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Exposure to Environmental Endocrine Disruptors and Child Development

John D. Meeker[1]

[1]Department of Environmental Health Sciences, University of Michigan School of Public Health, Ann Arbor, MI

Abstract

Exposure to exogenous chemicals can impact endocrine function at multiple sites and through numerous specific modes of action, which may have far-reaching impacts on human health and development. Widespread human exposure to numerous known or suspected endocrine disrupting chemicals (EDCs) has been documented in the US and worldwide, as have trends for increased rates of endocrine-related diseases and disorders among children. While human epidemiology studies of exposure to EDCs and children's health remain extremely limited, there is a growing body of evidence showing that exposure to a number of chemicals commonly found in consumer goods, personal care products, food, drinking water, and other sources may adversely impact child development through altered endocrine function. This narrative review provides a brief introduction to several common EDCs (with a specific focus on persistent organic pollutants, phthalates, bisphenol A, and contemporary use pesticides, which only represents a small number of all known or suspected EDCs), an overview of the state of the human evidence for adverse impacts of EDCs on child development (fetal growth, early reproductive tract development, pubertal development, neurodevelopment, and obesity), guidance for health care providers based on current knowledge, and recommendations for future research.

1. INTRODUCTION

The development and use of synthetic chemicals has grown exponentially since the 1940s, and there are now greater than 84,000 different chemicals in commerce.[1] While many of these chemicals have allowed for modern conveniences (e.g. plastics) or were developed to address safety (e.g. flame retardants) and other societal needs (e.g. pesticides) to improve our quality of life, recent advances in the fields of exposure science and analytical chemistry have documented widespread exposure to hundreds of these chemicals among men, women and children throughout the world. Depending on the chemical, exposure can occur through food, drinking water, air, soil and house dust, or through direct contact with various household materials or consumer products. Exposures among children are especially of concern since they have contact with potentially contaminated soil and dust; they have frequent hand-to-mouth or object-to-mouth activity; they eat, drink and breathe more per body weight compared to adults; and they are undergoing many rapid changes that are susceptible to even minute doses of environmental stressors.[2] Fetal and infant exposures are also of concern since many chemicals have been shown to pass through the placenta and/or can be passed from mother to infant through breast milk.

Address correspondence to: John Meeker, ScD, Department of Environmental Health Sciences, University of Michigan School of Public Health, 6635 SPH Tower, 109 S. Observatory St., Ann Arbor, MI 48109, Phone: 1-734-764-7184, Fax: 1-734-936-7283, meekerj@umich.edu.

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Numerous high production volume (HPV) chemicals - those produced or imported in the US in quantities of 1 million pounds or more per year (which currently number approximately 3,000) - are known or suspected endocrine disrupting chemicals (EDCs). EDCs can impact endocrine system through a multitude of specific mechanisms which can target different levels of the hypothalamic-pituitary-gonad/thyroid/adrenal axes, ranging from effects on hormone receptors to effects on hormone synthesis, secretion or metabolism; therefore, they can have far-reaching health implications throughout the life course.[3, 4] Transgenerational effects are also possible, as is now being observed in offspring of women who had been exposed to diethylstilbestrol (DES) *in utero* decades ago.[5] The realization that exposure to many environmental EDCs is now ubiquitous, coupled with proven or suggested trends for increased rates of certain endocrine-related diseases and disorders among children, has resulted in growing concern regarding potential links between the two among scientists, governments, physicians, and patients. Several scientific bodies, including the Endocrine Society, now support that EDCs can impact human health.[3] However, human studies investigating possible adverse health effects of EDCs, especially among children, are surprisingly deficient for most EDCs.

This review provides a brief introduction to several common EDCs, an overview of the state of the human evidence for adverse impacts of EDCs on child development, guidance for health care providers based on current knowledge, and recommendations for future research. As an overview, it does not provide indepth information on any of the individual exposures or outcomes introduced, and discusses only a small portion of all known or suspected EDCs. Seminal studies, select examples, and previous review articles focusing on various subtopics are referenced here, and the interested reader is directed toward those for additional detail.

