Endocrine-Disrupting Chemicals and Child Health

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Abstract

While definitions vary, endocrine-disrupting chemicals (EDCs) have two fundamental features: their disruption of hormone function and their contribution to disease and disability. The unique vulnerability of children to low-level EDC exposures has eroded the notion that only the dose makes the thing a poison, requiring a paradigm shift in scientific and policy practice. In this review, we discuss the unique vulnerability of children as early as fetal life and provide an overview of epidemiological studies on programming effects of EDCs on neuronal, metabolic, and immune pathways as well as on endocrine, reproductive, and renal systems. Building on this accumulating evidence, we dispel and address existing myths about the health effects of EDCs with examples from child health research. Finally, we provide a list of effective actions to reduce exposure and subsequent harm that are applicable to individuals, communities, and policy-makers.

INTRODUCTION

While definitions vary, endocrine-disrupting chemicals (EDCs) have two fundamental features: their disruption of hormone function and their contribution to disease and disability. As our understanding of epigenetics and other molecular mechanisms of toxicity has evolved, no longer can this definition be confined to synthetic chemicals that mimic natural hormones and act directly at receptors (1). It is increasingly appreciated that the endocrine system underlies nearly all human biological functions, and the developmental origins of human health and disease (DOHaD) hypothesis recognizes the long latency of EDC effects by programming metabolic and other functions (2).

When the pesticide dichloro-diphenyl-trichloroethane (DDT) and the pharmaceutical diethylstilbestrol were recognized as EDCs, scientists opined that endocrine toxicity was rare and limited to high-dose exposures. Over 1,000 synthetic chemicals are now recognized as EDCs, and this is an underestimate, as regulations do not routinely require testing for endocrine effects, and the few requirements are limited to sex and thyroid hormones. The unique vulnerability of children to low-level EDC exposures has eroded the Paracelsian notion that only the dose makes the thing a poison, requiring a paradigm shift in scientific and policy practice. Subsequent sections describe the biologically based flaws in the Paracelsian paradigm and the human evidence that confirms these flaws. While randomized trials are not widely available, sufficient evidence exists for urgent action by the public to eradicate these exposures to the maximum extent possible.

WHY ARE CHILDREN PARTICULARLY VULNERABLE TO EDC EXPOSURE?

Exposure to environmental hazards during the prenatal period, infancy, and childhood can have profound effects on the health and well-being of an individual. Considerable evidence has accumulated showing that EDCs can cross the placental barrier and reach the developing internal organs of the fetus. Conventionally, it was postulated that only polar chemicals can cross the placental barrier, but recent studies suggest that even larger molecules such as microplastics can cross placenta (3). Detectable concentrations of a wide variety of EDCs, including bisphenols, benzophenones, and parabens, across the maternal–fetal compartments suggest chemical exposures throughout human development (4, 5). Furthermore, neonatal exposures occur through breastfeeding and other external pathways (inhalation, dermal, and ingestion). A wide range of toxicants have been detected in human milk and infant formula (6). The early life stages (from conception to age 2 years) are critical windows of growth and development, characterized by the maturation and epigenetic programming of neuronal, metabolic, and immune pathways as well as endocrine, reproductive, and renal systems (7). These life stages are also sensitive to toxicants due to the immaturity in metabolic enzymes and lower capacity to eliminate toxic compounds, suggesting that metabolism and detoxification are not as efficient in infants and young children as they are in adults.

