Biosensor discovery of thyroxine transport disrupting chemicals. *Toxicol Appl Pharmacol*. 2008;232(1):150-160.
- 215. Wilson J, Berntsen HF, Zimmer KE, Verhaegen S, Frizzell C, Ropstad E, Connolly L. Do persistent organic pollutants interact with the stress response? Individual compounds, and their mixtures, interaction with the glucocorticoid receptor. *Toxicology letters*. 2016;241:121-132.
- Zhang Q, Wang J, Zhu J, Liu J, Zhao M. Potential Glucocorticoid and Mineralocorticoid Effects of Nine Organophosphate Flame Retardants. *Environ Sci Technol.* 2017;51(10):5803-5810.
- Net S, Sempere R, Delmont A, Paluselli A, Ouddane B. Occurrence, fate, behavior and ecotoxicological state of phthalates in different environmental matrices. *Environ Sci Technol.* 2015;49(7):4019-4035.
- Hannon PR, Flaws JA. The effects of phthalates on the ovary. Front Endocrinol (Lausanne). 2015;6:8.
- Di(2-ethylhexyl) phthalate. Report on carcinogens: carcinogen profiles / US Dept of Health and Human Services, Public Health Service, National Toxicology Program. 2011;12:156-159.
- 220. Blount BC, Milgram KE, Silva MJ, Malek NA, Reidy JA, Needham LL, Brock JW. Quantitative detection of eight phthalate metabolites in human urine using HPLC-APCI-MS/MS. *Analytical chemistry*. 2000;72(17):4127-4134.
- Wittassek M, Koch HM, Angerer J, Bruning T. Assessing exposure to phthalates the human biomonitoring approach. *Molecular nutrition & food research*. 2011;55(1):7-31.
- 222. Becker K, Seiwert M, Angerer J, Heger W, Koch HM, Nagorka R, Rosskamp E, Schluter C, Seifert B, Ullrich D. DEHP metabolites in urine of children and DEHP in house dust. *International journal of hygiene and environmental health*. 2004;207(5):409-417.
- 223. Kato K, Silva MJ, Reidy JA, Hurtz D, 3rd, Malek NA, Needham LL, Nakazawa H, Barr DB, Calafat AM. Mono(2-ethyl-5-hydroxyhexyl) phthalate and mono-(2-ethyl-5-oxohexyl) phthalate as biomarkers for human exposure assessment to di-(2-ethylhexyl) phthalate. *Environmental health perspectives*. 2004;112(3):327-330.
- 224. Krotz SP, Carson SA, Tomey C, Buster JE. Phthalates and bisphenol do not accumulate in human follicular fluid. *Journal of assisted reproduction and genetics*. 2012;29(8):773-777.
- Hernandez-Diaz S, Mitchell AA, Kelley KE, Calafat AM, Hauser R. Medications as a potential source of exposure to phthalates in the U.S. population. *Environmental health perspectives*. 2009;117(2):185-189.
- 226. Hernandez-Diaz S, Su YC, Mitchell AA, Kelley KE, Calafat AM, Hauser R. Medications as a potential source of exposure to phthalates among women of childbearing age. *Reproductive toxicology* (*Elmsford*, NY). 2013;37:1-5.
- 227. Aldyreva MV, Klimova TS, Iziumova AS, Timofeevskaia LA. [The effect of phthalate plasticizers on the generative function]. *Gigiena truda i professional'nye zabolevaniia*. 1975(12):25-29.
- 228. Meeker JD, Ferguson KK. Urinary phthalate metabolites are associated with decreased serum testosterone in men, women, and children from NHANES 2011-2012. *The Journal of clinical endocrinology and metabolism.* 2014;99(11):4346-4352.
- 229. Mathieu-Denoncourt J, Wallace SJ, de Solla SR, Langlois VS. Plasticizer endocrine disruption: Highlighting developmental and reproductive effects in mammals and non-mammalian aquatic species. *Gen Comp Endocrinol.* 2015;219:74-88.

- Kay VR, Chambers C, Foster WG. Reproductive and developmental effects of phthalate diesters in females. Critical reviews in toxicology. 2013;43(3):200-219.
- Grindler NM, Allsworth JE, Macones GA, Kannan K, Roehl KA, Cooper AR. Persistent organic pollutants and early menopause in U.S. women. *PloS one*. 2015;10(1):e0116057.
- 232. Messerlian C, Souter I, Gaskins AJ, Williams PL, Ford JB, Chiu YH, Calafat AM, Hauser R. Urinary phthalate metabolites and ovarian reserve among women seeking infertility care. *Human reproduction (Oxford, England)*. 2016;31(1):75-83.
