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# Mini Review: Transgenerational effects of Obesogens

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## Abstract

Obesity and associated disorders are now a global pandemic. The prevailing clinical model for obesity is overconsumption of calorie-dense food and diminished physical activity (the calories in - calories out model). However, this explanation does not account for numerous recent research findings demonstrating that a variety of environmental factors can be superimposed on diet and exercise to influence the development of obesity. The environmental obesogen model proposes that exposure to chemical obesogens during *in utero* and/or early life can strongly influence later predisposition to obesity. Obesogens are chemicals that inappropriately stimulate adipogenesis and fat storage, *in vivo* either directly or indirectly. Numerous obesogens have been identified in recent years and some of these elicit transgenerational effects on obesity as well as a variety of health endpoints after exposure of pregnant F0 females. Prenatal exposure to environmental obesogens can produce lasting effects on the exposed animals and their offspring to at least the F4 generation. Recent results show that some of these transgenerational effects of obesogen exposure can be carried across the generations via alterations in chromatin structure and accessibility. That some chemicals can have permanent effects on the offspring of exposed animals suggests increased caution in the debate about whether and to what extent exposure to endocrine disrupting chemicals and obesogens should be regulated.

## Introduction

The obesity pandemic is an escalating worldwide public health crisis, affecting over 650 million people across all race, age and socio-economic groups. Despite global recognition and endless health campaigns targeting caloric intake and physical activity, the trends in obesity and obesity-related diseases are steadily rising. Worldwide obesity tripled from 1975–2016 and obesity in the US alone more than doubled between 1980 and 2010 [1, 2]. These rates continue to rise, with the most recent statistics indicating that the fraction of obese adults in the US has reached nearly 40% [3, 4]. This burden of obesity falls most heavily on woman and some minority populations with the obesity rate in African American

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and Hispanic women exceeding 50% [4]. Alarmingly, childhood obesity rates have more than tripled in the US [5]. Even the percentage of obese 2- to 5-year-olds has more than doubled from 5% to 13.9% and among teens ages 12 to 19, the rate increased four-fold, from 5% to 20.6% [5]. Childhood obesity can be detrimental to physical and emotional health and is closely associated with negative social and health outcomes including poor self-esteem, academic performance and impaired cardiovascular health. Moreover, overweight children are likely to continue being overweight or obese into adulthood and the fraction of obese adults who successfully lose large amounts of weight and then maintain this weight loss is than 17% [6, 7]. Obesity is associated with the development of non-communicable diseases such as type 2 diabetes, cancer and cardiovascular disease which contribute greatly to the medical costs of obesity. These costs were recently estimated at more than $200 billion annually in the US [8] and the fraction of these costs that could be attributed to but a small number of known obesogens was substantial [9, 10]. The actual cost is likely to be significantly higher. This magnitude of the medical and human capital costs of obesity underscores the necessity of investigating all relevant factors to the obesity pandemic.

## The Energy Balance Dogma

On the surface, the cause of this obesity pandemic seems simple: too much caloric intake and not enough exercise. As a result, health professionals have led the general public to focus on weight management strategies that involve reducing an individual's net caloric balance through portion control and increasing physical exercise. However, this strategy has proven to be wholly inadequate at the population level as the number of obese people continues to rise worldwide. Moreover, the simplistic concept of increased caloric consumption and reduced exercise cannot explain the rapid rise in obesity. A key recent study examined NHANES data between 1988 and 2006 and found that even at the same levels of calorie consumption and energy expenditure via exercise, the average BMI was 2.3 $kg/m^2$ higher in 2006 than in 1988 [11]. In addition, the same NHANES data set refuted the idea of increased sedentary behaviour in the population by demonstrating that leisure time physical activity increased 47% in males and 120% in females between 1988 and 2006. Another series of studies demonstrated that exercise is consistently linked with increased fat mass in the long term [12, 13]. Thus, the energy imbalance model of calories consumed vs. calories expended is not sufficient to explain the uphill trend in obesity; other causes and risk factors should be considered. This has recently been recognized by representatives of the World Obesity Federation, World Economic Forum, the World Health Organization and several leading universities who wrote, "The established narrative on obesity relies on a simplistic causal model with language that generally places blame on individuals who bear sole responsibility for their obesity. This approach disregards the complex interplay between factors not within individuals' control (eg, epigenetic, biological, psychosocial) and powerful wider environmental factors and activity by industry (eg, food availability and price, the built environment, manufacturers' marketing, policies, culture) that underpin obesity" [14]. We could not agree more.

## Obesity lacks a single cause

Generally speaking, adult body weight is stable over time and normal physiological mechanisms balance metabolic control with hedonic inputs from the nervous system [15]. Thus, the brain can sense environmental cues, process metabolic inputs from multiple tissues and integrate these disparate data to manage body weight. In the typical situation, a temporary weight loss from illness or weight gain from holiday eating or the first year of university 10–15-pound weight gain is compensated and a “normal” weight is regained when these disturbances are remediated. This has led to the proposal that there is a type of “body weight set point” [15]. While this is not an immutable set point such as body temperature, it makes sense that body weight is managed around such a set point. One factor that argues strongly in favour of such a set point is the observation that obesity is rarely reversible once established. More than 83% of obese individuals who lost substantial amounts of weight through rigorous adherence to a regimen of dietary restriction and exercise gained it back within a few years [6, 7, 16]. In the absence of a body weight set point that these people had to fight (and failed), it is difficult to understand why such a small fraction of people who successfully remodelled their bodies could maintain this new normal. How and when might such a set point be established?

## The Developmental Nature of Obesity

A number of factors can play into the obesity equation, including diet [17], genetics [18, 19], smoking during pregnancy [20, 21], stress [22, 23], the microbiome [24–26] and timing of meal consumption [27, 28]. However, an ever growing body of evidence demonstrates that obesity can be orchestrated before a person is even born. The foetal origins hypothesis, first promulgated by David Barker, proposes that the 9 months *in utero* has the ability to shape individual health outcomes and future well-being trajectories [29, 30]. Barker showed that infants born small for gestational age (and presumably undernourished as fetuses, *in utero)* were more likely to become obese adults and suffer unfavourable metabolic and cardiovascular conditions in comparison with infants who were not subjected to a nutritionally poor environment [31, 32]. Barker called this the “thrifty phenotype” and posited that it reflected an imbalance between the nature of the foetal environment and the adult environment; the undernourished foetus adapted itself to a calorie poor environment but grew up to experience a calorie sufficient or calorie rich environment for which it was not prepared [30]. This provided a strong link between the prenatal environment and postnatal health outcomes and presumed the existence of “prenatal programming” which became known as the foetal origins model. Since it is also recognized that critical periods in development are not restricted to the *in utero* period, Gluckman and Hanson proposed the “Developmental Origins of Health and Disease” or DOHaD paradigm to reflect this fact [33–35].

A key tenet of the DOHaD and foetal origins models is that foetal and early life programming set the parameters of “normal” adult physiological function. Developmental disturbances can produce adult physiology that is outwardly normal but which has underlying functional deficits that can increase susceptibility to disease. An extensive set of studies in animals and humans have borne out a connection between poor prenatal nutrition

and increased risk of diseases such as obesity throughout the life course and even in subsequent generations [29, 36]. What is currently lacking is an understanding of the molecular details through which such developmental programming occurs. Recent studies have implicated epigenetic mechanisms which will be discussed further below [37–39].

Economists have expanded on the DOHaD hypothesis, investigating a broader range of foetal shocks and circumstances and have found a wealth of later-life outcomes including test scores, educational attainment and income, along with health that reflect these exposures. For example, adults with prenatal exposure to maternal fasting during Ramadan were 20% more likely to have mental and learning disabilities compared to adults that were never exposed [40]. The fact that these effects were observed with a relatively mild foetal shock (episodic periods of fasting) leads one to question how much of an effect other common exposures would produce. The 1918 influenza pandemic was a more severe prenatal stressor, and one-third of babies born in early 1919 had mothers who acquired the infection while pregnant [41]. Despite the short time period of exposure to the foetal stressor, the individuals exposed to the influenza *in utero* were 20% more likely to be disabled and experienced reduced educational attainment [41]. These are but two among many examples of diverse foetal exposures resulting in significant, persistent and unfavourable health outcomes.

To further support the importance of environmental effects on development, the escalating obesity trend in humans is mirrored in animals living in close proximity to humans. These include our pet cats and dogs but also feral rats living in cities and, crucially, rats, mice and primates living in research colonies where caloric intake is strictly controlled [42]. This puzzling finding highlights just how little is known about the factors influencing fat accumulation and shines a bright light on the potential role of the environment in addition to lifestyle choices as drivers of the obesity pandemic.

## Endocrine disrupting chemicals

The endocrine system plays many important roles in energy balance, fat deposition and fat distribution in the body. Insulin and glucagon produced in the pancreas modulate glucose uptake and usage; ghrelin and cholecystokinin affect metabolism in the gastrointestinal tract; glucagon, insulin and fibroblast growth factor 21 (FGF21) act in the liver to control metabolism, hunger and satiety. The brain itself is an endocrine organ that controls hedonic circuits that modulate food intake via reward mechanisms involving peptide hormones, neurotransmitters and growth factors as well as regulating metabolism [15, 43–45]. Sex hormones such as estradiol and testosterone can affect food intake, body weight, fat distribution and can alter the balance of glucose and insulin, lipogenesis and lipolysis, all of which affect energy metabolism and, ultimately obesity [reviewed in 46].

It is now widely accepted that endocrine-active chemicals in the environment can disrupt hormone function to influence health, particularly by altering developmetnal programming [reviewed in 47, 48]. The Endocrine Society defines an endocrine-disrupting chemical (EDC) as an exogenous chemical, or mixture of chemicals, that can interfere with any aspect of hormone action” [49]. This is distinct from the EPA and WHO definitions which add the

rather vague requirement that such effects must also be “adverse”. Endocrinologists and endocrine scientists recognize disruption of hormonal signalling as adverse, *per se* [49]. A general feature of endocrine signalling systems is that the endogenous hormones function at quite low levels (nano- to picomolar); therefore, molecules capable of disrupting them are expected to act at similar doses and not to exhibit threshold effects because endocrine signalling systems are typically already active [50].

