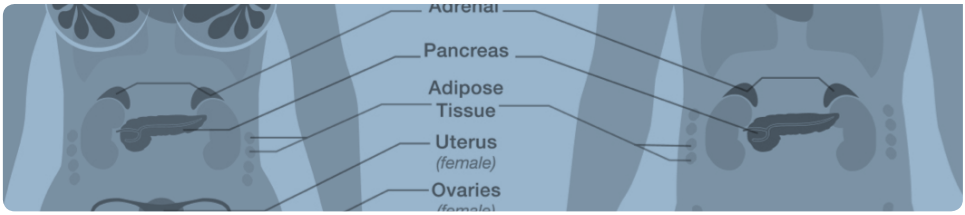

INTRODUCTION TO ENDOCRINE DISRUPTING CHEMICALS (EDCs)

A GUIDE FOR PUBLIC INTEREST ORGANIZATIONS AND POLICY-MAKERS

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ENDOCRINE SOCIETY
Hormone Science to Health

IPEN
a toxics-free future

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

ENDOCRINE SOCIETY
Hormone Science to Health

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.

IPEN
a toxics-free future

IPEN is a leading global network of 700 non-governmental organizations (NGOs) working in more than 100 developing countries and countries with economies in transition. IPEN works to establish and implement safe chemicals policies and practices to protect human health and the environment. It does this by building the capacity of its member organizations to implement on-the-ground activities, learn from each other's work, and work at the international level to set priorities and achieve new policies. Its mission is a toxics-free future for all.

IPEN has been engaged in the SAICM process since 2003, and its global network helped to develop the SAICM international policy framework. At its founding, in 1998, IPEN focused on advancing the development and implementation of the Stockholm Convention on persistent organic pollutants (POPs). Today, its mission also includes promoting safe chemicals management through the SAICM process (where it holds the public interest organization seat on the SAICM Bureau), halting the spread of toxic metals, and building a movement for a toxics-free future.

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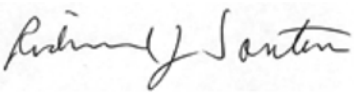
FOREWORD

Scientific understanding of the health impacts of endocrine-disrupting chemicals (EDCs) has been growing in recent years, and in 2012, this issue entered the international chemical policy arena via the Strategic Approach to International Chemicals Management (SAICM) as noted in Annex I. SAICM is a multi-stakeholder policy framework to foster the sound management of chemicals with a goal of ensuring that, by the year 2020, chemicals are produced and used in ways that minimize significant adverse impacts on the environment and on human health.

To raise global awareness about endocrine-disrupting chemicals (EDCs) the Endocrine Society and IPEN have joined together to develop this EDC Guide. The guide draws from each organization's strengths to present a more comprehensive picture of global EDC exposures and health risks than either could have done alone. Endocrine Society authors contributed the scientific and health-related content; IPEN provides knowledge of global policies and perspectives from developing and transition countries.

In preparing and distributing this guide, we hope to help global policymakers, government leaders, and public interest organizations throughout the world better understand what EDCs are and the impact EDCs have on human health. We further hope that greater awareness will lead to additional programs to enhance knowledge of EDCs, to foster new research into the effects of these chemicals, and to promote a greater appreciation for the critical need for endocrine principles to be applied in formulating EDC policy and regulations.

Sincerely,



Richard J. Santen, MD
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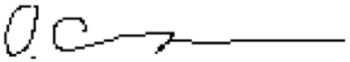

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EXECUTIVE SUMMARY

Scientific knowledge about endocrine-disrupting chemicals (EDCs) has been increasing rapidly in recent years. Along with evidence on the impact of these chemicals on human health, there is a growing body of literature that suggests that relying upon traditional scientific methods for assessing the human health impact of chemicals is inadequate when assessing EDCs and such methods, in fact, may result in dangerous and faulty policy.

EDCs are defined by the Endocrine Society as: "an exogenous [non-natural] chemical, or mixture of chemicals, that interferes with any aspect of hormone action." Hormones are natural chemicals produced in cells within endocrine glands, which are located throughout the body.

Hormones coordinate the development of every individual from a single fertilized cell to the many millions of specialized cells that make up the blood, bones, brain, and other tissues. More than a century of biological research has proven that as an individual develops, the changing hormonal needs of each organ require hormones to be present in precise amounts at particular times, and that the needs of each organ and tissue change through the life cycle. Circulating in very low concentrations, hormones regulate the body's 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. As a whole, the endocrine system is one of the body's major interfaces with the environment, allowing for development, adaptation and maintenance of bodily processes and health. In other words, they play key roles in determining the quality of life, and many hormones are absolutely essential for survival.

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

EDCs are a global and ubiquitous problem. Exposure occurs at home, in the office, on the farm, in the air we breathe, the food we eat, and the water we drink. Of the hundreds of thousands of manufactured chemicals, it is estimated that about 1000 may have endocrine-acting properties. Biomonitoring (measurement of chemicals in body fluids and tissues) shows nearly 100% of humans have a chemical body burden based on detectable levels in blood, urine, placenta and

umbilical cord blood, and body tissues such as adipose tissue (fat). Some common examples of EDCs include DDT and other pesticides; bisphenol A (BPA) and phthalates used in children's products, personal care products and food containers; and flame retardants used in furniture and floor coverings. In addition to the known EDCs, there are countless suspected EDCs or chemicals that have never been tested.

Exposures to known EDCs are relatively high in contaminated environments in which industrial chemicals leach into soil and water; are taken up by microorganisms, algae, and plants; and move into the animal kingdom as animals eat the plants, and bigger animals eat the smaller animals. Animals at the top of the food chain, including humans, have the highest concentrations of such environmental chemicals in their tissues.

There is good reason to suspect that increasing chemical production and use is related to the growing incidence of endocrine-associated pediatric disorders over the past 20 years, including male reproductive problems (cryptorchidism, hypospadias, testicular cancer), early female puberty, leukemia, brain cancer, and neurobehavioral disorders. At the same time, the global production of plastics grew from 50 million tons in the mid-1970s to nearly 300 million today, and sales for the global chemical industry have sharply increased from USD$171 billion in 1970 to over USD$4 trillion in 2013. Chemicals such as polychlorinated biphenyls (PCBs), BPA, and phthalates, are now detectable in serum, fat, and umbilical cord blood in humans around the globe. In fact, the concept of "better living through chemistry" was introduced by the chemical industry in the 1930s. This pervasive notion underlies the global escalation in chemicals production.

Over the last two decades there has been burgeoning scientific evidence based on field research in wildlife species, epidemiological data on humans, and laboratory research with cell cultures and animal models that provides insights into how EDCs cause biological changes, and how that may lead to disease. However, endocrinologists now believe that a shift away from traditional toxicity testing is needed. The prevailing dogma applied to chemical risk assessment is that "the dose makes the poison." These testing protocols are based on the idea that there is always a simple, linear relationship between dose and toxicity, with higher doses being more toxic, and lower doses less toxic. This strategy is used to establish a dose below which a chemical is considered "safe," and experiments are conducted to determine that threshold for safety. Traditional testing involves chemicals being tested one at a time on adult animals, and they are presumed safe if they did not result in cancer or death.

A paradigm shift away from this dogma is required in order to assess fully the impact of EDCs and to protect human health. Like natural hormones, EDCs

There is good reason to suspect that increasing chemical production and use is related to the growing incidence of endocrine-associated pediatric disorders over the past 20 years, including male reproductive problems (cryptorchidism, hypospadias, testicular cancer), early female puberty, leukemia, brain cancer, and neurobehavioral disorders.

exist in the body in combination due to prolonged or continual environmental exposures. Also like natural hormones, EDCs have effects at extremely low doses (typically in the part-per-trillion to part-per-billion range) to regulate bodily functions. This concept is particularly important in considering that exposures start in the womb and continue throughout the life cycle. A new type of testing is needed in order to reflect that EDCs impact human health even at the low levels encountered in everyday life.

Rather than the old toxicological method of a single-exposure, dose-response approach using pure compounds, it is vital that new risk assessment procedures simulate more closely what occurs in nature. Rather than pure compounds, we need to know the effects of combinations of compounds or mixtures. We also need to recognize that because certain life stages are particularly vulnerable to EDCs, especially early in development, testing EDC effects on adults, which is the norm in traditional risk assessment, may not extrapolate to the exposed fetus or infant.

1. MAJOR HEALTH AND SCIENCE INSTITUTIONS HIGHLIGHT CONCERNS ABOUT EDCs

Significant advances in research into endocrine-disrupting chemicals (EDCs) and their health effects have elevated concerns in recent years about these chemicals among a number of international scientific and health organizations. The Endocrine Society was the first 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. The Society's 2012 Statement of Principles on EDCs and Public Health Protection, letters to the European Commission (March 2013), and to the Secretariat of the Strategic Approach to International Chemicals Management (SAICM, June 2013) encouraging science-based action on EDCs further advanced awareness and understanding of EDCs.

Since the Endocrine Society's inaugural statement in 2009, the number of medical societies voicing concern over EDCs globally has grown in parallel with the body of literature revealing negative health effects of chemicals that interfere with hormone action. In the United States, the American Medical Association – the largest organization of US medical professionals – adopted a policy in November 2009 (D-135.982, Regulation of Endocrine-Disrupting Chemicals) calling for improved regulatory oversight of EDCs based on "comprehensive data covering both low-level and high-level exposures"*. In the same month, the American Public Health Association† called for "a precautionary approach to reducing American exposure to endocrine-disrupting chemicals." The American Chemical Society issued a 2012-2015 policy statement on testing for endocrine disruption‡, recommending

* https://ssl3.ama-assn.org/apps/ecomm/PolicyFinderForm.pl?site=www.ama-assn.org&uri=%2fresources%2fhtml%2fPolicyFinder%2fpolicyfiles%2fDIR%2fD-135.982.HTM

† http://www.apha.org/policies-and-advocacy/public-health-policy-statements/policy-database/2014/07/09/09/03/a-precautionary-approach-to-reducing-american-exposure-to-endocrine-disrupting-chemicals

‡ http://www.acs.org/content/dam/acsorg/policy/publicpolicies/promote/endocrinedisruptors/2012-05-testing-for-erine-disruption.pdf

The American Chemical Society issued a 2012-2015 policy statement on testing for endocrine disruption, recommending expanded education and research, updated testing protocols, and the development of safer alternatives to EDCs.

expanded education and research, updated testing protocols, and the development of safer alternatives to EDCs.

A number of international and global health organizations also have taken up the call for improved EDC policies. In February 2013, the World Health Organization (WHO) and United Nations Environment Programme (UNEP) launched their joint 2012 report on the state of the science of EDCs* (2). The report outlines the current understanding of EDCs and their effects on human health; it also recommends improved testing and reduced exposures to EDCs. Also in 2013, the Collegium Ramazzini – an international academy of renowned occupational and environmental health experts – issued a statement on EDCs in the European Union† calling for the expansion of the scope of the REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) legislation and more inclusive assessment of the totality of scientific evidence in regulatory decision-making. Again in 2013, a large group of independent scientists issued the Berlaymont Declaration expressing concern over EDCs and calling on the European Commission to improve its regulatory regime governing these chemicals‡. The Declaration has been signed by nearly 100 scientists from 19 countries, including Chile,

* http://www.who.int/ceh/publications/endocrine/en/

† http://www.collegiumramazzini.org/download/EDCs_Recommendations(2013).pdf

‡ http://www.brunel.ac.uk/__data/assets/pdf_file/0005/300200/The_Berlaymont_Declaration_on_Endocrine_Disrupters.pdf

China, Czech Republic, Mexico, South Africa, and several European Union member states.

The above examples are not an exhaustive list and do not include statements by large medical associations that address EDCs in the context of the larger universe of toxic chemicals. In October 2013, the American College of Obstetrics and Gynecology and the American Society of Reproductive Medicine issued a joint committee opinion "calling for timely action to identify and reduce exposure to toxic environmental agents"* (3). The British Royal College of Obstetrics and Gynaecology issued a 2013 Scientific Impact Paper on chemical exposures during pregnancy† "to inform women who are pregnant or breastfeeding of the sources and routes of chemical exposure in order for them to take positive action in regard to minimising harm to their unborn child" (4). Finally, the International Conference on Children's Health and Environment issued a 2013 Jerusalem Statement‡ on its "commitment to protect children's health from environmental hazards."

As the global scientific and medical community continues to express concern over EDCs and their harmful effects on human health, public policies should be grounded in the latest available scientific evidence.