- Tabacova S LR, Balabaeva L. Maternal exposure to phthalates and complications of pregnancy. *Epidemiology*. 1999(10).
- Radke EG, Braun JM, Meeker JD, Cooper GS. Phthalate exposure and male reproductive outcomes: A systematic review of the human epidemiological evidence. *Environment international*. 2018;121(Pt 1):764-793.
- 235. Kaul AF, Souney PF, Osathanondh R. A review of possible toxicity of di-2-ethylhexylphthalate (DEHP) in plastic intravenous containers: effects on reproduction. *Drug intelligence & clinical pharmacy.* 1982;16(9):689-692.
- 236. Agarwal DK, Lawrence WH, Turner JE, Autian J. Effects of parenteral di-(2-ethylhexyl)phthalate (DEHP) on gonadal biochemistry, pathology, and reproductive performance of mice. *Journal of toxicology and environmental health*. 1989;26(1):39-59.
- 237. Barakat R, Lin PP, Rattan S, Brehm E, Canisso IF, Abosalum ME, Flaws JA, Hess R, Ko C. Prenatal exposure to DEHP induces premature reproductive senescence in male mice. *Toxicological sciences : an official journal of the Society of Toxicology*. 2017.
- Gore AC, Krishnan K, Reilly MP. Endocrine-disrupting chemicals: Effects on neuroendocrine systems and the neurobiology of social behavior. *Hormones and behavior*. 2018.
- Quinnies KM, Harris EP, Snyder RW, Sumner SS, Rissman EF. Direct and transgenerational effects of low doses of perinatal di-(2-ethylhexyl) phthalate (DEHP) on social behaviors in mice. *PloS one*. 2017;12(2):e0171977.
- 240. Shoshtari-Yeganeh B, Zarean M, Mansourian M, Riahi R, Poursafa P, Teiri H, Rafiei N, Dehdashti B, Kelishadi R. Systematic review and meta-analysis on the association between phthalates exposure and insulin resistance. *Environmental science and pollution research international*. 2019.
- 241. Amin MM, Ebrahimpour K, Parastar S, Shoshtari-Yeganeh B, Hashemi M, Mansourian M, Poursafa P, Fallah Z, Rafiei N, Kelishadi R. Association of urinary concentrations of phthalate metabolites with cardiometabolic risk factors and obesity in children and adolescents. *Chemosphere*. 2018;211:547-556.
- 242. Lind L, Lind PM. Can persistent organic pollutants and plastic-associated chemicals cause cardiovascular disease? *Journal of internal medicine*. 2012;271(6):537-553.
- 243. He TT, Zhang T, Liu SB, Shi JC, Huang YS, Zheng HP, Liu WH. Toxicological effects benzotriazole to the marine scallop Chlamys nobilis: a 2-month exposure study. *Environmental science and pollution research international*. 2019;26(10):10306-10318.
- 244. Fent K, Chew G, Li J, Gomez E. Benzotriazole UV-stabilizers and benzotriazole: Antiandrogenic activity in vitro and activation of aryl hydrocarbon receptor pathway in zebrafish eleuthero-embryos. *The Science of the total environment*. 2014;482-483:125-136.
- 245. Liang X, Li J, Martyniuk CJ, Wang J, Mao Y, Lu H, Zha J. Benzotriazole ultraviolet stabilizers alter the expression of the thyroid hormone pathway in zebrafish (Danio rerio) embryos. *Chemosphere*. 2017;182:22-30.
- 246. Zhuang S, Lv X, Pan L, Lu L, Ge Z, Wang J, Wang J, Liu J, Liu W, Zhang C. Benzotriazole UV 328 and UV-P showed distinct antiandrogenic activity upon human CYP3A4-mediated biotransformation. *Environmental pollution (Barking, Essex : 1987).* 2017;220(Pt A):616-624.
- Weatherly LM, Gosse JA. Triclosan exposure, transformation, and human health effects. Journal of toxicology and environmental health Part B, Critical reviews. 2017;20(8):447-469.
- 248. Programme UE. UNEP-POPS-COP.8-SC-8-11. 2017.

- 249. Miller P, DiGangi J. TOXIC INDUSTRIAL CHEMICAL RECOMMENDED FOR GLOBAL PRO-HIBITION CONTAMINATES CHILDREN'S TOYS.14.
- 250. Petrlik J, Ismawati Y, DiGangi J, Arisandi P, Si M, Bell L, Beeler B. PLASTIC WASTE FLOODING INDONESIA LEADS TO TOXIC CHEMICAL CONTAMINATION OF THE FOOD CHAIN.40.