## The obesogen hypothesis

In 2006, Blumberg and Grün proposed the existence of chemicals, including EDCs, that could influence adipogenesis and obesity and be important, yet unsuspected players in the obesity pandemic. These “obesogens” can be defined by their function as chemicals that promote obesity in humans or animals [51]. The obesogen hypothesis extended the DOHaD paradigm for obesity by proposing that obesogens could act during development to predispose the exposed individual to obesity in adolescence or adulthood. In principle, obesogens can act directly on cells to increase the commitment or differentiation of adipocytes from stem cells or preadipocytes, thereby altering adipocyte number. They can also act by inducing adipocytes to increase triglyceride storage and/or by altering adipocyte homeostasis. The average adipocyte lives for ten years [52], therefore, altering the rate of adipocyte birth or death can influence the total number. Obesogens can also act indirectly to increase fat mass by changing basal metabolic rate, by modulating food intake via effects on the brain, pancreas, adipose tissue, liver, gastrointestinal tract, brain and muscle, by shifting energy balance to favour calorie storage, and by altering the composition of the microbiome [reviewed in 46, 53, 54]. Recent studies have established that obesogens can alter metabolic “set points” leading to obesity later in life, particularly when dietary composition or caloric intake is changed [55, 56]. Obesogens do not necessarily induce obesity alone, but they can alter developmental programming, affecting nuclear factors or other endocrine pathways during development in ways that lead to obesity later in life. It is important to note that not all EDCs are obesogens and not all obesogens are EDCs; there are dietary obesogens such as refined sugars that may not meet the strict definition of an EDC, but which are definitely obesogens.

## Mechanisms of obesogen action

An important outstanding question is the extent to which exposure to obesogens contributes to the obesity pandemic in humans. To address this important question, one must examine the data that support or refute the obesogen hypothesis and the extent to which these data are consistent with the importance of environmental obesogens in the aetiology of obesity. Moreover, it is critical to have extensive data from longitudinal epidemiological studies in humans, together with accurate and repeated measurements of obesogen levels at least throughout pregnancy (which are largely absent from the literature at the moment). Numerous reviews have been written on this topic based on data from human and animal studies [46, 53, 54, 57–62]. EDCs have been linked to obesity, and obesogens have been detected in humans [63–67] and animals [68–71]. It is important to note that no systematic effort has yet been undertaken to determine the number of potential obesogens that are present in the tens of thousands of chemicals in widespread use. These chemicals are

pervasive in the environment; therefore, it is crucial to understand which of them might be obesogens, how they disrupt developmental programming, predisposing individuals to obesity and related disorders. At this writing, about 50 chemicals have been identified that can act as obesogens, *in vivo* [46]. Unfortunately, we currently know very little about the molecular mechanisms through which most obesogens act but some examples of known obesogens follow together with the mechanisms through which some of them act.

## Obesogens reprogram stem cell fate

One of the first *bona fide*, *in vivo* obesogens to be identified was the antifouling agent, tributyltin (TBT). Organotins are widely used in industry and the related chemical, triphenyltin (TPT) is used in agriculture, primarily as a miticide. Although there are no biomonitoring efforts to monitor organotin exposure in humans, exposure likely occurs through dietary sources such as seafood and shellfish contaminated by TBT used in marine shipping applications or as fungicides for paper mills and industrial water systems. TPT use as a fungicide on high value food crops presents more opportunities for human exposure. TBT is present in vinyl plastics as a contaminant (non-intentionally added substance) of the heat stabilizer dibutyltin (DBT) and has been found at appreciable levels in house dust in the US [72, 73]. TBT binds directly to the “master regulator” of adipogenesis, peroxisome proliferator activated receptor gamma (PPARγ) and its heterodimeric partner, 9-cis retinoic acid receptor (RXR) at nanomolar (parts per billion) levels [70, 74, 75]. Several studies have shown that pre-adipocytes as well as mouse and human multipotent mesenchymal stromal cells (aka mesenchymal stem cells, MSCs) can be induced to differentiate into adipocytes by organotins such as TBT and TPT [70, 75] as well as the highly prevalent DBT [76, 77]. These results are largely dependent on the ability of these chemicals to activate PPARγ [78–80]. Adult mice exposed to TBT *in utero* displayed increased lipid accumulation in adipose depots, livers and testis [70, 81] and treatment of adolescent or adult mice, rats, goldfish and zebrafish led to increased fat deposition and hepatic steatosis [82–85]. Very few epidemiological studies of TBT levels exist, yet TBT continues to be found in house dust [73] and in seafood, [86] and at least one study shows increased ponderal index in human infants with the highest prenatal TBT exposure [87].

Several other chemicals have been identified as obesogens, *in vivo*. These include the fungicides triflumizole [79], tolylfluanid [88] and the plasticizer diethylhexyl phthalate [89]. Tolylfluanid was shown to act via the glucocorticoid receptor [88] whereas triflumizole acts through PPARγ [79]. Which receptor diethylhexyl phthalate acts through is unknown but the action may be via its metabolite monoethylhexylphthalate on PPARγ.

A variety of other potential obesogens have been identified that are known to act on preadipocytes or MSCs to promote adipogenic differentiation [90, 91]. It was recently shown that TBT and other chemicals that activate RXR, commit MSCs to the adipose lineage by activating RXR, but not PPARγ. TBT and pharmacological RXR agonists de-repress genes important for adipogenic commitment by decreasing deposition of the repressive chromatin mark, histone 3 lysine 27 trimethyl ($H3K27^{me3}$) in the promoters and regulatory regions of these genes, leading to increased expression of their mRNAs [92]. Therefore, it is likely that other RXR activators (these are collectively called ‘rexinoids’) such as the fungicide

fludioxonil or the surfactant SPAN-80 will produce similar effects. Intriguingly, a variety of other fungicides with widely divergent structures, including flusilazole, zoxamide and quinoxyfen are candidate obesogens, *in vitro* [90]. Other agrochemicals such as tebupirimfos, flusilazole, forchlorfenuron, acetamiprid and pymetrozine induce 3T3-L1 preadipocytes to differentiate into adipocytes in culture by mechanisms other than activating PPARγ [90]. Flame retardants, phthalates, plasticizers, parabens, alkylphenols and bisphenols can all differentiate 3T3-L1 cells to adipocytes *in vitro* [reviewed in 46]. Which of these candidate obesogens lead to increased fat accumulation *in vivo* remains unknown. However, the next chemical shown to induce the differentiation of fat cells, *in vitro*, that does not cause fat accumulation *in vivo*, will be the first.

## Obesogen exposure can produce unhealthy adipocytes

Considering how many chemicals increase the commitment or differentiation of adipocytes, it is reasonable to ask whether the adipocytes produced are normal and fully functional [93]. Such studies were prompted by the studies of Sargis and colleagues who investigated the effects of TBT vs. the pharmaceutical PPARγ activator, troglitazone on the differentiation and function of 3T3-L1 preadipocytes, *in vitro* [94]. TBT-induced adipocytes produced lower levels of adiponectin and CEBPα mRNA and protein than did troglitazone-induced adipocytes. The TBT-induced adipocytes displayed reduced GLUT4 expression but normal glucose uptake and they inferred that TBT had produced “unhealthy” adipocytes [94]. White adipocytes play an important role in metabolic health by removing glucose from the circulation when stimulated by insulin [95]. White adipose tissue (WAT) also releases important adipokines such as adiponectin [96]. Adiponectin expression is inversely correlated with risk of type 2 diabetes largely by suppressing gluconeogenesis and stimulating β-oxidation of fatty acids in the liver [97]. Pharmaceutical PPARγ activators are thought to promote the development of “healthy” adipocytes which are characterized by their production of healthy adipokines such as adiponectin, their sensitivity to glucose, their anti-inflammatory and non-fibrotic local microenvironment and by being normoxic and not hypertrophic [98, 99].

Shoucri and colleagues confirmed and extended these results to a stem cell model and addressed the mechanistic underpinnings of the obesogenic phenotype. They treated differentiating MSCs with the PPARγ activator rosiglitazone (ROSI), the RXR activator IRX4204 or the dual RXR/PPARγ agonist TBT and investigated the transcriptome and function of the adipocytes produced in this way. They showed that TBT- and 4204-treated cells accumulated essentially the same amount of fat as did ROSI-treated cells but that TBT- and 4204-induced adipocytes differed in a number of ways from ROSI-induced adipocytes [93]. TBT or 4204-induced adipocytes expressed reduced levels of GLUT4 accompanied by lower glucose uptake. They produced lower levels of adiponectin mRNA and protein and showed elevated levels of molecular markers of inflammation and fibrosis [93]. The TBT or 4204-treated cells were impaired in their respiratory function, measured *in vitro* and, as might be expected, contained fewer mitochondria [93]. Intriguingly, the TBT or rexinoid induced adipocytes were less able to produce thermogenic beige/brite fat. Taken together, these data show that while ROSI, TBT or rexinoid differentiated adipocytes all accumulated fat to similar levels, *in vitro*, the TBT or rexinoid differentiated cells did not respond to

normal signalling processes. This may be highly relevant to the observations that animals treated with these chemicals accumulate excess fat. To what extent other environmental obesogens produce normal or dysfunctional WAT and the mechanisms through which they accomplish this is an open and exciting question to address in the future.