2. Endocrine Disrupting Chemicals

2.1. Persistent Organic Pollutants

Persistent organic pollutants (POPs) are lipophilic chemicals with long half-lives that bioaccumulate up the food chain, and include polychlorinated biphenyls (PCBs), organochlorine pesticides (such as DDT, chlordane, and hexachlorobenzene), polybrominated diphenyl ethers (PBDEs) and other brominated flame retardants (BFRs), among others. PCBs are a class of chemicals that were widely used as transformer and hydraulic fluids, and as additives in paints, oils and building materials.[6] DDT and other organochlorine pesticides were widely used after World War II and were regarded at the time as safe and effective alternatives to arsenic-based pesticides. In response to reports of high concentrations in the environment due to their persistence, effects on wildlife, and the potential to harm human health, PCBs and some of the more heavily used organochlorine pesticides were banned in industrialized nations in the 1970s. The use of DDT still occurs in some developing countries as an effective and affordable method to combat malaria and other vector-borne illnesses. PBDEs and other flame retardants are found in furniture, carpet backing, electronics, and many other consumer products.[6] The use of PBDEs has recently been banned or is currently being phased out in the US and other countries. Due to their environmental ubiquity and persistence, human exposure to POPs can continue for decades after their use ceases. Continued exposures to PCBs and DDT in countries that have banned their use occur primarily through the diet (dairy, meat and higher trophic level fish), though PCB exposure from building materials used in the mid-20th century is also possible. PBDE exposures can also occur through the same dietary sources, though exposure to some congeners may occur to a greater extent through contact with house dust after they have leached from products in the home.

POPs have been associated with a wide range adverse health effects in studies of adults, including male and female reproductive problems, thyroid effects, obesity, diabetes, and

endocrine-related cancers.[7–9] Most of this evidence comes from research on PCBs and organochlorine pesticides, though a growing number of studies are now investigating health effects related to PBDE exposures.

2.2. Phthalates

Phthalates are a diverse class of widely used industrial chemicals. They are used as plasticizers to make plastics more flexible, and are also used as solubilizing or stabilizing agents. Phthalates can be found in an extensive array of products. Low molecular weight phthalates are found in personal care products, certain dietary supplements and medications, and other consumer goods. High molecular weight phthalates are found in flexible PVC commonly found in consumer products, food packaging, home furnishings and other building materials. Medical equipment can also contain phthalates, and elevated exposures have been documented among NICU infants.[10] Due to this widespread use urinary phthalate metabolites can be measured in virtually everyone.[6] Several phthalates are anti-androgenic, and in rodents have demonstrated significant adverse impacts on male reproductive development and numerous other endpoints at high doses.[11] In human studies of adults phthalates have been related to decreases in sex steroid and thyroid hormone levels, poor sperm quality, endometriosis, insulin resistance, obesity, and possibly breast cancer.[12, 13]

2.3. Bisphenol A (BPA)

Bisphenol A is a high production chemical that is used in the manufacture of polycarbonate plastics, epoxy resins, and thermal paper. Polycarbonate is a clear, rigid plastic that has been used for water bottles, and other items, while epoxy resins are found in the lining of many canned foods and in certain construction materials. As with phthalates, medical equipment may also contain BPA, as NICU infants have been shown to have elevated exposure levels.[14] For most people exposure to BPA occurs primarily through the diet, and measurable levels of BPA can be found in most people.[6] BPA has been known to be weakly estrogenic for 75 years, and recent animal studies have reported a diverse variety of developmental problems following early life exposure, such as altered reproductive organ development and neurobehavioral effects.[15] Human studies of BPA remain limited, though in adults there have been suggestive relationships with male and female reproductive endpoints, altered thyroid hormones and liver function, cardiovascular disease, and diabetes.[16]