Higher Exposures in Children Than in Adults

Human exposure studies have shown that infants and toddlers have higher exposure to EDCs than do adults. For example, human biomonitoring studies across ten countries have reported the higher exposure of children to bisphenol A (BPA), some phytoestrogens, perchlorate, polyaromatic hydrocarbons, and benzene metabolites when compared to adults (8). In addition, low metabolic capacity, higher consumption of water and food as well as inhalation rate per unit body mass than that of adults, higher intestinal absorption, and frequent object-to-mouth and hand-to-mouth activities contribute to elevated exposures in children. Children have physiologically
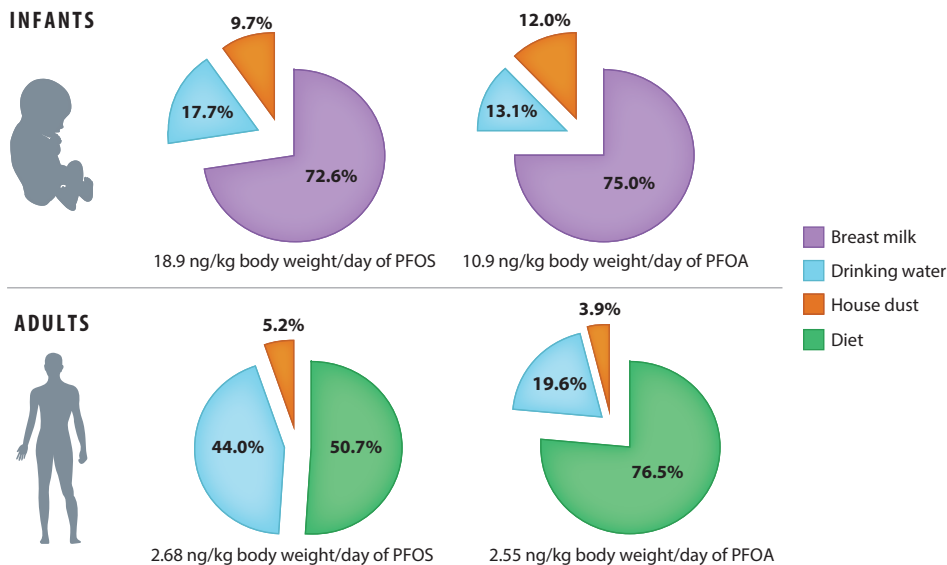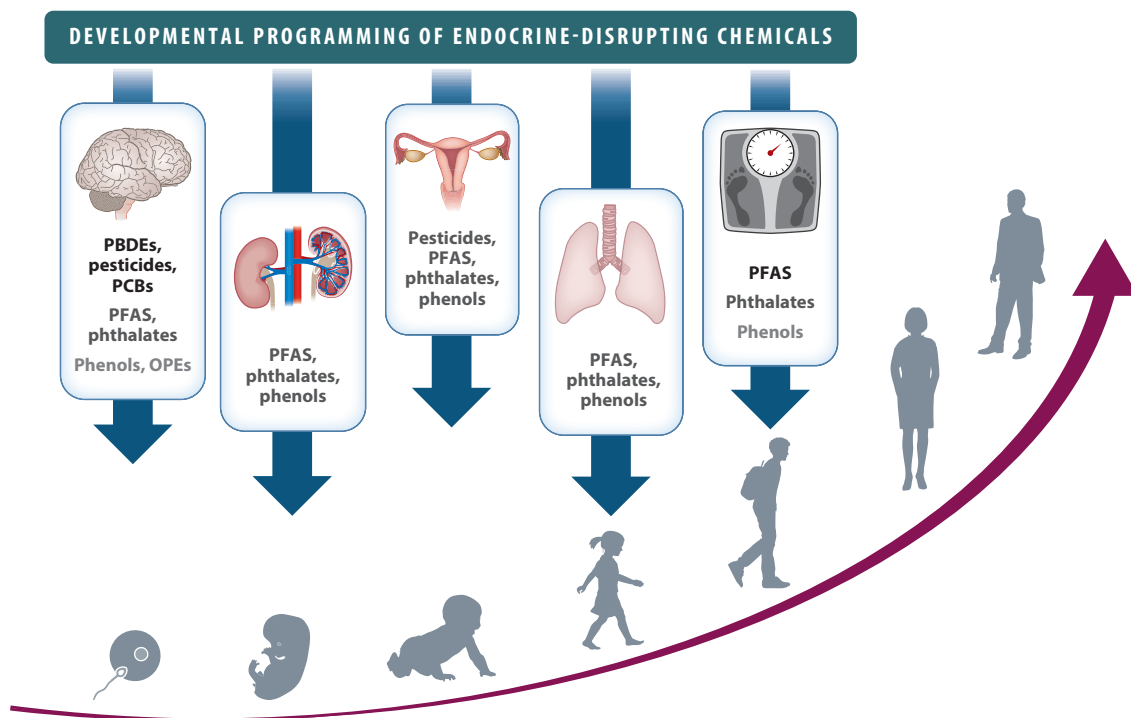
Figure 1

Estimated exposure doses and profiles of perfluorooctane sulfonate (PFOS) and perfluorononanoic acid (PFOA) in infants (6 kg) and adults (70 kg) from the United States. Data from Wu & Kannan (11).

thinner skin than do adults and also have greater skin surface area per unit body weight, which can result in higher dermal permeation and exposure to toxicants. In a study conducted in 2006 that measured serum levels of polybrominated diphenyl ether flame retardants (PBDEs) among family members, children had two- to fivefold-higher concentrations than did the parents (9). The role of indoor dust in contributing to elevated exposure to environmental toxicants in children has been a topic of interest for over a decade (10). The average estimated daily intake of PBDEs was one to two orders of magnitude higher in breastfed infants (86.4 ng/kg body weight/day) than in adults (2.9 ng/kg body weight/day) in the United States (10). Similarly, the estimated average daily intake of two legacy perfluoroalkyl substances (PFASs), perfluorooctane sulfonate (PFOS) and perfluorononanoic acid (PFOA), in infants from the United States was fivefold higher than that calculated for adults (11) (**Figure 1**). The calculated exposure doses for PFOS and PFOA in children were above the European Food Safety Authority's tolerable weekly intake of 4.4 ng/kg body weight/week. In fact, several EDCs of current concern, including phthalates and bisphenols, were shown to have higher exposure doses in children than in adults (12, 13). Other emerging contaminants, such as melamine and cyanuric acid exposures, are several-fold higher in infants and children than in adults (14). The results of exposure doses calculated through the analysis of breast milk, infant formula, or other environmental sources are supported by human biomonitoring data.

Unexpected Sources of Exposure

Elevated exposure in children to many emerging chemicals is due to the fact that these chemicals are used in a variety of consumer products and that the indoor environment, particularly indoor dust, is a sink for these chemicals. Many of the childcare products are often not tested for the presence of toxic substances. Studies have reported leaching of phthalates, bisphenols, and other EDCs marketed in baby teethers from the United States (15). Occurrence of bisphenols, phthalates, parabens, and other emerging EDCs has been reported in baby feeding bottles, infant

DEVELOPMENTAL PROGRAMMING OF ENDOCRINE-DISRUPTING CHEMICALS

PBDEs, pesticides, PCBs

PFAS, phthalates

Phenols, OPEs

PFAS, phthalates, phenols

Pesticides, PFAS, phthalates, phenols

PFAS, phthalates, phenols

PFAS

Phthalates

Phenols

Figure 2

Epidemiological evidence on developmental exposure to endocrine-disrupting chemicals and child health outcomes. Darker text represents stronger evidence. Abbreviations: OPE, organophosphate ester; PBDE, polybrominated diphenyl ether; PCB, polychlorinated biphenyl; PFAS, perfluoroalkyl substance.

clothing, sanitary wipes, and diaper creams (16, 17), products often used by infants and children. Use of cyanuric acid–based salt in swimming pools as a disinfectant stabilizer can result in the high exposure of children swimming in pools (18). Overall, there are myriad childcare products that can contribute to elevated exposure to EDCs in early life stages.