## Obesogens exposure can impair thermogenesis

An important recent advance in understanding adipocyte function was the discovery that thermogenic brown adipose tissue (BAT) is found in adult humans, albeit dispersed, rather than concentrated in discrete depots as in human infants [100]. Another key discovery was that white adipose tissue (WAT) can be induced to produce thermogenic fat, which has been termed beige or brite fat [101, 102]. Both the differentiation of *bona fide* brown adipocytes and the beiging of white adipocytes are characterized by the increased production of mitochondria. Thermogenesis relies on the presence of Uncoupling Protein 1 (UCP1) which uncouples cellular respiration from ATP synthesis to generate heat instead of ATP. There is some recent evidence that at least a few obesogens exert some of their functions by impeding the production or function of thermogenic adipocytes. La Merrill and colleagues showed that perinatal exposure to the insecticide dichlorodiphenyltrichloroethane (DDT) produces an interesting phenotype: adult female animals are intolerant to cold, have reduced core temperature accompanied by lower energy expenditure [103]. The authors ascribed much of this reduced BAT function to diminished expression of peroxisome proliferator-activated receptor γ coactivator 1α (Ppargc1α or PGC-1α) and iodothyronine deiodinase 2 (Dio2, which converts thyroxine, T4, to the more thermogenic triiodothyronine, T3). Secondly, as noted above, Shoucri and colleagues recently found that production of beige/brite fat cells from MSCs was inhibited by TBT or rexinoids [93]. These examples indicate that obesogens can influence obesity by impairing thermogenesis, *in vitro* and *in vivo*. This is an intriguing area for future study. The European Untion has recently funded several large grants through their Horizon 2020 program that aim to develop sensitive new assays to assess the effects of EDCs on metabolic endpoints. Among these are assays that will identify chemicals that affect thermogenesis which may allow the identification of more such chemicals.

## Can obesogens modulate metabolic setpoints?

Despite abundant evidence from animal models showing that obesogen exposure can elicit increased fat depot weight, adipocyte size and number, the human situation will undoubtedly be more complex. Humans have a number of contributing factors to obesity such as diet composition and caloric input, composition of the gut microbiome, circadian rhythms, type and amount of exercise, environmental stressors such as air pollution, noise and light pollution and some input from genetics. Moreover, these multiple influences interact with each other and with confounding factors such as prescription drugs, dietary supplements and individual variation. The common human lament of weight being easy to gain yet hard to lose, together with abundant evidence showing that sustained weight loss in obese individuals is rare, and that adding exercise to one's lifestyle without modifying caloric input results in increased body fat all support the existence of some sort of body weight set point. In this view, the combination of physical activity and caloric intake are key factors in

weight control and the effects of obesogen exposure are superimposed onto these other factors. That is, obesogen exposure alone may be insufficient to produce obesity, interactions with other factors such as diet may be critical.

Research in multiple laboratories has supported the existence of a body weight point that can be altered by obesogen exposure. Perinatal exposure to the estrogen, diethylstilbestrol led to weight gain at adulthood despite no detectable increase in food intake [104]. Prenatal nicotine exposure in rats produced adults that required less high-fat food to gain weight [105]. Exposure of F0 female mice to TBT throughout pregnancy and lactation led to males of the unexposed F4 generation gaining weight very rapidly when dietary fat was increased; they retained much of this extra fat even after their chow was returned to the previous low-fat diet [55]. The animals also over-expressed leptin and the authors inferred they were leptin-resistant [55]. A very important recent study in humans showed that caloric restriction in a clinical setting led to weight loss, irrespective of the type of diet but that individuals regained weight at different rates when dieting was ceased [56]. Intriguingly, those individuals who regained weight the most quickly had lower resting metabolic rates than those who regained weight more slowly and that the rapid weight regainers had the highest levels of perfluoroalkyl chemicals in their blood [56]. This provided the first link between metabolic rate in humans and chemical contaminants in blood. Resting metabolic rate is the biggest consumer of calories in human physiology; therefore, small alterations in this rate can have large consequences on body weight. In sum, these data support the concept of a metabolic set point that might be malleable by exposure to chemical obesogens.

## The effects of EDCs and obesogens can be heritable

One of the most startling results in the EDC field came in 2005 when Michael Skinner and colleagues showed that prenatal exposure to the anti-androgenic fungicide vinclozolin, or the estrogenic pesticide methoxychlor led to disease in various organs in the F4 generation [106]. More recently, when pregnant mice were treated with environmentally-relevant (nM) doses of TBT via their drinking water, effects were detected in the F1–F3 descendants of F0 mice exposed during pregnancy [81] or the F1–F4 descendants of animals treated during pregnancy and lactation [55]. Notably, unlike TBT, the pharmacological obesogen, ROSI which activates PPAR$\gamma$, could not produce such transgenerational effects on obesity, suggesting that despite its action through PPAR$\gamma$ in cell culture, additional or different targets of TBT were required to generate transgenerational effects [55, 81]. TBT exposure led to a transgenerational “thrifty phenotype” in F4 male (but not female) mice. This thrifty phenotpye as manifested as males being resistant to fat loss during fasting and showing an increased propensity to gain weight when dietary fat was increased. Since this phenotype was not manifested until diet challenge, it is clear that it does not result from the trivial explanation of fat animals producing fat offspring. The authors inferred that the thrifty phenotype was associated with changes in chromatin structure that led to subsequent alterations in DNA methylation and overexpression of leptin and important metabolic genes in white adipose tissue (WAT) [55]. In addition to these effects of TBT on obesity, Skinner and colleagues have shown that plastic components BPA, diethylhexyl and dibutyl phthalates [107], the pesticide methoxychlor [108], a mixed hydrocarbon mixture (jet fuel JP-8) [109] and the pesticide, DDT [110] can all cause transgenerational obesity in the rat model.

It is currently controversial which molecular mechanisms underlie transgeneral inheritance of any trait, including obesity. While most investigators in the EDC field believe that these effects are transmitted in an epigenetic manner, this idea has met with strong resistance in the genetics community [111]. However, it is clear that the normal development of mammalian germline cells depends on hormonally regulated functions of somatic cells supporting their survival and differentiation, thus it is reasonable to hypothesize that EDCs could affect epigenetic reprogramming of germline cells. Perhaps the strongest argument raised against the transmission of epigenetic marks such as DNA methylation is that genome-wide epigenetic reprogramming in mammalian germline cells should erase epimutations from the preceding generation [111–113]. Some investigators report stable transgenerational changes in DNA methylation [110, 114, 115]; others found that the same chemicals induced epimutations and alterations in gene expression in the F1 generation, but that these were not conserved in F2 prospermatogonia [116]. Other factors such as histone retention and small non-coding RNA inheritance have been invoked as being involved in transgenerational inheritance [117], but the mechanisms underlying the transfer of these factors across generations remain elusive. One possible model comes from the work of Chamorro-García and colleagues who proposed that changes in chromatin accessibility and large scale organization are transmitted across generations. In their model, altered accessibility of the chromatin to DNA and histone modifying enzymes can lead to secondary changes in DNA and/or histone methylation that can ultimately result in differential gene expression [55]. It remains to be seen just what changes in chromatin structure can be transmitted across generations and whether different chemical obesogens produce overlapping changes in chromatin structure.

## FUTURE DIRECTIONS

Obesity adds at least $200 billion to US healthcare costs annually [8], and the number of obese individuals continues to increase [4]. Thus, studies aimed at discovering the many mechanisms underlying the predisposition to obesity and related disorders are timely and important. Recent estimates of the impact of three obesogens on the cost of obesity to the EU inferred an annual cost of €18 billion [10]. A similar study was performed for the US population and estimated an annual cost of $5.9 billion [9]. These are likely to be gross underestimates since they only considered exposure to 3 obesogens. The number was limited to 3 because the number of prospective cohorts with suitable measurements of chemical levels to infer exposure was quite limited. Thus, we need appropriate studies to estimate the cost of the other ~50 known obesogens to world society and to what degree obesogen exposure influences obesity in humans. There are important knowledge gaps regarding the effects of multiple simultaneous or serial obesogen exposures as well as the interactions between obesogen exposure and established risk factors in obesity. Such factors include inflammation, disrupted circadian rhythms, oxidative stress, mitochondrial dysfunction, dietary composition, timing of eating and the regulation of appetite and satiety. These interactions could be critical in understanding the effects of obesogens on humans. We know very little about how to determine who has been exposed to obesogens during their development, or in their ancestry. Identifying biomarkers of exposure is a “Holy Grail” of obesogen research and will allow the establishment of strong links between obesogen

exposure, other risk factors and the eventual development of obesity and related disorders. Effects of obesogen and EDC exposure are at least in part epigenetic, yet we know relatively little about the underlying mechanisms and how the effects are transmitted across the generations. For example, how does exposure of pregnant F0 female mice lead to obesity in unexposed F3 and F4 males [55]? Is there a causal link between perfluoroalkyl chemicals and reduced resting metabolic rate [56]? Which molecular targets mediate the effects of obesogens on metabolic programming *in vivo*? Relatively little is known about the extent to which obesogen exposure programs dysfunctional adipose tissue that may readily store, but not mobilize fat. There is an extreme paucity of data on the effects of multiple or continuing exposures over the life course and across generations.

The obesogen field is only about 15 years old. Much has been learned about the potential effects of EDCs and obesogens in obesity. Perhaps the strongest evidence for the existance of chemical obesogens are the observations that a variety of pharmaceuticals have the side effects of making patients fat [reviewed in 46, 118]. Drugs are nothing more than chemicals that have been tested and validated to be effective against a particular condition; it is obvious that chemicals targeting the same molecular pathways should elicit similar effects. Several international workshops have been held to discuss the potential role of EDCs in obesity and metabolic diasease [10, 46, 119, 120]. There is wide agreement that obesogens exist and have the potential to influence obesity in humans. Thus, it would be prudent to consider policies and strategies aimed at reducing obesogen exposure in the population in addition to other preventive factors.

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## References

1. G. B. D. Obesity CollaboratorsAfshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, et al. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. N Engl J Med 2017;377:13–27. [PubMed: 28604169]
2. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010. JAMA : the journal of the American Medical Association 2012;307:491–7. [PubMed: 22253363]
3. Flegal KM, Kruszon-Moran D, Carroll MD, Fryar CD, Ogden CL. Trends in Obesity Among Adults in the United States, 2005 to 2014. JAMA : the journal of the American Medical Association 2016;315:2284–91. [PubMed: 27272580]
4. Hales C, Carroll M, Fryar CD, Ogden CL. Prevalence of Obesity Among Adults and Youth: United States, 2015–2016 Hyattsville, MD: U.S. Department of Health & Human Services, Statistics NCfH; 2017 October 2017. Report No.: NCHS Data Brief No 288, October 2017 Contract No.: Document Number|.
5. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011–2012. JAMA : the journal of the American Medical Association 2014;311:806–14. [PubMed: 24570244]
6. Fildes A, Charlton J, Rudisill C, Littlejohns P, Prevost AT, Gulliford MC. Probability of an Obese Person Attaining Normal Body Weight: Cohort Study Using Electronic Health Records. Am J Public Health 2015:e1–e6.