* http://www.acog.org/~/media/Committee%20Opinions/Committee%20on%20Health%20Care%20for%20Underserved%20Women/co575.pdf?dmc=1&ts=20140912T1804036966

† https://www.rcog.org.uk/en/guidelines-research-services/guidelines/sip37/

‡ http://www.isde.org/Jerusalem_Statement.pdf

2. INTRODUCTION TO THE HUMAN ENDOCRINE SYSTEM AND EDCs

I. BACKGROUND ON THE HUMAN ENDOCRINE SYSTEM

The endocrine system consists of a series of glands that are distributed throughout the body (Figure 1). Each gland produces one or more hormones. Hormones are natural chemicals that are produced in cells within a gland and released into the circulatory system, where they travel through the bloodstream until they reach a target tissue or organ. There, they bind to specific receptors, triggering a response such as production of another hormone, a change in metabolism, a

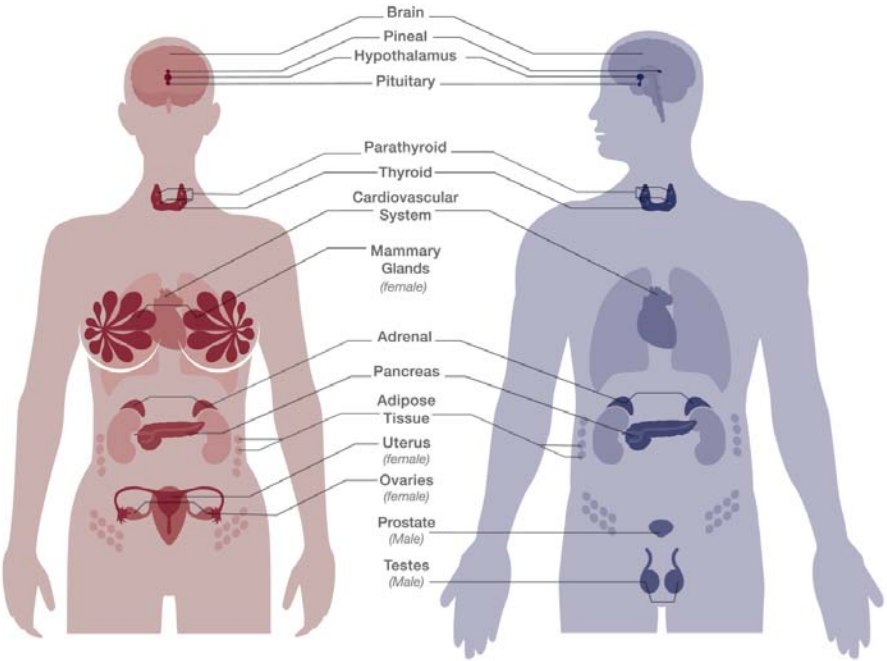


Figure 1. Diagram of major endocrine glands in the human body, shown in a female (left) and male (right).

behavioral response, or other responses, depending upon the specific hormone and its target. Some endocrine glands produce a single hormone, while others produce multiple endocrine hormones (Table 1). For example, the parathyroid gland produces a single known hormone (parathyroid hormone), whereas the pituitary gland makes eight or more hormones, including prolactin and growth hormone. Prolactin is involved in making breast milk, and it is only synthesized and released from the pituitary glands of women who are breast feeding their infants. By contrast, growth hormone is synthesized throughout life, as it is important for growth and development in childhood and for building and maintaining muscles and the skeleton in adulthood. It is also notable that some endocrine glands have other, non-endocrine functions. The pancreas is a good example: it produces the hormone insulin, which circulates in the blood and is necessary for normal regulation of blood sugar levels; and it makes digestive enzymes that go directly to the digestive tract and are not part of the endocrine system because they are not released into the blood. Clearly, endocrine systems and functions are complex and diverse, with each gland and hormone playing unique roles in health and well-being.

These examples, together with the additional information provided in Table 1, underscore a critical point about all endocrine systems: they are absolutely 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. Thus, as a whole, the endocrine system is one of the body's major interfaces with the environment, allowing for development, adaptation, and maintenance of bodily processes and health.

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. Aldosterone is also critical for life, and adrenal diseases affecting aldosterone function can be life-threatening. 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

Endocrine Gland	Location in the body	Major hormone(s) secreted by the gland	General effect(s)
Pituitary	Just under the brain, and above the roof of the mouth	1. Growth hormone 2. TSH 3. ACTH 4. LH 5. FSH 6. Prolactin 7. Oxytocin 8. Vasopressin	1. Growth 2. Metabolism 3. Stress and immune responses 4 & 5. Reproduction in both males and females 6. Milk production 7. Milk release during nursing, and uterine contraction during delivery of a baby 8. Electrolyte balance and blood pressure.
Pineal	Next to the base of the brain	Melatonin	24-hour biological rhythms of sleep, wakefulness and activity.
Thyroid	Both sides of the lower throat	1. Thyroid hormones 2. Calcitonin	1. Metabolism 2. Calcium balance.
Parathyroid	Adjacent to the thyroid gland	Parathyroid hormone	Calcium balance
Hypothalamus	Base of brain	1. GHRH 2. TRH 3. CRH 4. GnRH 5. Dopamine	1. Growth 2. Metabolism 3. Stress and immune responses 4. Reproduction 5. Lactation (dopamine is the prolactin-inhibiting hormone).
Pancreas	Abdomen	1. Insulin 2. Glucagon	1 & 2. Blood sugar and other nutrient regulation.
Adrenal	Above the kidney	1. Glucocorticoids (cortisol) 2. Mineralocorticoids (aldosterone) 3. Sex steroids (DHEA and others)	1. Stress and immune responses 2. Blood pressure and water balance 3. Growth of muscle and bone.
Ovary (female)	Abdomen	Sex steroids, especially estrogens and progesterone	Reproduction in females
Testis (male)	Scrotum	Sex steroids, especially androgens (testosterone)	Reproduction in males

The numbers of hormones in the third column, "Major hormone(s) secreted by the gland," corresponds to the numbers in the fourth column, "General effects," describing the functions of these hormones. Abbreviations: ACTH: adrenocorticotropic hormone; CRH: corticotropin-releasing hormone; DHEA: dehydroepiandrosterone; FSH: follicle-stimulating hormone; GHRH: growth hormone-releasing hormone; GnRH: gonadotropin-releasing hormone; LH: luteinizing hormone; TRH: thyrotropin-releasing hormone; TSH: thyroid-stimulating hormone.

II. WHAT ARE EDCs, HOW ARE THEY USED, AND WHERE ARE THEY FOUND?

EDCs were recently 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" (5). There are over 85,000 manufactured chemicals, of which thousands may be EDCs. A short list of representative EDCs and their applications is provided in Table 2. There are dozens of other processes and products that include EDCs, too numerous to include in this table.

TABLE 2. SOME KNOWN EDCS AND THEIR USES

Category/Use	Example EDCs
Pesticides	DDT, chlorpyrifos, atrazine, 2,4-D, glyphosate
Children's products	Lead, phthalates, cadmium
Food contact materials	BPA, phthalates, phenol
Electronics and Building materials	Brominated flame retardants, PCBs
Personal care products, medical tubing	Phthalates
Antibacterials	Triclosan
Textiles, clothing	Perfluorochemicals

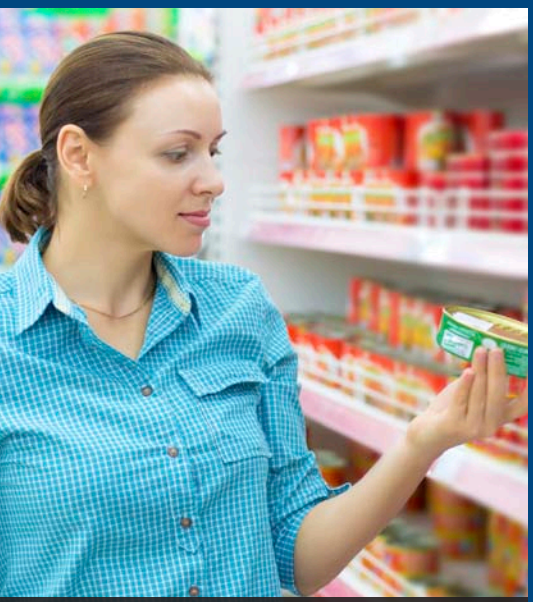
Abbreviations: BPA: bisphenol A; 2,4-D: 2,4-dichlorophenoxyacetic acid; DDT: dichlorodiphenyltrichloroethane; PCBs: polychlorinated biphenyls

People and animals come into contact with EDCs by a variety of routes (Table 3), including consumption of food and water, through the skin, by inhalation, and by transfer from mother to fetus (across the placenta) or mother to infant (via lactation) if a woman has EDCs in her body.

WHERE YOU CAN FIND EDCs

PESTICIDES

CHILDREN'S PRODUCTS



FOOD CONTACT MATERIALS

ELECTRONICS AND
BUILDING MATERIALS

TABLE 3. EXAMPLES OF EDC ROUTES OF EXPOSURES IN HUMANS

How we are exposed to EDCs	Where the EDCs come from	EDC example(s)
Oral consumption of contaminated food or water	Industrial waste or pesticides contaminating soil or groundwater	PCBs, dioxins, perfluorinated compounds, DDT
Oral consumption of contaminated food or water	Leaching of chemicals from food or beverage containers; pesticide residues in food or beverage	BPA, phthalates, chlorpyrifos, DDT
Contact with skin and/or inhalation	Household furniture treated with flame retardants	BFRs
Contact with skin and/or inhalation	Pesticides used in agriculture, homes, or for public disease vector control	DDT, chlorpyrifos, vinclozolin, pyrethroids
Intravenous	Intravenous tubing	Phthalates
Application to skin	Some cosmetics, personal care products, anti-bacterials, sunscreens, medications	Phthalates, triclosan, Parabens, insect repellants
Biological transfer from placenta	Maternal body burden due to prior/current exposures	Numerous EDCs can cross the placenta
Biological transfer from mother's milk	Maternal body burden due to prior/current exposures	Numerous EDCs are detected in milk

Abbreviations: BFR: brominated flame retardant; BPA: bisphenol A; PCBs: polychlorinated biphenyls

To understand how EDCs perturb the endocrine system, it is necessary to have some basic understanding of how natural hormones work in the body. The chemical composition and three-dimensional shape of each endocrine hormone is unique. Every hormone in turn has a corresponding receptor (or receptors) localized on the target cells. A receptor's shape is complementary to its hormone, similar to the way in which one key (hormone) is specific to a lock (receptor). The response of a given tissue or organ to a hormone is determined by the presence of receptors on target cells and receptor activation by hormone binding. The ability of a hormone to activate its receptor depends upon several factors, including how much hormone is synthesized and released by the endocrine gland, how it is transported through the circulation, how much reaches the target organ, and how potently and for how long the hormone can activate its receptor. These properties

are fundamental to normal hormonal signalling. EDCs can interfere with any – and all – of these steps.

EDCs often disrupt endocrine systems by mimicking or blocking a natural hormone. In the case of hormone mimics, an EDC can "trick" that hormone's receptor into thinking that the EDC is the hormone, and this can inappropriately activate the receptor and trigger processes normally activated only by a natural hormone. In the case of hormone blockers, an EDC can bind to a hormone's receptor, but in this case, the receptor is blocked and cannot be activated, even if the natural hormone is present.

The best known example is endocrine disruption of estrogenic hormones, which act upon the body's estrogen receptors (ERs). In both males and females, ERs are present in many cells in the brain, in bone, in vascular tissues, and in reproductive tissues. While estrogens are best understood for their roles in female reproduction, they are important for male reproduction, and are also involved in neurobiological functions, bone development and maintenance, cardiovascular functions, and many other functions. Natural estrogens exert these actions, after being released from the gonad (ovary-female or testis-male), by binding to ERs in the target tissues.

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

3. IMPACTS OF EDCs

I. HISTORICAL PERSPECTIVE ON EDCs

Since 1940 there has been an exponential increase in the number, and abundance, of manufactured chemicals, some of which have been released (intentionally or not) into the environment. This chemical revolution has irreversibly changed ecosystems in a manner that has had severe impacts on wildlife and human health. Rachel Carson's book *Silent Spring*, published in 1962, was the first public warning that environmental contamination, in particular the pesticide DDT, might be responsible for the reduced numbers of birds due to reproductive failure caused by this and other toxic chemicals.

However, whether chemical exposures caused toxicity in humans was unclear, with the exception of massive chemical spills or contamination. In addition, although it is now well-accepted 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 exposure. 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 malformations. Clearly, the fetus was vulnerable to pharmaceuticals given to the mother. The second breakthrough discovery was that of diesthylstilbestrol (DES) given to pregnant women to avert miscarriage. DES is similar in its properties to natural estrogen hormones. Girls who had been exposed to DES in the womb often had reproductive tract malformations and some developed rare reproductive cancers in adolescence that were normally only seen in postmenopausal women (6). 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 with DES as fetuses also demonstrated reproductive disorders in the offspring as they matured to adulthood. This cause-and-effect relationship between fetal DES, reproductive tract malformations, and cancer later in life in girls was tied together to experimental DES effects in mice, and the field of endocrine disruption was born.

Meanwhile, wild American alligators in Florida exposed to dicofol, an organochlorine pesticide chemically related to DDT, exhibited genital and reproductive malformations. The discovery of deformed frogs in Minnesota (US) by school children on a nature field trip further illuminated the problem of chronic pollution by agricultural runoff. Many other examples of associations between these and other EDCs have since been confirmed in wildlife of every class (7).

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.

Not surprisingly, chemical contamination of the environment has been proven to affect humans and further discussion of this will be provided below. But the most direct evidence for cause and effect came from several large-scale disasters in which humans were exposed to varying amounts of chemicals, including both high levels, which were acutely toxic, and lower levels, which have now been shown to cause more chronic, subtle, and long-lasting 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 school-children 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 remain to be seen, although there is evidence of estrogenicity from studies on mice and fish (8, 9). Another common route of human exposure is in agriculture with the routine seasonal spraying of crops with pesticides. This established practice can create a body burden that affects exposed workers, nearby residents, consumers of the food, and even future generations, as described below.

II. EDC EXPOSURES TO THE INDIVIDUAL, AND TO FUTURE GENERATIONS

Exposure to environmental chemicals is life-long. Animals and humans living in contaminated environments carry personal body burdens – the amount of chemicals contained in an individual's tissues – from direct exposure accumulated throughout their lives. Some of these EDCs 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. These measurements reflect contact with EDCs through food, water, skin absorption, and from the atmosphere. Fat is a particularly important reservoir for EDCs, as these chemicals' compositions tend to make them fat-soluble. In addition, measures of EDC body burdens reflect not only contemporary contact with EDCs; they also include past exposures, sometimes decades ago, to persistent chemicals such as PCBs and others. Beyond an individual's own lifetime of exposures is the inheritance of exposures to EDCs from his/her ancestors. For example, during pregnancy, some of the chemicals stored in a woman's body fat may cross the placenta and affect her developing embryo. Some EDCs are detectable in breast milk and can be passed to the suckling infant. In addition, there is now evidence that EDCs induce changes to germ cells – precursors to sperm and egg cells – making their effects heritable not just to one's own children, but also to grandchildren, great-grandchildren, and beyond. In other words, children can inherit the negative consequences induced by the exposures of their ancestors. This is very important, because it underscores the point that the introduction of a chemical into the environment, if it affects the germ cells, will be inherited long after the chemical is cleaned up or breaks down.

