14 Endocrine Disruptors as Obesogens

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Introduction

Substantial effort has been devoted to explaining secular trends in childhood obesity and metabolic risks to unhealthy diet and physical activity. It is plausible, for example, that a child who ingests 50 calories more per day would gain an additional 5 pounds as fat over a year, if that intake is not matched with an increase in energy expenditure [1]. If a similar dietary change has occurred over the cohort of American children, then dietary changes would account for a significant portion of the increase in childhood obesity.

While data from the National Health and Nutrition Examination Survey suggest that adult caloric intake increased over the period between 1971–1975 and 2003–2004 [2], the Bogalusa Heart Study found no such increase across the 10-year-old cohorts they followed from 1973 to 1994 [3], and more recent studies suggest that BMI is 2.7 points higher now than in 1986 at the same levels of caloric intake and energy expenditure [4]. Ecologic data from the Youth Risk Behavior Surveillance System provide somewhat stronger support for the notion that changes in physical activity patterns may explain the observed increases in obesity. Enrollment in physical education classes declined among high school students from 42% to 28.4% over the period 1991–2003. From 1977 to 2001, walking to school decreased from 20.2% to 12.5% (as a proportion of total trips) [5]. More recent data, however, reduce the likelihood of this secular trend contributing to changes in adolescent obesity [6].

While these and other studies are suggestive, the major conclusions drawn are that increased caloric intake and decreased exercise levels may have a partial role in the pathogenesis of obesity and metabolic risks. Since it is unlikely that the human genome has changed significantly in a single generation to have generated an increased susceptibility to excess weight gain in early life, we are left with the reality that factors in addition to diet and exercise represent important risks for obesity and metabolic disorders—environmental influences are among these important factors. In contrast to diet and physical activity, which can require intensive attention, effort, and costs to modify through behavioral and other interventions, government action can fundamentally transform the environmental influences to prevent disease and disability. The costs of regulations to limit environmental obesogens can also be much lower than the benefits to society.

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The notion that synthetic chemicals in the environment can disrupt metabolism was first and most definitively described with tributyltin (TBT), a fungicide used to prevent fouling of the hulls of ships [7–9]. In laboratory studies, TBT selectively activates peroxisome proliferator-activated receptor (PPARy) and its heterodimeric partners, the 9-cis retinoic acid receptor (RXR) [10]. PPARy has long been known as a target for pharmaceutical drugs intended to treat diabetes, adding to the plausibility that synthetic chemicals created for other purposes can influence these master receptors that organize carbohydrate and lipid metabolism [8]. In animal studies, TBT exposure in utero has produced adiposity in mice, with effects that can be transmitted transgenerationally, such that the "great-grandchildren" of mice exposed during pregnancy to TBT can become obese without additional exposure [11, 12].

Over the past two decades, rapidly accumulating scientific evidence has expanded this mechanistic framework to recognize that multiple pathways can be influenced by an even broader array of synthetic chemicals, with characteristic metabolic disruption across multiple endocrine organs and tissues [13, 14]. PPARs such as PPAR-gamma require heterodimerization with RXRs, binding together on target DNA to activate the expression of downstream genes [15]. Sex steroid pathways have also been proven to produce sex-specific effects on body mass [16].

The remainder of this chapter focuses on three categories of chemicals for which the evidence in laboratory, animal, and human studies is the most convincing: phthalates, bisphenols, and persistent organic pollutants. For each, we describe pathways of exposure and methods to limit exposure. We then close with a discussion of the disease burden and costs that can be traced to chemicals that contribute metabolic risks and opportunities for policy action to reduce exposures to the most hazardous chemicals that may contribute.

Phthalates

Phthalate esters have a diverse array of uses in consumer products, and they can be classified into two categories. Low molecular weight (LMW) phthalates are frequently added to shampoos, cosmetics, lotions, and other personal care products to preserve scent [17], whereas high molecular weight (HMW) phthalates are used to produce vinyl plastics used in many applications ranging from flooring, clear food wrap, and intravenous tubing [18]. Within the HMW category, di-2-ethylhexylphthalate (DEHP) is of particular interest because industrial processes to produce food frequently use plastic products containing DEHP [19], and its metabolites are often considered as a subcategory.

