Published in final edited form as:

Trends Endocrinol Metab. 2018 September ; 29(9): 607–625. doi:10.1016/j.tem.2018.06.003.

Obesogenic endocrine disrupting chemicals: identifying knowledge gaps

Almudena Veiga-Lopez^{1,*}, Yong Pu¹, Jeremy Gingrich^{1,2}, and Vasantha Padmanabhan^{3,4,5,6,*}

¹Department of Animal Science, College of Agriculture and Natural Resources, Michigan State University, East Lansing, Michigan, USA

²Department of Pharmacology and Toxicology, College of Natural Sciences, Michigan State University, East Lansing, Michigan, USA

³Department of Pediatrics, University of Michigan, Ann Arbor, Michigan, USA

⁴Department of Obstetrics and Gynecology, University of Michigan, Ann Arbor, Michigan, USA

⁵Department of Molecular and Integrative Physiology, University of Michigan, Ann Arbor, Michigan, USA

⁶Department of Environmental Health Sciences, University of Michigan, Ann Arbor, Michigan, USA

Abstract

Endocrine disrupting chemicals (EDCs) are compounds that are part of everyday consumer products and industrial manufacturing processes. EDCs can interfere with the endocrine system, including the adipose tissue. Accumulating evidence from epidemiological, animal and *in vitro* studies demonstrates that EDCs can alter body weight, adipose tissue expansion, circulating lipid profile, and adipogenesis, with some resulting in transgenerational effects. These outcomes appear to be mediated through multiple mechanisms from nuclear receptor binding to epigenetic modifications. A better understanding of the signaling pathways via which these EDCs contribute to an obesogenic phenotype, the interaction amongst complex mixtures of obesogenic EDCs, and the risks they pose relative to the obesity epidemic are still needed for risk assessment and development of prevention strategies.

Keywords

obesogens; endocrine disruptors; obesity; developmental origins of health and disease

*Correspondence should be addressed to: Almudena Veiga-Lopez, Department of Animal Science, Michigan State University, 474 S. Shaw Lane, Rm 1230F East Lansing, MI 48824, USA. Telephone: 517-432-7084; veiga@msu.edu. Vasantha Padmanabhan, Department of Pediatrics, University of Michigan, 7510 MSRB I, 1150 West Medical Center Drive, Ann Arbor, MI 48109-5718. Telephone: 734-647-0276; vasantha@umich.edu.

Disclosure statement: Authors have nothing to disclose.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

1. Introduction

In the past decades, prevalence of obesity has been increasing dramatically in developed countries and has now reached an all-time high, with 36.5% [1] of adults in the U.S. being obese and 70% being overweight or obese. Obesity now also affects 1 in every 6 children and adolescents (ages 2–19; [1]). In general, medical costs for people who have obesity are ~40% higher than of normal weight individuals [2], which is often driven by obesity-related, preventable conditions that are also on the rise. Obesity is a major player in the increased prevalence of co-morbidities, such as type 2 diabetes (> 30 million U.S. adults; [3]), metabolic syndrome (~34% of U.S. adults; [4]), non-alcoholic fatty liver disease (75% of chronic liver disease in the U.S.; [5, 6]), and cardiovascular disease [7]. Although the etiologies of these co-morbidities is multifactorial, the strong association with obesity points to the lipotoxic effects that the adipose tissue can exert on other systems.

2. The origin of obesity and risk factors

To date, in spite of 227 genetic variants having been identified to be associated with polygenic obesity [8], the heritability of obesity remains an enigma [9]. Contributing factors to the obesity epidemic include increase in caloric consumption, sedentary lifestyle and genetics. However, the abrupt and rapid increase in obesity prevalence in the 21st century calls for the investigation of additional risk factors, such as stress, social determinants, microbiota, and the environment, among others. Evidence pointing to the role of the environment on obesity prevalence is increasingly supported by 1) epidemiological observations of geographic disparity of obesity [1] and 2) experimental evidence supportive of ubiquitously present environmental **endocrine disrupting chemicals (EDCs)** (see Glossary) that can promote adipose tissue accumulation. The ever-increasing production of chemicals in the past few decades and their prolific use in consumer products worldwide [10], coupled in parallel with an increase in obesity prevalence, warrants careful investigation regarding the risks posed by these natural and man-made products to the obesity epidemic.

3. Obesogenic endocrine disrupting chemicals

EDCs are chemicals that interfere with the **endocrine system**, including adipose tissue. Historically considered as an organ whose main function is energy storage, the adipose tissue secretes numerous hormones and other factors such as leptin, adiponectin, resistin, adipisin, angiotensin, and free fatty acids. These are involved in a broad range of physiological actions including glucose and lipid metabolism, appetite control, vascular tone control, angiogenesis, and immunity [11]. EDCs that not only increase adipose mass / adipogenesis but also result in other metabolic dysfunctions are also referred to as **metabolic disrupting chemicals (MDCs)** [12]. While humans are exposed to a multitude of EDCs from a variety of sources (see Figure 1), the focus of this review is on six groups of obesogenic EDCs, herein referred to as **obesogens** (see Table 1). These include non-steroidal estrogens, organotins, parabens, phthalates, polychlorinated biphenyls, and bisphenols that have been found to have an impact on one or more of the following traits: 1) an increase in

adipose tissue mass by hypertrophy or hyperplasia, 2) a disruption of adipocyte function leading to increased lipid production 3) an induction of dyslipidemia, 4) a disruption in metabolic hormone profiles, 4) an increase in preadipocyte differentiation, or 5) an increase in the fate of mesenchymal stem cells to undergo **adipogenic differentiation**. In reviewing epidemiological and *in vivo* studies, the outcome variables considered relative to the effect of obesogens include: birth weight, catch up growth, body weight, body mass index (BMI), adipose tissue mass, adipocyte cell size and number, plasma lipid profile, and metabolic hormones. Outcomes reviewed for the *in vitro* studies focus on the ability of preadipocytes to differentiate into adipocytes, hypertrophy and hyperplasia, lipid accumulation, and molecular phenotyping of genes and proteins that regulate adipogenesis and differentiation of **mesenchymal stem cells (MSCs)**.

3.a. Non-steroidal estrogens

Non-steroidal estrogens include phytoestrogens such as isoflavones or coumestans, selective estrogen receptor modulators (SERMs) such as tamoxifen, and synthetic endocrine disruptors such as bisphenol A (discussed in section 3.f.). The classic example of non-steroidal estrogen is diethylstilbestrol (DES), an FDA-approved estrogen-replacement therapy prescribed between 1940 and 1980 to prevent miscarriage. Although mostly known for producing reproductive defects in offspring exposed to DES *in utero*, pioneering studies from Dr. Newbold's laboratory brought to attention DES as an obesogen [13]. In their studies, gestational days (GD 9–16) or early postnatal (postnatal day (PND) 1–5) exposure of CD1 mice to DES (1µg - 1 mg/kg/day) increased adipose tissue mass, triglycerides, as well as circulating leptin concentrations [13]. Similarly, exposure of C57BL/6J mice to DES (0.01–0.1 mg/kg BW) from GD 12 to PND 7 was found to increase body weight, adipose tissue mass, circulating triglyceride and glucose levels in female offspring at PND 60 [14]. DES (0.1 mg/day, sc) also increased daily weight gain by 15%, when administered for 8 weeks to growing lambs [15], a precocial species with developmental trajectory similar to humans [16]. *In vitro* studies have also documented that DES (1 to 10 µM), in a dose-dependent manner, stimulates 3T3-L1 preadipocyte differentiation, and activates the peroxisome proliferator-activated receptor gamma (*PPAR*γ) activity via estrogen receptor (ER) [14] (see Figure 2), a key regulatory event in cellular differentiation, development, and metabolism. DES was one of the first chemicals to be recognized for its obesogenic effects. Although its therapeutic use has been discontinued, mechanistic studies into the obesogenic nature of DES are still warranted due to the potential for transgenerational effects. Multi-/transgenerational effects of DES have been evidenced with other pathologies, such as occurrence of genital malformation in males [17, 18].

3.b. Organotins

Organotins are comprised of two main chemical families that share structural similarities [19, 20], butyltins and phenyltins, each comprised of several chemicals based on the number of alkyl or aryl chains and substitutions. Tributyltin (TBT) is the most studied organotin. TBT is a man-made organotin chemical used in the manufacturing of antifouling paints, as a preservative in papers and textiles, in agricultural pesticides, and as a stabilizer in plastic production [21]. TBT easily leaks into the environment [22, 23] and because of its lipophilic nature bioaccumulates in animal [22, 24] and human tissues [25, 26], including the placenta

[27] (see Table 1; [25, 28, 29]). To our knowledge, the only available epidemiological study investigating the effects of gestational TBT exposure demonstrated weight gain up to three months of age in newborns with increasing placental TBT concentrations [27]. The obesogenic nature of TBT has, for the most part, been demonstrated in fish, mice, and rats. The use of TBT in antifouling paints has directed a large number of studies on TBT exposure in aquatic species. Most TBT studies carried out in fish involved environmentally relevant doses (range: ~1–100 ng/l), and have demonstrated that TBT increases body weight, adipose tissue mass, triglycerides, and cholesterol [30–34]. The vulnerability of these species to TBT is further supported by the diversity of exposure windows (post fertilization days 5–15, pre-hatch to 9 months, and adult), all of which resulted in obesogenic effects [30–34].

In contrast to studies in aquatic species, studies in mice and rats have explored higher doses of TBT (range: 0.5–500 µg/kg BW) as opposed to environmentally relevant doses. Findings from these studies are also supportive of TBT's obesogenic nature, manifested as increase in body weight [35–39], adipose tissue mass [39–42], and leptin levels [41] in mice, with such effects evident following exposure during prenatal, perinatal, or postnatal periods. Importantly, recent studies also documented transgenerational inheritance of obesogenic effects [40, 41]. Studies demonstrating a lack of obesogenic effect of TBT are scarce [43].

Overall, TBT effects are evident after prenatal as well as postnatal exposures, highlighting the broad window of susceptibility for this EDC. While postnatal exposure to TBT results in partially reversible effects on glucose homeostasis [37], perinatal TBT exposure produces permanent and transgenerational (F1, F2, and F3) obesogenic effects in mice, which include increased adipose tissue mass, adipocyte hypertrophy and hyperplasia, and hepatic lipid accumulation [40]. Importantly, from a public health context, these effects have been shown to be transmitted to the F4 generation, when the F0 exposure window included the lactational period [41]. Two of these studies have demonstrated that TBT can have a sex-specific effect, with higher adipose tissue accumulation in males [40, 41], opening an area of research for further exploration. Most recently, perinatal administration (50 nM) of another organotin compound, dibutyltin (DBT), was found to increase body weight and reduce glucose tolerance [44] warranting further studies with this compound.