WHAT DOES EPIDEMIOLOGICAL EVIDENCE SHOW ON HEALTH EFFECTS OF EDC EXPOSURE IN CHILDREN?

Due to higher exposure rates in children and the potential harmful effects of exposure during sensitive windows of growth and development, epidemiological studies have addressed the impact on the programming of neuronal, metabolic, and immune pathways as well as on endocrine, reproductive, and renal systems (**Figure 2**). This large body of literature comprises high-quality longitudinal observational studies, and several national and international consortia are underway (19–21).

Neurodevelopmental Outcomes

Thyroid hormone has long been known to be crucial for brain development, and organizational and activational effects of sex hormones are also well established (22, 23). Epigenetic modification of genes encoding brain-derived neurotrophic factor and other proteins can also have implications for cognitive function and other neurobehavioral end points (24). Human studies of PBDEs,

organophosphate (OP) pesticides, and polychlorinated biphenyls, all of which are well known to disrupt thyroid functions, have shown that these compounds produce cognitive dysfunction, precipitating the regulation of these chemicals over the last few decades (25).

Evidence is accumulating for the developmental neurotoxicity of PFASs, as shown with the higher risk of problem behavior in offspring (26–28) and alternations in brain function as observed in magnetic resonance imaging (29), if exposure happens during the fetal period or early life. Inconsistent findings, for example, null or negative associations between higher PFAS exposure and less behavioral problems, which were reported in some studies, may arise from life birth bias and methodological differences (30, 31). Emerging evidence from prospective studies suggests that organophosphate esters (OPEs), plasticizers and replacements for PBDEs, and phthalates, which are estrogenic and antiandrogenic and have thyroid-disrupting properties (32–36), might also influence brain development. For instance, one longitudinal epidemiological study has found lower IQ and impaired working memory in children who were prenatally exposed to OPEs (37). OPEs have structural similarity to OP pesticides that might trigger similar downstream effects in thyroid disruption and oxidative stress (38). Also, two systematic reviews of birth cohort studies examining prenatal phthalate exposure suggest that phthalates are a potential risk factor for neurodevelopmental impairments, that is, in domains of cognition, behavior, and psychomotor development (39, 40). Both reviews raise concerns regarding methodological limitations that remain to be addressed in future studies, including exposure misclassification of nonpersistent chemicals, sex-specific effects, and the effects of chemical mixtures. While sex differences are expected, studies were small, resulting in inconsistent findings in boys and girls, depending on the neurodevelopmental outcomes.

A new paradigm is emerging in which studies of EDC exposure and neurodevelopmental outcomes apply a life course approach and examine exposures beyond the prenatal period that may also be impactful (41). Significant growth and maturation of the adolescent brain is influenced by hormonal changes that can be altered by exogenous chemical exposures (42). As such, informed by developmental neuroscience and toxicology, epidemiological studies have begun to design neurodevelopmental evaluations consistent with sensitive windows of exposure, accounting for embryonic cascades of brain processes, for example, proliferation, differentiation, and migration as well as postnatal pruning, synaptogenesis and network formation, protracted myelination, and maturation of white matter through adolescence.

Obesity and Metabolism

The thrifty phenotype hypothesis first described by Barker et al. (43) suggests that early-life adaptations to poor in utero nutritional conditions can produce a profile of maladaptation ex utero in which the ability to acquire energy results in increased adiposity beginning in childhood and cardiovascular risks later in life. It is now more widely appreciated that a broader array of influences, including EDC exposures, can induce intrauterine growth retardation and developmental metabolic programming, setting the stage for studies of effects on fetal growth as well as long-term effects on body mass, metabolic, and cardiovascular outcomes in later life (44).

Bisphenols are synthetic estrogens (45) that can reprogram mesenchymal cells away from bone to fat (46, 47) and antagonize adiponectin (48). Phthalates influence expression of peroxisome proliferator–activated receptors crucial to lipid and carbohydrate metabolism (49), are oxidative stressors (50), and have estrogenic and antiandrogenic effects in toxicological studies (51, 52). Despite experimental and toxicological evidence, a recent review did not identify the expected consistent relationships of prenatal phthalate and bisphenol exposures with child adiposity as found in epidemiological data (53). For phthalates, some studies did identify positive associations in girls

(54–56), and two others identified increases in adiposity that did not appear to differ by sex (57, 58). Four cohorts also reported childhood adiposity in relation to prenatal exposure to BPA (55, 56, 59, 60). In contrast, PFASs, which are also considered obesogens (61), have been associated with decrements in birth weight (62) as well as increases in child adiposity in multiple birth cohorts, although frequently with sexual dimorphism (63–66). Longer-chain PFASs, that is, PFOA and PFOS, have increasingly been replaced by shorter-chain PFASs such as perfluorobutanesulfonic acid, although evidence from a carefully conducted birth cohort in Shanghai suggests that it is a regrettable substitute and obesogen (67). A meta-analysis of ten cohort studies found an overall 25% increase in childhood overweight and increases in body mass index from PFOA exposure (68).