2.4. Contemporary use pesticides

Due to the long-lasting environmental issues related to the persistent organochlorine pesticides described earlier, nearly all pesticides used today are non-persistent. While they are designed to break down in a matter of hours or days, it has been shown that many non-persistent pesticides can remain for years after an application in homes and other indoor environments where they are protected from moisture, sunlight, and other degradation mechanisms. Exposure is multi-media, multi-pathway and multi-route, and can depend on the chemical, scenario, and population. Pesticides are known neurotoxins, especially in acute high-dose situations. Many commonly used pesticides are also known or suspected EDCs, though studies of potential endocrine effects have greatly lagged behind research focused on their designed mode of action (e.g. cholinesterase inhibition). Among all the types of pesticides (insecticides, herbicides, fungicides, rodenticides, etc.) the most human research has been conducted for insecticides. The most common classes of insecticides are organophosphates, carbamates, and pyrethroids. Of these the organophosphates, some of which have been banned or restricted for residential but not agricultural use in the US, have been the most studied class.

2.6. Other chemicals

There are many other types of known or suspected EDCs for which widespread human exposure has been documented. There is a large body of evidence showing that a number of heavy metals, such as lead, cadmium and mercury, may impact endocrine function in addition to their other modes of toxicity. There is also a growing list of emerging EDCs of concern which includes, among others, parabens, triclosan, perchlorate, alternative brominated and chlorinated flame retardants, and fluorinated organic compounds such as perfluorooctane octanoate (PFOA) and perfluorooctane sulfonate (PFOS). A handful of studies suggest that many of these emerging compounds may be associated with endocrine-related endpoints in animals and humans. However, the number of human studies that have been conducted for any one chemical or class of chemicals is sparse. Thus, the remainder of this article will focus on developmental endpoints associated with those EDCs introduced in previous paragraphs.

3. Developmental Endpoints Related to EDCs

3.1. Fetal growth and gestation length

Low birth weight (LBW) and preterm birth are the leading cause of infant mortality and precursors to future morbidity, and both have increased significantly in the US since 1990.[17] Numerous studies have assessed relationships between chemical exposures and birth weight which have been extensively reviewed.[18, 19] Studies among EDCs are more limited compared to those of agents related to ambient air pollution, such as particulate matter, carbon monoxide, ozone, nitrogen dioxide, and sulfur dioxide. There is some inconsistent evidence for reduced birth weight in association with exposure to POPs, organophosphate insecticides, and triazine herbicides. A meta-analysis of nearly 8,000 women from 12 European birth cohorts dating back to 1990 reported significant declines in birth weight in relation to markers of low-level exposure to PCBs, but not DDT.[20] More recently, evidence for reduced birth weight in relation to phthalates,[21] BPA,[22] and PBDE[23] has been reported, though several studies have also reported no associations. Since study designs and results have varied across studies, for most EDCs it is currently difficult to conclude whether a relationship exists between exposure and birth weight.

Few studies have investigated the potential relationship between EDC exposure and preterm birth, and most have focused on PCBs and organochlorine pesticides.[18, 19] Since the time these exhaustive literature reviews were published, a small nested case-control study taking place in Mexico City (n=60) reported higher concentrations of phthalates and BPA in third trimester urine of women who delivered preterm compared to women who delivered at term.[24, 25] For phthalates, this was consistent with two studies reporting inverse relationships between phthalates and gestation length.[26, 27] On the other hand, two studies have reported null or even positive associations between phthalates and gestation length.[28, 29] Future studies are needed on the relationship between EDCs and preterm birth, and should account for the heterogenous etiologies of preterm birth to enhance study precision.

3.2. Male reproductive tract development

There is evidence that birth anomalies of the male reproductive tract (cryptorchidism, hypospadias) may have increased in some countries in recent decades.[30] A leading hypothesis for a collection of linked conditions in human males exposed to EDCs *in utero* is termed “testicular dysgenesis syndrome (TDS)”. TDS represents a number of reproductive disorders of varying severity that are associated with disturbed gonadal development, including cryptorchidism, hypospadias, and smaller reproductive organs.[31] Later in life, the effects of TDS are hypothesized to manifest as a reduction in semen quality and infertility,