Strong evidence for TBT's obesogenic nature also comes from *in vitro* studies. TBT increases glucose uptake [45] and promotes adipogenic differentiation in preadipocytes [39, 42, 45–48] and MSCs. The obesogenic nature of TBT has been demonstrated in human MSC [49], human [50] and mice [51] embryonic-derived stem cells, mice bone marrow derived MSCs [52, 53], and mice adipose-derived stromal stem cells [54]. TBT-induced adipogenesis is reported to occur through activation of PPAR γ activity in preadipocytes [42, 45, 55, 56] and MSCs [53], although some studies have failed to validate this [47, 52] (see Figure 2). Since TBT activates several nuclear receptors (PPAR γ , liver X receptor, and retinoid X receptor) [20, 42, 51, 53], any differing responses may be a function of varying exposure windows, length, doses, and nature of cell culture systems and the receptors they activate. In addition, because TBT-induced adipogenesis in preadipocytes and human MSCs is associated with modifications in global methylation [49, 57], histone H3K27me3 methylation [52], and DNA methylation in adipogenic genes [49], such epigenetic

modifications may underlie the transgenerational effects of TBT [40, 41]. Recent work has also demonstrated that DBT enhances adipogenesis in mouse and human bone-marrow MSCs via PPAR γ [44] stressing the need to investigate the obesogenic nature of other non-TBT organotin chemicals.

Recent research in aquatic species is beginning to shed light into the cumulative obesogenic potential of the organotin chemicals [58]. A greater adipogenic effect (complete adipogenic differentiation) was observed when organotin compounds (TBT and triphenyltin) were used in combination rather than individually [58]. Thus, research focused on potential obesogenic effects of combinations of such compounds with structural similarities are warranted, both in epidemiological studies and animal models with similar developmental trajectory as humans.

3.c. Parabens

Alkyl esters of p-hydroxybenzoic acid, also known as parabens, are commonly used in food, beverage preservatives and personal care products [59], for which the primary route of exposure is transdermal. Their use in personal care products has resulted in U.S. women having a higher geometric mean than men for methyl-paraben (104 $\mu\text{g/l}$ and 29.8 $\mu\text{g/l}$) and propyl-paraben (20.4 $\mu\text{g/l}$ and 2.96 $\mu\text{g/l}$; see Table 1; [60, 61]). Available epidemiological studies have not yielded consistent outcomes relative to the obesity phenotype. For instance, studies with the French EDEN cohort demonstrated a positive association between urinary paraben (sum of total parabens) concentration and birth weight in male offspring [62] that persisted through the three-year study. In contrast, studies in an Indian cohort (where only obese individuals were studied), found no relationship between paraben exposure and childhood obesity [63]. Although ethnic susceptibility to paraben exposure or the limitation of the population to obese individuals in the Indian cohort may have played a role in these differing outcomes, the limited number of epidemiological studies available calls for further investigation to address the translational impact of parabens on obesity.

As opposed to the inconsistent findings from epidemiological studies, studies in animals provide evidence in support of parabens' obesogenic potential. For instance, post-weaning exposure (12 weeks, 100 mg/kg BW/day, PO) to methyl-paraben, but not butyl-paraben increases adiposity and serum leptin concentrations in C57BL/6J mice [64]. Both parabens also induced white adipose tissue gene expression (fatty acid synthase, fatty acid binding protein 4, and lipin 1) consistent with enhanced adipogenic potential [64]. In other studies, prenatal exposure (GD 7–21) to butyl-paraben (100 mg/kg BW/day, PO) reduced plasma leptin levels in both male and female fetal rats (adipose tissue mass not assessed) [65]. Considering that traditional paraben exposure in humans primarily occurs transdermally, the experimental route of exposure, namely oral gavage, in all these animal studies could be a confounding factor when translating these findings to humans due to first-pass metabolism in the gut.

In vitro studies provide the strongest support of the adipogenic nature of parabens. Methyl-, ethyl-, propyl- and butyl-paraben exposure (100 μM) promote adipogenesis, lipid accumulation, and PPAR γ upregulation in 3T3-L1 cells [66] with butyl- and benzyl-paraben inducing adipogenesis in a dose-dependent manner [67]. Additionally, exposure to methyl-,

ethyl-, propyl- and butyl-parabens promotes adipogenic differentiation in human adipose-derived multipotent stromal cells [66] and upregulates *PPAR γ* mRNA in C3H10T1/2 murine multipotent stem cells [68]. Multiple mechanisms have been reported in support of the adipogenic effect of parabens (see Figure 2). First, parabens can act as *PPAR γ* agonists [69] while *PPAR γ* antagonists suppress paraben-induced adipogenesis [66]. Second, and despite the controversy regarding the role of the glucocorticoid receptor (GR) in mediating obesity [70], parabens can also activate GR without direct binding or modulation of GR ligand binding in murine 3T3-L1 cells [66, 68]. Third, fatty acid amide hydrolase (FAAH) is the direct molecular target of butyl- and benzyl-paraben (1–50 μ M) through endocannabinoid-mediated adipogenesis [67]. Interestingly, the potency of parabens to induce obesogenic effects (adipogenesis and lipid accumulation) was found to increase with their linear alkyl chain length [66].

In contrast to *in vitro* studies that show all parabens (methyl-, ethyl-, propyl- and butyl-paraben) induce adipogenesis, epidemiological studies do not provide unequivocal evidence in support of paraben's obesogenic nature. Furthermore, one of the greatest limitations of experimental studies of paraben exposure relates to the higher dose range used (range: 1–100 mg/kg BW) relative to the U.S. adult median exposure concentrations (daily intakes for methyl-, n-propyl- and n-butyl-paraben are 47.5, 20.6 and 4.6 μ g/kg bw/day, respectively [71]. Additional experimental studies addressing environmentally relevant doses and transdermal route of exposure are needed to better assess human obesity risk to parabens.

3.d. Phthalates

Diesters of 1,2-benzenedicarboxylic acid, or phthalates, are used as industrial plasticizers of polyvinyl chloride to be used in floorings, vinyl upholstery, car interiors, and toys [72], plastic food packaging [73], as well as in cosmetic products such as lotions and perfumes [74]. Human exposure occurs primarily through ingestion or inhalation (see Table 1; [75–77]). Available epidemiological studies on phthalates relative to their impact on obesity are limited. The CHAMACOS cohort study reported a positive association between early life exposure (at 14 and 26 weeks of gestation) to diethyl phthalate (DEP), dibutyl phthalate (DBP) and di-(2-ethylhexyl)-phthalate (DEHP) and increase in childhood body weight, BMI, waist circumference, and percent body fat in 5–12 year old children, supportive of phthalates being developmental obesogens [78]. Another study also found a positive association between mono-3-carboxypropyl phthalate at 27 to 34 weeks of gestation and overweight/obese status in 4–7 year-old children [79]. These investigators also observed an inverse relationship between DEP and DEHP metabolites and BMI in girls, but not in boys, suggestive of sex-specific effects [79]. In contrast, the same group found no association between maternal phthalate concentrations between 25 to 40 weeks of gestation and percent body fat in 4–9 year-old children from New York City, nor did they find any effect of sex [80]. To what extent these differences are a function of the specific phthalate being studied, gestational time point of investigation (first vs. last trimester of pregnancy), and/or how the various phthalates interact in producing the final phenotype remains to be determined.

As most of the phthalate-associated obesogenic effects in epidemiologic studies relate to DEHP, or its metabolite mono-2-ethylhexyl phthalate (MEHP), *in vivo* studies with

animals, as well as *in vitro* research have primarily focused on these two compounds. The predominant exposure phenotype of mice exposed *in utero* to DEHP include non-sex specific increases in body weight, visceral fat mass, and circulating leptin, insulin and/or glucose concentrations [81, 82]. In contrast, another study using the same window of exposure reported no change in body weight despite increased visceral fat mass, and serum leptin, insulin and glucose concentrations [83]. Metabolic effects of prenatal DEHP exposure (increased body fat and adipocyte size) are sex-specific, with males being more affected and exacerbated by postnatal high fat diet [84]. An array of DEHP exposure concentrations (0.25–300 mg/kg BW/day), exposure windows (embryonic day (ED) 1–19, and embryonic day 12 to PND 7), and age of study outcomes (PND 21, PND 54, PND 60, PND 84) have been studied with most producing obesity-related phenotypic outcomes, suggesting multiple windows of susceptibility that extend beyond the prenatal period [81–84]. In general, mice exposed *in utero* to DEHP vary in phenotype between studies, even under similar exposure conditions. The different outcomes may relate to differences in genetic background, diet, window of exposure, or other factors, such as intrauterine position that could contribute to differences in androgen exposure [85]. Adult animals exposed orally to DEHP (5, 50, 500 mg/kg BW/day, for either 4 or 5 weeks, or 0.5, 5 and 500 mg/kg BW/day for 8 weeks) also present with increased body weight [82, 86, 87], increased visceral fat mass [82], and increased serum lipid, insulin, and leptin concentrations [86]. Mechanistically, a single DEHP dose (0.5 mg/kg BW) administered to 6-week-old mice was found to increase adipogenic gene expression [81]. Additionally, adipose tissue from these animals showed reduction in *UCP1* mRNA expression, suggestive of increased white adipocyte differentiation [87]. An increase in *JAK3/STAT5a* mRNA expression [86] was also evident suggesting that DEHP exposure promotes triglyceride accumulation by altering the signal transduction involved in lipid metabolism.

In utero exposure studies to MEHP are more limited but demonstrate that exposure to low (0.05 mg/kg BW/day, po), but not higher (0.25 or 0.5 mg/kg BW/day) doses from embryonic day 2 to PND7) elicit a similar response to DEHP; namely, increased body weight, increased fat mass, and increased circulating cholesterol, triacylglycerides, and glucose concentrations (observed at PND60) [88]. This effect appears to be sex-specific with an effect only observed in male offspring, [88]. The mechanisms by which DEHP induces sex specific effects are not yet known. A recent meta-analysis of 31 rodent studies on the impact of early life exposure to DEHP or MEHP for obesity related outcomes revealed a significant association between early life exposure to DEHP and MEHP and increased adipose tissue weight [89]. These findings provide an associative link between gestational phthalate exposure and offspring adiposity.

DEHP and MEHP also enhance adipogenic differentiation in 3T3-L1 preadipocytes and murine mesenchymal stem cells over a broad range of concentrations (1 – 100 μ M) [88, 90]. Although MEHP can activate both PPAR α and PPAR γ [91], its enhancement of adipogenesis appears to be through the PPAR γ pathway as is the case with DEHP [88, 90]. Additionally, a metabolomics study found exposure of human female subcutaneous preadipocytes to MEHP increased expression of genes involved in glyceroneogenesis and triglyceride uptake, synthesis, and storage [92]. Not all reports support the adipogenic nature

of DEHP, with some studies reporting a lack of adipogenic differentiation in bone marrow stromal cells [93] or 3T3-L1 preadipocytes [81].

