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THE POTENTIAL ROLE OF DEVELOPMENTAL CHEMICAL EXPOSURES IN CONTRIBUTING TO THE OBESITY EPIDEMIC

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Introduction:
The prevalence of obesity and overweight is increasing worldwide among adults, children and adolescences. Risk factors commonly considered to give rise to this epidemic include excess caloric intake, diet composition, decreased exercise, the built environment, and developmental as well as genetic susceptibility to these environmental factors. Whether developmental chemical exposure can contribute to risk of obesity, remains relatively under-examined. Persistent organic pollutants have been associated with obesity and obesity risk factors across a variety of species, including humans. In the majority of instances, a mechanistic basic is plausible for these associations.

Materials and methods:
This review surveys developmental exposures to numerous classes of POPs, including dioxin-like compounds, organochlorine pesticides, polyfluroalkyls, and polybrominated diphenyl ethers, for which aspects of obesity have been examined. For instance, adipose tissue mass and percent adiposity, body mass, and lipotoxicity were examined as potential outcomes consistent with the obesogen hypothesis. Although effects on insulin action are also known risk factors for obesity, we considered these outcomes as out of the scope of this survey. The survey is focused on human data and experimental research findings, including those of *in vivo* experimental models as well as ecotoxicology.

Results and discussion:
Despite the anticipated increased susceptibility to toxicants during the metabolic programming period, there are relatively few developmental studies of POP exposure and offspring obesity and lipotoxicity. Numerous epidemiology studies indicate a positive association between developmental exposure to dioxin like compounds and body weight of offspring[1]. Experimental studies of developmental dioxin-like effects on adiposity and lipotoxicity have mostly been preformed at doses high enough to cause wasting[1]. However in a one month study, chronic developmental exposure to the polychlorinated (PCB) mixture Aroclor 1254 was associated with increased body weights of mouse pups on postnatal days (PND) 16-20[2].

A recent review of PFOA epidemiologic studies consistently found PFOA was positively associated with elevated serum total cholesterol, although the magnitude of this modest association varied[3]. In a large cross sectional study of children living in an area with high PFOA levels, there were positive linear associations between PFOA and PFOS exposures with total cholesterol and LDL cholesterol; only PFOA was positively and linearly associated with HDL cholesterol and triglycerides[4]. Similarly, a NHANES cross sectional study of adolescent metabolic syndrome found PFNA was associated with a decreased odds of low HDL cholesterol, and most PFCs were associated with a decreased odds of high waist circumference[5]. An experimental lifecourse study of PFOA suggests these cross-sectional studies may be overly simplified. Mice exposed to low levels of perfluorooctanoic acid (PFOA) *in utero* had persistently increased body mass once mature[6]. By 18 months of age, there was a direct and inverse dose response relationship between *in utero* PFOA exposure and abdominal brown- and white- adipose tissue masses in the aged mice, respectively[6].

Developmental exposure to several persistent organochlorine pesticides has also been implicated in obesity. The majority of prospective studies of maternal exposures to DDE demonstrated a positive association with offspring obesity[1]. Likewise, mice prenatally exposed to DDT had higher body weights in the week after birth when the study ended,[7] and rats exposed to DDT during late gestation had excess hepatic lipid droplets as early as the first day of birth[8]. Cord blood HCB levels are also positively associated with childhood obesity[9], however no animal studies have confirmed this[10].

Polybrominated flame retardants are also emerging as a class of potential developmental obesogens in experimental models, although one human study did not find an association with obesity in adults[11] and we know of

no human studies of adult exposures. Prenatal exposure to brominated diethyl ether (BDE)-99 increased mouse birth weight[12], and pre- and post- natal exposure to BDE-47 increased rat body weights from birth to puberty (when the study ended) [13]. In another BDE-47 study, mice exposed 10 days after birth had increased body weights from postnatal day 47 until 4 months of age, when the study ended[14]. Penta-BDEs are also lipotoxic. Developing shrimp exposed to BDE-47 had increased cholesterol[15], and both male and female rats exposed to a penta-BDE mixture exhibited a dose response increase in plasma cholesterol[16].

Developmental exposure to chemical classes containing peroxisome proliferator activated receptor (PPAR) γ agonists and polyhalogenated hydrocarbons are possible risk factors for obesity. The association of these chemical classes with obesity is biologically plausible. PPARγ is considered a master regulator of adipogenesis as it is essential to the terminal differentiation of adipocytes[17]. AhR, the receptor held responsible for essentially all the effects of dioxin and dioxin-like compounds, appears to have an innate role in insulin and lipid homeostasis. AhR is activated by LDL and AhR knockout mice have higher serum LDL and insulin resistance[18, 19].

Many of the human studies reviewed were cross-sectional and most adjusted POP levels by serum lipids. These raise question to reverse causation. If POPs cause dyslipidemia, then POP levels should not be adjusted by blood lipids in multivariable models of outcomes for which dyslipidemia may be on the causal pathway (including obesity, diabetes and CVD, and the cancers for which obesity and diabetes increase risk such as breast cancer)[20]. Indeed a recent longitudinal epidemiology study found weaker, but still significant, associations between POPs and obesity when adjusting for serum triglycerides and cholesterol, which is consistent with triglycerides and cholesterol partially mediating the effects of POPs on adiposity[21]. Because methodological concerns arise when adjusting for serum lipids (over specified model/decreased precision) or not (does not estimate adipose- burden/possible exposure misclassification), directly using a PBPK model estimate of blood or tissue concentrations may be an alternative[22, 23]. Yet errors in the PBPK model estimates of POP levels could also contribute to decreased precision and exposure misclassification.

POPs such as dioxins, and DL-PCB, organochlorine pesticides, brominated flame retardants and perfluorinated compounds can act as obesogens in experimental models. All of these POPs have direct or indirect effects on PPARγ action and lipid metabolism. Cross-sectional epidemiologic studies demonstrating an association between lipophilic POPs and measures of adiposity may reflect reverse causation. Where it exists, longitudinal epidemiologic data supports an association between POPs and obesity, particularly developmental exposures. In order to further the obesogen hypothesis, epidemiologic model designs should reflect experimental evidence that the effects of POPs on lipids may be on the casual pathway to obesity.

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