Possible explanations for the inconsistent findings across the studies of EDCs and childhood obesity include (*a*) limited exposure assessment for nonpersistent chemicals, which introduces exposure imprecision and limits insight into effects that depend on the life stage; (*b*) a lack of fetal growth data to evaluate intrauterine effects; (*c*) the use of body mass index rather than specific measures of fat mass; (*d*) failure to measure specific end-organ changes; and (*e*) their lack of mechanistic insights to unravel complex and sexually dimorphic effects that may be explained by epigenetic variation and metabolic pathway programming. While inconsistencies of human findings (especially for nonpersistent chemicals) suggest a need to improve study designs, policy-makers should heed the warnings of the consistent animal and laboratory evidence rather than dismiss possible contributions.

Immune System and Asthma/Allergy

For centuries, the chief scientific paradigm has been that immunity arises from early-life exposure to viruses, bacteria, parasites, and other threats. Immune malfunctions or disorders are still chiefly thought to be genetically derived (primary) or to arise out of medication use, chronic conditions such as diabetes, or infections such as human immunodeficiency virus. EDCs are increasingly understood to modify immune responses to common infections or antibody response after vaccination, raising the possibility of modifiable risks and their mitigation (69). For example, higher exposure to PFASs has been associated with greater difficulties with common colds, gastroenteritis, and ear infections in children (70–72). In two studies, children with higher in utero and childhood exposure to PFASs were identified to have a lower antibody response to routine childhood immunizations and an increased risk of antibody levels below what is needed for long-term protection (70, 73). A limited number of epidemiological studies have examined the association of EDC exposure with cytokine response in humans and reported that higher prenatal phenol exposure was associated with elevated IL-6 in the circulation of both mother and offspring (74, 75). Differences in associations of maternal and infant cytokine levels with a single versus a mixture of EDCs confirm the importance of a mixture approach, when several EDC exposures commonly occur simultaneously (75).

Experimental data show that EDC exposure is also associated with a disrupted development and imbalance in T helper 1/T helper 2 pathways, leading to the progression of asthma and allergy in children (76). Two groups of EDCs that have been largely studied in relation to allergy and asthma in children are phthalates and phenols (77). Yet, despite extensive evidence from preclinical studies on bisphenols, for example (78), findings of epidemiological studies on the prospective association of phthalates and bisphenols with allergic disease have remained inconclusive, mainly because of heterogeneity in outcome assessments (allergic dermatitis or rhinitis, wheezing, or asthma) and the age of children (too young to manifest symptoms of asthma and allergy) (77). Relying on advanced biomarker assessments for better characterization of immune response, including an array of cytokines and chemokines and various cell types, is now possible with novel

methods, which require a very small amount of the biospecimen. Additionally, a more refined outcome assessment that is developmentally sensitive can be a direction for better understanding the role of EDCs in immune disruption and allergy/asthma in children.

Male Reproductive System

Testicular dysgenesis syndrome refers to a cluster of reproductive disorders of the male fetus, including poor semen quality, congenital reproductive malformations (cryptorchidism or hypospadias), and testicular cancer, that have been defined in experimental settings. Testicular descent and maturation of the male sex organs are mediated by Leydig cells, which produce hormone insulin-like factor 3 (INSL3) (79). EDCs produce estrogenic, antiandrogenic, and steroidogenic enzyme inhibitory effects that disrupt INSL3 function (80). Cryptorchidism, hypospadias, and testicular cancer share several common pathogenetic mechanisms that result from INSL3 dysregulation, and there is suggestive evidence that these conditions, as a whole, are increasing (81–83).

Increasing trends in abnormalities of the male reproductive system together with widespread EDC use in consumer products and experimental evidence on sex hormone disruption have been the basis for several prospective cohort studies that examine the associations of pre- and perinatal exposure to EDCs and male reproductive outcomes. These studies have shown associations of exposure to phthalates, particularly high–molecular weight phthalates such as di(2-ethylhexyl) phthalate (DEHP), diisononyl phthalate (DiNP), and some phenols, with hypospadias and other genital anomalies (84, 85), shorter penile size (86), decreased anogenital distance (85–88), hormonal abnormalities suggesting impairment of Leydig cells (89, 90), and testicular volumes (90). Null associations with anogenital distance or penile size as well as positive associations between higher prenatal phthalate exposure and shorter anogenital distance are also reported (91, 92). These studies faced major limitations in design and sample size. Most prominently, several of these studies relied on assessments of phthalates in maternal or cord serum samples instead of in urine, which is preferred for nonpersistent chemicals (85, 86, 90). Numbers of cases with genital anomalies were also small (84). One study reported associations between maternal prenatal phthalate levels and fetal testicular length, but only in African American boys (93). Evidence remains limited regarding an association of prenatal phthalate or phenol exposures with childhood testicular cancer (94). As prospective studies are moving toward longer follow-up of children prenatally exposed to phthalates, other concerns are emerging, including the potential impact of prenatal phthalate development on the onset and progression of sexual development and puberty (95).

In light of the strong biological plausibility described above, we need longitudinal studies with prenatal recruitment and large sample sizes that allow analysis in males only and the examination of genital anomalies with low prevalence in the general population. These studies are required to apply sensitive methods of exposure assessment and follow up with children through puberty to examine all potential impacts on male reproductive systems in children.