Mono-(2-ethylhexyl)phthalate (MEHP), a DEHP metabolite, increases expression of peroxisome proliferator-activated receptor (PPAR)-gamma [20] which plays key roles in lipid and carbohydrate metabolism, providing biological plausibility for the potential influence of DEHP metabolites in childhood obesity and insulin resistance. Laboratory studies have found that metabolites of phthalates promote release of interleukin-6, a pro-inflammatory cytokine [21], and oxidant stress [22]. This is important because oxidant stressors appear to diminish insulin-dependent glucose transport activity [23] and to modify the endothelial relaxant nitric oxide, promoting vasoconstriction, platelet adhesion, and release of inflammatory cytokines such as interleukin-1 [24, 25]. In experimental models and patients with primary hypertension, there is increased release of oxidant free radicals by endothelial cells throughout the body [26]. Emerging animal evidence also suggests that DEHP may produce arrhythmia [27], change metabolic profiles, and produce dysfunction in cardiac myocytes [28]. This raises the possibility of phthalates as a contributor to cardiovascular risk, independent of obesity.

Of the three cross-sectional studies in children and adolescents, one found no associations of urinary phthalate concentrations in 1209 children and adolescents in 1999–2002 NHANES with

unstandardized measurements of BMI (body mass index) or WC (waist circumference) [29] although patterns of association varied by age and gender. The second, in a population of largely Latino, New York City (NYC) children [30], examined urinary phthalates measured in 6–8-year-olds and associations with BMI and WC 1 year later, stratifying models to examine for effects within overweight/normal BMI subpopulations. While whole-sample associations were not observed, Teitelbaum and coworkers identified positive relationships with body mass measures in relationship to log-transformed phthalate metabolites for monoethyl phthalate, or MEP, and the sum of all LMW phthalate metabolites (MEP, mono-n-butyl-phthalate or MBP, mono-isobutyl phthalate or MiBP, and mono-(3-carboxypropyl) phthalate or MCPP). Finally, in the third study, analyses of NHANES 2003–2008 identified increases in odds of overweight, obese, and BMI Z-score associated with log-transformed LMW metabolites among non-Hispanic Blacks in stratified, multivariable models, but not in other subpopulations. Longitudinal studies exploring the relationship between prenatal phthalates and childhood growth discovered different results in males and females, predominantly resulting in negative associations with growth in males [31–33]. One limitation of all studies was the infrequency of phthalate measurements during pregnancy. This is important because pharmacokinetic studies in adults suggest that phthalates have a half-life in the range of 12–48 h, respectively [34], and fat deposition may disrupt kinetics as well [35].

Bisphenols

Bisphenol A (BPA) is used to manufacture polycarbonate resin and is a breakdown product of coatings that prevent metal corrosion in food and beverage containers [36]. A comprehensive, cross-sectional study of dust, indoor and outdoor air, and solid and liquid food in preschool age children [37] suggested that dietary sources constitute a major source of BPA exposure. Given the mild estrogenic activity of BPA [38], and the known association of obesity with increased estrogen levels in males [39], potentially gender-specific increases in weight gain are plausible. BPA also reduces the function of adiponectin, which protects against oxidant stress, insulin resistance, and heart disease [40]. BPA has been documented to trigger the differentiation of preadipocytes into adipocytes; to increase the quantity of stored fat [41]; to disrupt pancreatic β-cell function in vivo [42], producing insulin resistance and glucose intolerance [43]; and to affect glucose transport in mouse adipocytes. Disruption of these metabolic and hormonal processes has been documented in environmentally relevant doses [40, 41, 44].