- Hernandez-Ochoa I, Karman BN, Flaws JA. The role of the aryl hydrocarbon receptor in the female reproductive system. *Biochemical pharmacology*. 2009;77(4):547-559.
- 252. Karman BN, Basavarajappa MS, Craig ZR, Flaws JA. 2,3,7,8-Tetrachlorodibenzo-p-dioxin activates the aryl hydrocarbon receptor and alters sex steroid hormone secretion without affecting growth of mouse antral follicles in vitro. *Toxicol Appl Pharmacol.* 2012;261(1):88-96.
- 253. Eskenazi B, Warner M, Marks AR, Samuels S, Gerthoux PM, Vercellini P, Olive DL, Needham L, Patterson D, Jr., Mocarelli P. Serum dioxin concentrations and age at menopause. *Environmental health perspectives*. 2005;113(7):858-862.
- 254. Warner M, Eskenazi B, Olive DL, Samuels S, Quick-Miles S, Vercellini P, Gerthoux PM, Needham L, Patterson DG, Mocarelli P. Serum dioxin concentrations and quality of ovarian function in women of Seveso. *Environmental health perspectives*. 2007;115(3):336-340.
- 255. Karman BN, Basavarajappa MS, Hannon P, Flaws JA. Dioxin exposure reduces the steroidogenic capacity of mouse antral follicles mainly at the level of HSD17B1 without altering atresia. *Toxicol Appl Pharmacol.* 2012;264(1):1-12.
- 256. Chain EPoCitF. Scientific Opinion Cadmium in Food. EFSA Journal. 2009;980:1-139.
- 257. Chain EPoCitF. Scientific Opinion on Lead in Food. EFSA Journal. 2010;8(4):1570.
- Varga B, Zsolnai B, Paksy K, Naray M, Ungvary G. Age dependent accumulation of cadmium in the human ovary. *Reproductive toxicology (Elmsford, NY)*. 1993;7(3):225-228.
- IARC. Inorganic and Organic Lead Compounds. IARC Monographs n the Evaluation of Carcinogenic Risks to Humans. Vol Volume 872004.
- 260. Jarup L. Hazards of heavy metal contamination. Br Med Bull. 2003;68:167-182.
- IARC. Cadmium and cadmium compounds. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol Volume 100C2012.
- Byrne C, Divekar SD, Storchan GB, Parodi DA, Martin MB. Metals and breast cancer. J Mammary Gland Biol Neoplasia. 2013;18(1):63-73.
- Ali I, Damdimopoulou P, Stenius U, Halldin K. Cadmium at nanomolar concentrations activates Raf-MEK-ERK1/2 MAPKs signaling via EGFR in human cancer cell lines. *Chem Biol Interact*. 2015;231:44-52.
- 264. Gao X, Yu L, Moore AB, Kissling GE, Waalkes MP, Dixon D. Cadmium and proliferation in human uterine leiomyoma cells: evidence of a role for EGFR/MAPK pathways but not classical estrogen receptor pathways. *Environmental health perspectives*. 2015;123(4):331-336.
- Martin MB, Reiter R, Pham T, Avellanet YR, Camara J, Lahm M, Pentecost E, Pratap K, Gilmore BA, Divekar S, Dagata RS, Bull JL, Stoica A. Estrogen-like activity of metals in MCF-7 breast cancer cells. *Endocrinology*. 2003;144(6):2425-2436.
- 266. Gray JM, Rasanayagam S, Engel C, Rizzo J. State of the evidence 2017: an update on the connection between breast cancer and the environment. *Environmental health* : a global access science source. 2017;16(1):94.
- 267. Gollenberg AL, Hediger ML, Lee PA, Himes JH, Louis GM. Association between lead and cadmium and reproductive hormones in peripubertal U.S. girls. *Environmental health perspectives*. 2010;118(12):1782-1787.
- Liu Y, Tellez-Rojo MM, Sanchez BN, Zhang Z, Afeiche MC, Mercado-Garcia A, Hu H, Meeker JD, Peterson KE. Early lead exposure and pubertal development in a Mexico City population. *Environment international*. 2019;125:445-451.

- Williams PL, Bellavia A, Korrick SA, Burns JS, Lee MM, Sergeyev O, Hauser R, Russian Children's Study T. Blood lead levels and timing of male sexual maturity: A longitudinal study of Russian boys. *Environment international*. 2019;125:470-477.