Phthalates can exert an anti-androgenic effect, not through the androgen receptor, but through PPAR α . The resulting decrease in androgen activity has been proposed as a mechanism of phthalate-induced obesity [94] (see Figure 2). Other phthalates, such as dicyclohexyl phthalate (DCHP) [95] and benzyl butyl phthalate (BBP) [96, 97] can also enhance adipogenic differentiation in 3T3-L1 preadipocytes [95, 96] and the C3H10T1/2 mouse mesenchymal stem cell line [97]. The mechanism by which DCHP induces adipogenic differentiation differs from that of DEHP and MEHP and has been reported to be through activation of glucocorticoid activity [95]. To our knowledge, no epidemiological study assessing the obesogenic effect of either of these two phthalates is available.

The strongest support for both MEHP and DEHP as obesogenic EDCs come from animal and *in vitro* studies. However, in translating findings to human, it needs to be recognized, that the exposure range used in *in vivo* studies in animals (0.25 – 500 mg/kg BW/day) is significantly higher than the estimated U.S. adult daily exposure (0.001 – 0.03 mg/kg BW/day) [76]. On the other hand, available *in vitro* studies highlight the potential for enhanced adipogenesis at environmentally relevant doses and suggest mechanisms by which this may occur. Overall, studies involving environmentally relevant doses of DEHP and MEHP, as well as other phthalates (DCHP, BBP) with reported *in vitro* adipogenic potential, are required to better assess human obesity risk from exposures to phthalates individually or in combination.

3.e. Polychlorinated biphenyls

Persistent organic pollutants (POPs) are chemicals widely used as pesticides and industrial solvents. POPs are lipophilic, highly stable, with a low decomposition rate, making them highly persistent in the environment. Polychlorinated biphenyls (PCBs) are amongst the 12 chemicals recognized as POPs in the 2001 Stockholm Convention [98]. PCBs are a large family of over 200 chemicals employed in a variety of industrial products such as transformers, cable insulation, lubricants, hydraulic fluids, or fiberglass [99]. PCB concentrations in human serum range from 0.0075 – 75.5 ng/g [100] (see Table 1; [100, 101]). Primary route of exposure of PCBs is oral [102]. PCBs primarily accumulate in adipose tissue [103] thus having the potential to be released into circulation during lipolysis [104]. Over 10 PCBs have been identified to have a dioxin-like toxicity, but with different obesogenic potential. Importantly, a positive association between dietary intake of PCBs and higher incidence of obesity has been found in a prospective Spanish study comprised of over 12,000 individuals [105]. Similarly, PCB-138 and PCB180 were associated with increased child BMI z-scores and PCB-138 with overweight risk in a Spanish birth cohort (470 children) [106]. Furthermore, serum and adipose tissue levels of PCBs have been positively associated with the visceral to subcutaneous adipose tissue ratio in adult individuals [107]. In stark contrast, low-level exposure to PCB-153 has been associated with lower birth weight in a study including 12 European birth cohorts and 7,990 individuals [108]. A smaller cohort with 145 participants also observed a negative correlation between serum levels of PCB-153, PCB-180, PCB-170 and BMI and total and subcutaneous abdominal

adipose tissue [109]. These studies highlight the daunting complexity of understanding the obesogenic effects of PBCs relative to the vast family of congeners, the opposing obesogenic effects reported amongst members the PCB family (see next paragraph), and their dose-dependency.

The effects of PCBs on adipogenesis is congener specific. *In vitro* data shows PCB-101, PCB-153 [110], PCB-118 [111], and PCB-138 [111] stimulate adipogenesis in preadipocytes, while PCB-126 [112] suppresses adipogenic differentiation of human preadipocytes. PCB-153, but not PCB-77, also stimulates proliferation of human subcutaneous preadipocytes [113]. Data on other PCBs is less clear. For instance, epidemiological data shows circulating PCB-180 was negatively correlated with BMI in adults [109], but gestational exposure to PCB-180 was positively associated with the risk of being overweight at 7 years of age [106]. This is of importance, as PCBs can cross the placental barrier and reach concentrations in fetal circulation up to 50% of that observed in maternal circulation [114, 115]. Divergence between epidemiological studies may relate to dose-dependency of effects, as has been observed *in vitro*. For instance, PCB-180 stimulates 3T3-L1 adipogenesis at 1 μ M, but not at lower doses [110], while the opposite was observed with PCB-77 exposure where low (3.4 μ M) concentrations increased adipogenesis, but high concentrations (68 μ M) decreased adipogenesis [116].

Multiple mechanisms appear to underlie the obesogenic nature of PCBs (see Figure 2). Some PCBs are agonists of the aryl hydrocarbon receptor (AhR), a ligand dependent transcription factor known to modulate adipogenesis [116, 117]. Exposure of human preadipocytes to PCB-126 and 3T3-L1 preadipocytes to PCB-77 reduces adipogenic differentiation, an effect that can be blocked by AhR binding [112, 116]. PCB77-induced increase in body weight and circulating cholesterol in adult mice appears to be mediated via AhR [116]. Additional mechanisms that have been linked to PCB's obesogenicity include the NF κ B pathway [118] and fat-specific protein 27 [111].

Although studies have provided compelling evidence for the obesogenic nature of some PCBs (PCB-101, PCB-118, PCB-138, PCB-153), but not others (PCB-77, PCB-126, PCB-180), information regarding the cumulative obesogenic burden of all PCBs in unison remains incomplete. With over 200 congeners that comprise this chemical family makes this task especially complex. The obesogenicity of PCBs is congener specific and much remains to be investigated. Considering that 1) PCBs can cross the placental barrier [114, 115], 2) preconceptional maternal and paternal exposure to PCBs have an impact on birth weight [119], a risk factor for adult onset disease, 3) some PCBs can disrupt offspring's lipid homeostasis and increase adipose tissue mass [110, 111, 116–118], and 4) PCB exposure can induce epigenetic changes [120], the contribution of epigenetic mechanisms underlying developmental programming effects on adipose tissue and adipogenic differentiation due to PCBs is also warranted.

3.f. Bisphenols

Bisphenols are synthetic lipophilic chemicals used in the manufacturing of plastics and epoxy resins. This class includes several related compounds namely BPA, BPAF, BPAP, BPB, BPC, BPE, BPF, BPS, and BPZ. Bisphenol A (BPA), the most studied representative

of this group, is prevalent in human serum, umbilical cord blood, breast milk and urine [121–124] with human exposures occurring through oral, dermal, and inhalatory routes [125] (see Table 1; [126–128]). In the last decade, we [129, 130] and others [131] have investigated the effects of BPA on birth and body weight, and adiposity. Because of the intense focus on BPA, several reviews addressing the link between BPA and obesity from an epidemiological standpoint already exist [132–136]. Most available epidemiological studies are cross-sectional and point to a link between BPA exposure in adults and an increased risk of being overweight or obese. However, these findings need to be considered in the context of other studies showing either a decreased risk of being overweight or obese, or no association. Additionally, early-life exposure studies suggest a link between BPA exposure and excess adiposity and an increased risk of being overweight or obese. These studies demonstrate a sex- or ethnicity-specific effect, or no association. Factors underlying the differing results observed among studies are multifactorial, and likely the result of differences in study protocol, unaccounted for residual confounding factors, or reverse causality, e.g. individuals who are obese have a different dietary pattern that increases their exposure risk. The major caveat of these cross-sectional studies is that most use only a single measure of BPA exposure which may result in exposure misclassification. Many of the cross-sectional studies also failed to consider latency of effects. Due to the ubiquity and short half-life of BPA, even prospective cohort studies face the challenge of unaccounted confounding factors. As such, more epidemiological evidence is needed to gain a better understanding of early BPA exposure levels.

Similarly, over a hundred animal studies have focused on understanding whether BPA has an obesogenic effect during developmental exposures. One of the latest systematic reviews and meta-analysis that included 61 publications suggest that early-life exposure (during gestation and/or lactation up to postnatal day 21) to BPA may increase adiposity and circulating lipid levels in rodents [137] with stronger associations in males [138, 139] and at doses below the U.S. reference dose (50 µg/kg BW/day). Multigenerational obesogenic effect has also been reported for BPA [140]. Other non-rodent studies have also pointed to the obesogenicity of perinatal exposures to BPA [129, 141]. However, the recent National Toxicology Program (NTP) draft report that used rats as the animal model (2.5 – 25,000 µg/kg/day from GD6 through postnatal life) found no effect of any of the doses studied on body weight but an increase in retroperitoneal fat pad in females with only the 2.5 µg/kg dose [142]. It is important to recognize that obesogenic effects of BPA has been found to be non-monotonic, with increased adipocyte volume and glucose intolerance observed with low doses (5 µg/kg BW/day during GD 9 to GD18), but not higher doses in male mice [143]. As such, based on current body of BPA studies, the lack of obesogenic effects in the NTP study may be a function of doses examined relative to other studies.

The most consistent evidence in support of the obesogenic effect of BPA comes from *in vitro* studies. BPA increases adipogenic differentiation in 3T3-L1 preadipocytes after short (3 days; [95]) or long (8–14 days; [144–146]) exposures, at high (25–80 µM; [145, 147]) or environmentally relevant doses (0.01–10 nM; [144, 148, 149]). BPA was also found to be associated with increased triglyceride secretion [150, 151]. BPA increases adipogenesis in human primary cultured preadipocytes [152] and adipose-derived stromal stem cells [153]. However, this effect was not observed in human or mouse mesenchymal stromal stem cells

[144] or mouse embryonic stem cells [90]. Receptor binding and luciferase reporter assays have demonstrated BPA's adipogenic ability to be mediated through ER [152, 153] or the glucocorticoid receptor (GR) [95, 149, 150] (see Figure 2). However, other reports have observed GR-independent effects of BPA-induced adipogenesis [152]. BPA and its halogenated analogs (tetrabromobisphenol A [TBBPA] and tetrachlorobisphenol A [TCBPA]) target PPAR γ in multiple species [154] and modulate adipogenesis in 3T3-L1 cells [145]. Other proposed pathways include the modulation of the p38/mitogen-activated protein kinase (MAPK) [150], protein kinase B (Akt) pathway [155], c-Jun N-terminal kinase (JNK)/p38 [156] and mammalian target of rapamycin (mTOR) signaling pathways [157]. How obesogenic effects of BPA are programmed during early life exposures is not fully understood. It has been postulated to be modulated through endoplasmic reticulum stress [158], microRNA [150], and global DNA methylation [147]. Bisphenol S (BPS), the second most prevalent bisphenol viewed as a replacement to BPA, has recently been demonstrated to increase postnatal body weight after neonatal exposure [159] and also increase adipogenesis *in vitro* by targeting PPAR γ [145] and ER [160], thus raising concerns as to its applicability as a replacement chemical; these observations are similar to those in other endocrine organs, such as the placenta [161].