III. EDCs AND ENDOCRINE DISEASE

It has been estimated that, globally, upwards of 24% of human diseases and disorders are attributable to environmental factors (10) and that the environment plays a role in 80% of the most deadly diseases, including cancer and respiratory and cardiovascular diseases (11). Because perturbation of the endocrine system is fundamental to the most prevalent of these diseases, EDCs may be primary contributors. The incidence of endocrine-associated pediatric disorders, including male reproductive problems (cryptorchidism, hypospadias, testicular cancer), early female puberty, leukemia, brain cancer, and neurobehavioral disorders, have all risen rapidly over the past 20 years. The prevalence of developmental disability in US children increased from 12.84% to 15.04% between 1997-2008 (12). The preterm birth rate in the US, UK 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.

The increased endocrine disease rates parallels increased production of manufactured chemicals. Global production of plastics grew from 50 million tons in the mid-1970s to nearly 300 million tons today. Similar trends hold for other chemical sources including pesticides, fire retardants, solvents, and surfactants. Sales for the global chemical industry have sharply increased from USD$171 billion in 1970 to over USD$4 trillion in 2013 (13). These and other chemicals such as PCBs, BPA, and phthalates, are detectable in human serum, fat, and umbilical cord blood (14-16).

THE PRETERM BIRTH RATE IN THE US, UK 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.

While associations between increased human chemical exposures and increased disease rates are suggestive they do not 'prove' that the two are linked. Data from cell-based studies, animal studies, and other experimental systems over the past few decades, however, have provided a wealth of evidence supporting this direct link. 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 be unethical and impossible for testing the impact of toxicants on humans. Conclusions about EDC-related health effects, therefore, have to be made using data from epidemiology studies, which can only reveal associations, and by making inferences about human risk from experimental data obtained from animals or cell-based models. An additional challenge is that humans are exposed to a complex mixture of chemicals across the lifespan, making it difficult to establish if health effects result from exposure to a few problematic chemicals or a collective combination of chemicals. Thus, although environmental exposures are recognized to contribute to endocrine-related disorders, finding a 'smoking gun' linking any specific EDC to any specific disease is difficult.

In many ways, the present debate about EDCs parallels the long and contentious debate surrounding the risks of smoking. Tobacco smoke was first shown to cause lung cancer in 1950, but debate about this link and how to regulate tobacco raged for decades, with executives from the biggest tobacco companies famously testifying before the US Congress in 1994 that the evidence showing cigarette smoking

CHILDHOOD NEUROPSYCHIATRIC DISORDERS INCLUDE DEPRESSION, MOOD DISORDERS, LEARNING DISABILITIES, EXECUTIVE FUNCTION DEFICITS, AND CONDUCT DISORDERS.

caused diseases such as cancer and heart disease was inconclusive. Today smoking remains the single biggest cause of cancer in the world and kills one person every 15 minutes (17). For EDCs the available data linking chemicals or a class of chemicals to chronic disease is, in some cases, comparable in strength and breadth to the evidence linking smoking with lung cancer. Thus, despite the insistence by some groups that the evidence is inconclusive, the body of data revealing EDC-related health effects is sufficient to warrant concern that EDCs adversely impact public health.

NEUROLOGICAL AND BEHAVIORAL DISORDERS

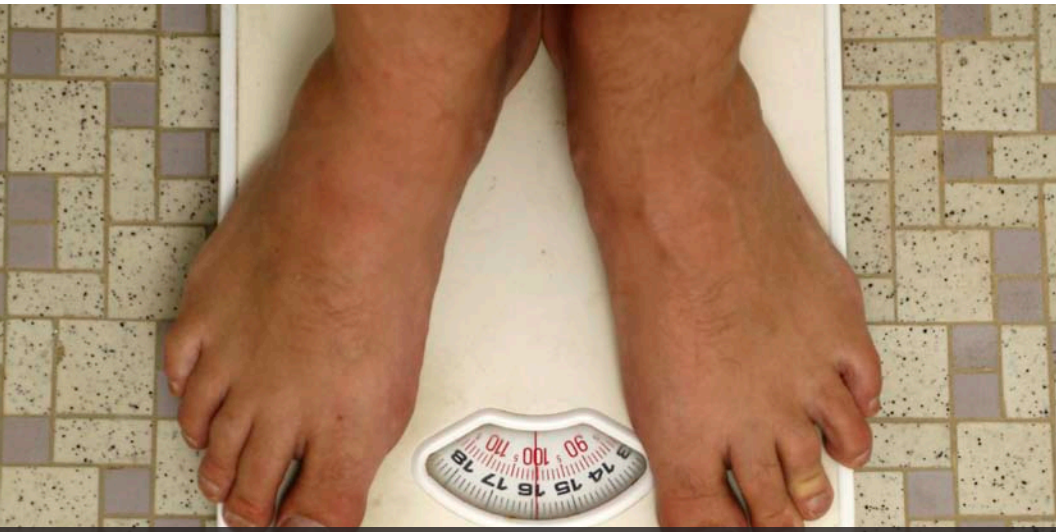
Numerous public health agencies including the World Health Organization, the United Nations, and the National Toxicology Program in the US have expressed concern about EDC effects on the brain and behavior (18, 19). Childhood neuropsychiatric disorders are increasing in prevalence with as many as 1 in 6 children in the US now diagnosed with at least one (12). These disorders include attention deficit hyperactivity disorder (ADHD) and Autism Spectrum Disorder (ASD), as well as depression and other mood disorders, learning disabilities, executive function deficits, and conduct disorders.

As a class, PCBs have the strongest and longest-known associations with neurological disorders. In humans, there is evidence for impaired neurodevelopment (20, 21), lower IQ, and problems with attention, memory, and fine motor skills such as writing. Some of these studies were completed in communities living near the Arctic, a place long thought to be pristine but now known to bioconcentrate PCBs and other persistent pollutants to some of the highest levels on the planet (22). Some PCB metabolites alter thyroid activity, long recognized to elevate risk of impaired neural development. Similarly, polybrominated diphenyl ethers (PBDEs) are associated with reduced IQ, and other cognitive deficits (23). PBDEs affect neurotransmitter activity, synaptic organization, and neuron viability suggesting

that they impact not only brain development but also brain aging. Links have been reported between pesticide exposures and neurodegenerative disorders such as Parkinson's Disease (24) and with depressive behaviors (25). Brominated flame retardants, perfluorinated compounds, and pesticides (organophosphates such as chlorpyrifos and organochlorines), are linked to ADHD, ASD, and related learning disabilities (26), but the evidence remains inconclusive. Experimental animal data show numerous neurobiological changes caused by EDCs, including neuronal development, properties of synaptic organization, neurotransmitter synthesis and release, and structural organizational effects on the developing brain. In conjunction with a growing literature on behavioral effects of EDC exposures, especially during development, these studies underscore the brain as a vulnerable target of EDCs (27).

OBESITY, METABOLIC DYSFUNCTION AND RELATED DISORDERS

Obesity rates are rising rapidly globally. While lifestyle factors such as diet and activity level are clearly primary contributors, accumulating evidence suggests that other factors, including chemical exposures, may also be playing a role. Chemicals referred to as "obesogens" are thought to enhance weight gain by altering or



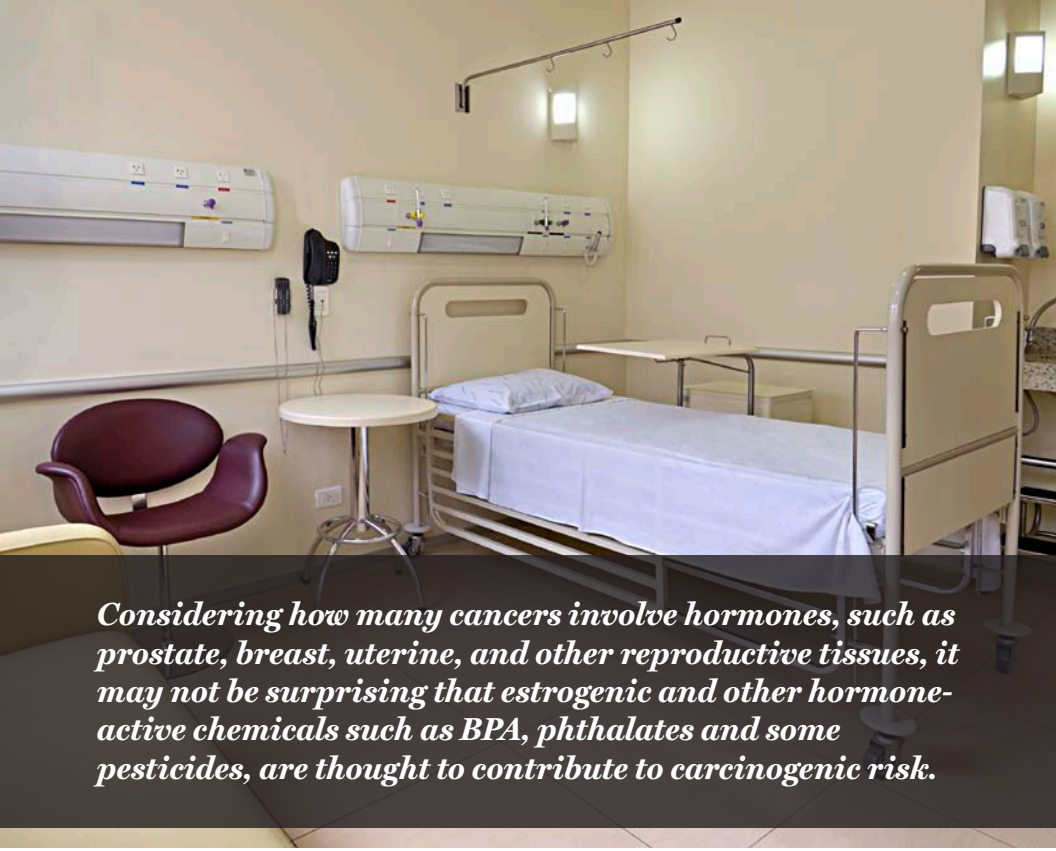
Chemicals referred to as "obesogens" are thought to enhance weight gain by altering or reprogramming key parts of the endocrine system governing metabolism, energy balance, and appetite, resulting in obesity and its related adverse health outcomes.

reprogramming key parts of the endocrine system governing metabolism, energy balance, and appetite, resulting in obesity and its related adverse health outcomes (28-31). Laboratory animal work shows that developmental exposure is particularly effective in predisposing an individual to weight gain and subsequent related adverse health outcomes including type-2 diabetes, cardiovascular disease, altered lipid metabolism and altered glucose sensitivity (32-34).

The most well studied obesogenic EDCs to date are tributyltin (TBT) and triphenyltin (TPT) (30); these and other chemicals act through hormone receptors called PPARγ (34). Disruption of thyroid hormone function is another mechanism by which obesogenic chemicals can act, due to the thyroid gland's important role in normal maintenance of metabolism. Some effects of PCBs and PBDEs may be mediated via the thyroid axis (35, 36). A brominated flame retardant, Firemaster 550, was shown to alter thyroid hormone levels in pregnant rats and their offspring, with the pups growing up to develop obesity, cardiac disease, early puberty and insulin resistance (37). Although that work needs to be repeated and extended, it is noteworthy that Firemaster 550 is now one of the most commonly used fire retardants in the US; it is a ubiquitous contaminant of household dust, and biomonitoring studies have identified Firemaster 550 in human urine (38). Although the field of environmental obesogens is relatively new, phthalates, perfluorinated compounds, BPA, dioxins, and some pesticides are emerging as potential obesogens, meriting further study.

REPRODUCTIVE DISORDERS

Among the strongest associations between EDC exposures and adverse outcomes are those for reproductive development, physiology, and pathology. The increased prevalence over the past 50 years of hormone-sensitive cancers (e.g. breast, prostate), compromised fertility, early puberty, decreased sperm counts, genital malformations, and unbalanced sex ratios (39) are at least partially attributable to increased chemical abundance and exposures. The increase in early puberty in girls, while contributed to by many factors including nutrition, stress, and ethnicity, may in part be due to exposures to estrogenic EDCs (40, 41). Such estrogenic compounds are also associated with uterine fibroids, ovarian dysfunction, and subfertility in humans and in animal models (39, 42, 43). BPA is linked with reduced egg quality and other aspects of egg viability in patients seeking fertility treatment (44, 45) – effects which closely parallel those seen in animal models (46). Danish women under 40 working in the plastics industry were more likely to have sought fertility assistance than unexposed women of the same age (47). In men, sperm counts have declined as much as 50% over the last half century in certain regions (48, 49). Several chemicals, most notably phthalates, are associated with a variety



Considering how many cancers involve hormones, such as prostate, breast, uterine, and other reproductive tissues, it may not be surprising that estrogenic and other hormone-active chemicals such as BPA, phthalates and some pesticides, are thought to contribute to carcinogenic risk.

of adverse effects on the male urogenital tract, including cryptorchidism, hypospadias, prostate disease and testicular cancer (50).

CANCER

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

The list of known chemical carcinogens is long and includes metals, vinyl chloride, benzidine (used in dyes), solvents such as benzene, polycyclic aromatic hydro-

carbons (PAHs), dioxins, fibers and dust (silica, asbestos, etc.), some pesticides including those on the Stockholm Convention's list of Persistent Organic Pollutants, and numerous pharmaceuticals including the synthetic estrogens. Some (although not all) of these chemicals are EDCs. Considering how many cancers involve hormones, such as prostate, breast, uterine, and other reproductive tissues, it may not be surprising that estrogenic and other hormone-active chemicals such as BPA, phthalates and some pesticides, are thought to contribute to carcinogenic risk (51, 52).