7. Fothergill E, Guo J, Howard L, Kerns JC, Knuth ND, Brychta R, et al. Persistent metabolic adaptation 6 years after "The Biggest Loser" competition. Obesity (Silver Spring) 2016;24:1612–9. [PubMed: 27136388]
8. Cawley J, Meyerhoefer C. The medical care costs of obesity: an instrumental variables approach. J Health Econ 2012;31:219–30. [PubMed: 22094013]
9. Attina TM, Hauser R, Sathyanarayana S, Hunt PA, Bourguignon JP, Myers JP, et al. Exposure to endocrine-disrupting chemicals in the USA: a population-based disease burden and cost analysis. Lancet Diabetes Endocrinol 2016;4:996–1003. [PubMed: 27765541]
10. Legler J, Fletcher T, Govarts E, Porta M, Blumberg B, Heindel JJ, et al. Obesity, diabetes, and associated costs of exposure to endocrine-disrupting chemicals in the European Union. J Clin Endocrinol Metab 2015;100:1278–88. [PubMed: 25742518]
11. Brown RE, Sharma AM, Ardern CI, Mirdamadi P, Mirdamadi P, Kuk JL. Secular differences in the association between caloric intake, macronutrient intake, and physical activity with obesity. Obes Res Clin Pract 2016;10:243–55. [PubMed: 26383959]
12. Melanson EL, Keadle SK, Donnelly JE, Braun B, King NA. Resistance to exercise-induced weight loss: compensatory behavioral adaptations. Med Sci Sports Exerc 2013;45:1600–9. [PubMed: 23470300]
13. Sawyer BJ, Bhammar DM, Angadi SS, Ryan DM, Ryder JR, Sussman EJ, et al. Predictors of fat mass changes in response to aerobic exercise training in women. J Strength Cond Res 2015;29:297–304. [PubMed: 25353081]
14. Ralston J, Brinsden H, Buse K, Candeias V, Caterson I, Hassell T, et al. Time for a new obesity narrative. Lancet 2018;392:1384–6. [PubMed: 30316458]
15. Yu Y-H, Vasselli JR, Zhang Y, Mechanick JI, Korner J, Peterli R. Metabolic vs. hedonic obesity: a conceptual distinction and its clinical implications. Obesity Reviews 2015;16:234–47. [PubMed: 25588316]
16. Kraschnewski JL, Boan J, Esposito J, Sherwood NE, Lehman EB, Kephart DK, et al. Long-term weight loss maintenance in the United States. Int J Obes (Lond) 2010;34:1644–54. [PubMed: 20479763]
17. Hall KD, Heymsfield SB, Kemnitz JW, Klein S, Schoeller DA, Speakman JR. Energy balance and its components: implications for body weight regulation. The American journal of clinical nutrition 2012;95:989–94. [PubMed: 22434603]
18. Herbert A The fat tail of obesity as told by the genome. Curr Opin Clin Nutr Metab Care 2008;11:366–70. [PubMed: 18541993]
19. Li S, Zhao JH, Luan J, Luben RN, Rodwell SA, Khaw KT, et al. Cumulative effects and predictive value of common obesity-susceptibility variants identified by genome-wide association studies. The American journal of clinical nutrition 2010;91:184–90. [PubMed: 19812171]
20. Behl M, Rao D, Aagaard K, Davidson TL, Levin ED, Slotkin TA, et al. Evaluation of the association between maternal smoking, childhood obesity, and metabolic disorders: a national toxicology program workshop review. Environmental health perspectives 2013;121:170–80. [PubMed: 23232494]
21. Power C, Jefferis BJ. Fetal environment and subsequent obesity: a study of maternal smoking. Int J Epidemiol 2002;31:413–9. [PubMed: 11980805]
22. Garruti G, Cotecchia S, Giampetruzzi F, Giorgino F, Giorgino R. Neuroendocrine deregulation of food intake, adipose tissue and the gastrointestinal system in obesity and metabolic syndrome. J Gastrointestin Liver Dis 2008;17:193–8. [PubMed: 18568142]
23. Torres SJ, Nowson CA. Relationship between stress, eating behavior, and obesity. Nutrition 2007;23:887–94. [PubMed: 17869482]
24. Noble EE, Hsu TM, Jones RB, Fodor AA, Goran MI, Kanoski SE. Early-Life Sugar Consumption Affects the Rat Microbiome Independently of Obesity. J Nutr 2017;147:20–8. [PubMed: 27903830]
25. Palleja A, Kashani A, Allin KH, Nielsen T, Zhang C, Li Y, et al. Roux-en-Y gastric bypass surgery of morbidly obese patients induces swift and persistent changes of the individual gut microbiota. Genome Med 2016;8:67. [PubMed: 27306058]

26. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature 2006;444:1027–31. [PubMed: 17183312]
27. Garaulet M, Gomez-Abellan P. Timing of food intake and obesity: a novel association. Physiol Behav 2014;134:44–50. [PubMed: 24467926]
28. Garaulet M, Gomez-Abellan P, Alburquerque-Bejar JJ, Lee YC, Ordovas JM, Scheer FA. Timing of food intake predicts weight loss effectiveness. Int J Obes (Lond) 2013;37:604–11. [PubMed: 23357955]
29. Barker DJ. The origins of the developmental origins theory. Journal of internal medicine 2007;261:412–7. [PubMed: 17444880]
30. Hales CN, Barker DJ. The thrifty phenotype hypothesis. Br Med Bull 2001;60:5–20. [PubMed: 11809615]
31. Barker DJ. Fetal origins of coronary heart disease. BMJ (Clinical research ed) 1995;311:171–4.
32. Barker DJ, Winter PD, Osmond C, Margetts B, Simmonds SJ. Weight in infancy and death from ischaemic heart disease. Lancet 1989;2:577–80. [PubMed: 2570282]
33. Gluckman PD, Hanson MA. Living with the past: evolution, development, and patterns of disease. Science 2004;305:1733–6. [PubMed: 15375258]
34. Gluckman PD, Hanson MA, Bateson P, Beedle AS, Law CM, Bhutta ZA, et al. Towards a new developmental synthesis: adaptive developmental plasticity and human disease. Lancet 2009;373:1654–7. [PubMed: 19427960]
35. Hanson MA, Gluckman PD. Developmental origins of health and disease--global public health implications. Best practice & research Clinical obstetrics & gynaecology 2015;29:24–31. [PubMed: 25225058]
36. Hanson M, Godfrey KM, Lillycrop KA, Burdge GC, Gluckman PD. Developmental plasticity and developmental origins of non-communicable disease: Theoretical considerations and epigenetic mechanisms. Prog Biophys Mol Biol 2011;106:272–80. [PubMed: 21219925]
37. Godfrey KM, Sheppard A, Gluckman PD, Lillycrop KA, Burdge GC, McLean C, et al. Epigenetic gene promoter methylation at birth is associated with child's later adiposity. Diabetes 2011;60:1528–34. [PubMed: 21471513]
38. Lillycrop KA. Effect of maternal diet on the epigenome: implications for human metabolic disease. Proc Nutr Soc 2011;70:64–72. [PubMed: 21266093]
39. Barouki R, Melén E, Herceg Z, Beckers J, Chen J, Karagas M, et al. Epigenetics as a mechanism linking developmental exposures to long-term toxicity. Environ Int 2018;114:77–86. [PubMed: 29499450]
40. Almond D, Mazumder B. Health Capital and the Prenatal Environment: The Effect of Ramadan Observance During Pregnancy. American Economic Journal: Applied Economics 2011;3:56–85.
41. Almond D, Currie J. Killing Me Softly: The Fetal Origins Hypothesis. J Econ Perspect 2011;25:153–72. [PubMed: 25152565]
42. Klimentidis YC, Beasley TM, Lin HY, Murati G, Glass GE, Guyton M, et al. Canaries in the coal mine: a cross-species analysis of the plurality of obesity epidemics. Proceedings Biological sciences / The Royal Society 2011;278:1626–32.
43. Jager G, Witkamp RF. The endocannabinoid system and appetite: relevance for food reward. Nutrition research reviews 2014;27:172–85. [PubMed: 24933167]
44. Schellekens H, Finger BC, Dinan TG, Cryan JF. Ghrelin signalling and obesity: at the interface of stress, mood and food reward. Pharmacology & therapeutics 2012;135:316–26. [PubMed: 22749794]
45. Volkow ND, Wang GJ, Tomasi D, Baler RD. Obesity and addiction: neurobiological overlaps. Obesity reviews : an official journal of the International Association for the Study of Obesity 2013;14:2–18. [PubMed: 23016694]
46. Heindel JJ, Blumberg B, Cave M, Machtinger R, Mantovani A, Mendez MA, et al. Metabolism disrupting chemicals and metabolic disorders. Reprod Toxicol 2017;68:3–33. [PubMed: 27760374]

47. Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, Hauser R, Prins GS, Soto AM, et al. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. Endocr Rev 2009;30:293–342. [PubMed: 19502515]
48. Gore AC, Chappell VA, Fenton SE, Flaws JA, Nadal A, Prins GS, et al. EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals. Endocr Rev 2015;36:E1–E150. [PubMed: 26544531]
49. Zoeller RT, Brown TR, Doan LL, Gore AC, Skakkebaek NE, Soto AM, et al. Endocrine-disrupting chemicals and public health protection: a statement of principles from The Endocrine Society. Endocrinology 2012;153:4097–110. [PubMed: 22733974]
50. Vandenberg LN, Colborn T, Hayes TB, Heindel JJ, Jacobs DR Jr., Lee DH, et al. Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses. Endocr Rev 2012;33:378–455. [PubMed: 22419778]
51. Grun F, Blumberg B. Environmental obesogens: organotins and endocrine disruption via nuclear receptor signaling. Endocrinology 2006;147:S50–5. [PubMed: 16690801]
52. Spalding KL, Arner E, Westermark PO, Bernard S, Buchholz BA, Bergmann O, et al. Dynamics of fat cell turnover in humans. Nature 2008;453:783–7. [PubMed: 18454136]
53. Janesick A, Blumberg B. Endocrine disrupting chemicals and the developmental programming of adipogenesis and obesity. Birth Defects Res C Embryo Today 2011;93:34–50. [PubMed: 21425440]
54. Janesick AS, Blumberg B. Obesogens: an emerging threat to public health. Am J Obstet Gynecol 2016;214:559–65. [PubMed: 26829510]
55. Chamorro-Garcia R, Diaz-Castillo C, Shoucri BM, Kach H, Leavitt R, Shioda T, et al. Ancestral perinatal obesogen exposure results in a transgenerational thrifty phenotype in mice. Nat Commun 2017;8:2012. [PubMed: 29222412]
56. Liu G, Dhana K, Furtado JD, Rood J, Zong G, Liang L, et al. Perfluoroalkyl substances and changes in body weight and resting metabolic rate in response to weight-loss diets: A prospective study. PLoS Med 2018;15:e1002502. [PubMed: 29438414]
57. Braun JM, Gennings C, Hauser R, Webster TF. What Can Epidemiological Studies Tell Us about the Impact of Chemical Mixtures on Human Health? Environmental health perspectives 2016;124:A6–9. [PubMed: 26720830]
58. Darbre PD. Endocrine Disruptors and Obesity. Curr Obes Rep 2017;6:18–27. [PubMed: 28205155]
59. Janesick AS, Shioda T, Blumberg B. Transgenerational inheritance of prenatal obesogen exposure. Mol Cell Endocrinol 2014;398:31–5. [PubMed: 25218215]
60. Le Magueresse-Battistoni B, Labaronne E, Vidal H, Naville D. Endocrine disrupting chemicals in mixture and obesity, diabetes and related metabolic disorders. World journal of biological chemistry 2017;8:108–19. [PubMed: 28588754]
61. Stegemann R, Buchner DA. Transgenerational Inheritance of Metabolic Disease. Seminars in cell & developmental biology 2015;43:131–40. [PubMed: 25937492]
62. Stojanoska MM, Milosevic N, Milic N, Abenavoli L. The influence of phthalates and bisphenol A on the obesity development and glucose metabolism disorders. Endocrine 2017;55:666–81. [PubMed: 27822670]
63. Stahlhut RW, van Wijgaarden E, Dye TD, Cook S, Swan SH. Concentrations of urinary phthalate metabolites are associated with increased waist circumferece and insulin resistance in adult U.S. males. Environmental health perspectives 2007;115:876–82. [PubMed: 17589594]
64. Hatch EE, Nelson JW, Qureshi MM, Weinberg J, Moore LL, Singer M, et al. Association of urinary phthalate metabolite concentrations with body mass index and waist circumference: a cross-sectional study of NHANES data, 1999–2002. Environ Health 2008;7:27. [PubMed: 18522739]
65. Trasande L, Attina TM, Blustein J. Association between urinary bisphenol A concentration and obesity prevalence in children and adolescents. JAMA : the journal of the American Medical Association 2012;308:1113–21. [PubMed: 22990270]
66. Li DK, Miao M, Zhou Z, Wu C, Shi H, Liu X, et al. Urine bisphenol-A level in relation to obesity and overweight in school-age children. PLoS One 2013;8:e65399. [PubMed: 23776476]

67. Tang-Peronard JL, Andersen HR, Jensen TK, Heitmann BL. Endocrine-disrupting chemicals and obesity development in humans: a review. Obesity reviews : an official journal of the International Association for the Study of Obesity 2011;12:622–36. [PubMed: 21457182]
68. Newbold RR, Padilla-Banks E, Jefferson WN. Environmental estrogens and obesity. Mol Cell Endocrinol 2009;304:84–9. [PubMed: 19433252]
69. Vom Saal FS, Nagel SC, Coe BL, Angle BM, Taylor JA. The estrogenic endocrine disrupting chemical bisphenol A (BPA) and obesity. Mol Cell Endocrinol 2012;354:74–84. [PubMed: 22249005]
70. Grun F, Watanabe H, Zamanian Z, Maeda L, Arima K, Cubacha R, et al. Endocrine-disrupting organotin compounds are potent inducers of adipogenesis in vertebrates. Mol Endocrinol 2006;20:2141–55. [PubMed: 16613991]
71. Hines EP, White SS, Stanko JP, Gibbs-Flournoy EA, Lau C, Fenton SE. Phenotypic dichotomy following developmental exposure to perfluorooctanoic acid (PFOA) in female CD-1 mice: Low doses induce elevated serum leptin and insulin, and overweight in mid-life. Mol Cell Endocrinol 2009;304:97–105. [PubMed: 19433254]
72. Fromme H, Mattulat A, Lahrz T, Ruden H. Occurrence of organotin compounds in house dust in Berlin (Germany). Chemosphere 2005;58:1377–83. [PubMed: 15686755]
73. Kannan K, Takahashi S, Fujiwara N, Mizukawa H, Tanabe S. Organotin compounds, including butyltins and octyltins, in house dust from Albany, New York, USA. Arch Environ Contam Toxicol 2010;58:901–7. [PubMed: 20379706]
74. le Maire A, Grimaldi M, Roecklin D, Dagnino S, Vivat-Hannah V, Balaguer P, et al. Activation of RXR-PPAR heterodimers by organotin environmental endocrine disruptors. EMBO Rep 2009;10:367–73. [PubMed: 19270714]
75. Kanayama T, Kobayashi N, Mamiya S, Nakanishi T, Nishikawa J. Organotin compounds promote adipocyte differentiation as agonists of the peroxisome proliferator-activated receptor gamma/retinoid X receptor pathway. Mol Pharmacol 2005;67:766–74. [PubMed: 15611480]
76. Chamorro-Garcia R, Shoucri BM, Willner S, Kach H, Janesick A, Blumberg B. Effects of Perinatal Exposure to Dibutyltin Chloride on Fat and Glucose Metabolism in Mice, and Molecular Mechanisms, in Vitro. Environmental health perspectives 2018;126:057006. [PubMed: 29787037]
77. Milton FA, Lacerda MG, Sinoti SBP, Mesquita PG, Prakasan D, Coelho MS, et al. Dibutyltin Compounds Effects on PPARgamma/RXRalpha Activity, Adipogenesis, and Inflammation in Mammalians Cells. Front Pharmacol 2017;8:507. [PubMed: 28824431]
78. Li X, Ycaza J, Blumberg B. 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;127:9–15. [PubMed: 21397693]
79. Li X, Pham HT, Janesick AS, Blumberg B. Triflumizole is an obesogen in mice that acts through peroxisome proliferator activated receptor gamma (PPARgamma). Environmental health perspectives 2012;120:1720–6. [PubMed: 23086663]
80. Kirchner S, Kieu T, Chow C, Casey S, Blumberg B. Prenatal exposure to the environmental obesogen tributyltin predisposes multipotent stem cells to become adipocytes. Mol Endocrinol 2010;24:526–39. [PubMed: 20160124]
81. Chamorro-Garcia R, Sahu M, Abbey RJ, Laude J, Pham N, Blumberg B. Transgenerational inheritance of increased fat depot size, stem cell reprogramming, and hepatic steatosis elicited by prenatal exposure to the obesogen tributyltin in mice. Environmental health perspectives 2013;121:359–66. [PubMed: 23322813]
82. Zhang J, Sun P, Kong T, Yang F, Guan W. Tributyltin promoted hepatic steatosis in zebrafish (Danio rerio) and the molecular pathogenesis involved. Aquat Toxicol 2016;170:208–15. [PubMed: 26674369]
83. Zhang J, Sun P, Yang F, Kong T, Zhang R. Tributyltin disrupts feeding and energy metabolism in the goldfish (Carassius auratus). Chemosphere 2016;152:221–8. [PubMed: 26971175]
84. Zuo Z, Chen S, Wu T, Zhang J, Su Y, Chen Y, et al. Tributyltin causes obesity and hepatic steatosis in male mice. Environ Toxicol 2011;26:79–85. [PubMed: 19760618]