Female Reproductive System

Buck Louis et al. (96) described a similar ovarian dysgenesis syndrome, comprising alterations in ovarian structure and function, endometriosis, fibroids, infertility, and polycystic ovarian syndrome. They provided evidence on the particular role of the developmental exposure to EDCs and in utero hormone disruption. Though the conditions themselves may not fully manifest in childhood, the exposures that induce these effects appear to occur in early life. The prenatal and early-life hormonal environment can also influence mammary gland development and susceptibility to breast cancer (97). Studies identified an increased risk of polycystic ovarian syndrome in association with exposure to BPA and PFASs, reinforced links between phthalates

and endometriosis, and suggested associations of PFASs with endometriosis and of OP pesticides and PFASs with breast cancer (53). In addition, increases in premenopausal breast cancer have been identified in association with levels of DDT found in early postpartum samples in women exposed to DDT before the age of 14 (98). The collective evidence on developmental exposure to EDCs and ovarian dysgenesis syndrome has directed research on the origin of fecundity and chronic diseases in the female population (99). Several EDCs that affect human fecundity are no longer in production, but newer replacements may have similar reproductive consequences, as shown with OPE exposure in women seeking in vitro fertilization (100).

Kidney Structure and Function

Built on the concept of the DOHaD, Brenner et al. (101) conceptualized a framework on developmental programming of the kidney. This framework was grounded on data showing that low birthweight and hypertension cluster with chronic kidney disease in highly affected populations. Most nephrons form by the mid-third trimester, and so prematurity compromises normal kidney development and leads to the birth of infants with a reduced number of functional units (102). Albuminuria and hypertension ensue when oxidative and environmental stressors cumulatively injure the kidney, with the reduced renal parenchyma compromising adaptive responses and increasing the risk of progression to chronic kidney disease.

As such, findings of experimental studies came as no surprise, which showed nephrotoxicity of fetal exposure to EDCs, including BPA, phthalates, and PFASs (103–105). However, the impact of EDC exposure on kidney development and function in children, encompassing diminished glomerular function or development of chronic kidney disease, received attention in epidemiological studies only recently (106). These studies built on mounted evidence that EDCs induce oxidative stress and enzymatic changes and cause DNA damage and direct cytotoxicity in the kidney (107). In observational studies of children with chronic kidney disease, BPA and phthalates were not associated with clinical outcomes but were associated with increased tubular injury and oxidative stress biomarkers (108, 109). In highly exposed children, serum levels of PFOS, PFOA, and perfluorohexanesulfonate were cross-sectionally associated with indicators of kidney function (estimated glomerular filtration rate and serum uric acid) (110–112), but prospective associations were lacking, which suggests that higher serum PFASs are likely a consequence of decreased kidney function rather than the cause. In the general population, most studies performed to date have been cross-sectional and have reported an increase in albumin/creatinine ratio by BPA and DEHP levels, but they had inconsistent findings regarding albuminuria (113–115). Overall, reverse causation limited conclusions from cross-sectional studies of childhood exposure to PFASs, phenols, and phthalates. Moreover, studies that examine developmental effects of fetal exposure to EDCs on kidney, despite biological plausibility, remain sparse (106). Such prospective studies that use standardized biomarkers of kidney function, combine examination of subclinical and clinical renal end points (e.g., fetal kidney development as detected in gestational ultrasound), and apply repeated exposure assessments will address the reverse causation and shed light on proposed mechanisms of action. Investigation of a potential dose-response relationship will also be critical in studies of populations with chronic kidney disease.

New Tools and Technical Challenges in Epidemiological Studies

Major methodological challenges in epidemiological studies of EDC exposure and child health—irrespective of outcomes—include exposure misclassification of nonpersistent chemicals, a single-pollutant rather than a chemical mixture approach, and lack of mechanistic insights. In

the past several years, sensitive methods (e.g., sample pooling) have been developed that use and combine repeatedly collected biospecimens for better characterization of exposure to chemicals with short half-lives in the human body (116). As cohorts simultaneously measure several environmental contaminants, statistical methods are also widely available to address exposure to a mixture of chemicals, built on the fact that different chemical exposures happen simultaneously in real life. The diversity of available methods allows researchers to select the most appropriate methods, depending on the study question and the number of available exposures (117). Using the right matrix for the measurement of exposure biomarkers and selection of the right target tissue, depending on health outcomes of interest, are major considerations, particularly in longitudinal studies on brain influences of EDCs or kidney impairments. Another important consideration is accounting for exposure pathways for environmental contaminants when studying hazardous health effects. An example of that is manganese, an essential element, which can be neurotoxic if inhaled (118). In response to a need for more mechanistic insights, technological advances allow assessments of multi-omics at a low price and in large numbers of individuals, and as such, national and international consortia have applied available tools to address the downstream biological alterations associated with EDC exposure in child health research.

DISPELLING AND ADDRESSING EDC MYTHS

As the evidence builds for the case of EDC effects on children's health, a number of misperceptions continue to be advanced; these myths have prevented swift actions to protect public health. Like many other environmental exposures, including tobacco, asbestos, and lead, building an iron-clad case demonstrating that exposures cause harm requires decades of study, leaving millions of children to be exposed in the meantime.

How Do We Know that EDC Exposures Cause Disease and Dysfunction?

One of the biggest criticisms of environmental epidemiology studies is that they cannot demonstrate empirically that a chemical exposure causes the disease of interest in exposed populations. This has always been a limitation of environmental epidemiology, and many of these same criticisms were lobbed by the tobacco industry when the earliest human studies revealed associations between exposure to cigarette smoke and diseases such as lung cancer and heart disease. Yet today, no one honestly questions that exposure to cigarette smoke causes these diseases (and many others).