and an increased risk for testicular cancer. The evidence for widespread endocrine disruption among males is thus further fueled by reports of significant secular declines in semen quality[32] and testosterone,[33] as well as increased rates of testicular cancer,[34] in men over the past 50 years or so. Several studies have assessed relationships between EDCs, particularly POPs, and male genital birth defects with inconsistent findings which have been reviewed previously.[19, 30] More recently, a large case-control study (n=471 cases and 490 controls) of maternal occupation reported significantly increased risk of hypospadias associated with exposure to hairspray and phthalates, some of which are anti-androgenic.[35] Another recent case-control study reported increased risk of hypospadias and cryptorchidism in relation to parental occupational exposure to pesticides, though the number of cases in the study was relatively small (14 hypospadia, 18 cryptorchidism).[36] A relationship between PBDE measured in breast milk, but not placenta, and risk of cryptorchidism was also reported in a Danish case-control study of 95 cryptorchid boys.[37]

More subtle measures of reproductive tract development have been studied in relation to EDCs in recent years. A landmark US study reported reduced anogenital distance (a marker for insufficient fetal androgenization), penis size, and incomplete testicular descent in 106 2–24 month old boys in relation to several urinary phthalate metabolites measured in third trimester maternal urine.[38] A newer Japanese study that measured phthalate metabolites in 111 pregnant women also reported inverse associations with anogenital distance in male infants.[39] Finally, a Danish study reported significant decreases in serum measures of free testosterone and Leydig cell function in 3 month-old boys in relation to phthalates in maternal breast milk.[40] Thus, there is evidence that phthalates and possibly other EDCs disrupt early male reproductive development, but additional studies are needed.

3.3. Pubertal development

A secular decline in the age at onset of puberty and an increased frequency of precocious puberty has been observed over the past couple of decades in the US and other countries.[41, 42] These trends are considered to be a significant public health concern since precocious puberty is a risk factor for endocrine-related diseases in adulthood. The trends cannot be fully explained by known predictors (e.g. living conditions, BMI), and exposure to EDCs have been hypothesized to be a significant contributor.[43, 44] Several studies have reported an association between exposure to POPs and precocious puberty or earlier menarche in girls, and delayed puberty in boys; however, there have also been a number of studies that have not observed these relationships.[45]

There has been a lack of research on non-persistent EDCs and pubertal development. Several phthalates were found to be elevated in serum of girls with premature thelarche compared to controls in a small study in Puerto Rico.[46] However, the study has been criticized on several aspects of the study design, including the potential for sample contamination when measuring phthalates in serum. A more recent US study of pubertal development among 1,151 girls aged 6 to 8 years at enrollment reported subtle but statistically suggestive positive associations between low molecular weight urinary phthalate metabolites and breast and pubic hair development.[47] The authors also reported a weak inverse relationship between high molecular weight phthalate and pubic hair stage, but no associations between BPA and pubertal development. Among boys, a small study conducted in Turkey reported that plasma concentrations of high molecular weight phthalates were significantly higher in 11 to 15 year olds with pubertal gynecomastia compared to a control group.[48] Additional studies on EDC exposure and pubertal development are greatly needed due to the current lack of human data.

3.4. Neurodevelopment

Neurodevelopmental disorders are prevalent in the US and worldwide, with evidence that rates of certain disorders, such as attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorders (ASD) have been increasing in recent years.[49–52] While it is likely that these trends are attributable to numerous factors, including changes in diagnostic practices, there is growing evidence that exposure to EDCs may play a significant role. Sex steroid hormones are vital to central nervous system development. Thus, developing neuroendocrine systems may be particularly sensitive to EDC exposure.[53] Longitudinal and/or cross-sectional human studies have related exposure to EDCs, both *in utero* and during early childhood, and neurodevelopmental disorders such as decreased IQ, poorer memory, ASD, ADHD, and other behavioral problems.[54] These data are most robust for PCBs[55] and pesticides.[56] However, there is recent evidence that certain phthalates may be associated with each of these endpoints[13, 54] as well as reduced masculine play in boys,[57] that gestational BPA exposure may be associated with poorer executive function and behavior in 3 year-old girls,[58] and that gestational exposure to PBDEs could be related to lower scores on tests of mental development in the first few years of life.[59]