85. Zuo Z, Wu T, Lin M, Zhang S, Yan F, Yang Z, et al. Chronic exposure to tributyltin chloride induces pancreatic islet cell apoptosis and disrupts glucose homeostasis in male mice. Environ Sci Technol 2014;48:5179–86. [PubMed: 24693970]
86. Mattos Y, Stotz WB, Romero MS, Bravo M, Fillmann G, Castro IB. Butyltin contamination in Northern Chilean coast: Is there a potential risk for consumers? Sci Total Environ 2017;595:209–17. [PubMed: 28384577]
87. Rantakokko P, Main KM, Wohlfart-Veje C, Kiviranta H, Airaksinen R, Vartiainen T, 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;13:45. [PubMed: 24899383]
88. Regnier SM, Kirkley AG, Ye H, El-Hashani E, Zhang X, Neel BA, et al. Dietary exposure to the endocrine disruptor tolylfluanid promotes global metabolic dysfunction in male mice. Endocrinology 2015;156:896–910. [PubMed: 25535829]
89. Hao C, Cheng X, Guo J, Xia H, Ma X. Perinatal exposure to diethyl-hexyl-phthalate induces obesity in mice. Front Biosci (Elite Ed) 2013;5:725–33. [PubMed: 23277027]
90. Janesick AS, Dimastrogiovanni G, Vanek L, Boulos C, Chamorro-Garcia R, Tang W, et al. On the Utility of ToxCast and ToxPi as Methods for Identifying New Obesogens. Environmental health perspectives 2016;124:1214–26. [PubMed: 26757984]
91. Foley B, Doheny DL, Black MB, Pendse SN, Wetmore BA, Clewell RA, et al. Editor's Highlight: Screening ToxCast Prioritized Chemicals for PPARG Function in a Human Adipose-Derived Stem Cell Model of Adipogenesis. Toxicol Sci 2017;155:85–100. [PubMed: 27664422]
92. Shoucri BM, Martinez ES, Abreo TJ, Hung VT, Moosova Z, Shioda T, et al. Retinoid X Receptor Activation Alters the Chromatin Landscape To Commit Mesenchymal Stem Cells to the Adipose Lineage. Endocrinology 2017;158:3109–25. [PubMed: 28977589]
93. Shoucri BM, Hung VT, Chamorro-Garcia R, Shioda T, Blumberg B. Retinoid X Receptor Activation During Adipogenesis of Female Mesenchymal Stem Cells Programs a Dysfunctional Adipocyte. Endocrinology 2018;159:2863–83. [PubMed: 29860300]
94. Regnier SM, El-Hashani E, Kamau W, Zhang X, Massad NL, Sargis RM. Tributyltin differentially promotes development of a phenotypically distinct adipocyte. Obesity (Silver Spring) 2015;23:1864–71. [PubMed: 26243053]
95. Saltiel AR, Kahn CR. Insulin signalling and the regulation of glucose and lipid metabolism. Nature 2001;414:799–806. [PubMed: 11742412]
96. Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. Nat Rev Immunol 2011;11:85–97. [PubMed: 21252989]
97. Li S, Shin HJ, Ding EL, van Dam RM. Adiponectin levels and risk of type 2 diabetes: a systematic review and meta-analysis. JAMA : the journal of the American Medical Association 2009;302:179–88. [PubMed: 19584347]
98. Kusminski CM, Bickel PE, Scherer PE. Targeting adipose tissue in the treatment of obesity-associated diabetes. Nat Rev Drug Discov 2016;15:639–60. [PubMed: 27256476]
99. Fibrosis and Adipose Tissue Dysfunction (2013).
100. Harms M, Seale P. Brown and beige fat: development, function and therapeutic potential. Nat Med 2013;19:1252–63. [PubMed: 24100998]
101. Nam M, Cooper MP. Role of Energy Metabolism in the Brown Fat Gene Program. Front Endocrinol (Lausanne) 2015;6:104. [PubMed: 26175716]
102. Kajimura S, Saito M. A new era in brown adipose tissue biology: molecular control of brown fat development and energy homeostasis. Annu Rev Physiol 2014;76:225–49. [PubMed: 24188710]
103. La Merrill M, Karey E, Moshier E, Lindtner C, La Frano MR, Newman JW, et al. Perinatal exposure of mice to the pesticide DDT impairs energy expenditure and metabolism in adult female offspring. PLoS One 2014;9:e103337. [PubMed: 25076055]
104. Newbold RR, Padilla-Banks E, Snyder RJ, Jefferson WN. Developmental exposure to estrogenic compounds and obesity. Birth Defects Res A Clin Mol Teratol 2005;73:478–80. [PubMed: 15959888]

105. Somm E, Schwitzgebel VM, Toulotte A, Cederroth CR, Combescure C, Nef S, et al. Perinatal exposure to bisphenol a alters early adipogenesis in the rat. Environmental health perspectives 2009;117:1549–55. [PubMed: 20019905]
106. Anway MD, Cupp AS, Uzumcu M, Skinner MK. Epigenetic transgenerational actions of endocrine disruptors and male fertility. Science 2005;308:1466–9. [PubMed: 15933200]
107. Manikkam M, Tracey R, Guerrero-Bosagna C, Skinner MK. Plastics Derived Endocrine Disruptors (BPA, DEHP and DBP) Induce Epigenetic Transgenerational Inheritance of Obesity, Reproductive Disease and Sperm Epimutations. PLoS One 2013;8:e55387. [PubMed: 23359474]
108. Manikkam M, Haque MM, Guerrero-Bosagna C, Nilsson EE, Skinner MK. Pesticide methoxychlor promotes the epigenetic transgenerational inheritance of adult-onset disease through the female germline. PLoS One 2014;9:e102091. [PubMed: 25057798]
109. Tracey R, Manikkam M, Guerrero-Bosagna C, Skinner MK. Hydrocarbons (jet fuel JP-8) induce epigenetic transgenerational inheritance of obesity, reproductive disease and sperm epimutations. Reprod Toxicol 2013;36:104–16. [PubMed: 23453003]
110. Skinner MK, Manikkam M, Tracey R, Guerrero-Bosagna C, Haque M, Nilsson EE. Ancestral dichlorodiphenyltrichloroethane (DDT) exposure promotes epigenetic transgenerational inheritance of obesity. BMC Med 2013;11:228. [PubMed: 24228800]
111. Whitelaw E Disputing Lamarckian epigenetic inheritance in mammals. Genome Biol 2015;16:60. [PubMed: 25853737]
112. Franklin TB, Mansuy IM. Epigenetic inheritance in mammals: evidence for the impact of adverse environmental effects. Neurobiology of disease 2010;39:61–5. [PubMed: 19931614]
113. Heard E, Martienssen RA. Transgenerational epigenetic inheritance: myths and mechanisms. Cell 2014;157:95–109. [PubMed: 24679529]
114. Skinner MK, Guerrero-Bosagna C, Haque MM. Environmentally induced epigenetic transgenerational inheritance of sperm epimutations promote genetic mutations. Epigenetics 2015;10:762–71. [PubMed: 26237076]
115. Haque MM, Nilsson EE, Holder LB, Skinner MK. Genomic Clustering of differential DNA methylated regions (epimutations) associated with the epigenetic transgenerational inheritance of disease and phenotypic variation. BMC Genomics 2016;17:418. [PubMed: 27245821]
116. Iqbal K, Tran DA, Li AX, Warden C, Bai AY, Singh P, et al. Deleterious effects of endocrine disruptors are corrected in the mammalian germline by epigenome reprogramming. Genome Biol 2015;16:59. [PubMed: 25853433]
117. Skinner MK, Ben Maamar M, Sadler-Riggleman I, Beck D, Nilsson E, McBirney M, et al. Alterations in sperm DNA methylation, non-coding RNA and histone retention associate with DDT-induced epigenetic transgenerational inheritance of disease. Epigenetics Chromatin 2018;11:8. [PubMed: 29482626]
118. Heindel JJ, Blumberg B. Environmental Obesogens: Mechanisms and Controversies. Annu Rev Pharmacol Toxicol 2018.
119. Heindel JJ, vom Saal FS, Blumberg B, Bovolin P, Calamandrei G, Ceresini G, et al. Parma consensus statement on metabolic disruptors. Environ Health 2015;14:54. [PubMed: 26092037]
120. Lind L, Lind PM, Lejonklou MH, Dunder L, Bergman A, Guerrero-Bosagna C, et al. Uppsala Consensus Statement on Environmental Contaminants and the Global Obesity Epidemic. Environmental health perspectives 2016;124:A81–3. [PubMed: 27135406]
121. Janesick A, Schug TT, Heindel JJ, Blumberg B. Environmental pollutants and obesity. In: Bray GA, Bouchard C, editors. Handbook of obesity : epidemiology, etiology, and physiopathology, Third Edition. 3rd ed. Boca Raton: CRC Press; 2014 p. 471–88.
122. Chamorro-Garcia R, Kirchner S, Li X, Janesick A, Casey SC, Chow C, et al. Bisphenol A diglycidyl ether induces adipogenic differentiation of multipotent stromal stem cells through a peroxisome proliferator-activated receptor gamma-independent mechanism. Environmental health perspectives 2012;120:984–9. [PubMed: 22763116]
123. Choi J, Eom J, Kim J, Lee S, Kim Y. Association between some endocrine-disrupting chemicals and childhood obesity in biological samples of young girls: a cross-sectional study. Environ Toxicol Pharmacol 2014;38:51–7. [PubMed: 24908636]

124. Schmidt JS, Schaedlich K, Fiandanese N, Pocar P, Fischer B. Di(2-ethylhexyl) Phthalate (DEHP) Impairs Female Fertility and Promotes Adipogenesis in C3H/N Mice. Environmental health perspectives 2012.
125. Wang YF, Chao HR, Wu CH, Tseng CH, Kuo YT, Tsou TC. A recombinant peroxisome proliferator response element-driven luciferase assay for evaluation of potential environmental obesogens. Biotechnol Lett 2010;32:1789–96. [PubMed: 20665227]
126. Legeay S, Faure S. Is bisphenol A an environmental obesogen? Fundam Clin Pharmacol 2017;31:594–609. [PubMed: 28622415]
127. Yanagisawa R, Koike E, Win-Shwe TT, Yamamoto M, Takano H. Impaired lipid and glucose homeostasis in hexabromocyclododecane-exposed mice fed a high-fat diet. Environmental health perspectives 2014;122:277–83. [PubMed: 24398136]
128. Kamstra JH, Hruba E, Blumberg B, Janesick A, Mandrup S, Hamers T, et al. Transcriptional and epigenetic mechanisms underlying enhanced in vitro adipocyte differentiation by the brominated flame retardant BDE-47. Environ Sci Technol 2014;48:4110–9. [PubMed: 24559133]
129. Fang M, Webster TF, Ferguson PL, Stapleton HM. Characterizing the peroxisome proliferator-activated receptor (PPARgamma) ligand binding potential of several major flame retardants, their metabolites, and chemical mixtures in house dust. Environmental health perspectives 2015;123:166–72. [PubMed: 25314719]
130. Tung EW, Boudreau A, Wade MG, Atlas E. Induction of adipocyte differentiation by polybrominated diphenyl ethers (PBDEs) in 3T3-L1 cells. PLoS One 2014;9:e94583. [PubMed: 24722056]
131. Chappell VA, Janesick A, Blumberg B, Fenton SE. Tetrabromobisphenol-A Promotes Early Adipogenesis and Lipogenesis in 3T3-L1 Cells. Toxicol Sci 2018;166:332–44. [PubMed: 30496566]
132. Watt J, Schlezinger JJ. Structurally-diverse, PPARgamma-activating environmental toxicants induce adipogenesis and suppress osteogenesis in bone marrow mesenchymal stromal cells. Toxicology 2015;331:66–77. [PubMed: 25777084]
133. Woeller CF, Flores E, Pollock SJ, Phipps RP. Editor's Highlight: Thy1 (CD90) Expression is Reduced by the Environmental Chemical Tetrabromobisphenol-A to Promote Adipogenesis Through Induction of microRNA-103. Toxicol Sci 2017;157:305–19. [PubMed: 28329833]
134. Cano-Sancho G, Smith A, La Merrill MA. Triphenyl phosphate enhances adipogenic differentiation, glucose uptake and lipolysis via endocrine and noradrenergic mechanisms. Toxicol In Vitro 2017;40:280–8. [PubMed: 28163246]
135. Pillai HK, Fang M, Beglov D, Kozakov D, Vajda S, Stapleton HM, et al. Ligand binding and activation of PPARgamma by Firemaster(R) 550: effects on adipogenesis and osteogenesis in vitro. Environmental health perspectives 2014;122:1225–32. [PubMed: 25062436]
136. Tung EWY, Ahmed S, Peshdary V, Atlas E. Firemaster(R) 550 and its components isopropylated triphenyl phosphate and triphenyl phosphate enhance adipogenesis and transcriptional activity of peroxisome proliferator activated receptor (Ppargamma) on the adipocyte protein 2 (aP2) promoter. PLoS One 2017;12:e0175855. [PubMed: 28437481]
137. Tung EWY, Peshdary V, Gagne R, Rowan-Carroll A, Yauk CL, Boudreau A, et al. Adipogenic Effects and Gene Expression Profiling of Firemaster(R) 550 Components in Human Primary Preadipocytes. Environmental health perspectives 2017;125:097013. [PubMed: 28934090]
138. Wang D, Yan S, Yan J, Teng M, Meng Z, Li R, et al. Effects of triphenyl phosphate exposure during fetal development on obesity and metabolic dysfunctions in adult mice: Impaired lipid metabolism and intestinal dysbiosis. Environ Pollut 2019;246:630–8. [PubMed: 30605818]
139. Soubry A, Hoyo C, Butt CM, Fieuws S, Price TM, Murphy SK, et al. Human exposure to flame-retardants is associated with aberrant DNA methylation at imprinted genes in sperm. Environ Epigenet 2017;3:dvx003.
140. Green AJ, Graham JL, Gonzalez EA, La Frano MR, Petropoulou SE, Park JS, et al. Perinatal triphenyl phosphate exposure accelerates type 2 diabetes onset and increases adipose accumulation in UCD-type 2 diabetes mellitus rats. Reprod Toxicol 2017;68:119–29. [PubMed: 27421578]