To date, the epidemiologic evidence for the role of BPA in childhood obesity has been chiefly cross-sectional. The first study leveraged NHANES 2003–2008, identifying relationships of quartile and logarithm-transformed urinary concentrations with BMI Z-score and obesity. Controlling for race/ethnicity, age, caregiver education, poverty/income ratio, gender, serum cotinine, caloric intake, television watching, and urinary creatinine, children in the lowest BPA quartile had a lower estimated prevalence of obesity (10.3%; 95% CI, 7.5–13.1) than those in the second, third, or fourth quartiles (20.1%, 95% CI, 14.5–25.6%; 19.0%, 95% CI, 13.7–24.2%; and 22.3%, 95% CI, 16.1–27.9%, respectively). Obesity was not associated with exposure to other environmental phenols commonly used in other consumer products, such as sunscreens and soaps. However, explanations of the association could not rule out the possibility that obese children ingest food with higher BPA content or that obese children have greater adipose stores of BPA [45].

Three more recent longitudinal studies have yielded positive, albeit not completely consistent results, although these studies were all limited by infrequent measurements of BPA in pregnancy [46–48]. This is important because pharmacokinetic studies in adults suggest that BPA has a short half-life in the range of 4–43 h [34], and fat deposition may disrupt kinetics of BPA elimination [49]. Studies with serial BPA measurements have

identified Pearson correlation coefficients in the range of 29–56% over 1–6-month periods [50–52]. Similarly, data from Generation R, a prospective, longitudinal multiethnic birth cohort study which has longitudinally followed 9778 pregnancies and children born between 2002 and 2006, suggest that reliability of a single urine specimen as a marker of pregnancy-wide BPA exposure is modest, as estimated by the intraclass correlation coefficient (0.32) in 80 women in which samples were analyzed at <18, 18–25, and >25 weeks gestation. While we note that weak indices of early exposure should bias estimates of association toward the null [53–55], this post hoc justification has limits. There remains a need for studies of individual subjects with biospecimens from time points when BPA and phthalate exposure could more plausibly and permanently disrupt metabolic and/or endocrine homeostasis, producing chronic caloric imbalance.

The "thrifty phenotype" hypothesis first described by Barker and coworkers [56, 57] suggests that early-life adaptations to poor in utero nutritional conditions can produce a profile of maladaptation after birth in which the ability to acquire energy results in increased adiposity beginning in childhood and cardiovascular risks later in life. A recent association of phthalates with low birth weight (LBW), as well as data associating increases in BPA with reductions in estimated fetal weight, would be consistent with this idea, although the thrifty phenotype hypothesis remains largely unexplored. Most typically, studies have examined risk factors for obesity insofar as they affect the trajectory of postnatal growth; however, this approach fails to recognize the different trajectories of fetal growth and potentially more impactful moments of exposure. Increasingly precise ultrasonographic approaches to estimating fetal weight at different periods in gestation now permit comparison of estimated fetal weight against optimal fetal weights customized by individual profiles and detection of health consequences of different nutritional and chemical exposures [58, 59].

Persistent Organic Pollutants

Persistent organic pollutants (POPs) are a diverse class of chemical contaminants, which degrade slowly and are widely distributed in the environment [60]. We focus here on four categories of POPs for which exposures persist at levels relevant for possible disruption of developmental metabolic processes.

Organochlorine pesticides (OCPs) such as dichlorodiphenyltrichloroethane (DDT), chlordane, and lindane have been banned through the Stockholm Convention [61], and concentrations of DDT and its main metabolite, dichlorodiphenyldichloroethylene (DDE), are reported to be decreasing in the environment [62]. However, current levels of DDE are known to be antiandrogenic [63], raising the possibility of sexually dimorphic effects on body mass, in addition to the estrogenicity of DDT [64], and effects on adipocyte differentiation [65].

Polychlorinated biphenyls (PCBs) were banned by the US Environmental Protection Agency in 1979, yet exposures continue in the United States due to latent environmental contamination of food (fish in particular) [66], soil [67], and water [68]. Low levels of PCB have long been known to inhibit thyroid hormone [69], which plays a critical role in human metabolism. Dioxin-like PCBs are also potent aryl hydrocarbon receptor (AhR) agonists, inducing xenobiotic metabolizing enzymes that can augment generation of reactive oxygen species [70], which are well known as major mechanisms underlying cardiometabolic risks.