The question of which EDCs have the greatest impact, and when in life (prenatal, childhood, adult) EDC exposure most significantly contributes to cancer risk, remain unresolved issues. Studies using cellular and animal models have revealed that early life exposure to chemicals such as BPA, phthalates, perflourinated compounds, PCBs, and some pesticides can heighten cancer risk later in life (52). Emerging epidemiological studies are beginning to establish correlative relationships in humans (53). Establishing such links in humans is difficult because it requires having information about exposures that may have occurred years or even decades earlier. There is no question, however, that based on the critical and broad effects of the environment on cancer prevalence and manifestation, minimizing chemical exposures will have a tremendous positive impact on cancer risk and probability of survival.

OTHER DISEASES AND DISORDERS

Animal work and epidemiological studies in humans indicate that EDC exposure contributes to other health conditions including cardiovascular disease and diabetes. 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, and even autism. The immune and endocrine systems often work together in responding to environmental challenges, and the convergence of their signaling pathways may underlie some of the inflammatory effects.

TABLE 4. TRADITIONAL CONCEPTS IN CHEMICAL TESTING AND WHY THEY ARE INADEQUATE TO DETERMINE ENDOCRINE-DISRUPTING ACTIVITY.

Traditional Approach to Chemical Testing: 'The Dose is the Poison'	**Why this approach is insufficient for Endocrine-Disrupting Chemicals**
Tests individual chemicals one at a time	Every person in the world now carries a body burden of chemicals that did not exist before 1940. Many more are being produced and released into the environment each year. Testing chemicals one at a time can't keep pace with exposure and doesn't take into account how combinations of chemicals within the body are impacting human development or health.
Assumes individual chemicals have a "safe or acceptable" level of exposure below which there are no adverse effects	The endocrine system regulates virtually every aspect of human health from development in the womb, to growth, to reproduction, and overall health. Recent science shows that even very small amounts of these chemicals or mixtures of these chemicals disrupt the endocrine system, reducing intelligence, disrupting reproductive systems, and causing other health problems. There may, in fact, be no safe level, especially when individuals have hundreds of these chemicals in their bodies.
Tests are focused on adult animals	Hormones regulate body systems beginning in the womb and throughout life. Tests conducted only on adult animals can't capture the impact of chemicals on the endocrine system throughout the body's life cycle.
Presumes doses below the amounts which cause test animals to die or develop a target disease (usually cancer) are 'safe'	Endocrine-disrupting chemicals have many impacts beyond death or disease.

4. RECENT ADVANCES IN THE SCIENCE OF EDCs, AND THE NEED FOR A NEW SCIENTIFIC PARADIGM TO EVALUATE EDC RISK

There is widespread, conclusive agreement about the hazards posed by cigarette smoke, lead, radioactive materials, and many chemicals. Decades of laboratory research, together with clinical evidence in individuals and epidemiological data from human populations, have provided conclusive evidence for cause-and-effect links between exposure and disease or death. In the case of chemical assessment and management, the ability to directly link an exposure to an adverse health outcome, or death, can be proven in cases of known exposures to high levels of a particular chemical. For example, the large-scale examples described earlier of industrial contamination (Seveso) and cooking oil (Yusho, Yucheng) resulted in severe birth defects and neurocognitive impairments in children born to women who, while pregnant, consumed the contaminated oil or were directly exposed to dioxins. Thus, traditional toxicological testing has been very important in identifying and characterizing such chemicals that pose a threat to humans and wildlife. However, because most people are exposed to a variety of EDCs, usually at low doses, in mixtures, and at different life stages, the ability to directly relate a disease in adulthood – for example, type 2 diabetes – to exposures to EDCs during life, especially during critical developmental periods, is much more difficult. The following sections describe how a new way of thinking is needed to properly understand effects of EDC exposures and their long-term manifestations as impaired quality of life, chronic disease, and cancers (Table 4). An additional brief summary of these concepts is provided at the end of this section (Box 2).

We now know that direct exposures of an individual to EDCs cause a range of behavioral, endocrine, and neurobiological problems. This requires a paradigm shift in how to conduct risk assessment.

I. THE NEED FOR A PARADIGM SHIFT TO MOVE OUR SCIENTIFIC UNDERSTANDING OF EDCs FORWARD

The Chemical Revolution was accompanied by environmental contamination leading to cancers, heavy metal poisoning, and air and water pollution. This in turn led to the need for testing to create general safety standards. Toxicological testing of pure chemicals at varying dosages successfully flagged certain chemicals in the environment that caused overt toxicity, cancers, and death. Based on information from dose-response curves, efforts were made to determine a threshold below which exposures did not result in any obvious acute toxicity, and to use this information to extrapolate downwards to establish a 'safe' level of exposure. We now know that the type of testing and the range of doses used in standard toxicological risk assessment are often inaccurate when applied to EDCs (54). The 'old science' approach makes several assumptions and is based on testing protocols that are not realistic. For example, most testing is performed in adult animals (e.g.

rats) using acute exposures to a single chemical. However, all humans and animals are exposed to a variety of EDCs in varying levels and mixtures throughout their lives. Thus, while the traditional toxicological methods can be useful, they must be transcended in identifying EDCs and determining their consequences.

Over the last two decades there has been burgeoning scientific evidence based on field research in wildlife species, epidemiological data on humans, and laboratory research with animal models, providing insights into how EDCs cause biological changes, and how that may lead to disease. We now know that direct exposures of an individual to EDCs cause a range of behavioral, endocrine, and neurobiological problems. This requires a paradigm shift in how to conduct risk assessment. For example, rather than the old toxicological method of a single-exposure, dose-response approach using pure compounds, it is vital that new risk assessment procedures simulate more closely what occurs in nature. Rather than single compounds, we need to know the effects of combinations of compounds or mixtures. We also need to recognize that because certain life stages are particularly vulnerable to EDCs, especially early in development, that testing EDCs in adults may not extrapolate to the exposed fetus or infant. We will elaborate upon these concepts below.

II. DEVELOPMENTAL EXPOSURE AND WINDOWS OF VULNERABILITY

Hormones coordinate the development of every individual, from a single fertilized cell to the many millions of specialized cells that make up the blood, bones, brain, and other tissues. These endogenous chemicals, first from the mother, the placenta, and from the developing fetus itself, circulate in very low concentrations, typically in the part-per-trillion to part-per-billion range. Hormones signal when genes need to be active and when to be silent. As complexity builds, the ever-changing mixture of natural hormones ensures normal development; too little or too much leads to disease and pathology. More than a century of biological research has proven that the programming and regulation of life processes require hormones in particular amounts at particular times and, further, that each organ's and tissues' needs change through the life cycle.

Early life, especially the fetus and infant, is a period of vulnerability, when any disruption to natural processes may change, sometimes irreversibly, the structure and/or function of a physiological system. The *timing* of release, in addition to the *amount* of hormone, is absolutely crucial to normal development. It stands to reason, then, that because EDCs interfere with hormone actions, their exposures during a sensitive developmental period can have both immediate as well as more

BOX 1: THE DEVELOPMENTAL ORIGINS OF HEALTH AND DISEASE (DOHAD)

DOHaD, also referred to as the "Fetal basis of adult disease" (FeBAD), is based on scientific evidence that the roots of many diseases and dysfunctions occur very early in life, especially the embryo, fetus, infant, and child. For example, under- or over-nutrition of a pregnant woman has an influence on the fetus's propensity to develop metabolic disorders including obesity, diabetes, and others, later in life. This research has since been extended to environmental influences such as cigarette smoking, pollution, and environmental chemicals. Other evidence has shown that the developing germ cells – precursors to the sperm and egg cells of the fetus – are quite vulnerable to disruptions from even low doses of EDCs. More recently, the nervous system, the development of which begins in early gestation and continues well into childhood, has been found to be very sensitive to EDC exposures. Certain cancers, especially reproductive cancers, seem to have their origins in early life. While the manifestation of disease or disorder may not be apparent at birth, following a latent period the results of these exposures become evident, often in adolescence, adulthood or aging. Thus, DOHaD is a key concept in understanding the influence of EDC exposures during these vulnerable periods.

latent consequences. The timing of exposure is key to understanding which organ or tissue may be affected, as the development of different parts of the body occurs at different rates. Thus, an organ that is developing during the time of the harmful exposure is more likely to be affected than an organ that has already completed development.

The outcomes of exposures during vulnerable periods may be physical malformations, functional defects, or both. Consider again the example of DES given to pregnant women, whose female fetuses often had structural malformations of the reproductive tract, together with an increased propensity for rare vaginocervical carcinomas later in life. Another very real and complex aspect of the windows of vulnerability concept is that the same exposure can have different effects depending on when in development the exposure occurred. For instance, in rodents, first trimester exposure of a fetus to the pesticide chlorpyrifos, a known EDC, can alter thyroid structure and function in the offspring when they become adults, while second trimester exposure to chlorpyrifos can increase insulin levels in the adult offspring.

Some disturbances in hormone levels may not cause obvious structural changes, but may still lead to functional changes, disease, or dysfunction, later in life. This concept of windows of vulnerability is referred to variously as the "Fetal basis of adult disease (FeBAD)" or the "Developmental origins of health and disease (Do-

HAD)" (Box 1). This field is well accepted by researchers who acknowledge that children are more vulnerable than adults to EDCs because their bodies are still developing. Children are also at greater risk of exposures than adults for a number of reasons including that: 1) they are exposed to many fat-soluble contaminants in breast milk or in formula; 2) they put their hands and objects in their mouth far more often than adults; 3) they live and play close to the ground; and 4) they have greater skin area relative to their body weight than adults allowing for more absorption of chemicals (55). The harm of exposures to children is thus due to differences in the ways they may be exposed, their developmental vulnerability, and a longer life expectancy with a much longer horizon for exposure to manifest as disease. Furthermore, they have limited understanding of danger, and are politically powerless to avoid exposures.

While this discussion has focused on the particular vulnerability of the embryo, fetus, infant, and child, every phase of the life cycle, from childhood to adolescence, adulthood, and aging, is sensitive to hormones and EDCs. Traditional toxicological testing invokes the concept that "the dose makes the poison" (Table 4). The new scientific insights of EDCs suggests that "the timing makes the poison" in considering the vulnerability of the developing organism.

III. THRESHOLDS, LOW DOSES, AND THE CONCEPT OF NO SAFE DOSE

The assumption that each chemical has a 'safe or acceptable exposure' has led to the generally accepted dogma that every compound has a threshold, and that exposures to levels below that threshold are safe. The 'old science' paradigm on which this conclusion is based emphasizes a carcinogenic/survival index, tests only single pure compounds, ignores mixture effects, and presumes a threshold dosage below which there is no observed adverse effect (NOAEL). In the tests to determine a safe threshold, different concentrations of a single chemical are administered. Toxicity is usually established in a two-year chronic study in rodents (usually adults) that determines the dosage at which one-half of the animals die or develop the target disease (usually a cancer). From this point studies establish the highest dose that has no observable toxicity (again, the endpoint is usually cancer or organ failure). This dosage in turn is divided by an arbitrary 'safety factor', usually 100. For chemicals that have received little testing, an additional factor of 10 (leading to a safety factor of 1000) might be utilized. The definition of 'safe' is extrapolated from these studies of death and dying despite the fact that other, more subtle effects may be induced even at these lower levels. Without actually looking for perturbations in an endpoint that is not as obvious as death, it is not possible to know if hormone levels are being affected, and whether/how that might change

the predisposition to develop a disease. Considering that the consequences of some endocrine disorders may not be observed for weeks, months, or years, the inability of toxicological testing to quantify such non-observable outcomes is a serious limitation of this approach to determining risk.

The "safe exposure threshold" approach began to be questioned in the 1980s as scientists began to better understand how natural hormones work in the body, how precisely the synthesis and release of hormones is regulated by our endocrine glands and how the body changes during development. (For example, there are periods of life when an individual may normally have no exposure at all to a particular natural hormone, and exposure to an EDC acts upon pathways that would otherwise be completely inactive at that life stage. At these times, even in very low concentrations, any exogenous EDC will exceed the body's natural endogenous hormone levels, which are zero). This led to a call for the development of biologically (vs. hypothetical) based dose-response models that could realistically reflect how the body responds to hormones and chemicals.

The development of accurate risk assessments of safety has been hindered by the cost of biological testing in animals. However, the first, and most important, experiment proving that there can be no threshold for EDCs (56) took place in the 1990s. In the red-eared slider turtle, it is the temperature during the mid-trimester of development that determines whether the individual will develop as a male or a female, similar to how the X and Y chromosome determine sex in humans. With that exception, (sex chromosome vs. temperature), the remaining biological processes of sexual development are remarkably similar between turtles and humans. This makes the turtle a unique biomedical model of sex determination.

Importantly, the effect of temperature can be overcome by application of hormones (57) or EDCs (56, 58) to the embryo. To test whether or not low dosages of hormones or EDCs can alter whether an individual becomes a male or a female, 2400 turtle eggs were exposed to an EDC that mimics estrogen's effects during a key developmental period when sex is determined (56). For example, if estrogen, or an estrogenic EDC such as a PCB, is added to eggs that are incubated at a temperature that normally produces only males, all of the offspring will be females. Further, these females will be sterile when they grow up. Using this model, a key experiment was performed demonstrating that extraordinarily low dosages of hormones or EDCs, given at key developmental periods when sex is determined, can permanently change whether an individual becomes a male or a female (56).

To understand this, recall that estrogen is a natural hormone that affects an organism at very low concentrations. Therefore, any additional exposure to a synthetic

BOX 2: SUMMARY OF GAPS BETWEEN MODERN SCIENCE AND REGULATORY POLICY

Although consensus is building on how exposures to EDCs are relevant to humans, not all controversies have been resolved. One issue revolves around the difficulty in understanding how very low dose exposures are biologically relevant. This concept is easier to understand in the context of development. There are times in life when there is literally no exposure to a natural hormone; thus, any exposure to even minute amounts of hormonally active substances will by definition change target cells that are sensitive to hormones. As basic scientists and clinicians with expertise in endocrinology have become increasingly involved in research and practice on EDCs, the evidence for low-dose effects is growing. Nevertheless, there is still a gap between endocrine science and regulatory policy. It is important that decisions about regulation of chemicals be based on the most modern scientific understanding of how hormones act, and how EDCs perturb these actions.