Some of the earliest environmental epidemiology studies, relying on a cross-sectional study design, provided evidence that specific EDCs might be associated with harm to health; these initial studies are often easiest to conduct in large populations, but the simultaneous timing of exposure and effect evaluation precludes the establishment of causal relationships. Yet, few studies of EDCs stop with a cross-sectional study design; today, the number of cohort studies evaluating early-life exposures and diseases that manifest months, years, or decades later continues to increase (19–21). This study design, which allows for the temporal relationship between exposure and effect to be more clearly delineated, has helped to build the case that EDCs cause health harm.

Bradford Hill (119) provided his views on how to build a case for a causal relationship between (typically uncontrolled) environmental exposures and disease. His nine principles can be utilized to evaluate and weigh the evidence for EDCs, although some of these viewpoints must be adapted based on the features of EDCs (**Table 1**). One of Bradford Hill's principles that has proven to be helpful to understand the harm from EDCs is the concept of coherence, where effects observed in environmental epidemiology studies are compared to effects observed in controlled laboratory

Table 1 Using the Bradford Hill criteria to evaluate causal relationships for EDCs and child health effects

Viewpoint	Explanation	Consideration for EDCs
Temporality	The cause must be experienced before the effect	EDC exposures should be documented prior to the health outcome; this is not possible in a cross-sectional study design
Strength of association	Associations are more likely to be causal if there is a larger effect size	NA
Reproducibility	Associations are more likely to be causal if they are observed in different populations	Other environmental features (e.g., exposures to other pollutants) might differ between populations, which can confound effects that are observed (or not)
Specificity	Associations are more likely to be causal if they produce more specific effects on a disease	The effects of tobacco on health were dismissed for many years because it was not understood how one exposure could have so many effects; with hormones having such wide-ranging and diverse effects at different stages of development, disruption of hormone action can similarly have wide-ranging and diverse effects
Biological gradient	Greater exposure is expected to be associated with a greater effect	Both hormones and EDCs have been shown to induce nonmonotonic dose responses
Coherence	Associations are more likely to be causal if there are similar responses in epidemiology and laboratory studies	NA
Plausibility	A plausible link between the exposure and the effect increases the likelihood that there is a causal relationship	It is often difficult or impossible to demonstrate mechanisms in humans (individuals or populations)
Experimental evidence	Experimental evidence can support causal relationships; for example, if exposures are decreased due to a temporary shift in environmental conditions, but then exposures return to baseline, if disease follows a similar pattern, this evidence supports a causal relationship	NA
Analogy	Associations are more likely to be causal if similar exposures produce similar effects	For EDC studies, analogous data can be available for chemical classes and/or chemical analogs

Abbreviations: EDC, endocrine-disrupting chemical; NA, not applicable.

experiments. Although controlled exposures to EDCs in human populations are typically not possible, a large body of evidence is now available from laboratory animals, and in many cases the effects observed in rodents are consistent with the diseases evaluated in humans (2).

Are the Effects of EDCs Actually Adverse?

One of the arguments that has been made by industry advocates is that the effects of EDCs are not concerning because they are not adverse. In animal studies, adverse effects are defined by the International Programme on Chemical Safety as "a change in morphology, physiology, growth, development or lifespan of an organism which results in impairment of functional capacity or impairment of capacity to compensate for additional stress or increase in susceptibility to the harmful effects of other environmental influences" (120, p. 46). The ambiguity in this definition, and the

lack of transparency in how this definition is employed, has led environmental health scientists to propose that regulatory agencies should use upstream events, for example, early biological effects that occur in a disease pathway prior to development of the overt disease (121). Other efforts have focused on the addition of these upstream events to standardized toxicity testing protocols used in controlled laboratory experiments (122).

There are some diseases, such as cancer, that are associated with EDCs that are clearly adverse and thus cannot be easily dismissed (123). Other diseases and dysfunctions, such as obesity, have been dismissed as nonadverse by regulatory agencies such as the US Food and Drug Administration (FDA) (124). Presumably, this is because obesity is not a lethal condition, even though it is associated with increased mortality, health-care costs, and risk for other fatal health conditions (including cancer). Still other effects of EDCs have been dismissed because the effects are immeasurable on the level of individuals but significant at the level of populations, such as IQ or anogenital distance, a measure that is directly related to prenatal exposures to antiandrogens and associated with decreased male fertility (91, 125). Finally, many studies of EDCs have shown associations between exposures and markers of disease rather than the frank disease itself. For example, studies relevant to asthma often look at wheeze, a symptom of the condition, and studies examining kidney health evaluate markers of oxidative stress in the blood, an easily accessed measurement indicative of kidney function. Certainly, it should be argued, if an outcome is used by a clinician in the diagnosis of a disease or a determination of disease risk, it should similarly be considered as evidence of an adverse effect when associations are revealed in environmental epidemiology studies. Similarly, if an outcome were to require pharmaceutical treatment or other medical intervention, it should be considered adverse.

Another challenge that has only recently been revealed is the FDA's statements that an effect should be observed in both males and females to be considered adverse (126). Different effects of EDCs have been observed on neurobehavioral and immune measurements in males and females in both human populations and laboratory animals [described in the sections above and elsewhere (127)]. The failure to observe the same effects of EDCs on male and female children is an indefensible reason to dismiss these effects.

How Important Is Timing?