Polybrominated diphenyl ethers (PBDEs) are structurally similar to PCBs and have been extensively used as flame retardants in household products, such as textiles, foam, and electronic devices [60, 71, 72]. Although California and other states have banned penta- and octa-brominated PBDEs, deca-PBDEs remain in use and are found in computers, television sets, mobile phones, construction materials, polyurethane foam mattresses, cushions, carpets, and draperies. Deca-PBDEs are readily metabolized into lower-brominated forms, and one such compound, PBDE 47, increases adipocyte differentiation in a dose-dependent manner [73]. Rats perinatally exposed to PBDEs displayed similar responses upon stressful stimulation in later life, including increased systolic BP and cardiovascular reactivity [74]. PBDE exposures in animal studies have induced oxidative stress-mediated hepato- and nephrotoxicity [75], in addition to decreased vasopressin levels, which

indirectly impact BP via regulation of blood volume, plasma osmolality, and water retention [76].

Perfluoroalkyl compounds (PFCs) are fluorine-based halogenated hydrocarbons with powerful surfactant and water-repelling properties. PFCs are used as surfactants and stain-resistant coatings on many products, including upholstery, carpet, food packaging, and nonstick cookware, among others [77]. Four longer-chain PFCs (≥8 carbon) were scheduled to be phased out at the end of 2015 [78], yet numerous PFCs continue to be used, and effects of past longer-chain PFC exposures remain relevant given the 7–15-year half-lives of these chemicals. A study of PFC use trends between 1996 and 2010 in Sweden reported increases (11%/year) in perfluoroalkylbutane sulfonate (PFBS), a four-carbon substitute for the longer-chain PFOS. PFBS is increasingly being identified as a food contaminant, suggesting that diet may be a relevant route of exposure [79]. PFCs are reported to activate the nuclear receptors, PPAR-alpha and PPAR-gamma, which play key roles in lipid and glucose metabolism, providing biological plausibility for PFC-induced childhood obesity and insulin resistance. In cell cultures using the 3T3-L1 preadipocyte system, multiple PFCs increased cell number, increased total triglyceride, and altered expression of genes associated with adipocyte differentiation and lipid metabolism [79, 80]. Developmental PFC exposures in mice have also been found to increase leptin and insulin levels in midlife [81]. Microvascular endothelial cell culture studies have also shown that PFC exposure increases reactive oxidative species and induces endothelial permeability [82], which plays a critical role in ischemic renal injury [83].

Epidemiologic studies of POPs have yielded results suggesting substantial contribution to obesity and other metabolic outcomes in youth. Pooled analyses of multiple European birth cohorts have associated prenatal PCB-153 (but not DDE) with decreased birth weight [84] and DDE with accelerated infant weight gain [85]. While associations of prenatal OCP/PCB exposures were absent in the Collaborative Perinatal Project [86], increases in obesity among Mexican-American boys in the CHAMACOS study were associated with DDT and DDE levels in pregnancy [87]. Prenatal DDT exposure has been associated with hypertension diagnosed in women <50 in the California-based Child Health and Development Studies [88].

Few studies have examined PBDE early-life exposures in relationship to postnatal body mass and cardiovascular outcomes. A small cross-sectional study of 43 children found that serum PBDE levels were related to increased cardiovascular stress responses [89]. The CHAMACOS cohort identified positive associations of maternal PBDE with BMI Z-score in boys, with negative associations in girls, as well as an inverse association of PBDE at age 7 with simultaneously measured BMI Z-score [90].

Perfluorooctanoic acid (PFOA) levels in pregnant women have been associated with increases in pregnancy-induced hypertension [91–93]. There is also some evidence that PFCs may impact birth weight and early life growth trajectories [94, 95]. Infants in the Norwegian Mother and Child Cohort Study (MoBa) with higher levels of PFCs in utero were found to have slightly lower birth weight than those exposed to lower levels [94]. Danish infants exposed in utero to PFCs tended to weigh less at 5 and 12 months of age than less exposed children, and this effect was more pronounced in boys [95]. More research is required to elucidate these effects and whether they are related to long-term impacts on BMI [96, 97]. However, the relationship between altered fetal growth, early-life growth restriction, and CVD in adulthood has been widely accepted, due to the work from the Dutch Winter Hunger Study and, more recently, the Biafran famine [98, 99]. Although longitudinal studies of a population exposed to PFCs due to emissions from a chemical plant did not associate antecedent PFC exposure with increases in obesity [100], these antecedent exposures may not reflect effects in the general population, and were modeled from resident address and water measurements, which have modest predictive value in children (62%) [101].