EDC that mimics estrogen's effects may result in levels that by default exceed the threshold for adverse effects in that organism. To test the traditional toxicological hypothesis of safe levels of exposure, a huge study was performed involving more than 2400 eggs (57). What was found was that even the lowest dose of exogenous estradiol increased the proportion of expected females by more than 10% beyond the temperature control. The most striking feature of these studies is that it represented the first evidence that a threshold dose may not exist when an exogenous EDC mimics an endogenous hormone by acting through the same endogenous mechanism.

The work with turtles is important for two reasons. First, it puts to rest the argument that it is not possible to determine 'no threshold,' as these studies incontrovertibly prove no threshold. Second, the biological processes of development in this species can be directly extrapolated to all other species, including humans. Since the early work in turtles, there have been many studies showing that even extremely low dosages of EDCs can alter biological outcomes and, importantly, that the effects of low doses cannot be predicted by the effects observed at high doses (54).

IV. MIXTURES

In a laboratory the emphasis is on rigorous control of the environment, so that elements can be manipulated and outcomes assessed. For example, some work is conducted in homogeneous cultures of a cell line, grown under identical conditions

from one culture plate to the next. Animal work is conducted in a laboratory with row after row of cages of mice, each genetically identical to the others, with a very specific type of bedding, food, water, light cycle, and controlled temperature. The essence of traditional toxicological methods is the administration of a single, pure chemical in exact dosages, with all other conditions equal to allow comparison of the chemical to a control (placebo) group.

However, the world is not like a laboratory. Humans are genetically unique (other than identical twins); they live in very different environments; they migrate to new environments; each person has his/her own dietary and nutritional exposures, etc. Each person is exposed to mixtures of EDCs at various developmental periods – that is, each person has a unique "exposome," the sum of everything to which he or she is exposed. The 'new science' of EDCs recognizes these realities: that exposure in nature is chronic; that EDCs are ubiquitous and global; and that there is bioaccumulation and biomagnification of EDCs up the food chain. Furthermore, with the exception of occupational exposures, it is rare that environmental exposure involves pure compounds. Instead, exposures involve mixtures of compounds, as well as degradation products of single compounds.

Thus, modern science must include studies on effects of single compounds, but more importantly, their mixtures, to better approximate the additive or synergistic effects of compounds in the body. There is still some controversy as to whether EDCs exhibit synergistic activity. The heat of that debate stems from the fact that a number of EDCs have a lower potency than natural hormones and, when considered individually, these chemicals may exist in the environment in concentrations believed to be too low to be of concern. However, in the absence of a so-called 'safe dose', these low environmental levels may still have biological actions. Much debate in this area has been based on the old science of extrapolating low-dose effects from high-dose experiments, rather than on real life physiology of hormone actions, or the real-world nature of exposures – the modern paradigm shift that is needed in understanding biological actions of EDCs.

5. EXPOSURE OF HUMANS TO EDCs

EDCs are a global and ubiquitous problem. Exposure occurs at home, in the office, on the farm, in the air we breathe, the food we eat, and the water we drink. Of the hundreds of thousands of manufactured chemicals, it is estimated that about 1000 may have endocrine-acting properties. Biomonitoring (measurement of chemicals in body fluids and tissues) show nearly 100% of humans have a chemical body burden. In addition to the known EDCs, there are countless suspected EDCs or chemicals that have never been tested.

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

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

Exposure to EDCs may also be in the form of pesticides, algicides, and other chemicals designed to kill unwanted organisms. Spraying of homes, agricultural crops, and ponds releases airborne and sedimented chemicals that are inhaled, get on skin, and are ingested from sprayed food. It is not surprising that some of these chemicals are EDCs.

DDT and chlorpyrifos, the first banned in many parts of the world but the second still registered in most countries, appears below.

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

The following sections include examples of commonly used EDCs from three categories: pesticides (DDT, chlorpyrifos), products (children's products – inor-

BOX 3: HUMAN HEALTH CONSEQUENCES OF EXPOSURE TO DDTS

- Reduced fertility
- Urogenital birth defects (males)
- Impaired breast feeding
- Type 2 diabetes
- Cancer

ganic lead; electronics – brominated flame retardants), and food contact materials (BPA). These are just a few of the many known sources of EDCs (see Tables 2 and 3). Other categories include personal care products (phthalates, triclosan, mercury, alkylphenol polyethoxylates), textiles and clothing (perfluorochemicals), and building products (high-volume use of brominated flame retardants and chemicals in insulation), among others.

A) PESTICIDES

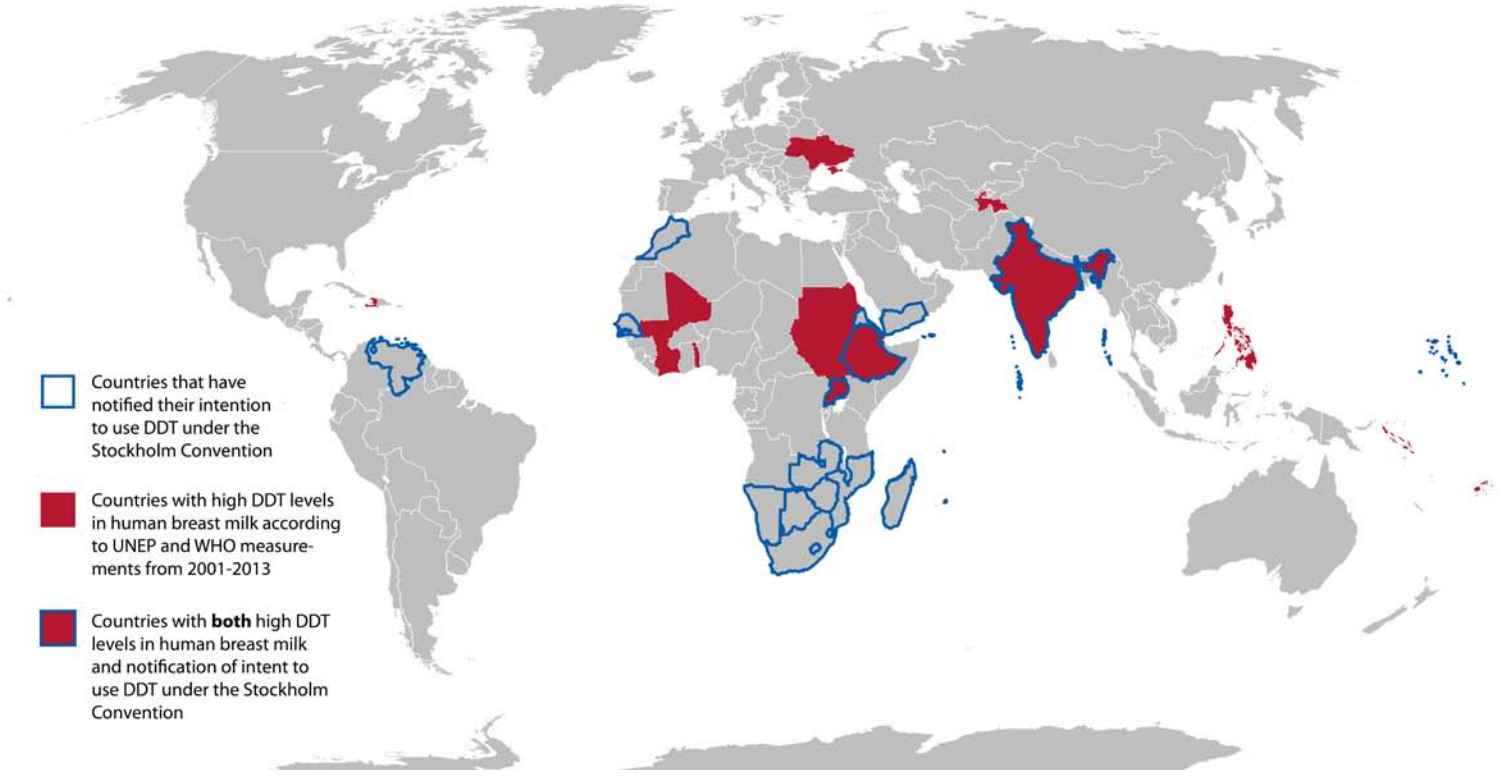
i. DDT

Where it is used

DDT is an organochlorine insecticide that was used extensively worldwide in the 1940s, 1950s and 1960s. Its use included insect control in the commercial and private production of crops and livestock, and in homes, gardens, public places, and institutions. Due to DDT's toxicity to wildlife and its persistence, numerous countries banned DDT use in the 1970s. Despite this, DDT is still used extensively, particularly in India and Africa, for controlling insects that transmit human diseases such as malaria, leishmaniasis, dengue and Chagas disease.

The Stockholm Convention on Persistent Organic Pollutants (POPs), which was adopted in 2001 and is now ratified by 179 countries, was intended to restrict global use of DDT to disease vector control in accordance with WHO guidelines as an Indoor Residual Spray until viable alternatives are available. Although the goal was to reduce and ultimately eliminate all use, global use has not changed significantly since the Stockholm Convention went into effect (59). Moreover, despite the restriction of DDT to its use in vector control only, monitoring reports suggest

FIGURE 2 LEVELS OF DDT IN HUMAN MILK



Data reflects survey results over the period 2001-2013 and current DDT registry information from the Stockholm Convention

illegal agricultural use may still be occurring in some countries such as India, Ethiopia, and Ghana (60-63).

As of December 2013, countries that have notified their intention to use DDT under the Stockholm Convention are Botswana, Eritrea, Ethiopia, India, Madagascar, Marshall Islands, Mauritius, Morocco, Mozambique, Namibia, Senegal, South Africa, Swaziland, Uganda, Venezuela, Yemen, and Zambia*. Myanmar has withdrawn its notification of DDT use, and China has notified discontinuation of production and use†. Ethiopia, India, and Namibia have notified actual or proposed production of DDT‡.

Where people are exposed, evidence of exposure, and where risks are

People who live and work in areas where DDT is being used to control malaria are exposed to DDT and its metabolite DDE (together termed DDTs) in their home and workplace. For instance, South African adults living in homes sprayed with DDT have an average blood DDT concentration of just under 100 ug/g serum lipid, compared to less than 10 μgDDT/g in people living in nearby communities without DDT spraying (64, 65).

The majority of people worldwide are still exposed to DDTs through their food supply. DDTs are stored in animal fats, and consequently the foods that frequently contain the highest levels of DDTs are meat, fish, poultry, eggs, cheese, butter and milk. DDTs remain widespread food contaminants, and the levels can be substantial in areas of continued DDT use and production, as well as past production (66). Due to the longer half-life of DDE than DDT, there may be detectable DDE even if the shorter half-life DDT is no longer detectable (67). As a testament to the public health benefits of banning DDT use, average blood DDE concentration of people in countries with long-time bans is < 1 ug/g serum lipid, compared with serum levels of DDE in people living in dwellings sprayed with DDT (215 μgDDE/g serum lipid (67).

Children have higher levels of DDTs in their bodies than adults living nearby, whether they live in a community actively using DDT (61), or in a country that banned it long ago (67). Exposure can begin in the fetus through placental trans-

* Stockholm Convention ,DDT Register Pursuant to Paragraph 1 of Part II of Annex B of the Stockholm Convention: http://chm.pops.int/Implementation/Exemptions/AcceptablePurposesDDT/tabid/456/Default.aspx

† Stockholm Convention, Withdrawal from the DDT Register http://chm.pops.int/Implementation/Exemptions/AcceptablePurposesDDT/DDTRegisterWithdrawnnotifications/tabid/2684/Default.aspx

‡ Stockholm Convention, DDT Register. See link to Annex B above.

fer, or in a breastfeeding infant (68). According to measurements conducted by the United Nations Environmental Programme and the World Health Organization from 2001- 2013, high DDT levels in human breast milk were found in Ethiopia (2013), Tajikistan (2009), Solomon Islands (2011), India (2009), Haiti (2005), Pacific States (2011), Hong Kong SAR (2002), Mauritius (2009), Mali (2009), Moldova (2009), Togo (2010), Uganda (2009), Fiji (2002), Sudan (2006), Philippines (2002), Ukraine (2001), Djibouti (2011), Côte d'Ivoire (2010), and others (listed from highest level first) (Figure 2). However, breast feeding has very important health benefits to children, including decreased risk of infections, Sudden Infant Death Syndrome, and childhood obesity (69). The World Health Organization recommends women breast-feed their children for at least the first two years of life.

Elderly people also tend to have higher levels of DDTs because the DDTs accumulate throughout life and because exposures in the past tended to be much greater than in the present in many countries. Indeed, age is often the most powerful predictor of levels of DDTs (70). For instance, in a community living near an old DDT manufacturing plant, average adults had 159 ng DDT/ml serum, while the average DDT level in people over 70 years old was 350 ng/ml (66). This raises the possibility that elderly persons, who also have a higher chronic disease burden, may have a greater sensitivity to their DDT burden than younger adults, and this should be kept in mind when working with populations exposed to DDTs.

The persistence of DDTs from prior use, coupled with global migration patterns of humans, both contribute to high levels of DDTs in people even in countries with long-time bans. It takes between four and 10 years for concentrations of DDTs in people to decrease by half (the so-called "half-life" (71)). Hence, while monitoring studies have established that banning DDT succeeds in lowering human exposure, levels of DDTs can remain high in people years later (67). For instance, more than 30 years after DDT was banned in the United States and near the time of the phase-out and ban of DDT in Mexico, agricultural workers who migrated from Mexico had much higher levels of DDTs than typically seen in the US. Further, people living in a US community 10 km from a manufacturing plant site that used to produce DDT also had substantially higher levels of DDTs in their bodies than the general population (66). Thus even countries that do not use DDT should recognize the possibility of higher exposures to DDTs within their population, such as in migrants and in people living in communities that are near sites of previous DDT production.