Thyroid hormones also play an essential role in neurodevelopment in addition to many other functions related to growth and metabolism. Rates of thyroid dysfunction, including congenital hypothyroidism, have been on the rise over the past several decades.[60] There is a growing list of EDCs that have been found capable of disrupting thyroid function. Both human and animal studies suggest that PCBs, PBDEs, pesticides, phthalates, and BPA, in addition to numerous other EDCs, may disrupt thyroid signaling through diverse mechanisms.[61, 62] More research is needed to establish dose-response relationships between EDCs and adverse neurodevelopment, as well as to determine the most sensitive stages and precise biological mechanisms involved.

3.5. Obesity

The prevalence of overweight and obesity is rapidly increasing in the US and worldwide.[63, 64] In addition to diet, physical activity and genetics, environmental "obesogens" may play a role in these trends. Obesogens are defined as chemicals that inappropriately alter lipid homeostasis to promote adipogenesis and lipid accumulation, and experimental evidence showing that numerous chemicals may impart these effects is growing.[64, 65] Human studies of environmental exposures in relation to obesity among children are lacking. They are primarily limited to studies of POPs and results have been inconsistent.[64, 66] Cord blood PCB and DDE concentrations were associated with increased BMI or change in BMI from ages 1 to 3 years in a Belgian prospective study.[67] In a cross-sectional study of adolescents, three serum PCB congeners (138, 153, 180) were associated with decreased BMI, but a fourth (118) was positively associated with BMI, among 14 and 15 year olds.[68] Several studies have reported null results as well.[64] For nonpersistent EDCs, research has been limited to two cross sectional studies that have reported suggestive positive associations between certain phthalates and BMI in girls.[66, 69] More research is needed to more adequately assess whether EDC exposure is associated with childhood obesity and related conditions (metabolic syndrome, diabetes, and future cardiovascular disease).

4. Clinical Perspectives

Based on the available data it is currently impossible to determine individual-level risk and whether there are "safe" levels of exposure to EDCs. Although the effect estimates or expected changes in developmental markers reported in individual studies may seem subtle, because exposure is ubiquitous a seemingly small shift in the population distribution for

these measures in relation to exposure is of great public health concern. Given the range of potential serious developmental effects described above, efforts to reduce EDC exposure as a precaution among pregnant women and children are warranted. The first level of concern is for those highly exposed, and physicians should obtain occupational and environmental exposure history information. Occupational exposure history for the parents may shed light on potentially important *in utero* exposures. Current "take home" exposures may also occur for some children, where the parent's clothing or other articles contaminated from the workplace can lead to exposures in the home or car. Patient or parent accounts of product overuse, hobbies, home-based businesses, or contaminated locations where children spend time are some examples of potentially useful environmental history information.[70]

Because exposure to the chemicals described here occurs among virtually everyone as they go about their normal activities, all patients could be advised to take certain steps in an attempt to reduce exposure. They can purchase consumer goods or personal care products labeled phthalate-free or BPA- free, which are becoming more commonly available. However, this trend has been primarily due to marketing purposes and products containing these chemicals are generally not required to be labeled as such.[71] For BPA and high molecular weight phthalates, replacing foods in the diet that involve plastic food packaging with "fresh" alternatives may reduce exposure by over 50%.[72] Among fresh foods, replacing a diet of conventional produce with organic produce may significantly reduce exposure to organophosphate pesticides for children who are exposed primarily through residues in food.[73] For legacy POPs like PCBs and DDT that are no longer used in most countries, as well as for more contemporary POPs such as PBDEs, consuming a diet lower in animal fats may reduce exposure. Individuals who live near polluted waters should also adhere to local fishing advisories. Since homes, offices, daycares and cars still have many products that contain PBDEs, and other flame retardants are being used in new products, careful product selection and cleaning practices to reduce indoor dust exposure (e.g., cleaning carpets and dusty surfaces regularly, using a vacuum cleaner with a HEPA filter) may help reduce exposure.[74]