141. Lassiter TL, Brimijoin S. Rats gain excess weight after developmental exposure to the organophosphorothionate pesticide, chlorpyrifos. Neurotoxicol Teratol 2008;30:125–30. [PubMed: 18166376]
142. Slotkin TA. Does early-life exposure to organophosphate insecticides lead to prediabetes and obesity? Reprod Toxicol 2011;31:297–301. [PubMed: 20850519]
143. Howell G 3rd, Mangum L. Exposure to bioaccumulative organochlorine compounds alters adipogenesis, fatty acid uptake, and adipokine production in NIH3T3-L1 cells. Toxicol In Vitro 2011;25:394–402. [PubMed: 21044676]
144. Kim J, Sun Q, Yue Y, Yoon KS, Whang KY, Marshall Clark J, et al. 4,4'-Dichlorodiphenyltrichloroethane (DDT) and 4,4'-dichlorodiphenyldichloroethylene (DDE) promote adipogenesis in 3T3-L1 adipocyte cell culture. Pestic Biochem Physiol 2016;131:40–5. [PubMed: 27265825]
145. Mangum LH, Howell GE 3rd, Chambers JE. Exposure to p,p'-DDE enhances differentiation of 3T3-L1 preadipocytes in a model of sub-optimal differentiation. Toxicol Lett 2015;238:65–71. [PubMed: 26200599]
146. Routti H, Lille-Langoy R, Berg MK, Fink T, Harju M, Kristiansen K, et al. Environmental Chemicals Modulate Polar Bear (Ursus maritimus) Peroxisome Proliferator-Activated Receptor Gamma (PPARG) and Adipogenesis in Vitro. Environ Sci Technol 2016;50:10708–20. [PubMed: 27602593]
147. Cano-Sancho G, Salmon AG, La Merrill MA. Association between Exposure to p,p'-DDT and Its Metabolite p,p'-DDE with Obesity: Integrated Systematic Review and Meta-Analysis. Environmental health perspectives 2017;125:096002. [PubMed: 28934091]
148. Smith A, Yu X, Yin L. Diazinon exposure activated transcriptional factors CCAAT-enhancer-binding proteins alpha (C/EBPalpha) and peroxisome proliferator-activated receptor gamma (PPARgamma) and induced adipogenesis in 3T3-L1 preadipocytes. Pestic Biochem Physiol 2018;150:48–58. [PubMed: 30195387]
149. Sargis RM, Johnson DN, Choudhury RA, Brady MJ. Environmental endocrine disruptors promote adipogenesis in the 3T3-L1 cell line through glucocorticoid receptor activation. Obesity (Silver Spring) 2010;18:1283–8. [PubMed: 19927138]
150. Janderova L, McNeil M, Murrell AN, Mynatt RL, Smith SR. Human mesenchymal stem cells as an in vitro model for human adipogenesis. Obes Res 2003;11:65–74. [PubMed: 12529487]
151. Lehmann JM, Lenhard JM, Oliver BB, Ringold GM, Kliewer SA. Peroxisome proliferator-activated receptors alpha and gamma are activated by indomethacin and other non-steroidal anti-inflammatory drugs. J Biol Chem 1997;272:3406–10. [PubMed: 9013583]
152. Hartman JK, Beames T, Parks B, Doheny D, Song G, Efremenko A, et al. An in vitro approach for prioritization and evaluation of chemical effects on glucocorticoid receptor mediated adipogenesis. Toxicol Appl Pharmacol 2018;355:112–26. [PubMed: 29782964]
153. Chen JQ, Brown TR, Russo J. Regulation of energy metabolism pathways by estrogens and estrogenic chemicals and potential implications in obesity associated with increased exposure to endocrine disruptors. Biochim Biophys Acta 2009;1793:1128–43. [PubMed: 19348861]
154. Levin ED. Fetal nicotinic overload, blunted sympathetic responsivity, and obesity. Birth Defects Res A Clin Mol Teratol 2005;73:481–4. [PubMed: 15959889]
155. Park SS, Skaar DA, Jirtle RL, Hoyo C. Epigenetics, obesity and early-life cadmium or lead exposure. Epigenomics 2017;9:57–75. [PubMed: 27981852]
156. Green AJ, Hoyo C, Mattingly CJ, Luo Y, Tzeng JY, Murphy SK, et al. Cadmium exposure increases the risk of juvenile obesity: a human and zebrafish comparative study. Int J Obes (Lond) 2018;42:1285–95. [PubMed: 29511319]
157. Sun H, Wang N, Nie X, Zhao L, Li Q, Cang Z, et al. Lead Exposure Induces Weight Gain in Adult Rats, Accompanied by DNA Hypermethylation. PLoS One 2017;12:e0169958. [PubMed: 28107465]
158. Shin YY, Ryu IK, Park MJ, Kim SH. The association of total blood mercury levels and overweight among Korean adolescents: analysis of the Korean National Health and Nutrition Examination Survey (KNHANES) 2010–2013. Korean J Pediatr 2018;61:121–8. [PubMed: 29713358]

159. Lee HW, Pyo S. Acrylamide induces adipocyte differentiation and obesity in mice. Chem Biol Interact 2019;298:24–34. [PubMed: 30409764]
160. Du L, Heaney AP. Regulation of adipose differentiation by fructose and GluT5. Mol Endocrinol 2012;26:1773–82. [PubMed: 22827929]
161. Tappy L Fructose-containing caloric sweeteners as a cause of obesity and metabolic disorders. J Exp Biol 2018;221.
162. Halldorsson TI, Rytter D, Haug LS, Bech BH, Danielsen I, Becher G, et al. Prenatal exposure to perfluorooctanoate and risk of overweight at 20 years of age: a prospective cohort study. Environmental health perspectives 2012;120:668–73. [PubMed: 22306490]
163. Hartman TJ, Calafat AM, Holmes AK, Marcus M, Northstone K, Flanders WD, et al. Prenatal Exposure to Perfluoroalkyl Substances and Body Fatness in Girls. Child Obes 2017;13:222–30. [PubMed: 28128969]
164. Liu S, Yang R, Yin N, Wang YL, Faiola F. Environmental and human relevant PFOS and PFOA doses alter human mesenchymal stem cell self-renewal, adipogenesis and osteogenesis. Ecotoxicol Environ Saf 2019;169:564–72. [PubMed: 30476818]
165. Ma Y, Yang J, Wan Y, Peng Y, Ding S, Li Y, et al. Low-level perfluorooctanoic acid enhances 3 T3-L1 preadipocyte differentiation via altering peroxisome proliferator activated receptor gamma expression and its promoter DNA methylation. J Appl Toxicol 2018;38:398–407. [PubMed: 29094436]
166. Lobato NS, Filgueira FP, Akamine EH, Davel AP, Rossoni LV, Tostes RC, et al. Obesity induced by neonatal treatment with monosodium glutamate impairs microvascular reactivity in adult rats: role of NO and prostanoids. Nutr Metab Cardiovasc Dis 2011;21:808–16. [PubMed: 20554176]
167. Bunyan J, Murrell EA, Shah PP. The induction of obesity in rodents by means of monosodium glutamate. Br J Nutr 1976;35:25–39. [PubMed: 1106764]
168. Pereira-Fernandes A, Demaegdt H, Vandermeiren K, Hectors TL, Jorens PG, Blust R, 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:e77481. [PubMed: 24155963]
169. Pereira-Fernandes A, Dirinck E, Dirtu AC, Malarvannan G, Covaci A, Van Gaal L, et al. Expression of obesity markers and Persistent Organic Pollutants levels in adipose tissue of obese patients: reinforcing the obesogen hypothesis? PLoS One 2014;9:e84816. [PubMed: 24427296]
170. Hu P, Chen X, Whitener RJ, Boder ET, Jones JO, Porollo A, et al. Effects of parabens on adipocyte differentiation. Toxicol Sci 2013;131:56–70. [PubMed: 22956630]
171. Hu P, Overby H, Heal E, Wang S, Chen J, Shen CL, et al. Methylparaben and butylparaben alter multipotent mesenchymal stem cell fates towards adipocyte lineage. Toxicol Appl Pharmacol 2017;329:48–57. [PubMed: 28527915]
172. Kolatorova L, Sramkova M, Vitku J, Vcelak J, Lischkova O, Starka L, et al. Parabens and their relation to obesity. Physiol Res 2018;67:S465–S72. [PubMed: 30484673]
173. Jordao R, Garreta E, Campos B, Lemos MF, Soares AM, Tauler R, et al. Compounds altering fat storage in Daphnia magna. Sci Total Environ 2016;545–546:127–36.
174. Wang ML, Lin SH, Hou YY, Chen YH. alpha-Naphthoflavone Increases Lipid Accumulation in Mature Adipocytes and Enhances Adipocyte-Stimulated Endothelial Tube Formation. Nutrients 2015;7:3166–83. [PubMed: 25942489]
175. Chang JW, Chen HL, Su HJ, Lee CC. Abdominal Obesity and Insulin Resistance in People Exposed to Moderate-to-High Levels of Dioxin. PLoS One 2016;11:e0145818. [PubMed: 26752053]
176. Agay-Shay K, Martinez D, Valvi D, Garcia-Esteban R, Basagana X, Robinson O, et al. Exposure to Endocrine-Disrupting Chemicals during Pregnancy and Weight at 7 Years of Age: A Multi-pollutant Approach. Environmental health perspectives 2015;123:1030–7. [PubMed: 25956007]
177. Arsenescu V, Arsenescu RI, King V, Swanson H, Cassis LA. Polychlorinated biphenyl-77 induces adipocyte differentiation and proinflammatory adipokines and promotes obesity and atherosclerosis. Environmental health perspectives 2008;116:761–8. [PubMed: 18560532]