There is elevated exposure to DDTs in circumpolar countries because these chemicals are semi-volatile and undergo long-range transport, meaning they rise into the air in temperate regions and deposit at the earth's surface in colder regions.

These environmental sources of DDTs accumulate in animals and are amplified up the food chain. In fact, intake of DDTs by Inuit people is comparable to that of people living in regions using DDT to control malaria (72).

Several aspects of climate change predictions indicate that exposure to DDTs will increase over the next decades, although the processes are complex. Climate change is expected to increase the incidence of malaria, potentially leading to increased demand for and use of DDT (73). Melting glaciers contributed 46% of the DDTs entering the Canadian Archipelago, and over 60% of the DDTs entering Canadian subalpine lakes; melting sea ice and permafrost provide further DDT (74, 75). Climate change also increases partitioning of POPs from water and soil to the atmosphere and higher wind speeds increase airborne transport, so deposition in the Arctic is likely to increase again. Because DDTs accumulate at the top of the food chain to levels that are thousands of times higher than at the bottom, and hundreds of thousands fold higher than in the water, it is likely that DDTs released from melting glaciers will increase concentrations of DDTs in people who eat from the Arctic food chain. Additionally, exposure to EDCs has been demonstrated to affect the thyroid hormone system, which due to its role in maintenance of body temperature would likely affect the ability of Arctic wildlife to adapt to climate change (76).

Science on why DDT is an EDC

DDT was one of the first recognized EDCs, with a broad range of effects on reproduction and hormonal systems. It was used indiscriminately as a pesticide for decades, until attention was called to its devastation of entire ecosystems by Rachel Carson in her landmark book, *Silent Spring*. Laboratory animal studies and human observations consistently show associations between DDTs and negative health consequences, making DDTs one of the most widely accepted classes of EDCs. In animals and cell lines, DDTs modify the thyroid, estrogen, androgen, renin-angiotensin, insulin, and neuroendocrine systems. These pathways are involved in normal functioning of reproductive, cardiovascular, and metabolic processes, among others. Some effects of DDTs are as estrogen mimics, and DDTs also interfere with androgen (testosterone) pathways in the body (77). In mammals (including humans), gonads of females (ovaries) and males (testes) make estrogens and androgens, albeit at different levels. Females have higher estrogens and lower androgens, and males have higher androgens and lower estrogens. By disrupting the body's major normal sex hormones individually, and by causing changes in the ratios of sex hormones, DDTs are associated with a plethora of reproductive problems. Numerous studies indicate that high exposure to DDTs reduces male, and possibly female, fertility, including in humans (67). For instance, men living

in homes with indoor DDT spraying have decreased sperm quality (64) that may lead to diminished fertility. There is also some evidence to suggest that exposure to DDTs shorten the lactation period (67). A brief summary of these and other health effects of DDT in humans is provided in Box 3.

Like most EDCs, the health consequences of DDT exposures are most pronounced when exposure occurs in developing fetuses and children. When girls are exposed to DDTs early in life before the breast is fully matured, this is associated with increased risk of breast cancer later in life (78). Several human studies indicate that DDT increases risk of urogenital birth defects such as cryptorchidism (failure of the testes to descend), and a rat study also showed that fetal DDT exposure caused male reproductive abnormalities (67). Evidence that early life exposure to DDTs may contribute to an earlier onset of puberty (menarche) in girls, together with adult studies showing that DDTs are associated with longer menstrual cycles and earlier menopause, suggest that DDT may disrupt the menstrual cycle across life (67). A recent study of rats showed that high doses of DDT to grandparent rats increased obesity of their rat grandchildren (79); though the dose was much higher than found in people, it certainly calls attention to the potential effect that high DDT use worldwide in the middle of last century may be having on the current worldwide obesity epidemic.

Negative Endocrine Health Outcome: Type 2 Diabetes (T2D)

Numerous epidemiological studies have demonstrated a strong positive association between the DDT metabolite DDE and T2D risk (80). These studies came from countries that have banned DDT use for decades, and also from areas contaminated with higher levels of DDTs. The diabetes epidemic continues to grow dramatically in countries where DDT is still in use, such as in South Africa and India (81-83). These documented human associations are corroborated by studies demonstrating that both low prenatal- and high adult- exposure to DDT caused features of T2D in adult rodents (84-86). Indeed experimental studies have shown that DDT increases circulating blood glucose, a hallmark of diabetes, in part by increasing enzymes that make glucose (85). Under normal circumstances, increased glucose levels cause the pancreas to produce insulin, which in turn reduces glucose. Mice exposed to DDT become insulin resistant, a central feature of T2D, because their DDT exposure reduces the normal ability of the pancreas to secrete insulin in response to high glucose (84).

ii. Chlorpyrifos

Where it is used

Organophosphorus pesticides (OPs) are some of the most commonly used insecticides worldwide, and chlorpyrifos is a typical OP. It is used to control household pests such as cockroaches, flies, termites, fire ants, mosquitoes, and lice. Chlorpyrifos is used agriculturally to combat pests on cotton, grain, seed, nut, fruit, wine, and vegetable crops. It is also used in forestry, nurseries, food processing plants, on golf courses, and in water supplies to combat larvae, especially mosquitoes. It has numerous other uses, such as impregnated bags to cover ripening bananas in plantations, in cattle ear tags, and in paint. It is acutely toxic to some species that are beneficial to agriculture, such as earthworms and honeybees.

Where people are exposed, and where risks are

Relative to organochlorine pesticides, chlorpyrifos degrades more rapidly in the environment. However, it can still be persistent, meeting the Stockholm Convention criteria for persistence under some circumstances [e.g. (87-91)]. Its regular use in agriculture and home gardens can cause its accumulation in soil, water, food, and air (92). After residential applications, chlorpyrifos is detected in flooring, furniture, toys, dust, and air (93). In a study of urban apartments, chlorpyrifos lingered on absorbent and soft surfaces for as long as two weeks after application, including areas not directly sprayed (93). Furthermore, all indoor air and dust samples collected in a study of homes and day cares in the United States had chlorpyrifos present, even though the majority had not used pesticides for at least a week (94). In one study, chlorpyrifos was still measured in the air inside houses eight years after it had been applied for termite control (95).

There is some evidence that chlorpyrifos can accumulate up the food chain in certain species, and it has been measured in fish in the Arctic as a result of global transport (87, 96-98). Residues are commonly found in vegetables, fruit, rice, and cereal products in many countries. It is also found in fish, dairy products, drinking water, and even soft drinks in some countries. A survey of chlorpyrifos in pasteurized milk from Mexico found that 8% of milk sampled exceeded the regulatory threshold, a sizable proportion when considering how common milk is among households with children (99).

Biomonitoring/body burden studies (evidence of exposure)

Chlorpyrifos is relatively short lived in people (half is removed from the blood and fat in about 24 and 60 hours, respectively). Instead of accumulating in the body,

There is some evidence that chlorpyrifos can accumulate up the food chain in certain species, and it has been measured in fish in the Arctic as a result of global transport.

chlorpyrifos transforms to metabolites that can also cause harm. Chlorpyrifos and its metabolites have been found in urine, maternal and cord blood, the meconium (first feces) of newborn infants, breast milk, cervical fluid, sperm, and infants' hair (100-105).

Exposure to chlorpyrifos occurs from agricultural and household use, use on livestock and pets, and through residues in food and water. It can result from spray drift, and inhalation of air and dust in vehicles, homes, and childcare centers and other buildings in which it is used. A survey of schoolchildren in Chile found that 80% of them had metabolites of chlorpyrifos in their urine; and this was associated with eating fruits and vegetables (106).

OPs are detectable in nearly all agricultural workers who have been examined, including those from countries where the use of OPs is declining (107). A biomonitoring study conducted in Egypt among agricultural workers who primarily work with chlorpyrifos found that their OP exposure levels varied according to the extent of OP contact within their job duties (107). Elevated levels of chlorpyrifos metabolites have been have been found in the urine of both adults and children involved in banana plantation work and small-scale farming in Nicaragua (108).

The primary route of chlorpyrifos exposure is thought to be through the skin for most occupational chlorpyrifos exposures. However, measurements of chlorpyrifos levels in ambient air breathed by farmers in Tambon Bang Rieng, Thailand, found that farmers were inhaling concentrations up to 0.61 mg/m^3, more than twice the acceptable daily intake for all routes of exposure (109).

Residential use of chlorpyrifos is a major source of exposure to non-agricultural workers and to children. One study of cities in the United States estimated that 140 μgof daily chlorpyrifos exposure comes from food while daily chlorpyrifos exposure from air was 27 times that amount (93). Children are at further risk of chlorpyrifos exposure through air because after chlorpyrifos treatment, its concentrations are greater closer to the floor in the low areas where children breathe compared to the areas where adults breathe (92). Indeed, infants in United States homes treated with chlorpyrifos absorbed approximately 2.7 mg/kg (92), and the urinary metabolites of chlorpyrifos were about 120 ng metabolite/kg body weight per day in children (94). This is appreciably higher than the levels of urinary metabolites of chlorpyrifos found in pregnant women in both the United States and Mexico (average 1.4-1.8 ng/ml, respectively) (110).

Science on why chlorpyrifos is an EDC

Developmental neurotoxicity is the primary adverse health outcome observed in experimental and human observational studies of chlorpyrifos, and these effects

are at least partially caused through cholinesterase- and endocannabinoid- signaling (111). The neurotransmitter acetylcholine is involved in signaling of nerve cells in the brain, and it is metabolized by the enzyme cholinesterase. The endocannabinoid pathways of the brain are also important for neural functions. This is why chlorpyrifos's most potent effects are on the brain. Developmental exposures to chlorpyrifos at levels typically observed in people caused hyperactivity and reduced learning in rodents, the latter associated with changes in thyroid hormone (112, 113). Additional endocrine disruption by chlorpyrifos is suggested by changes in the endocrine adrenal gland weight and structure in rodent experiments.

Cholinergic symptoms, e.g. salivation, urination, defecation, gastrointestinal distress, and vomiting that are caused by nervous system damage, are present in acute chlorpyrifos poisonings of adult people, and nerve damage was observed weeks later. Adult agricultural workers use OP pesticides as mixtures, and workers with moderate OP exposure, inclusive of chlorpyrifos, also have signs of neurotoxicity, such as impaired peripheral nervous system function (114). Two studies of US residents exposed to mixtures of pesticides found that chlorpyrifos was associated with Parkinson's disease (115, 116). Although it is difficult to find human studies that have examined the neurotoxicity effects of chlorpyrifos in isolation from other pesticides, a study of chlorpyrifos applicators found they did not perform as well on neurological tests compared to people with much lower chlorpyrifos exposure (117). They also reported memory problems, fatigue, and loss of muscle strength (117).

Developmental susceptibility appears to be an important risk factor for human neurotoxicity associated with exposure to chlorpyrifos. Indeed the majority of scientific experts on a scientific panel on chlorpyrifos toxicity agreed that chlorpyrifos should be banned from home use due to resulting neurodevelopment defects (92). For example, prenatal and childhood chlorpyrifos exposures are linked to attention deficit hyperactivity disorder, and impaired mental- and motor- skill development in young children (92, 110). Extensive animal studies also support a strong role of chlorpyrifos in causing neurotoxicity during development* (118).

Emerging experimental evidence indicates that developmental exposure to chlorpyrifos also alters the regulation of lipid and glucose metabolism. Developing rats exposed to doses comparable to levels typical in people had elevated cholesterol, triglycerides, and insulin in adulthood (119). These findings raise the possibility that people exposed to chlorpyrifos would have increased risk of type 2 diabetes and cardiovascular disease. To date, this prediction has not yet been evaluated in well-designed human studies.

* http://www.panap.net/sites/default/files/monograph-chlorpyrifos.pdf

Negative Endocrine Health Outcome: Thyroid Disruption

Most studies of chlorpyrifos focus on its nervous system toxicity, but reports on its effects on the thyroid hormone system are emerging, and suggest that chlorpyrifos may be a risk factor for hypothyroidism. A chlorpyrifos metabolite was associated with decreased thyroid stimulating hormone and increased T4 in men in one study (120), and had the opposite association with these thyroid hormones of men in another study (120). Experimental studies in animals also indicate that developmental chlorpyrifos exposure alters the thyroid hormone system (121). Very low prenatal chlorpyrifos exposure, below the level that produces any cholinergic toxicity or behavioral changes, reduced brain thyroxine levels from early life into adulthood in rats (121). This is consistent with several studies in mice demonstrating that developmental chlorpyrifos exposure also decreased circulating thyroid hormones in male and female mice (122, 123). Other actions of chlorpyrifos, including neuroendocrine, estrogenic, and androgenic effects, have been reported.

B) CHEMICALS IN PRODUCTS

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

Consumers have little to no choice in whether or not they are exposed to chemicals in these products, because there is generally not full disclosure about these items' chemical constituents. Some of these chemicals are released into the air and remain in the indoor environment, particularly in poorly ventilated buildings. From the air, some chemicals can settle out into carpets and dust. This is of great concern with infants and children who often pick up and put items from the floor into their mouths, or eat food that has fallen on the floor. Personal care products are applied to skin, and there are also chemicals in toothpastes and antimicrobial soaps that are absorbed or even ingested in small amounts.