4. Concluding Remarks and Future Perspectives

While the review of the available literature points to detrimental effects of several classes of EDCs relative to increased weight and higher adiposity (see Figure 3 for composite summary of phenotypic outcomes reviewed), several limitations need to be overcome prior to linking their contribution to the obesity epidemic. These limitations span epidemiological (Box 1), animal (Box 2), and *in vitro* (Box 3) studies. It is important to emphasize that differences in mode and dose of exposure, window of exposure, developmental time point of investigation, species, strain, sex differences, diet, and other life style factors could have all contributed to the inconsistencies that exist in the current body of literature.

Box 1

Epidemiological studies. Limitations and future directions

Limitations	<ul style="list-style-type: none"> • Many studies investigate a single EDC • Outcome assessment is often limited to single time point • Fail to consider exposure relative to critical periods of differentiation (susceptibility windows) • Fail to take into account complexity of confounding variables • Fail to address cumulative EDC burden and interactions • Fail to consider latency of EDC effect • Fail to take into account ethnic disparity • Fail to integrate modulatory role of additional factors (diet, stress, etc.)
Future Directions	<ul style="list-style-type: none"> • Assess multiple exposures and their interactions • Address genetic susceptibility • Study EDC effects in the context of diet, stress etc.

- Apply sophisticated statistical models to assess complex exposures

Box 2

Animal studies. Limitations and future directions

Limitations

- Studies often restricted to a single EDC at doses that are not environmentally relevant
- Fail to consider critical windows of organ development
- Study single strain without considering genetic susceptibility
- Often fail to address sex-specific effects
- Fail to take into account the mother as the experimental unit
- Fail to address latency of effects
- Fail to assess cumulative burden
- Fail to consider dietary interactions

Future Directions

- Assess multiple doses spanning environmentally relevant to occupational level exposures
- Explore mixture effects
- Explore sex-specific effects
- Distinguish organizational vs. activational effects
- Undertake longitudinal phenotyping across the life span
- Validate non-monotonic dose responses
- Consider potential for interaction with diet, stress
- Explore modulation via second hit (postnatal diet, stress, etc.)
- Identify biomarkers for risk assessment and development of prevention strategies

Box 3

In vitro studies. Limitations and future directions

Limitations

- Cell lines are not reflective of responses of primary cells
- Cell lines do not predict sex-specific responses
- *In vitro* studies cannot address organizational effects
- 2D systems are not reflective of cellular interactions and tissue structural properties

Future Directions

- Develop organotypic systems that better mimic *in vivo* cellular interactions
- Primary cells procured for *in vitro* studies should take into account developmental time points of relevance
- Investigate EDC mixture effects
- Findings from *in vitro* studies need to be validated *in vivo*

Longitudinal epidemiological studies establishing positive associations between perinatal exposure to EDCs and increased adipose tissue mass in children are often conducted in specific populations where a single exposure is investigated at a single point in time without consideration of the exposure window as it relates to timing of organ differentiation, latency of effect or cumulative burden, and with correlations drawn based on a snapshot of the EDC exposure. This is especially important for EDCs with a short half-life, such as bisphenols, parabens, or phthalates. Many of these studies should measure internal EDC exposure at more than one time point to assess cumulative EDC burden.

Considering that humans are exposed to not a single, but a multitude of chemicals [162, 163] that may have additive, synergistic, or opposing effects [164, 165], it is important that studies undertake a more comprehensive screening of exposure interactions between various environmental EDCs. Thus far, only a handful of studies have addressed the impact of exposure to EDC mixtures [133, 166–168]. Another drawback of most epidemiological studies is the lack of consideration of confounding factors. Since genetic susceptibility stemming from ethnicity, lifestyle, diet, stress, habitat, and mobility between rural vs. urban areas, among others can influence the impact of EDCs, these should be carefully considered in these investigations. To assess the risk posed by exposure to environmental EDCs on obesity outcome variables, epidemiologic studies need to capitalize on sophisticated statistical models and novel algorithms, and assess the life course impact of heterogeneous exposures on obesity outcome variables, as well as their effects on multimodal mediators. In addition, when considering the implications for public health, in cases of uncertainty, risk assessment agencies have the social responsibility to follow the precautionary principle.

Studies with animal models, necessary to address causality, should test multiple doses that cover exposures from low to environmentally relevant doses in the general population to occupational exposure levels. This is especially important in view of the non-monotonic responses of organ systems to such exposures [169–171]. Also of importance is the consideration of appropriate animal models [172] in the context of the developmental window of the organ system being studied as it relates to humans. For instance, in humans, nonhuman primates and ruminants, ovarian development gets completed *in utero*, while it continues to develop postnatally in altricial species [16]. As such, prior to translating findings from studies in altricial species, such as mice and rats, additional testing in precocial species with a developmental trajectory similar to humans is a much-warranted step. All animal studies should consider appropriate exposure levels, include positive and negative controls, include varying species / strains to address genetic susceptibility differences, perform detailed phenotyping at several developmental time points, assess sex-differences, consider cycle stage when reproductively mature females are studied, and investigate differences due to dietary modulation. When litter bearing animals are used, it is also important to consider the mother as the experimental unit rather than the offspring. Since effects of *in utero* EDC exposure on fetal developmental trajectory may involve modulation of the maternal/fetal steroidal environment, a classic programming factor, rodent studies need to also consider the fetal intrauterine position during development [85]. Animal studies should also begin to address mixture effects to provide proof of concept for exposure interactions. Studies of targeted mixture studies should take into account human exposure levels in formulating such mixtures. Furthermore, to gain an understanding of the true

impact of “real life” exposure to environmental chemicals, which is likely to be comprised of both known and unknown EDCs, models such as biosolid exposure models [173] should also be considered. When focusing on developmental programming, adults should be carefully phenotyped to establish a pathology before investigating early time points in the fetus such as *in utero* development. Animal studies should clearly distinguish organizational (permanent) vs. activational (transient) effects and the potential for interactions between both effects. Ultimately, animal studies should identify biomarkers of disease susceptibility to EDC exposures.

In vitro studies often rely on transformed cell lines that, although easily accessible and yield highly reproducible results, are not always good predictors of responses by primary cells. In addition, studies using primary cells are warranted, as sex-specific responses cannot be addressed by cell lines. In addition, the majority of studies continue to rely on classic *in vitro* systems (i.e. suspensions, monolayer cultures, etc.), which assume cells exist in isolation and thus fail to recreate the cellular interactions that occur at a tissue level. The emerging introduction of novel systems capable of recreating the complex cell environments that occur *in vivo*, namely ‘organ-on-a-chip’ offer a breadth of possibilities to study the complex cellular interactions contributing to the response to chemical exposures. See ‘Outstanding Questions’ section for a summary of emerging questions as they relate to the three study types (epidemiological, animal, and *in vitro* studies).

Outstanding questions

- Careful longitudinal phenotypic profiling in the context of critical periods of susceptibility to obesogenic EDCs are needed. To achieve this, epidemiological association studies should be coupled with causal investigations in animal models taking into account similarity in developmental trajectory of organ systems.
- What are the underlying mechanisms (cellular reprogramming, epigenetic, and other) by which life course exposures to EDCs result in latent, long-term, and transgenerational effects?
- As humans are often exposed to multiple combinations of EDCs, what are the possible additive, synergistic, or opposing effects of these mixtures on human health?
- There is a need for careful linkage of epidemiologic association studies (accounting for various confounders and sex-specific differences) with studies of causalities undertaken in cellular and animal models to unequivocally establish a link to the obesity epidemic.
- What are the best intervention strategies to overcome the deleterious effects of identified obesogenic EDCs?

To move the field forward partnerships across disciplines are critical. A prime example are studies conducted under the realm of the Children’s Centers co-funded by the National Institutes of Environmental Health and the Environmental Protection Agency that

incorporate epidemiologic and animal studies that address association and causality. These studies are the test ground for not only establishing the link between exposures to obesity epidemic, but for identifying community level intervention strategies. Epidemiologists should partner with basic scientists so that appropriate tissues such as fat and/or muscle biopsies can be collected for later probing of underlying mechanisms. This will help relate associations discovered in epidemiological studies to mechanisms. Additionally, such investigations can be paralleled with studies addressing causalities in animal models and novel *in vitro* organ systems in partnership with, for instance, bioengineering colleagues. Investigators setting up longitudinal studies following developmental EDC insults should strive to identify collaborators with expertise in various organs/systems to enable procurement of an integrative system level perspective of exposure outcomes. Significant advances in the field will only come from establishing causality and identifying risks posed by EDCs. As such, efforts should be directed towards developing research teams comprised of epidemiologists, basic scientists, bioengineers, and biostatisticians that enable interdisciplinary collaborations targeted towards a common goal.

Acknowledgments

Funding source: Research reported in this publication was supported the National Institute of Environmental Health Sciences of the National Institute of Health (1K22 ES026208 to A.V-L.) and (R01-ES016541, R01 ES017500, and P01 ES022844 to V.P.), Michigan State University (MSU) General Funds, MSU AgBioResearch, and the United States Department of Agriculture (USDA) National Institute of Food and Agriculture (Hatch project MICL02383). Jeremy Gingrich was partially supported by the BioMolecular Sciences graduate program at MSU and a National Institute of Environmental Health Sciences of the National Institute of Health T32-ES07255.

We would like to thank the free photo source pixabay.com for access to images used in this review.

Glossary

Adipogenic differentiation

Complex process by which preadipocytes transition into lipid-filled, insulin-responsive adipocytes. This process is controlled by transcription factors, including peroxisome proliferator-activated receptor gamma (PPAR γ), CCAAT/enhancer-binding proteins (C/EBPs), and sterol regulatory element binding protein (SREBP).

Endocrine disrupting chemicals (EDCs)

Natural or man-made chemicals that can interfere with the endocrine system. This includes alterations in hormone production, secretion, and/or action.

Endocrine system

The set of glands that produce and secrete hormones into the bloodstream or surrounding fluids to reach distant target organs and integrate body functions such as growth, behavior, reproduction, and/or metabolism.

Mesenchymal stem cells (MSCs)

Multipotent stromal cells that can differentiate into several cell types. These include, adipocytes (fat cells), myocytes (muscle cells), osteoblasts (bone cells), and chondrocytes (cartilage cells).

Metabolic disrupting chemicals (MDCs)

EDCs that not only increase adipose mass / adipogenesis but also result in other metabolic dysfunctions, such as insulin resistance, glucose intolerance, hepatic steatosis, and/or metabolic syndrome.

Obesogens

EDCs that can increase adipose tissue mass by hypertrophy or hyperplasia, preadipocyte differentiation or the fate of mesenchymal stem cells to undergo adipogenic differentiation and/or disrupt adipocyte function leading to increased lipid production.