178. Henriquez-Hernandez LA, Luzardo OP, Valeron PF, Zumbado M, Serra-Majem L, Camacho M, et al. Persistent organic pollutants and risk of diabetes and obesity on healthy adults: Results from a cross-sectional study in Spain. Sci Total Environ 2017;607–608:1096–102.

179. Temkin AM, Bowers RR, Magaletta ME, Holshouser S, Maggi A, Ciana P, et al. Effects of Crude Oil/Dispersant Mixture and Dispersant Components on PPARgamma Activity in Vitro and in Vivo: Identification of Dioctyl Sodium Sulfosuccinate (DOSS; CAS #577–11-7) as a Probable Obesogen. Environmental health perspectives 2016;124:112–9. [PubMed: 26135921]

180. Bowers RR, Temkin AM, Guillette LJ, Baatz JE, Spyropoulos DD. The commonly used nonionic surfactant Span 80 has RXRalpha transactivation activity, which likely increases the obesogenic potential of oil dispersants and food emulsifiers. Gen Comp Endocrinol 2016;238:61–8. [PubMed: 27131391]

181. Kassotis CD, Kollitz EM, Ferguson PL, Stapleton HM. Nonionic Ethoxylated Surfactants Induce Adipogenesis in 3T3-L1 Cells. Toxicol Sci 2018;162:124–36. [PubMed: 29106673]

**Table 1 -**

List of known obesogens and potential obesogens with selected endpoints and references. The reader should also consult references in previous review articles [46, 121]

| major use category | chemical | *in vitro* | *in vivo* | human | Endpoints | Reference |
|---|---|---|---|---|---|---|
| **plastics** | BADGE | + | | | Induce adipogenic differentiation in MSC's and in preadipocytes | [122] |
| | MEHP | + | + | | Increased adipogenesis, stimulates 3T3-L1 cells, increased lipid accumulation | [63, 64, 123] |
| | DEHP | + | + | | Increased adipocytes, lipid accumulation | [63, 64, 89, 123, 124] |
| | BBP | + | | | Increased LA in 3T3-L1 cells | [123, 125] |
| | BPA | + | + | + | Increased obesity in adults; increased LA in 3T3-L1 cells | Reviewed in [126] |
| **flame retardant** | hexabromocyclododecane | | + | | Impaired Lipid and Glucose Homeostasis | [127] |
| | BDE-47 | + | + | + | Disruption of glucose homeostasis; upregulation of denovo lipogenesis genes | [128–130] |
| | TBBPA | + | + | | Increased lipid accumulation and adipocyte number | [131–133] |
| | Triphenyl Phosphate | + | + | | Lipid accumulation; increased body weight and fat mass in mice | [134–137] |
| | FM-550 | + | + | | Lipid accumulation; weight gain | [134, 135, 137–140] |
| **pesticide** | Chlorpyrifos | | + | | Weight gain and hyperinsulinemia in rats | [141, 142] |
| | Quinoxyfen | + | | | Induce adipogenesis and adpogenic gene expression in 3T3-L1 cells | [90] |
| | Forchlorfenuron | + | | | Induce adipogenesis and adpogenic gene expression in 3T3-L1 cells | [90] |
| | Flusilazole | + | | | Induce adipogenesis and adpogenic gene expression in 3T3-L1 cells | [90] |
| | Fludioxonil | + | | | Induce adipogenesis and adpogenic gene expression in 3T3-L1 cells and MSCs | [90] |
| | acetamiprid | + | | | Induce adipogenesis and adpogenic gene expression in 3T3-L1 cells | [90] |
| | tebupirimfos | + | | | Induce adipogenesis and adpogenic gene expression in 3T3-L1 cells | [90] |
| | Triflumizole | + | + | | Induce adipogenesis and adpogenic gene expression in 3T3-L1 cells, MSCs and in mice | [79, 90] |
| | spirodiclofen | + | | | Induce adipogenesis and adpogenic gene expression in 3T3-L1 cells | [90] |
| | pymetrozine | + | | | Induce adipogenesis and adpogenic gene expression in 3T3-L1 cells | [90] |
| | DDE | + | + | + | Adipogenesis in 3T3-L1 cells, increased weight gain *in vivo* | [143–146] |
| | DDT | + | + | * | Adipogenesis in 3T3-L1 cells, increased weight gain, *in vivo*, transgenerational obesity | [110, 143–146], reviewed in [147] |
| | Diazinon | + | | | Induces adipogenesis in 3T3-L1 cells | [148] |

| major use category | chemical | *in vitro* | *in vivo* | human | Endpoints | Reference |
|---|---|---|---|---|---|---|
| | Halosulfuron-methyl | + | | | Induces adipogenesis in human adipose-derived stromal cells | [91] |
| | Diclofop-methyl | + | | | Induces adipogenesis in human adipose-derived stromal cells | [91] |
| | zoxamide | + | | | Induces adipogenesis in 3T3-L1 cells | [90] |
| | Fentin Hydroxide | + | | | Stimulates 3T3-L1 adipogenesis, lipid accumulation | [75, 91] |
| | Lactofen | + | | | Induces adipogenesis in human adipose-derived stromal cells | [91] |
| | tolyfluanid | + | + | | Induce adipogenesis in 3T3-L1 cells, increases fat mass in mice | [88, 149] |
| **drugs** | Rosiglitazone, pioglitazone | + | + | + | Induces adipogenesis in 3T3-L1 preadipocytes, MSCs, rodents and humans | Reviewed in [46] |
| | Indomethicin | + | | | Increased adipogenesis in C3H10T1/2 cells, MSCs, rodents and humans | [150, 151] |
| | triamcinolone | | | | Induces adipogenesis in human adipose-derived stromal cells | [152] |
| | dexamethasone | + | | | Induces adipogenesis in human adipose-derived stromal cells | [152] |
| | corticosterone | + | | | Induces adipogenesis in human adipose-derived stromal cells | [152] |
| | prednisone | + | | | Induces adipogenesis in human adipose-derived stromal cells | [152] |
| | melengestrol acetate | + | | | Induces adipogenesis in human adipose-derived stromal cells | [152] |
| | diethylstilbestrol | + | + | | Increased fat mass in mice and rats | [104, 153] |
| | Nicotine | | + | + | Increased body weight; reduced leptin; impaired glucose homeostasis | [105, 154] |
| **Metals** | Cadmium | | + | + | Increased BMI in humans, increased lipid accumulation in zebrafish | [155, 156] |
| | Lead | | + | + | Increased BMI in humans, increased adiposity in rats | [155, 157] |
| | Mercury | | | + | Increased BMI in humans | [158] |
| **Food/ packaging** | acrylamide | + | + | | Increased lipid accumulation in 3T3-L1 cells, increased fat mass in mice | [159] |
| | fructose | + | + | + | Induces adipopgenesis in 3T3-L1 cells, Increased body weight in humans and animals | [160] reviewed in [161] |
| | Perfluoroalkyl substances | + | + | + | Induces/potentiates adipogenesis in 3T3-L1, increased adiposity in rodents and humans | [71, 162–165] |
| | Monosodium glutamate | | + | + | Increased obesity in rodents | [166, 167] |
| **Personal care products** | Alkylphenols | + | + | + | Increased adipogenesis in 3T3-L1 cells, increased fat depot size in rodents, found in obese patients | [123, 168, 169] |
| | Parabens | + | + | + | Increased adipogenesis in 3T3-L1 cells | [168, 170–172] |

| major use category | chemical | *in vitro* | *in vivo* | human | Endpoints | Reference |
|---|---|---|---|---|---|---|
| **organotins** | dibutyltin (DBT) | + | + | | Increased adipogenesis in 3T3-L1 cells and MSCs, obesity in mice | [76, 77] |
| | Tributyltin (TBT) | + | + | | Increased adipogenesis in 3T3-L1 cells and MSCs, transgenerational obesity in mice | [55, 70, 75, 80, 81] |
| | Triphenyltin, fentin (TPT) | + | + | | Lipid accumulation | [75, 91, 173] |
| **persistent organic pollutants** | Alpha napthoflavone | + | | | Increases lipid accumulation in mature adipocytes | [174] |
| | Tetrachlorodibenzodioxin (TCDD) | | + | + | Increased adipogenesis in 3T3-L1 cells; diabetes in adults | [175] |
| | Polychlorinated biphenyls PCB-77, PCB-138, PCB-180 | | + | + | Increase in body mass | [176–178] |
| **Surfactant/ emulsifiers** | dioctyl sodium sulfosuccinate (DOSS) | + | | | Increased adipogenesis in 3T3-L1 cells | [179] |
| | SPAN-80 | + | | | Increased adipogenesis in 3T3-L1 cells | [180] |
| | Alkylphenol ethoxylates | + | | | Increased adipogenesis in 3T3-L1 cells | [181] |