BOX 4: PHTHALATES

Phthalates are a class of plasticizers used to soften polyvinyl chloride (PVCs), add fragrance to a product, or enhance pliability in plastics and other products. Phthalates are classified as low molecular weight (3-6 carbon backbone) and high molecular weight (>6 carbon backbone), with the low molecular weight classes thought to pose the most significant health risks. Phthalates act by interfering with androgen (testosterone) production. Because androgens are critical to male development, including genital development, boys are thought to be most vulnerable to exposure. However, androgens also play important roles in females, making phthalates relevant to both sexes. Use of some phthalates has been restricted from toys since 1999 in the EU and 2008 in the US. Phthalates are found in:

- Shampoo, lotion, nail polish and other personal care products;
- Cosmetics;
- Baby products including lotion, shampoo, powders and teethers;
- Toys;
- Scented products such as candles, detergent and air fresheners;
- Automobiles (phthalates are responsible for the 'new car' smell);
- Medical equipment including tubing, blood bags, and plastics in the NICU;
- Building materials including vinyl flooring, wall paper, paint, glue and adhesives;
- Enteric coatings of pharmaceuticals;
- Art supplies including paint, clay, wax and ink.

Phthalate exposure is linked to:

- Genital abnormalities in boys;
- Reduced sperm counts;
- Decreased 'male typical' play in boys;
- Endometriosis;
- Elements of metabolic disruption including obesity.

We will focus here on two representative classes of products: children's products and electronics. For each one we have selected one example: Heavy metals and more specifically lead, in the case of children's products; and brominated flame retardants (BFRs) in the case of electronics. Lead is a widely-accepted toxicant, and lead exposure to children in particular is strongly associated with neurological and cognitive dysfunctions, at lower levels it may also act as an EDC. BFRs are in an assortment of items that come into common contact with humans through computers and other electronics, fabrics, and clothing. There are many other chemicals in these products – such as cadmium and phthalates (Box 4) in children's products, too numerous to mention in this guide.

i. Children's products – Inorganic lead

Where it is used

Lead is a naturally occurring element found in the Earth's crust, and its widespread occurrence in the environment is largely the result of human activity. Majors sources of environmental lead pollution include mining, smelting, refining, and informal recycling of lead; use of leaded petrol (gasoline); production and use of lead-acid batteries and paints; jewelry making, soldering, ceramics, and leaded glass manufacture in informal and cottage (home-based) industries; electronic waste; and use in water pipes and solder. Significant sources of exposure to lead still remain, particularly in developing and transition countries (124). Experiences in developed countries demonstrate that reductions in the use of lead in petrol (gasoline), paint, plumbing, and solder can result in substantial reductions in lead levels in the blood.

Where people are exposed, evidence of exposure, and where risks are

Lead may enter the body via ingestion of contaminated food, water, and house dust; and inhalation of lead-contaminated air. Smoking tobacco may also increase lead exposure. Other important cultural sources of lead exposure include lead-glazed pottery, some traditional medicines, and makeup (e.g. kohl). Blood lead levels reflect current exposure while bone lead levels may be a better marker of long term exposure since lead accumulates in skeletal bone over time, comprising 90-95% of lead burden in adults and 80-95% in children (125). The distribution of lead worldwide is greatest in developing regions, particularly within those countries that still use leaded gasoline. Additional subpopulations that may face elevated risks include children of lower-income families living in degraded housing, communities living in 'hotspots' (such as certain industrial activities), and occupational groups (126). Exposures and risks may also vary by life stage; pregnant

women and young children are particularly at risk from lead toxicity. Bone lead stores are mobilized in pregnancy and lactation for women with prior lead exposure, which is a concern since lead released into maternal blood and breast milk can adversely affect the fetus or newborn (127). Young children represent another vulnerable subpopulation (Box 5) because in children: 1) the intake of lead per unit body weight is higher, 2) more dust may be ingested, 3) lead absorption in the gastrointestinal tract is higher, 4) the blood–brain barrier is not yet fully developed and 5) neurological effects occur at lower exposure levels than in adults (124).

Science on why lead is an EDC

Lead is a toxicant that affects multiple body systems, including the neurological, haematological, gastrointestinal, cardiovascular, and renal systems. Lead exposure is estimated to account for 0.6% of the global burden of disease, due to its adverse effects on mental retardation in children and consequences of elevated blood pressure in adults (128). Chronic, low-level lead exposure also has adverse health effects in children and adults and no blood lead level threshold for these effects has been identified (127).

Although most knowledge on lead focuses on its properties as a heavy metal, lead is also an EDC. It is a known reproductive toxicant (129), and can act on endocrine systems (130). Lead has the ability to activate the estrogen receptor and initiate transcription of estrogen-activated genes; corresponding estrogenic changes have been observed in experimental animal models. Animal models, in vitro studies, and human epidemiological studies, support adverse female reproductive function

BOX 5: LEAD IN CHILDREN'S PRODUCTS

In many countries, an important route of entry for chemicals and metals is through consumer products, especially products aimed at children. More than 100 out of 569 (18%) children's products tested by IPEN (2012) in Armenia, Belarus, Kazakhstan, Kyrgyzstan, Russia, and Ukraine contained lead levels that exceeded local regulation limits for lead in soil. In the Philippines, 15% of 435 children's products tested by IPEN in 2011 contained lead at or above the US regulatory limit. Similar tests by IPEN of 500 children's products in five cities in China in 2011 revealed 48 products (10%) that contained lead at or above the regulatory limit in China and 82 products (16%) that exceeded the 90 ppm regulatory limit for lead content in paint used in the US and Canada (http://www.ipen.org/site/toxics-products-overview).

effects of lead exposure. In humans, lead alters reproductive hormones in peripubertal girls (131) and healthy premenopausal women (132).

Negative Endocrine Health Outcome: Female Reproductive Health

Epidemiologic studies report associations between lead exposure and reproductive health impacts in women across the lifespan (133). Most of these studies examine effects of low-level, chronic exposures in US women. Two cross-sectional studies showed that low-level lead exposure is associated with delayed onset of key pubertal events such as menarche (first menstrual bleeding), breast development, and pubic hair development (134, 135). In a recent study, low-level cumulative lead exposure (measured by bone lead levels) was associated with early menopause among 434 women (136). Two other studies that examined the association between lead exposure and age at menopause found similar results. One was a study among former smelter workers who were found to have earlier menopause compared to community-based controls (137). The second study was a cross-sectional analysis of 1,782 nationally representative US women among whom increased odds of earlier natural menopause was seen with higher blood lead levels (138). The collective evidence on delayed pubertal timing coupled with those on earlier menopause suggests that lead exposure, even at low levels, may shorten women's reproductive lifespan.

ii. Electronics

Where they are used

Polybrominated diphenyl ethers (PBDEs) are persistent organic pollutants (POPs) that have widely been used as flame retardants in consumer products since the 1970s including computers, electronics and electrical equipment, textiles, foam furniture, insulating foams, and other building materials (139). Historically, three different mixtures known as PentaBDE, OctaBDE, and DecaBDE have been commercially available. The predominant use of PentaBDE has been in polyurethane foam within furniture, while OctaBDE and DecaBDE have been used in electronics and other plastic products. In many countries PentaBDE and OctaBDE have been phased out and replaced by other brominated flame retardants, including Firemaster 550, tetrabromobisphenol A (TBBPA) and hexabromocyclododecane (HBCD) (38, 140). Due to their persistent and bioaccumulative properties, and ability to transport long distances, PentaBDE, OctaBDE and HBCD have been added to Annex A of the Stockholm Convention for global elimination (141). DecaBDE is currently under evaluation for addition to the Convention and is still

widely available in developing countries. A brief summary on the recent San Antonio Statement on brominated flame retardants (BFRs) is provided in Box 6.

Where people are exposed, evidence of exposure, and where risks are

BFRs are not chemically bound to products and are therefore released into the environment where they may enter the human body via ingestion and inhalation of contaminated house dust and/or food. Even though PBDE exposures in Europe and the US are declining since they were phased out over a decade ago (142), they remain a public health concern since PBDEs have long elimination half lives in the body (143, 144), may persist in the indoor environment (145), and can biomagnify in the food web (146). Additionally, there may be a slow replacement time for PBDE-containing consumer products in the home. An additional source of PBDE exposure in developing countries is the processing of 20 – 50 million tons of waste primarily in Africa and Asia*.

The listing of PBDEs in the Stockholm Convention includes specific exemptions that allow for recycling and the use in articles of recycled materials containing these chemicals (141). 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). For example, one study of recycled

* http://www.basel.int/Implementation/PartnershipProgramme/PACE/Overview/tabid/3243/Default.aspx

plastics in India found concentrations of Deca-PBDE detected in 50% of samples examined (148). The contamination of recycled plastic products with BFRs also occurs in Europe. For example, a recent study found DecaBDE, TBBPA, and a variety of other flame retardant chemicals in recycled black thermo cups and kitchen utensils on the European market (149).

Sources and routes of exposure can vary by life stage and by individual PBDEs (144, 150). For example, serum concentrations of BDE-47, -99, and -100 (characteristic of PentaBDE)(151) are highly correlated with dust exposures (140, 152). In contrast, BDE-153 [a minor component of PentaBDE and OctaBDE (151)] shows strong correlations with dietary exposures (including breast milk) and less consistent relationships with dust exposures. Children, on average, have three times higher concentrations than adults (153); this is likely due to exposures from breast milk and increased dust intake due to their hand to mouth behaviors and close time on the ground (154).

Exposures in North America are an order of magnitude higher than in Europe and Asia (155). 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

BOX 6: SAN ANTONIO STATEMENT

Nearly 150 scientists from 22 countries have now signed the "San Antonio Statement on Brominated and Chlorinated Flame Retardants" presented at the 30th International Symposium on Halogenated Persistent Organic Pollutants, held in 2010 in San Antonio, Texas. The San Antonio Statement addresses the growing concern in the scientific community about the persistent, bioaccumulative, and toxic properties of brominated and chlorinated organic flame retardants (BFRs and CFRs, respectively) and the exposure to humans and wildlife as a result of intensive use.

The scientist signatories are experts on the health effects and environmental fate of BFRs and CFRs and environmental contaminants in general. The International Panel on Chemical Pollution (IPCP), an international network of scientists working on various aspects of chemical pollution, also has approved the statement.

The statement calls attention to a continuing pattern of substituting one dangerous flame retardant for another, and recommends improved use and disposal of BFRs and CFRs, use of safer alternatives, as well as better labeling and availability of information about BFRs and CFRs in consumer products. Finally it calls for more scientific attention to the actual need for flame retardants in products.

congeners are also found among low-income communities (154) and those occupationally exposed (157). Occupations with higher exposures include firefighting, 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).

Science on why BFRs are EDCs

BFRs are potential EDCs because both the original compounds as well as their break-down metabolites may interfere with the thyroid system. Thyroid hormones (TH) play a critical role in fetal and childhood development (162). In animal studies, PentaBDE mixture as well as their components reduce thyroid hormones in developing and adult rodents, possibly by activating liver enzymes that increase TH clearance from serum (163-165). Metabolites of PBDEs called hydroxylated PBDEs [OH-PBDEs (166)] have more potent actions on the thyroid system, and structural similarities between PBDEs and thyroid hormones enable the chemicals to interact with thyroid hormones-binding proteins (167). In addition, some OH-PBDEs can bind to thyroid and estrogen hormone receptors (168, 169).

Several epidemiological studies find that PBDE exposures during early life are associated with thyroid hormone disruption during early life, and that the developing fetus is particularly vulnerable (170-173). Pregnancy represents a period of increased demand on the thyroid gland. Serum TH levels increase by almost 50 percent during the first trimester (174). TH insufficiency during pregnancy can impair the health of mother and offspring (175). Even modest reductions in maternal thyroid hormone during early pregnancy are associated with long lasting developmental deficits in their children, including reduced IQ (176). Thus, PBDE exposure may impair the function of the thyroid gland of pregnant women, something that could have lifelong effects on the neurobiological health of their offspring.

Negative Endocrine Health Outcome – Adverse neurodevelopmental outcomes

One of the greatest public health concerns of PBDEs is neurodevelopmental toxicity. Experimental, animal, and human studies find that PBDEs can cause neurodevelopmental toxicity both by altering brain development directly and by interfering with thyroid hormone regulation (23). In human studies, prenatal and/or early postnatal exposures to PBDEs are associated with neurodevelopmental harm in children including deficits in concentration, fine motor coordination,

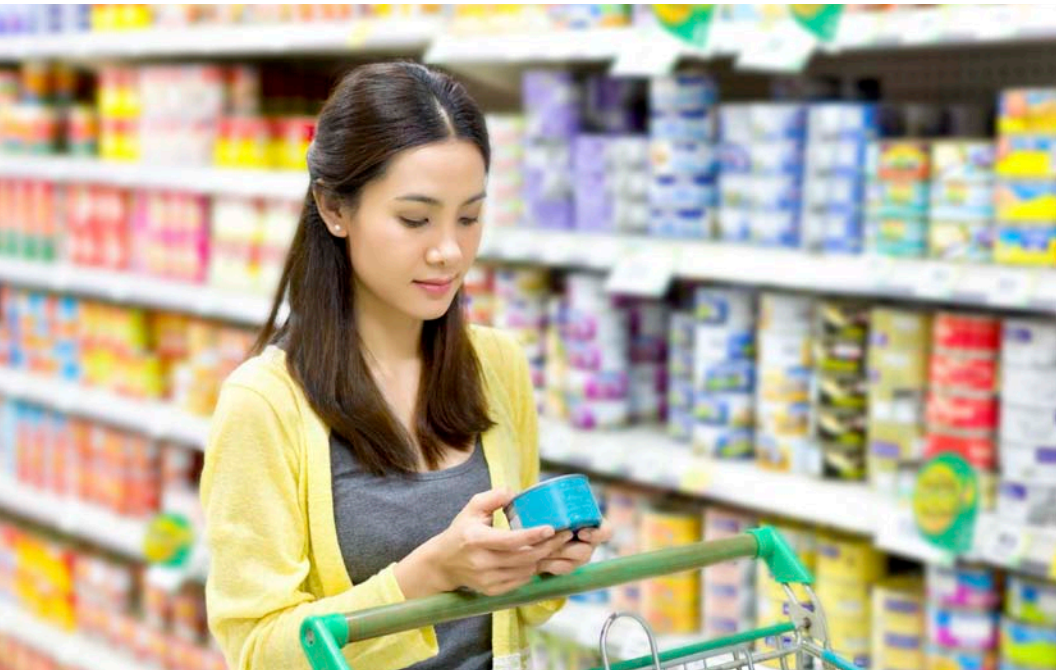
and cognition (177-179). For example, in the largest study to date, Eskenazi et al. (178) examined associations between prenatal and childhood PBDE exposures and neurobehavioral development at 5 and 7 years of age among a Californian migrant farmworker community in the US. They found that a ten-fold increase in both prenatal and childhood PBDE exposures were associated with an average reduction in five IQ points among seven-year-old children. These neurodevelopment effects are similar in magnitude to those observed due to lead and polychlorinated biphenyl ethers (PCBs) during early development.