References

1. Ogden CL, et al. Prevalence of Obesity Among Adults and Youth: United States, 2011–2014. NCHS Data Brief. 2015; (219):1–8.
2. Finkelstein EA, et al. Annual medical spending attributable to obesity: payer- and service-specific estimates. Health Aff (Millwood). 2009; 28(5):w822–31. [PubMed: 19635784]
3. CDC. Type 2 Diabetes. 2017.
4. Moore JX, et al. Metabolic Syndrome Prevalence by Race/Ethnicity and Sex in the United States, National Health and Nutrition Examination Survey, 1988–2012. Prev Chronic Dis. 2017; 14:E24. [PubMed: 28301314]
5. Hassan K, et al. Nonalcoholic fatty liver disease: a comprehensive review of a growing epidemic. World J Gastroenterol. 2014; 20(34):12082–101. [PubMed: 25232245]
6. Younossi ZM, et al. Changes in the Prevalence of the Most Common Causes of Chronic Liver Diseases in the United States From 1988 to 2008. Clinical Gastroenterology and Hepatology. 2011; 9(6):524–U109. [PubMed: 21440669]
7. Benjamin EJ, et al. Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. Circulation. 2018
8. Pigeyre M, et al. Recent progress in genetics, epigenetics and metagenomics unveils the pathophysiology of human obesity. Clinical Science. 2016; 130(12):943–986. [PubMed: 27154742]
9. Waalen J. The genetics of human obesity. Translational Research. 2014; 164(4):293–301. [PubMed: 24929207]
10. BR, editor BASF. Change in global chemical production (excluding pharmaceuticals) from 2011 to 2017, by region. 2017. 502018
11. Coelho M, et al. Biochemistry of adipose tissue: an endocrine organ. Arch Med Sci. 2013; 9(2): 191–200. [PubMed: 23671428]
12. Heindel JJ, et al. Metabolism disrupting chemicals and metabolic disorders. Reprod Toxicol. 2017; 68:3–33. [PubMed: 27760374]
13. Newbold RR, et al. Environmental estrogens and obesity. Mol Cell Endocrinol. 2009; 304(1–2): 84–9. [PubMed: 19433252]
14. Hao C, et al. The endocrine disruptor diethylstilbestrol induces adipocyte differentiation and promotes obesity in mice. Toxicol Appl Pharmacol. 2012; 263(1):102–10. [PubMed: 22710028]
15. Muir LA, et al. Effects of exogenous growth hormone and diethylstilbestrol on growth and carcass composition of growing lambs. J Anim Sci. 1983; 56(6):1315–23. [PubMed: 6874614]
16. Padmanabhan V, Veiga-Lopez A. Animal models of the polycystic ovary syndrome phenotype. Steroids. 2013; 78(8):734–40. [PubMed: 23701728]
17. Fenichel P, et al. The history of Diethylstilbene(R) (Diethylstilbestrol) told to grandchildren--the transgenerational effect. Ann Endocrinol (Paris). 2015; 76(3):253–9. [PubMed: 25934356]
18. Kalfa N, et al. Prevalence of hypospadias in grandsons of women exposed to diethylstilbestrol during pregnancy: a multigenerational national cohort study. Fertil Steril. 2011; 95(8):2574–7. [PubMed: 21458804]

19. Fang L, et al. The importance of environmental factors and matrices in the adsorption, desorption, and toxicity of butyltins: a review. *Environ Sci Pollut Res Int.* 2017; 24(10):9159–9173. [PubMed: 28160180]
20. Brtko J, Dvorak Z. Triorganotin compounds--ligands for "rexinoid" inducible transcription factors: biological effects. *Toxicol Lett.* 2015; 234(1):50–8. [PubMed: 25683035]
21. Antizar-Ladislao B. Environmental levels, toxicity and human exposure to tributyltin (TBT)-contaminated marine environment. a review. *Environ Int.* 2008; 34(2):292–308. [PubMed: 17959247]
22. Shue MF, et al. Tributyltin distribution and producing androgenic activity in water, sediment, and fish muscle. *J Environ Sci Health B.* 2014; 49(6):432–8. [PubMed: 24762181]
23. Kannan K, et al. Organotin compounds, including butyltins and octyltins, in house dust from Albany, New York, USA. *Arch Environ Contam Toxicol.* 2010; 58(4):901–7. [PubMed: 20379706]
24. Strand J, Jacobsen JA. Accumulation and trophic transfer of organotins in a marine food web from the Danish coastal waters. *Sci Total Environ.* 2005; 350(1–3):72–85. [PubMed: 16227074]
25. Kannan K, et al. Occurrence of butyltin compounds in human blood. *Environmental Science & Technology.* 1999; 33(10):1776–1779.
26. Nielsen JB, Strand J. Butyltin compounds in human liver. *Environ Res.* 2002; 88(2):129–33. [PubMed: 11908938]
27. Rantakokko P, et al. Association of placenta organotin concentrations with growth and ponderal index in 110 newborn boys from Finland during the first 18 months of life: a cohort study. *Environ Health.* 2014; 13(1):45. [PubMed: 24899383]
28. Lo S, et al. Dithioerythritol (DTE) prevents inhibitory effects of triphenyltin (TPT) on the key enzymes of the human sex steroid hormone metabolism. *J Steroid Biochem Mol Biol.* 2003; 84(5):569–76. [PubMed: 12767282]
29. Valenzuela A, et al. Speciation analysis of organotin compounds in human urine by headspace solid-phase micro-extraction and gas chromatography with pulsed flame photometric detection. *Talanta.* 2014; 125:196–203. [PubMed: 24840433]
30. Zhang J, et al. Tributyltin disrupts feeding and energy metabolism in the goldfish (*Carassius auratus*). *Chemosphere.* 2016; 152:221–8. [PubMed: 26971175]
31. den Broeder MJ, et al. Altered Adipogenesis in Zebrafish Larvae Following High Fat Diet and Chemical Exposure Is Visualised by Stimulated Raman Scattering Microscopy. *International Journal of Molecular Sciences.* 2017; 18(4)
32. Ouadah-Boussouf N, Babin PJ. Pharmacological evaluation of the mechanisms involved in increased adiposity in zebrafish triggered by the environmental contaminant tributyltin. *Toxicology and Applied Pharmacology.* 2016; 294:32–42. [PubMed: 26812627]
33. Lyssimachou A, et al. The Mammalian "Obesogen" Tributyltin Targets Hepatic Triglyceride Accumulation and the Transcriptional Regulation of Lipid Metabolism in the Liver and Brain of Zebrafish. *Plos One.* 2015; 10(12)
34. Zhang J, et al. Lipid accumulation, oxidative stress and immune-related molecules affected by tributyltin exposure in muscle tissues of rare minnow (*Gobiocypris rarus*). *Fish Shellfish Immunol.* 2017; 71:10–18. [PubMed: 28962884]
35. Penza M, et al. The environmental chemical tributyltin chloride (TBT) shows both estrogenic and adipogenic activities in mice which might depend on the exposure dose. *Toxicol Appl Pharmacol.* 2011; 255(1):65–75. [PubMed: 21683088]
36. Si JL, et al. Peripubertal Exposure to Low Doses of Tributyltin Chloride Affects the Homeostasis of Serum T, E2, LH, and Body Weight of Male Mice. *Environmental Toxicology.* 2011; 26(3):307–314. [PubMed: 20052771]
37. Li BS, et al. Tributyltin in male mice disrupts glucose homeostasis as well as recovery after exposure: mechanism analysis. *Archives of Toxicology.* 2017; 91(10):3261–3269. [PubMed: 28397090]
38. Zuo ZH, et al. Tributyltin Causes Obesity and Hepatic Steatosis in Male Mice. *Environmental Toxicology.* 2011; 26(1):79–85. [PubMed: 19760618]
39. Bertuloso BD, et al. Tributyltin chloride leads to adiposity and impairs metabolic functions in the rat liver and pancreas. *Toxicology Letters.* 2015; 235(1):45–59. [PubMed: 25819109]

40. Chamorro-Garcia R, et al. Transgenerational inheritance of increased fat depot size, stem cell reprogramming, and hepatic steatosis elicited by prenatal exposure to the obesogen tributyltin in mice. *Environ Health Perspect.* 2013; 121(3):359–66. [PubMed: 23322813]
41. Chamorro-Garcia R, et al. Ancestral perinatal obesogen exposure results in a transgenerational thrifty phenotype in mice. *Nature Communications.* 2017:8.
42. Grun F, et al. Endocrine-disrupting organotin compounds are potent inducers of adipogenesis in vertebrates. *Molecular Endocrinology.* 2006; 20(9):2141–2155. [PubMed: 16613991]
43. Asakawa H, et al. Enhanced Inhibitory Effects of TBT Chloride on the Development of F-1 Rats. *Archives of Environmental Contamination and Toxicology.* 2010; 58(4):1065–1073. [PubMed: 19937321]
44. Chamorro-Garcia R, et al. Effects of Perinatal Exposure to Dibutyltin Chloride on Fat and Glucose Metabolism in Mice, and Molecular Mechanisms, in Vitro. *Environ Health Perspect.* 2018; 126(5): 057006. [PubMed: 29787037]
45. Regnier SM, et al. Tributyltin differentially promotes development of a phenotypically distinct adipocyte. *Obesity.* 2015; 23(9):1864–1871. [PubMed: 26243053]
46. Pereira-Fernandes A, et al. Unraveling the mode of action of an obesogen: Mechanistic analysis of the model obesogen tributyltin in the 3T3-L1 cell line. *Molecular and Cellular Endocrinology.* 2013; 370(1–2):52–64. [PubMed: 23428407]
47. Inadera H, Shimomura A. Environmental chemical tributyltin augments adipocyte differentiation. *Toxicol Lett.* 2005; 159(3):226–34. [PubMed: 15993011]
48. Li X, et al. The environmental obesogen tributyltin chloride acts via peroxisome proliferator activated receptor gamma to induce adipogenesis in murine 3T3-L1 preadipocytes. *J Steroid Biochem Mol Biol.* 2011; 127(1–2):9–15. [PubMed: 21397693]
49. van den Dungen MW, et al. Persistent organic pollutants alter adipocyte differentiation DNA methylation during human. *Toxicology in Vitro.* 2017; 40:79–87. [PubMed: 28011154]
50. Wang RY, et al. Development of a Three-Dimensional Adipose Tissue Model for Studying Embryonic Exposures to Obesogenic Chemicals. *Annals of Biomedical Engineering.* 2017; 45(7): 1807–1818. [PubMed: 27815650]
51. Biemann R, et al. Tributyltin affects adipogenic cell fate commitment in mesenchymal stem cells by a PPARgamma independent mechanism. *Chem Biol Interact.* 2014; 214:1–9. [PubMed: 24513447]
52. Shoucri BM, et al. Retinoid X Receptor Activation Alters the Chromatin Landscape To Commit Mesenchymal Stem Cells to the Adipose Lineage. *Endocrinology.* 2017; 158(10):3109–3125. [PubMed: 28977589]
53. Baker AH, et al. Tributyltin engages multiple nuclear receptor pathways and suppresses osteogenesis in bone marrow multipotent stromal cells. *Chem Res Toxicol.* 2015; 28(6):1156–66. [PubMed: 25932594]
54. Kirchner S, et al. Prenatal Exposure to the Environmental Obesogen Tributyltin Predisposes Multipotent Stem Cells to Become Adipocytes. *Molecular Endocrinology.* 2010; 24(3):526–539. [PubMed: 20160124]
55. Li X, et al. The environmental obesogen tributyltin chloride acts via peroxisome proliferator activated receptor gamma to induce adipogenesis in murine 3T3-L1 preadipocytes. *Journal of Steroid Biochemistry and Molecular Biology.* 2011; 127(1–2):9–15. [PubMed: 21397693]
56. Pereira-Fernandes A, et al. Evaluation of a screening system for obesogenic compounds: screening of endocrine disrupting compounds and evaluation of the PPAR dependency of the effect. *PLoS One.* 2013; 8(10):e77481. [PubMed: 24155963]
57. Sales LB, et al. Effects of endocrine disrupting chemicals on in vitro global DNA methylation and adipocyte differentiation. *Toxicology in Vitro.* 2013; 27(6):1634–1643. [PubMed: 23603478]
58. Lutfi E, et al. Tributyltin and triphenyltin exposure promotes in vitro adipogenic differentiation but alters the adipocyte phenotype in rainbow trout. *Aquat Toxicol.* 2017; 188:148–158. [PubMed: 28527383]
59. Wong KH, Durrani TS. Exposures to Endocrine Disrupting Chemicals in Consumer Products-A Guide for Pediatricians. *Curr Probl Pediatr Adolesc Health Care.* 2017; 47(5):107–118. [PubMed: 28526231]