Healthcare providers are encouraged to practice primary prevention by learning about EDC exposure sources and potential health impacts. Several resources are available for health professionals and patients, including handouts designed by university-based Pediatric Environmental Health Specialty Units (PEHSU)(http://www.aoec.org/PEHSU/facts.html), a pediatric environmental health toolkit from the Physicians for Social Responsibility (http://www.psr.org/resources/pediatric-toolkit.html), the "Green Book" on Pediatric Environmental Health from the American Academy of Pediatrics (http://ebooks.aap.org/product/pediatric-environmental-health-3rd-edition), and guidance on collecting pediatric exposure history from the National Environmental Education Foundation (http://www.neefusa.org/health/PEHI/index.htm).[16] Hospitals may help prevent exposures among sensitive populations through their purchasing practices, such as seeking out PVC-free products for use in the NICU.[75] Finally, clinicians are encouraged to consult with physicians or other professionals trained in environmental and occupational health as needed to address specific exposures or potential environmentally related health conditions. A resource for clinician referrals the PEHSU network of pediatric environmental health providers (http://www.aoec.org/pehsu.htm).

5. Regulatory Perspectives

While the steps listed here may help reduce exposure to some extent, exposure to most EDCs is multi-source, multi-pathway, and multi-route. Individual exposure scenarios depend on many factors, many of which are not modifiable through personal choices and activities. Thus, the most effective way to reduce risk is at the regulatory level. The

regulatory framework for controlling chemical risks in the US is considered outdated and ineffective.[76] An extremely small proportion of chemicals in current use have been thoroughly tested for endocrine disrupting potential, and there has been little motivation for chemical producers to assess this during product development and registration. In 1996, the US EPA enacted legislation requiring special considerations be given to child susceptibility in the risk assessment of pesticides but not other industrial or consumer chemicals.[1] The 1996 legislation also mandated that pesticides and certain drinking water contaminants be screened for endocrine activity which resulted in implementation of the EPA Endocrine Disrupting Screening Program.[77] In 2009 EPA finally ordered producers to conduct the first set of endocrine screening tests for a truncated list of chemicals, but at the time this article was written data from these new tests were still not available.[78] In addition to data on health risks, data on exposure sources and pathways are also needed to inform the most effective and cost-efficient regulations. For example, several phthalates have been banned from use in children's toys in the US. However, the most sensitive exposure period may be to the developing fetus, which would likely not be reduced with legislation only geared toward children's toys. Finally, there must be caution when replacing chemicals deemed high-risk with new chemicals for which we know less about the potential toxicity.

6. Conclusions and Future Research Needs

There is a growing body of evidence showing that exposure to a number of chemicals may adversely impact child development through altered endocrine function. However, many of the potential exposure-response relationships described here have not been adequately explored. For those that have been investigated in multiple studies, results have been inconsistent across studies. There are many possible explanations for variability in study findings, including differences in sample size, study design, study populations, life stage, data analysis approaches, and/or strategies for attaining data on exposure, endpoint, and important covariates. Many studies on EDCs to date among both children and adults are cross-sectional; there is a great need for well-designed longitudinal studies that measure both exposure and developmental endpoints at multiple potentially sensitive time points. For non-persistent EDCs it is especially important for studies to consider intra-individual variability in exposure levels over time. Future research aimed at explaining sexually dimorphic impacts of EDCs on development is also needed, as are studies capable of exploring health effects resulting from exposure to multiple EDCs simultaneously to more closely reflect the reality of being exposed to chemical mixtures. Research that combines molecular epidemiology and toxicology approaches should be conducted to establish causality and to elucidate specific biological mechanisms of EDCs in humans, individual susceptibility factors, and the stages of development most sensitive to exposure. Finally, more research is needed in the area of exposure science to enable more precise effect estimates in epidemiology studies used for risk assessment, as well as to provide solid data on important exposure sources and pathways for risk management. The US National Children's Study (http://www.nationalchildrensstudy.gov) and Centers for Children's Environmental Health & Disease Prevention Research (http://www.niehs.nih.gov/research/supported/centers/prevention/) are important sources of cutting-edge research for developing new information on these topics.

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