C) FOOD CONTACT MATERIALS

i. Bisphenol A

Where it is used

BPA is found in a variety of food containers such as hard, rigid plastics, and the epoxy-based linings of canned foods. Until the past few years, most rigid, reusable plastic containers, such as water bottles, were made of polycarbonate and contained BPA. Now, alternative, BPA-free products, made from different materials, are readily available. Because of rising health concerns, use of BPA in some plastic containers, such as baby bottles, is now banned in many countries and being voluntarily reduced or phased out in others. BPA remains a common component of the epoxy resins that line the interior of canned foods such as soup, canned vegetables, and beans. This liner is important because it helps protect the contents from contamination by pathogens, which can cause serious food-borne illnesses such as



BOX 7: BPA IN RUSSIA

In 2010, The Chapaevsk Medical Association (CMA) tested 21 food samples from three Russian cities for levels of BPA, and found that 81% of the samples were contaminated. Canned infant food was found to have some of the highest levels of contamination. Results were shared at several seminars and workshops with physicians, chemists, government officials, industry leaders, and other NGOs. Among other recommendations, CMA suggests continued bio-monitoring in humans (particularly infants) for BPA levels, implementing epidemiological impact studies in the general public, and starting a public information and awareness campaign about the dangers of BPA in foods and consumer products. Source: http://www.ipen.org/project-reports/survey-bisphenol-russian-foods

botulism. Not all can linings contain BPA but it is impossible for the consumer to know which do and which do not. BPA can leach from these linings into the food, thereby exposing consumers. Other common household products containing BPA include polycarbonate eyeglasses, thermal paper receipts, and plastic water pipes.

Where people are exposed, evidence of exposure, and where the risks are

BPA is a high-volume production chemical, and global production is predicted to exceed 5.4 million metric tons by 2015. Exposure appears to be universal (Box 7); the US Centers for Disease Control have estimated that greater than 96% of all Americans have BPA in their bodies (180). BPA has been found in urine, blood, umbilical cord blood and amniotic fluid. Because children are more likely to eat and drink from plastics, spend so much time on the floor, and put so many items in their mouths, exposure levels are typically higher in children than adults. Conversely, people who use fewer plastics, personal care products, and make other lifestyle changes that reduce contact with BPA-containing items have lower body burdens (181, 182).

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

BPA is used in so many products that exposure is thought to be ubiquitous, and nearly continual. Unlike DDT and some other EDCs, BPA is rapidly metabolized and does not bioaccumulate in the body, so reducing exposure can rapidly reduce body burden. Several studies have shown that basic lifestyle changes, such as minimizing the use of canned foods and plastic containers, can rapidly reduce BPA levels in urine and other body fluids (181, 182). Increasing availability of BPA-free plastics and can linings will also likely reduce exposure, but concerns have been raised about the replacement compounds and if they too might be EDCs (183).

Although the introduction of BPA-free food containers to global markets is clearly advantageous for reducing human exposure, BPA remains a high-volume production chemical so alternative sources of exposure remain a significant concern. Environmental contamination is also a persistent problem. Unfortunately, less than 1/3 of all plastic bottles are recycled in the US, so much of it ends up in landfills or aquatic systems. In 2000, BPA was detected in 41% of 139 US streams in 30 states (184) and this trash ultimately ends up in the ocean. Greater than 90% of all ocean trash is plastic, and it can linger there for decades or longer (185). The situation is even worse in developing countries. BPA, leaching from some of this trash, has been detected in seawater and marine species meaning that it will continue to remain a significant environmental contaminant as it will take centuries for all of this plastic trash to weather and degrade.

Science on why BPA is an EDC

BPA is one of the most extensively-studied and well-known EDCs. First synthesized in 1891, BPA was identified as an estrogen mimic in the early 1930's so its endocrine-disrupting properties have been recognized for decades. BPA can interfere with estrogen signaling via several different mechanisms. It can bind to and stimulate estrogen receptors (ERs), albeit more weakly compared to natural estrogens (186, 187). BPA exposure, even low levels, can alter the density of estrogen receptors in tissues such as the brain (188), an effect that consequently alters the sensitivity of that tissue to natural estrogens. Because estrogen plays a critical role in the development of numerous tissues, including the brain, mammary gland, and even the testis, interference with estrogen activity during development can result in permanent changes that affect reproductive functions later in life. For example, early life exposure to BPA alters the density of neurons that produce an important neurotransmitter, dopamine, in a hypothalamic brain region critical to female ovulation and behavior (189, 190). This is one of many examples of effects of BPA on tissues that are sensitive to estrogens. Considering that males and females both produce and respond to natural estrogens, but that there are consider-

able sex differences in these processes, it is not surprising that BPA actions are not identical between the sexes.

A biological molecular mechanism by which BPA acts is through DNA methylation. Every human (except identical twins) has a unique set of genes. Within our bodies, expression of those genes – that is, whether they are activated and lead to expression of a protein within a cell – differs considerably. For example, the genetic material (DNA) is identical between a skin cell and a nerve cell, but the proteins that are produced in these very different tissues are unique for each cell type. It is the *expression* of genes that determines these differences. DNA methylation is the addition of a small chemical group, called a methyl group, to DNA. The amount and location of these methyl groups determines whether a gene is expressed, and levels of expression. Several EDCs, among which there is the most information for BPA, induce such changes in genes. BPA causes DNA methylation changes in neuroendocrine pathways fundamental to reproductive health, energy balance, and behavior, including estrogen-sensitive pathways (46, 191-193). Altered patterns of DNA methylation in key genes related to cell growth may be a potential mechanism explaining why developmental exposure to human-relevant, low levels of BPA heighten risk of uterine and prostate cancer in animal models (194-196). Similar disruptions have also been identified in the liver, brain, and ovary.

BPA was subsequently shown, using a variety of cell-based models, to disrupt the action of other steroid hormones including testosterone and thyroid hormone. In monkeys, BPA blocks the androgen-dependent enhancement of dendritic spines in the hippocampus, an effect which suggests BPA may interfere with neural plasticity (197). Human studies have shown associations between elevated androgen levels with BPA levels in men, women, and infants, an effect which remains poorly explained but may result from altered androgen metabolism, disruption of feedback loops regulating androgen production, or enhanced androgen production by the ovary (198). It has also been observed in vitro that BPA may be 80 times more potent on estrogen related receptor gamma (ERRγ) than classical estrogen receptors (199). Little is known about the functional role of ERRγ but it is highly expressed in fetal brain and placenta, a distribution that supports the concern that the fetus is particularly sensitive to BPA.

Negative Endocrine Heath Outcome: Behavior and Reproductive Health

As of 2014, nearly 100 epidemiological studies have been published associating BPA with human health effects, most notably disorders of reproduction, behavior and energy balance (198). Most support the prevailing concern that developmental exposure has the most profound effects. BPA has been linked with reduced oocyte

quality in women undergoing fertility assistance, including in vitro fertilization (44, 45), effects which are consistent with ovarian effects observed in animal models (200). Evidence from animal models, including non-human primates whose reproductive biology is virtually identical to that of humans, has also shown that developmental BPA exposure compromises ovarian development, uterine structure, and embryo implantation (201-203). Elevated BPA levels have been associated with polycystic ovarian syndrome (PCOS) and elevated androgen levels, a hallmark of this common reproductive disorder of women. Although BPA has been associated with other disorders of female fertility including endometriosis, miscarriage, premature birth, and low birth weight, the evidence is equivocal and the available studies suffer from design weaknesses including small samples sizes and effect sizes. Similarly, in men, BPA has been linked to reduced sperm quality and sexual function following exposure in an occupational setting but there is not sufficient evidence to establish if BPA has similar effects at the doses to which the general public is exposed.

Several agencies including the WHO and the National Toxicology Program have expressed concern regarding the impact of BPA on fetal brain development and behavior. Evidence from numerous animal models has shown that developmental BPA exposure elevates anxiety, aggression, and other behaviors (204), effects which have now been reported in children (205-207). This has led some to hypothesize that BPA may contribute to behavioral disorders such as ADHD and ASD (26, 208). Impacts on brain sexual differentiation and synaptic plasticity have also been observed in animals.

Linkages between BPA and cardiovascular disease and hypertension are fairly robust, documented in numerous epidemiological studies, and are supported by mechanistic studies in animals (198, 209). Importantly, this is an endpoint for which there is strong evidence associating adult (rather than developmental) BPA exposure with disease. Significant correlations have been reported in a range of populations and are consistent across study cohorts, an observation that strengthens confidence in the relationship. Because associations with obesity are tenuous, cardiovascular effects appear to be direct rather than a secondary outcome of increased body weight.

ANNEX I

Resolution on endocrine-disrupting chemicals adopted at the 3rd International Conference on Chemicals Management

The following resolution on EDCs was adopted by consensus agreement of more than 80 governments, along with various intergovernmental organizations, public interest non-governmental organizations, and the industry at the 3rd International Conference on Chemicals Management, held in Nairobi, Kenya, 17–21 September 2012.*

Endocrine-disrupting chemicals

Mindful of the overarching goal of the Plan of Implementation of the World Summit on Sustainable Development, as set out in paragraph 23, of ensuring that by 2020 chemicals are produced and used in ways that minimize significant adverse impacts on the environment and human health,†

Mindful also of the non-binding, voluntary and multi-stakeholder nature of the Strategic Approach to International Chemicals Management, which is aimed at achieving the sound management of chemicals throughout their life-cycles,

Recognizing the potential adverse effects of endocrine disruptors on human health and the environment,

Recognizing also the need to protect humans, and ecosystems and their constituent parts that are especially vulnerable, as set forth in, inter alia, paragraph 14 (b) of the Overarching Policy Strategy of the Strategic Approach,

Considering the particular needs of developing countries and countries with economies in transition,

Recognizing the continuing efforts by Strategic Approach stakeholders, including Governments, intergovernmental organizations and civil society, the scientific

* Resolution III/2: Emerging policy issues; F: Endocrine-disrupting chemicals; 3rd International Conference on Chemicals Management, Nairobi, Kenya, 17–21 September 2012 http://www.saicm.org/images/saicm_documents/iccm/ICCM3/Meeting%20documents/iccm3%2024/K1283429e.pdf

† Report of the World Summit on Sustainable Development, Johannesburg, South Africa, 26 August–4 September 2002 (United Nations publication, Sales No. E.03.II.A.1 and corrigendum), chap. I, resolution 2, annex.

community, public interest non-governmental organizations, trade unions and the health sector,

1. **Agrees** that international cooperation to build awareness and understanding and promote actions on endocrine-disrupting chemicals is an emerging policy issue;

2. **Considers** that information dissemination and awareness-raising on endocrine-disrupting chemicals are particularly relevant and that improving the availability of and access to information on such chemicals is a priority;

3. **Recognizes** the current knowledge gaps on exposure to and the effects of endocrine-disrupting chemicals;

4. **Also recognizes** the current difficulties faced by some countries in mobilizing the resources required to tackle endocrine-disrupting chemicals as an emerging policy issue;

5. **Decides** to implement cooperative actions on endocrine-disrupting chemicals with the overall objective of increasing awareness and understanding among policymakers and other stakeholders;

6. **Invites** the participating organizations of the Inter-Organization Programme for the Sound Management of Chemicals, within their respective mandates as part of their programmes of work, to lead and facilitate the cooperative actions on endocrine-disrupting chemicals in an open, transparent and inclusive manner by building on existing activities of all participants in the Strategic Approach that will:

   (a) Provide up-to-date information and scientific expert advice to relevant stakeholders for the purpose of identifying or recommending potential measures that could contribute to reductions in exposures to or the effects of endocrine-disrupting chemicals, in particular among vulnerable populations, through, inter alia, timely updates to the 2012 report on the state of the science of endocrine-disrupting chemicals, published jointly by the United Nations Environment Programme and the World Health Organization, with particular attention to the needs of developing countries and countries with economies in transition;

   (b) Raise awareness and facilitate science-based information exchange, dissemination and networking on endocrine-disrupting chemicals through, inter alia, activities at all levels and the use of the Strategic Approach clearing house;

(c) Provide international support for activities to build capacities in countries, in particular developing countries and countries with economies in transition, for generating information and for assessing issues related to endocrine-disrupting chemicals in order to support decision-making, including the prioritization of actions to reduce risks;

(d) Facilitate mutual support in research, the development of case studies and advice on translation of research results into control actions;

7. **Also invites** the participating organizations of the Inter-Organization Programme for the Sound Management of Chemicals to develop a plan of work for the cooperative actions on endocrine-disrupting chemicals and in consultation with participants of the Bureau of the Conference, in its development and to publish the plan on the Strategic Approach clearing house website;

8. **Requests** all interested stakeholders and organizations to provide support, including expertise and financial and in-kind resources, on a voluntary basis, for the cooperative actions, including by participating in developing and making available relevant information and guidance;

9. **Invites** the participating organizations of the Inter-Organization Programme for the Sound Management of Chemicals to report on the cooperative actions on endocrine-disrupting chemicals and its achievements and recommendations for further possible cooperative actions for the consideration of the Conference at its fourth session.

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