60. Calafat AM, et al. Urinary concentrations of four parabens in the U.S. population: NHANES 2005–2006. *Environ Health Perspect.* 2010; 118(5):679–85. [PubMed: 20056562]
61. Ye XY, et al. Parabens as urinary biomarkers of exposure in humans. *Environmental Health Perspectives.* 2006; 114(12):1843–1846. [PubMed: 17185273]
62. Philippat C, et al. Prenatal exposure to phenols and growth in boys. *Epidemiology.* 2014; 25(5): 625–35. [PubMed: 25061923]
63. Xue J, et al. Urinary levels of endocrine-disrupting chemicals, including bisphenols, bisphenol A diglycidyl ethers, benzophenones, parabens, and triclosan in obese and non-obese Indian children. *Environ Res.* 2015; 137:120–8. [PubMed: 25531816]
64. Hu P, et al. Differential effects on adiposity and serum marker of bone formation by post-weaning exposure to methylparaben and butylparaben. *Environ Sci Pollut Res Int.* 2016; 23(21):21957–21968. [PubMed: 27535158]
65. Boberg J, et al. Impact of diisobutyl phthalate and other PPAR agonists on steroidogenesis and plasma insulin and leptin levels in fetal rats. *Toxicology.* 2008; 250(2–3):75–81. [PubMed: 18602967]
66. Hu P, et al. Effects of parabens on adipocyte differentiation. *Toxicol Sci.* 2013; 131(1):56–70. [PubMed: 22956630]
67. Kodani SD, et al. Parabens inhibit fatty acid amide hydrolase: A potential role in paraben-enhanced 3T3-L1 adipocyte differentiation. *Toxicol Lett.* 2016; 262:92–99. [PubMed: 27659731]
68. Hu P, et al. Methylparaben and butylparaben alter multipotent mesenchymal stem cell fates towards adipocyte lineage. *Toxicol Appl Pharmacol.* 2017; 329:48–57. [PubMed: 28527915]
69. Taxvig C, et al. Differential effects of environmental chemicals and food contaminants on adipogenesis, biomarker release and PPARgamma activation. *Mol Cell Endocrinol.* 2012; 361(1–2):106–15. [PubMed: 22526026]
70. John K, et al. The glucocorticoid receptor: cause of or cure for obesity? *Am J Physiol Endocrinol Metab.* 2016; 310(4):E249–57. [PubMed: 26714851]
71. Moos RK, et al. Daily intake and hazard index of parabens based upon 24h urine samples of the German Environmental Specimen Bank from 1995 to 2012. *Journal of Exposure Science and Environmental Epidemiology.* 2017; 27(6):591–600. [PubMed: 27901017]
72. Koch HM, Calafat AM. Human body burdens of chemicals used in plastic manufacture. *Philos Trans R Soc Lond B Biol Sci.* 2009; 364(1526):2063–78. [PubMed: 19528056]
73. Garcia Ibarra G, et al. Identification of intentionally and non-intentionally added substances in plastic packaging materials and their migration into food products. *Anal Bioanal Chem.* 2018
74. Hubinger JC, Havery DC. Analysis of consumer cosmetic products for phthalate esters. *J Cosmet Sci.* 2006; 57(2):127–37. [PubMed: 16688376]
75. Myridakis A, et al. Phthalate esters, parabens and bisphenol-A exposure among mothers and their children in Greece (Rhea cohort). *Environment International.* 2015; 83:1–10. [PubMed: 26072145]
76. Program NT. Services, U.S.D.o.H.a.H. NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Di(2-Ethylhexyl) Phthalate (DEHP). 2006. 0-III-76
77. Saravanabhavan G, et al. Biomonitoring of phthalate metabolites in the Canadian population through the Canadian Health Measures Survey (2007–2009). *International Journal of Hygiene and Environmental Health.* 2013; 216(6):652–661. [PubMed: 23419587]
78. Harley KG, et al. Association of prenatal urinary phthalate metabolite concentrations and childhood BMI and obesity. *Pediatr Res.* 2017; 82(3):405–415. [PubMed: 28426647]
79. Buckley JP, et al. Prenatal Phthalate Exposures and Body Mass Index Among 4- to 7-Year-old Children: A Pooled Analysis. *Epidemiology.* 2016; 27(3):449–58. [PubMed: 26745610]
80. Buckley JP, et al. Prenatal Phthalate Exposures and Childhood Fat Mass in a New York City Cohort. *Environ Health Perspect.* 2016; 124(4):507–13. [PubMed: 26308089]
81. Hao C, et al. Perinatal exposure to diethyl-hexyl-phthalate induces obesity in mice. *Front Biosci (Elite Ed).* 2013; 5:725–33. [PubMed: 23277027]
82. Schmidt JS, et al. Effects of di(2-ethylhexyl) phthalate (DEHP) on female fertility and adipogenesis in C3H/N mice. *Environ Health Perspect.* 2012; 120(8):1123–9. [PubMed: 22588786]

83. Gu H, et al. In utero exposure to di-(2-ethylhexyl) phthalate induces metabolic disorder and increases fat accumulation in visceral depots of C57BL/6J mice offspring. *Exp Ther Med*. 2016; 12(6):3806–3812. [PubMed: 28105114]
84. Strakovsky RS, et al. In utero growth restriction and catch-up adipogenesis after developmental di (2-ethylhexyl) phthalate exposure cause glucose intolerance in adult male rats following a high-fat dietary challenge. *J Nutr Biochem*. 2015; 26(11):1208–20. [PubMed: 26188368]
85. Vom Saal FS. TRIENNIAL REPRODUCTION SYMPOSIUM: Environmental programming of reproduction during fetal life: Effects of intrauterine position and the endocrine disrupting chemical bisphenol A. *J Anim Sci*. 2016; 94(7):2722–36. [PubMed: 27482660]
86. Jia Y, et al. Effects of Di-(2-ethylhexyl) Phthalate on Lipid Metabolism by the JAK/STAT Pathway in Rats. *Int J Environ Res Public Health*. 2016; 13(11)
87. Lv Z, et al. DEHP induces obesity and hypothyroidism through both central and peripheral pathways in C3H/He mice. *Obesity (Silver Spring)*. 2016; 24(2):368–78. [PubMed: 26663559]
88. Hao C, et al. The endocrine disruptor mono-(2-ethylhexyl) phthalate promotes adipocyte differentiation and induces obesity in mice. *Biosci Rep*. 2012; 32(6):619–29. [PubMed: 22953781]
89. Wassenaar PNH, Legler J. Systematic review and meta-analysis of early life exposure to di(2-ethylhexyl) phthalate and obesity related outcomes in rodents. *Chemosphere*. 2017; 188:174–181. [PubMed: 28886551]
90. Biemann R, et al. Endocrine disrupting chemicals affect the adipogenic differentiation of mesenchymal stem cells in distinct ontogenetic windows. *Biochem Biophys Res Commun*. 2012; 417(2):747–52. [PubMed: 22197818]
91. Hurst CH, Waxman DJ. Activation of PPARalpha and PPARgamma by environmental phthalate monoesters. *Toxicol Sci*. 2003; 74(2):297–308. [PubMed: 12805656]
92. Ellero-Simatos S, et al. Combined transcriptomic-(1)H NMR metabolomic study reveals that monoethylhexyl phthalate stimulates adipogenesis and glyceroneogenesis in human adipocytes. *J Proteome Res*. 2011; 10(12):5493–502. [PubMed: 22017230]
93. Chiu CY, et al. *J Orthop Res*. 2017. Plasticizer di(2-ethylhexyl)phthalate interferes with osteoblastogenesis and adipogenesis in a mouse model.
94. Kim SH, Park MJ. Phthalate exposure and childhood obesity. *Ann Pediatr Endocrinol Metab*. 2014; 19(2):69–75. [PubMed: 25077088]
95. Sargis RM, et al. Environmental endocrine disruptors promote adipogenesis in the 3T3-L1 cell line through glucocorticoid receptor activation. *Obesity (Silver Spring)*. 2010; 18(7):1283–8. [PubMed: 19927138]
96. Yin L, et al. Benzyl butyl phthalate promotes adipogenesis in 3T3-L1 preadipocytes: A High Content Cellomics and metabolomic analysis. *Toxicol In Vitro*. 2016; 32:297–309. [PubMed: 26820058]
97. Sonkar R, et al. Benzyl butyl phthalate induces epigenetic stress to enhance adipogenesis in mesenchymal stem cells. *Mol Cell Endocrinol*. 2016; 431:109–22. [PubMed: 27164441]
98. Convention S. [accessed March 20, 2018] Stockholm Convention on Persistent Organic Pollutants (POPs) as amended in 2009. 2009. <http://chm.pops.int/TheConvention/Overview/TextoftheConvention/tabid/2232/Default.aspx>
99. Europe, W.R.O.f. Polychlorinated biphenyls (PCBs). Denmark: 2000. 1–22.
100. Cave M, et al. Polychlorinated Biphenyls, Lead, and Mercury Are Associated with Liver Disease in American Adults: NHANES 2003–2004. *Environmental Health Perspectives*. 2010; 118(12): 1735–1742. [PubMed: 21126940]
101. Genuis SJ, et al. Biomonitoring and Elimination of Perfluorinated Compounds and Polychlorinated Biphenyls through Perspiration: Blood, Urine, and Sweat Study. *ISRN Toxicol*. 2013; 2013:483832. [PubMed: 24083032]
102. Li L, et al. Revisiting the Contributions of Far- and Near-Field Routes to Aggregate Human Exposure to Polychlorinated Biphenyls (PCBs). *Environ Sci Technol*. 2018
103. Yu GW, et al. Persistent organic pollutants in serum and several different fat compartments in humans. *J Environ Public Health*. 2011; 2011:417980. [PubMed: 21647350]
104. Louis C, et al. PCB-153 Shows Different Dynamics of Mobilisation from Differentiated Rat Adipocytes during Lipolysis in Comparison with PCB-28 and PCB-118. *Plos One*. 2014; 9(9)