- Popovic M, McNeill FE, Chettle DR, Webber CE, Lee CV, Kaye WE. Impact of occupational exposure on lead levels in women. *Environmental health perspectives*. 2005;113(4):478-484.
- Eum KD, Weisskopf MG, Nie LH, Hu H, Korrick SA. Cumulative lead exposure and age at menopause in the Nurses' Health Study cohort. *Environmental health perspectives*. 2014;122(3):229-234.
- 272. Telisman S, Cvitkovic P, Jurasovic J, Pizent A, Gavella M, Rocic B. Semen quality and reproductive endocrine function in relation to biomarkers of lead, cadmium, zinc, and copper in men. *Environmental health perspectives*. 2000;108(1):45-53.
- 273. Pollack AZ, Schisterman EF, Goldman LR, Mumford SL, Albert PS, Jones RL, Wactawski-Wende J. Cadmium, lead, and mercury in relation to reproductive hormones and anovulation in premenopausal women. *Environmental health perspectives*. 2011;119(8):1156-1161.
- 274. Buck Louis GM, Sundaram R, Schisterman EF, Sweeney AM, Lynch CD, Gore-Langton RE, Chen Z, Kim S, Caldwell KL, Barr DB. Heavy metals and couple fecundity, the LIFE Study. *Chemosphere*. 2012;87(11):1201-1207.
- Tulic L, Vidakovic S, Tulic I, Curcic M, Bulat Z. Toxic Metal and Trace Element Concentrations in Blood and Outcome of In Vitro Fertilization in Women. *Biol Trace Elem Res.* 2019;188(2):284-294.
- 276. Wdowiak A, Mazurek PA, Wdowiak A, Bojar I. Low frequency electromagnetic waves increase human sperm motility A pilot study revealing the potent effect of 43 kHz radiation. *Int J Occup Med Environ Health*. 2018;31(6):723-739.
- 277. Bloom MS, Kim K, Kruger PC, Parsons PJ, Arnason JG, Steuerwald AJ, Fujimoto VY. Associations between toxic metals in follicular fluid and in vitro fertilization (IVF) outcomes. *Journal of assisted reproduction and genetics*. 2012;29(12):1369-1379.
- 278. Al-Saleh I, Coskun S, Mashhour A, Shinwari N, El-Doush I, Billedo G, Jaroudi K, Al-Shahrani A, Al-Kabra M, El Din Mohamed G. Exposure to heavy metals (lead, cadmium and mercury) and its effect on the outcome of in-vitro fertilization treatment. *International journal of hygiene and environmental health*. 2008;211(5-6):560-579.
- 279. Izah SC, Inyang IR, Angaye TCN, Okowa IP. A Review of Heavy Metal Concentration and Potential Health Implications of Beverages Consumed in Nigeria. *Toxics*. 2016;5(1).
- Hirano S, Suzuki KT. Exposure, metabolism, and toxicity of rare earths and related compounds. Environmental health perspectives. 1996;104 Suppl 1:85-95.
- 281. de Araujo JFP, Podratz PL, Merlo E, Sarmento IV, da Costa CS, Nino OMS, Faria RA, Freitas Lima LC, Graceli JB. Organotin Exposure and Vertebrate Reproduction: A Review. *Front Endocrinol (Lausanne)*. 2018;9:64.
- 282. Lagadic L, Katsiadaki I, Biever R, Guiney PD, Karouna-Renier N, Schwarz T, Meador JP. Tributyltin: Advancing the Science on Assessing Endocrine Disruption with an Unconventional Endocrine-Disrupting Compound. *Reviews of environmental contamination and toxicology*. 2018;245:65-127.
- 283. https://www.unenvironment.org/explore-topics/chemicals-waste/what-we-do/emerging-issues/ scientific-knowledge-endocrine-disrupting
- 284. https://www.sciencedirect.com/science/article/pii/S0045653520307724
- Weak Controls: European E-waste Poisons Africa's Food Chain. IPEN, 2019. https://ipen.org/documents/weak-controls
- Plastic Waste Poisons Indonesia's Food Chain. IPEN, 2019. https://ipen.org/documents/plastic-waste-poisons-indonesias-food-chain-full-report
- 287. Hagai Levine, Niels Jørgensen, Anderson Martino-Andrade, Jaime Mendiola, Dan Weksler-Derri, Irina Mindlis, Rachel Pinotti, Shanna H Swan. Temporal trends in sperm count: a systematic review and meta-regression analysis. *Human Reproduction Update*, Volume 23, Issue 6, November-December 2017, Pages 646–659, https://doi.org/10.1093/humupd/dmx022



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