The developmental origins of diseases have become better understood over the last several decades, with increasing numbers of studies demonstrating that disruptions experienced during early development contribute to diseases that manifest later in life (128). The strongest evidence for the DOHaD hypothesis has come from several disciplines, including the fields of nutrition (with many studies from children of the Dutch famine), endocrinology (with many studies examining the health of women exposed to the synthetic estrogenic pharmaceutical diethylstilbestrol in the womb), and radiation biology (with many studies examining cancer outcomes in children exposed to radionucleotides in Chernobyl and in Japanese cities after the dropping of the atomic bombs).

Endocrinologists have especially come to appreciate the divergent roles of hormones depending on the timing of exposure (129). Hormone exposures during adult periods are generally thought to induce activational effects, for example, responses that occur only when the hormone is administered and cease once administration stops. Hormonal contraceptives are consistent with an activational role of hormones, blocking ovulation and implantation during pharmaceutical intake but with fertility returning soon after intake stops. During critical windows of development, however, hormones have organizational effects, for example, exposures during this period induce permanent alterations to cell and tissue differentiation (130). EDCs are similarly expected to have

activational and organizational effects on individuals and on specific tissues and organs; each tissue will have unique periods of vulnerability, depending on the role and timing of endogenous hormones in the development of these organs. For example, even modest changes (∼30%) to circulating maternal thyroid hormone levels for a 3-day period of gestation in the rat are sufficient to induce structural abnormalities in the brains of the offspring; disruptions to maternal thyroid hormone levels during later periods of gestation do not induce these effects, reflecting the critical period for this specific effect (131).

The timing of exposures to EDCs is clearly very important in dictating the effects that are observed. One of the challenges for epidemiology studies, especially when evaluating nonpersistent chemicals, is whether the timing of exposure evaluation is sufficient to evaluate the appropriate critical periods (132). For chemicals with a long half-life (e.g., those that bioaccumulate, where concentrations in fluids and tissues evaluated on one day are highly predictive of concentrations measured within weeks, months, or years), a single time-point is often sufficient to characterize exposures while minimizing exposure mischaracterization. Yet many other chemicals have half-lives of a few hours, and exposures can vary greatly from day to day. For these nonpersistent chemicals, it is likely more appropriate to use multiple biomonitoring samples and a sampling strategy that accounts for the differences in intake across the vulnerable period of interest (116).

If EDC Exposures Are Low, Can They Really Cause Harm?

Perhaps one of the most pervasive myths that has been perpetuated for EDCs is that human exposures to these chemicals are so low that there is no need for concern. Of course, the thousands of environmental epidemiology studies that are now available should dispel this myth; even when exposures are limited to so-called low levels, they are associated with harm, and to suggest otherwise is to dismiss these thousands of studies as spurious (133).

Even the label low dose has been described as a misnomer (129). Where hormones are able to exert potent organizational effects at circulating levels in the parts-per-trillion and low parts-per-billion range, concentrations of many EDCs in human tissues and fluids are in the parts-per-billion and even parts-per-million range (134). Still, in 2017, the National Academies of Sciences, Engineering, and Medicine (NASEM) evaluated whether there was sufficient evidence to support the conclusion that EDCs act at low doses using systematic review methodologies (135). The NASEM panel selected two case studies, the effect of phthalates on male reproductive tract development and the effect of PBDEs on neurodevelopment. With differing levels of confidence for animal and human studies, the NASEM panel concluded that these two EDCs induce adverse effects at low doses, consistent with the conclusions from endocrinologists (136).

One of the biggest challenges for the evaluation and regulation of EDCs is the use of high-dose laboratory animal testing to calculate levels of exposure for human populations that are not thought to cause harm (or not thought to unreasonably increase the risk of harm) (133). Regulatory agencies rely on the results of studies conducted according to internationally recognized test guidelines, which typically evaluate overt signs of toxicity such as alterations to body weight, organ weight, organ histopathology, or hematology measures. They look for administered doses that do not cause these effects in laboratory animals and then divide those no-effect doses by a number ranging from 3 to 1,000 (usually referred to as an adjustment factor) to account for uncertainty and variability. This mathematical manipulation produces a level of exposure that is thought to have minimal hazard; so long as human exposures remain below this threshold, risk is considered acceptable (137). For many EDCs, these approaches have produced no-effect doses in the range of milligrams per kilogram per day and acceptable daily intake doses in the range of micrograms per kilogram per day, yet effects are documented with intake levels below these thresholds.

Clearly, the methods that have been used to identify supposedly safe doses for humans are insufficient for these purposes. One reason may be that the overt signs of toxicity evaluated in animal studies are inappropriate to predict the effects of EDCs on hormone-mediated diseases. Another may be that the premise of a threshold is flawed and that high doses cannot be used to predict effects of lower doses due to the presence of nonmonotonic dose responses.

WHAT ARE EFFECTIVE ACTIONS TO REDUCE EXPOSURE AND HARM?

Considering the high vulnerability of fetuses and children to adverse health effects of EDCs, the question is whether effective actions can reduce exposure and subsequently harm in these populations. Small-scale pilot studies have identified promising interventions to reduce EDC exposures. An organic diet intervention has decreased urinary OP levels in children (138), and adolescent girls have modified personal care product use to lower urinary paraben, phthalate, and phenol levels (139). Other studies have reduced BPA and DEHP exposures through a dietary intervention (140) and lowered PBDEs, PFASs, and OPE flame retardants through household renovation (141). Notably, these interventions were successful in low- and high-income populations, suggesting that the cost of these interventions is not a prohibitive factor at the individual level. Based on these preliminary but promising data, simple steps are proposed to reduce exposure (**Figure 3**).