105. Donat-Vargas C, et al. Association between dietary intakes of PCBs and the risk of obesity: the SUN project. *Journal of Epidemiology and Community Health*. 2014; 68(9):834–841. [PubMed: 24759782]
106. Agay-Shay K, et al. Exposure to Endocrine-Disrupting Chemicals during Pregnancy and Weight at 7 Years of Age: A Multi-pollutant Approach. *Environ Health Perspect*. 2015; 123(10):1030–7. [PubMed: 25956007]
107. Dirinck EL, et al. Exposure to persistent organic pollutants: relationship with abnormal glucose metabolism and visceral adiposity. *Diabetes Care*. 2014; 37(7):1951–8. [PubMed: 24963112]
108. Govarts E, et al. Birth weight and prenatal exposure to polychlorinated biphenyls (PCBs) and dichlorodiphenyldichloroethylene (DDE): a meta-analysis within 12 European Birth Cohorts. *Environ Health Perspect*. 2012; 120(2):162–70. [PubMed: 21997443]
109. Dirinck E, et al. Obesity and Persistent Organic Pollutants: Possible Obesogenic Effect of Organochlorine Pesticides and Polychlorinated Biphenyls. *Obesity*. 2011; 19(4):709–714. [PubMed: 20559302]
110. Ferrante MC, et al. Polychlorinated biphenyls (PCB 101, PCB 153 and PCB 180) alter leptin signaling and lipid metabolism in differentiated 3T3-L1 adipocytes. *Toxicology and Applied Pharmacology*. 2014; 279(3):401–408. [PubMed: 24978599]
111. Kim HY, et al. Polychlorinated biphenyls exposure-induced insulin resistance is mediated by lipid droplet enlargement through Fsp27. *Arch Toxicol*. 2017; 91(6):2353–2363. [PubMed: 27837308]
112. Gadupudi G, et al. PCB126 inhibits adipogenesis of human preadipocytes. *Toxicol In Vitro*. 2015; 29(1):132–41. [PubMed: 25304490]
113. Chapados NA, et al. Increased proliferative effect of organochlorine compounds on human preadipocytes. *Mol Cell Biochem*. 2012; 365(1–2):275–8. [PubMed: 22350817]
114. Soechitram SD, et al. Fetal exposure to PCBs and their hydroxylated metabolites in a Dutch cohort. *Environmental Health Perspectives*. 2004; 112(11):1208–1212. [PubMed: 15289169]
115. Park JS, et al. Placental transfer of polychlorinated biphenyls, their hydroxylated metabolites and pentachlorophenol in pregnant women from eastern Slovakia. *Chemosphere*. 2008; 70(9):1676–1684. [PubMed: 17764717]
116. Arsenescu V, et al. Polychlorinated biphenyl-77 induces adipocyte differentiation and proinflammatory adipokines and promotes obesity and atherosclerosis. *Environmental Health Perspectives*. 2008; 116(6):761–768. [PubMed: 18560532]
117. Shimada T, et al. Suppression of adipocyte differentiation by *Cordyceps militaris* through activation of the aryl hydrocarbon receptor. *American Journal of Physiology-Endocrinology and Metabolism*. 2008; 295(4):E859–E867. [PubMed: 18664595]
118. Wu H, et al. Polychlorinated biphenyls-153 induces metabolic dysfunction through activation of ROS/NF-kappa B signaling via downregulation of HNF1b. *Redox Biology*. 2017; 12:300–310. [PubMed: 28285191]
119. Robledo CA, et al. Preconception maternal and paternal exposure to persistent organic pollutants and birth size: the LIFE study. *Environ Health Perspect*. 2015; 123(1):88–94. [PubMed: 25095280]
120. Anzalone DA, et al. Polychlorinated biphenyls (PCBs) alter DNA methylation and genomic integrity of sheep fetal cells in a simplified in vitro model of pregnancy exposure. *Toxicology in Vitro*. 2018; 46:39–46. [PubMed: 28964899]
121. Calafat AM, et al. Exposure to bisphenol A and other phenols in neonatal intensive care unit premature infants. *Environ Health Perspect*. 2009; 117(4):639–44. [PubMed: 19440505]
122. Mendonca K, et al. Bisphenol A concentrations in maternal breast milk and infant urine. *Int Arch Occup Environ Health*. 2014; 87(1):13–20. [PubMed: 23212895]
123. vom Saal FS, Welshons WV. Evidence that bisphenol A (BPA) can be accurately measured without contamination in human serum and urine, and that BPA causes numerous hazards from multiple routes of exposure. *Molecular and Cellular Endocrinology*. 2014; 398(1–2):101–113. [PubMed: 25304273]
124. Huang RP, et al. Bisphenol A concentrations in human urine, human intakes across six continents, and annual trends of average intakes in adult and child populations worldwide: A thorough literature review. *Science of the Total Environment*. 2018; 626:971–981. [PubMed: 29898562]

125. Vandenberg LN, et al. Human exposure to bisphenol A (BPA). *Reprod Toxicol*. 2007; 24(2):139–77. [PubMed: 17825522]
126. Ye X, et al. Urinary Concentrations of Bisphenol A and Three Other Bisphenols in Convenience Samples of U.S. Adults during 2000–2014. *Environ Sci Technol*. 2015; 49(19):11834–9. [PubMed: 26360019]
127. Wan Y, et al. Spatial distribution of bisphenol S in surface water and human serum from Yangtze River watershed, China: Implications for exposure through drinking water. *Chemosphere*. 2018; 199:595–602. [PubMed: 29459349]
128. Gerona RR, et al. Bisphenol-A (BPA), BPA glucuronide, and BPA sulfate in midgestation umbilical cord serum in a northern and central California population. *Environ Sci Technol*. 2013; 47(21):12477–85. [PubMed: 23941471]
129. Veiga-Lopez A, et al. Developmental programming: interaction between prenatal BPA exposure and postnatal adiposity on metabolic variables in female sheep. *Am J Physiol Endocrinol Metab*. 2016; 310(3):E238–47. [PubMed: 26646100]
130. Veiga-Lopez A, et al. Gender-Specific Effects on Gestational Length and Birth Weight by Early Pregnancy BPA Exposure. *J Clin Endocrinol Metab*. 2015; 100(11):E1394–403. [PubMed: 26406292]
131. Birks L, et al. Occupational Exposure to Endocrine-Disrupting Chemicals and Birth Weight and Length of Gestation: A European Meta-Analysis. *Environ Health Perspect*. 2016; 124(11):1785–1793. [PubMed: 27152464]
132. Caporossi L, Papaleo B. Bisphenol A and Metabolic Diseases: Challenges for Occupational Medicine. *Int J Environ Res Public Health*. 2017; 14(9)
133. Braun JM. Early-life exposure to EDCs: role in childhood obesity and neurodevelopment. *Nat Rev Endocrinol*. 2017; 13(3):161–173. [PubMed: 27857130]
134. Ranciere F, et al. Bisphenol A and the risk of cardiometabolic disorders: a systematic review with meta-analysis of the epidemiological evidence. *Environ Health*. 2015; 14:46. [PubMed: 26026606]
135. Oppeneer SJ, Robien K. Bisphenol A exposure and associations with obesity among adults: a critical review. *Public Health Nutrition*. 2015; 18(10):1847–1863. [PubMed: 25311796]
136. LaKind JS, et al. Bisphenol A and indicators of obesity, glucose metabolism/type 2 diabetes and cardiovascular disease: A systematic review of epidemiologic research. *Critical Reviews in Toxicology*. 2014; 44(2):121–150. [PubMed: 24392816]
137. Wassenaar PNH, et al. Systematic Review and Meta-Analysis of Early-Life Exposure to Bisphenol A and Obesity-Related Outcomes in Rodents. *Environ Health Perspect*. 2017; 125(10):106001. [PubMed: 28982642]
138. van Esterik JC, et al. Programming of metabolic effects in C57BL/6JxFVB mice by exposure to bisphenol A during gestation and lactation. *Toxicology*. 2014; 321:40–52. [PubMed: 24726836]
139. Xu X, et al. Changed preference for sweet taste in adulthood induced by perinatal exposure to bisphenol A-A probable link to overweight and obesity. *Neurotoxicol Teratol*. 2011; 33(4):458–63. [PubMed: 21704699]
140. Susiarjo M, et al. Bisphenol a exposure disrupts metabolic health across multiple generations in the mouse. *Endocrinology*. 2015; 156(6):2049–58. [PubMed: 25807043]
141. Riu A, et al. Halogenated Bisphenol-A Analogs Act as Obesogens in Zebrafish Larvae (*Danio rerio*). *Toxicological Sciences*. 2014; 139(1):48–58. [PubMed: 24591153]
142. Program, N.T. Draft NTP Research Report on the CLARITY-BPA Core Study: A perinatal and chronic extended-dose-range study of bisphenol A in rats. 2018:1–249.
143. Angle BM, et al. Metabolic disruption in male mice due to fetal exposure to low but not high doses of bisphenol A (BPA): evidence for effects on body weight, food intake, adipocytes, leptin, adiponectin, insulin and glucose regulation. *Reprod Toxicol*. 2013; 42:256–68. [PubMed: 23892310]
144. Chamorro-Garcia R, et al. Bisphenol A diglycidyl ether induces adipogenic differentiation of multipotent stromal stem cells through a peroxisome proliferator-activated receptor gamma-independent mechanism. *Environ Health Perspect*. 2012; 120(7):984–9. [PubMed: 22763116]