Prevention of Obesogenic Exposures

While uncertainty exists about mechanisms of effect as well as timing of exposures that may contribute to early-life adiposity, there are

safe and simple steps that practitioners can take to advise families to reduce exposure. Choosing personal care products labeled as "phthalate-free" has reduced urinary levels of MEP by 27% in young girls in one study [102]. A fresh food intervention has produced even larger reductions in exposure [103]. Consumption of a diet according to World Health Organization recommendations has been associated with lower levels of PFCs and PCBs [104, 105].

Ultimately, policy action to regulate endocrine-disrupting chemicals could produce more rapid reductions in childhood obesity and net economic benefits to society. While the FDA recently banned its use in baby bottles and sippy cups, it recently declined to ban BPA in other food uses [106]. Natural and synthetic alternatives to BPA exist, and a recent estimate suggests that naturally derived oleoresin linings cost 2.2 cents more than those derived using BPA [107]. If 100 billion aluminum cans are produced annually [108], then the incremental cost of replacing BPA with oleoresin would be $2.2 billion. In one scenario based on reduction of BPA, 6200 cases of childhood obesity and $748 million in annual associated costs could be prevented by substitution of BPA with an alternative free of health effects [109].

It should be noted that endocrine-disrupting chemicals have a broad array of effects across the life course, and there are additional benefits to protecting against chemical obesogen exposures insofar as these exposures have other associated health effects. Recent studies suggest that the costs of EDCs annually are €163 billion in Europe and $340 billion in the United States [110, 111]. Of these costs, metabolic effects comprise €15 billion and $5 billion, respectively. These are likely to be underestimated because the researchers examined less than 5% of known EDCs (for which the most data were available), and only a subset of medical conditions linked to these EDCs, and did not include costs of suffering and other indirect consequences of conditions downstream of obesity.

Editor's Comments and Question

Experiments done many years ago at the National Institute of Environmental Health Sciences[a] demonstrated that neonatal treatment with diethylstilbestrol (DES) causes obesity in rodents. Bisphenol A (BPA) has structural similarities to DES, exerts adipogenic effects in vitro, and induces weight gain in rodents treated in the perinatal period. These findings suggest that exposure to BPA during a critical developmental window may "program" the development of obesity, insulin resistance, and possibly type 2 diabetes, at least in rats and mice. This has been more difficult to prove in humans, in part because (a) a critical window for toxic exposure in humans has not yet been defined and (b) longitudinal studies have not yet confirmed the hypothesis that exposure of human infants to BPA in pregnancy programs weight gain in childhood [46 and 47].

Nevertheless, the ubiquity of BPA and other endocrine disruptors, and their potential ramifications for reproductive development and malignancy[b], has for good reasons raised concerns among the public. In response, manufacturers have in some cases replaced BPA in their products with bisphenol S or related compounds. Are these compounds any safer than BPA?

Additional References for Editor's Comments and Question

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Authors' Response

In the absence of regulatory action to limit BPA exposure, BPA is already being replaced with synthetic alternatives that have been identified in paper products [57] and human urine [58], including bisphenol S (BPS). The current regulatory framework does not require comparison of newer chemicals such as BPS for similarity in structure-function relationships and potential toxicity to BPA [59]. Much less is therefore known about BPS than BPA regarding public health consequences of exposure.

The few studies that have had the opportunity to study BPS have identified similar genotoxicity and estrogenicity to BPA [60–65] and greater resistance to environmental degradation than BPA [66, 67]. Substitution of BPA with BPS may therefore yield the same consequences for obesity and cardiometabolic conditions. Regulatory agencies should consider the potential toxicity of as-yet untested substitutes for BPA in deciding how to further restrict BPA in food uses.

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