The social costs of the disease burden due to EDCs is on the order of $340 billion per year in the United States (2.3% of GDP) and €163 billion per year in Europe (1.2% of GDP) (142, 143), suggesting large potential benefits of prevention via policy change. Yet, many of the known sources of EDC exposures remain poorly addressed at the community and systems levels, in public health practice, nationally, and internationally. For example, the FDA has still not banned BPA in aluminum cans, despite a study that estimated that substitution of BPA in aluminum cans with a lining free of health effects could produce as much as fivefold greater benefits ($13.8 billion) than the cost of a naturally derived alternative, oleoresin ($2.2 billion) (144). The failure of this publication and its findings to produce sustained change in policy or public health practice can be attributed

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Safe and simple steps to limit exposure to persistent organic pollutants*

- Use stainless steel or cast iron cookware.
- Replace old furniture that has exposed foam or cover it with a slipcover.
- Outdoor air has lower concentrations of chemicals that accumulate from electronics, carpeting and the like. Recirculating the air a few minutes every day gets rid of chemical residues.
- Vacuum regularly with a HEPA filter and mop with a wet mop to prevent dust from accumulating.

* Including perfluoroalkyl substances and brominated flame retardants

Safe and simple steps to limit exposure to bisphenols and phthalates

- Avoid canned foods.
- Reduce the use of plastics, particularly those intended for single use.
- Don't microwave plastic containers or put them in the dishwasher.
- Avoid plastic bottles with the numbers 3, 6, or 7.
- Do not reuse single-use plastics.
- If plastic food containers are etched, it's time to throw them away.

Figure 3

Safe and simple steps to limit exposure to endocrine-disrupting chemicals.

in part to the absence of a real-life intervention on which the impact of BPA replacement could be modeled. While robust data were available from an intervention study to model decreases in urinary BPA levels (140), the small-scale intervention did not focus solely on the elimination of canned foods but more broadly on the elimination of food packaging. The dietary intervention did substantially reduce urinary BPA levels, yet the researchers prepared the food for the intervention. A real-life behavioral intervention would also need to account for availability and costs of alternative food sources and adherence to the suggested behavioral change outside the home (e.g., meals at work/school), among other factors. A fuller accounting of the impact of a change in manufacturing practices to eliminate BPA from can linings would also need to account for the feasibility of substituting BPA with oleoresin or some other alternative free of health effects. A further barrier is that few large-scale intervention studies have been executed to assess real-life benefits of prevention.

The policy failure on EDCs is evident in the emergence of new chemicals that have been introduced as replacements for chemicals of concern without a regulatory framework that fully evaluates their potential effects on children. Chemically similar bisphenols (e.g., bisphenol S) have replaced BPA (45). OPEs have replaced PBDEs in electronics (145). DiNP, diisodecyl phthalate, and 1,2-cyclohexane dicarboxylic acid diisononyl ester are replacing DEHP in food packaging (146). Neonicotinoids are being used as insecticides, replacing OPs and pyrethroids (147). Short-chain PFASs are increasingly replacing their long-chain analogs (148) and have already been associated with gestational diabetes (149).

A recent review identified four major opportunities for policy-level intervention to prevent EDC exposures: improvements in testing and identifying EDCs, stronger efforts to evaluate effects of exposures, limiting exposures through a hazard-based approach, and establishing an International Agency for Research on EDCs. For testing and identifying EDCs, a two-tiered premarket testing system was proposed to prevent regrettable substitutes and new hazards: a first tier of high-throughput in vitro screening for agonist and antagonist activities of a broad range of receptors, as well as receptor-independent mechanisms, followed by a second tier with more sensitive in vivo assays focusing on end points relevant to human diseases and relevant critical windows. Insofar as a risk-based approach remains the policy paradigm, a broader and stronger human biomonitoring platform is needed, particularly to address gaps in low- and middle-income countries. This platform can also inform educational campaigns about safe and simple steps to limit exposure. Requiring industry disclosure of ingredients is also crucial.

For many EDCs, data are lacking to support using risk-based approaches, hampering other regulatory actions. There is often a lag from identifying new exposures to completing human studies of effects, especially for disease outcomes with longer latencies such as diabetes or cancers. Nonmonotonic exposure-response relationships exist for many EDCs, making it impossible to extrapolate to no adverse effect levels. In addition, while some risk-based approaches try to account for age-related vulnerability, they falsely presume that the population sensitivity can be quantified a priori. Precedents for hazard-based evaluation exist in Europe for persistent and bioaccumulative pollutants—carcinogens as well as EDCs.

There is also an urgent need to establish a new international agency, or to broaden the International Agency for Research on Cancer (IARC)'s scientific charge, to study the effects of endocrine disruption. Established in 1965, IARC was tasked with evaluating the evidence of carcinogenesis due to environmental hazards and has since authored monographs describing mechanistic, animal, and epidemiologic evidence. A recent consensus on the key characteristics of EDCs followed a framework similar to one that has been used by IARC expert panels describing key characteristics of carcinogens (150). The presence of an independent global organization that can bring together diverse experts for collaborative reports on EDCs would foster global movement on regulations

and further support the post-2020 process of the Strategic Approach to International Chemicals Management.

CONCLUSION

EDCs contribute to disease and disability in children, with consistent evidence from laboratory, animal, and epidemiologic studies meeting coherence and other key criteria for causality, particularly for neurodevelopmental diseases and dysfunctions. Preventing these exposures requires individual-level and governmental interventions. A hazard-based approach to regulation would be supported by a strong premarket testing framework and an independent body of scientists that reviews evidence for action.

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