145. Ahmed S, Atlas E. Bisphenol S- and bisphenol A-induced adipogenesis of murine preadipocytes occurs through direct peroxisome proliferator-activated receptor gamma activation. *Int J Obes (Lond)*. 2016; 40(10):1566–1573. [PubMed: 27273607]
146. Valentino R, et al. Bisphenol-A impairs insulin action and up-regulates inflammatory pathways in human subcutaneous adipocytes and 3T3-L1 cells. *PLoS One*. 2013; 8(12):e82099. [PubMed: 24349194]
147. Bastos Sales L, et al. Effects of endocrine disrupting chemicals on in vitro global DNA methylation and adipocyte differentiation. *Toxicol In Vitro*. 2013; 27(6):1634–43. [PubMed: 23603478]
148. Ariemma F, et al. Low-Dose Bisphenol-A Impairs Adipogenesis and Generates Dysfunctional 3T3-L1 Adipocytes. *PLoS One*. 2016; 11(3):e0150762. [PubMed: 26942597]
149. Atlas E, et al. Bisphenol A increases aP2 expression in 3T3L1 by enhancing the transcriptional activity of nuclear receptors at the promoter. *Adipocyte*. 2014; 3(3):170–9. [PubMed: 25068083]
150. Xie X, et al. MiR-21a-5p suppresses bisphenol A-induced pre-adipocyte differentiation by targeting map2k3 through MKK3/p38/MAPK. *Biochem Biophys Res Commun*. 2016; 473(1): 140–146. [PubMed: 26996129]
151. Helies-Toussaint C, et al. Is bisphenol S a safe substitute for bisphenol A in terms of metabolic function? An in vitro study. *Toxicol Appl Pharmacol*. 2014; 280(2):224–35. [PubMed: 25111128]
152. Boucher JG, et al. Bisphenol A induces differentiation of human preadipocytes in the absence of glucocorticoid and is inhibited by an estrogen-receptor antagonist. *Nutr Diabetes*. 2014; 4:e102. [PubMed: 24418828]
153. Ohlstein JF, et al. Bisphenol A enhances adipogenic differentiation of human adipose stromal/stem cells. *J Mol Endocrinol*. 2014; 53(3):345–53. [PubMed: 25143472]
154. Riu A, et al. Peroxisome proliferator-activated receptor gamma is a target for halogenated analogs of bisphenol A. *Environ Health Perspect*. 2011; 119(9):1227–32. [PubMed: 21561829]
155. Kidani T, et al. Bisphenol A downregulates Akt signaling and inhibits adiponectin production and secretion in 3T3-L1 adipocytes. *J Atheroscler Thromb*. 2010; 17(8):834–43. [PubMed: 20467186]
156. Geng S, et al. Curcumin attenuates BPA-induced insulin resistance in HepG2 cells through suppression of JNK/p38 pathways. *Toxicol Lett*. 2017; 272:75–83. [PubMed: 28300666]
157. Boucher JG, et al. Identification of mechanisms of action of bisphenol a-induced human preadipocyte differentiation by transcriptional profiling. *Obesity (Silver Spring)*. 2014; 22(11): 2333–43. [PubMed: 25047013]
158. Pu Y, et al. *Endocrinology*. 2017. Sex-specific modulation of fetal adipogenesis by gestational bisphenol A and bisphenol S exposure.
159. Ahsan N, et al. Comparative effects of Bisphenol S and Bisphenol A on the development of female reproductive system in rats; a neonatal exposure study. *Chemosphere*. 2018; 197:336–343. [PubMed: 29407803]
160. Boucher JG, et al. Bisphenol S Induces Adipogenesis in Primary Human Preadipocytes From Female Donors. *Endocrinology*. 2016; 157(4):1397–407. [PubMed: 27003841]
161. Gingrich J, et al. Gestational bisphenol S impairs placental endocrine function and the fusogenic trophoblast signaling pathway. *Arch Toxicol*. 2018
162. Woodruff TJ, et al. Environmental chemicals in pregnant women in the United States: NHANES 2003–2004. *Environ Health Perspect*. 2011; 119(6):878–85. [PubMed: 21233055]
163. Mitro SD, et al. Cumulative Chemical Exposures During Pregnancy and Early Development. *Curr Environ Health Rep*. 2015; 2(4):367–78. [PubMed: 26341623]
164. Kortenkamp A. Ten years of mixing cocktails: a review of combination effects of endocrine-disrupting chemicals. *Environ Health Perspect*. 2007; 115(Suppl 1):98–105. [PubMed: 18174957]
165. Sun L, et al. Transcriptional responses in male Japanese medaka exposed to antiandrogens and antiandrogen/androgen mixtures. *Environ Toxicol*. 2016; 31(11):1591–1599. [PubMed: 26098908]

166. Biemann R, et al. Adipogenic effects of a combination of the endocrine-disrupting compounds bisphenol A, diethylhexylphthalate, and tributyltin. *Obes Facts*. 2014; 7(1):48–56. [PubMed: 24503497]
167. Carnevali O, et al. Dietary administration of EDC mixtures: A focus on fish lipid metabolism. *Aquat Toxicol*. 2017; 185:95–104. [PubMed: 28208108]
168. Kassotis CD, et al. Endocrine-Disrupting Activity of Hydraulic Fracturing Chemicals and Adverse Health Outcomes After Prenatal Exposure in Male Mice. *Endocrinology*. 2015; 156(12): 4458–73. [PubMed: 26465197]
169. Vandenberg LN, et al. Regulatory decisions on endocrine disrupting chemicals should be based on the principles of endocrinology. *Reprod Toxicol*. 2013; 38:1–15. [PubMed: 23411111]
170. Solecki R, et al. Scientific principles for the identification of endocrine-disrupting chemicals: a consensus statement. *Arch Toxicol*. 2017; 91(2):1001–1006. [PubMed: 27714423]
171. Lagarde F, et al. Non-monotonic dose-response relationships and endocrine disruptors: a qualitative method of assessment. *Environ Health*. 2015; 14:13. [PubMed: 25971433]
172. Stokes WS. Selecting appropriate animal models and experimental designs for endocrine disruptor research and testing studies. *ILAR J*. 2004; 45(4):387–93. [PubMed: 15454677]
173. Evans NP, et al. Reproduction Symposium: does grazing on biosolids-treated pasture pose a pathophysiological risk associated with increased exposure to endocrine disrupting compounds? *J Anim Sci*. 2014; 92(8):3185–98. [PubMed: 24948646]

Highlights

- This review addresses the risks posed by 6 classes of endocrine disrupting chemicals, namely non-steroidal estrogens, organotins, parabens, phthalates, polychlorinated biphenyls, bisphenols and the mechanisms by which these environmental exposures may contribute to the obesity epidemic.
- Most animal studies carried out with obesogenic EDCs have not carefully accounted for environmental exposure levels, developmental susceptibility windows translatable to humans, and/or sex-specific effects.
- Studies with obesogenic EDCs have focused on one EDC or one class of EDC, and failed to consider negative interactions, additivity, and synergism amongst the different classes of EDCs.
- Epidemiologic studies, which point to the association with obesity and not causality, have focused on specific populations and not considered latency of effects.
- The link between environmental obesogenic EDCs and the obesity epidemic remains to be proven.

Figure 1. Sources of obesogenic endocrine disrupting chemicals (EDCs). Each chemical class (bold) is shown along with the most common exposure source(s), namely industrial and common consumer products. Note: some EDCs share sources of origin.

Figure 2.

Mechanisms of actions of obesogenic endocrine disrupting chemicals (EDCs). EDCs and the generic formula for the EDC class and that of a representative chemical (*italics*) of each of the six classes of EDC, is shown in blue boxes. Potential mediators (receptors, endoplasmic reticulum stress, epigenetic mechanisms) by which obesogenic effects (increased weight, adipose tissue mass, and/or adipogenesis) that have been demonstrated to be induced for each class of EDC are linked by arrows to the EDC classes. Abbreviations: AhR: aryl hydrocarbon receptor, Akt: protein kinase B, AR: androgen receptor, BPA: bisphenol A, DES: diethylstilbestrol, ER: estrogen receptor, ER stress: endoplasmic reticulum stress, FAAH: fatty acid amide hydrolase, FSP27: fat-specific protein 27, JNK: c-Jun N-terminal kinase, GR: glucocorticoid receptor, LXR: liver X receptor, MAPK: p38/ mitogen-activated protein kinase, miRNA: microRNA, NF- κ B: nuclear factor kappa-light-chain-enhancer of activated B cells, mTOR: mammalian target of rapamycin, PPAR γ : peroxisome proliferator-activated receptor gamma, RXR: retinoid X receptor, TBT: tributyltin.

Figure 3.

Schematic summarizing known obesogenic effects (increased birth weight / weight gain, increased adipose tissues / obesity, increased lipid and/or triglycerides in circulation, and increased adipogenic differentiation) of the six classes of EDCs listed in center box. The summary was developed based on the literature summarized in the text of the review and includes evidence from epidemiological, animal, and *in vitro* studies. The six EDC classes (e.g.: organotins (TBT) in purple) are represented by different colors. Solid arrows linking the obesogen with a specific effect (arrows color coded to match the EDC class) indicates demonstrated obesogenic effect. Dotted line represents conflicting evidence in the literature. Absence of a link for a specific EDC represents no demonstrated effect.

Table 1

List of obesogenic chemicals and exposure levels.

Type	Chemical	Abbreviation	Source	Range of human exposure
Non-steroidal estrogen	diethylstilbestrol	DES	n/a	Administered dose: < 5 mg, po
Parabens	butylparaben	BP	Urine	0.2 – 1,240 µg/L
	methylparaben	MP	Urine	56.4 µg/L ^{GM}
	ethylparaben	EP	Urine	1 – 1,110 µg/L
	propylparaben	PP	Urine	7.91 µg/L ^{GM}
	benzylparaben	BzP	Urine	< 0.10 – 0.5 ng/mL
Phenols	bisphenol A	BPA	Urine	0.36 – 2.07 µg/mL ^{GM}
		uBPA	Umb cord	< LOD - 52.26 ng/mL
		sBPA	Umb cord	< LOD - 9.37 ng/mL
		gBPA	Umb cord	< LOD - 3.05 ng/mL
	bisphenol S	BPS	Mat blood	5.90 µg/L ^{GM}
Phthalates	mono 2-ethylhexylphthalate	MEHP	Urine	4.27 µg/L ^{GM}
	di 2-ethylhexylphthalate	DEHP	Serum	< 5.7 ng/mL
	benzylbutylphthalate	BBP	Urine	6.9 µg/L ^{GM} (measured BBP with surrogate metabolite mBzP)
	dicyclohexylphthalate	DCHP	Urine	< 0.2 ng/mL (measured DCHP with surrogate metabolite MCHP)
Polychlorinated biphenyls	polychlorinated biphenyls (coplanar)	PCBs	Serum	0.0075 – 22.8 ng/g
	PCBs (non-dioxin-like)	PCBs	Serum	0.19 – 75.55 ng/g
	PCB-28, 52, 66, 101, 110	PCBs	Urine	6.1 – 30.3 ng/mL
	PCB-52, 118, 138, 153, 180	PCBs	Blood	17.9 – 57.1 ng/mL
Organotins	tributyltin	TBT	Blood	< 1 – 85 ng/mL
	tributyltin	TBT	Urine	0.0008 - 0.0028 ng/mL
	triphenyltin	TPT	Serum	0.17 – 0.67 ng/mL
	triphenyltin	TPT	Urine	0.0049 – 0.016 ng/mL

GM superscript refers to geometric mean. Abbreviations: gBPA: BPA glucuronide, GM: geometric mean, LOD: level of detection, mBzP: Mat blood: maternal blood, Mono-benzyl phthalate, MCHP: Monocyclohexyl phthalate, sBPA: BPA sulfate, and uBPA: unconjugated BPA, umb cord: umbilical cord. References for paraben [58,59], phthalates [73–75], phenols [123–125], polychlorinated biphenyls [97,98], and organotins [24,27,28].