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## **Mini Review: Transgenerational effects of Obesogens**

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### **DISCLOSURE STATEMENT**

B.B. is a named inventor on U.S. patents related to PPAR $\gamma$  and other nuclear receptors, some of which have been licensed to for profit entities. None of these present any conflict on interest.

M.K.L. has no conflicts to declare.

## 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 and Hispanic women exceeding 50% [4]. Alarming, 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<sup>2</sup> higher in 2006 than in 1988 [11]. In addition, the same NHANES data set refuted the idea of increased sedentary behavior 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 favor 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 remodeled 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 fetal 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 unfavorable 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 fetal environment and the adult environment; the undernourished fetus 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 fetal 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 fetal origins models is that fetal 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 for 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].

o 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 developmental 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 signaling as adverse, *per se* [49]. A general feature of endocrine signaling 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 signaling 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 favor 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 the obesogen hypothesis and the extent to which these data are consistent with the importance of environmental obesogens in the etiology 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 (PPAR $\gamma$ ) 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 PPAR $\gamma$  [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 PPAR $\gamma$  [79]. Which receptor diethylhexyl phthalate acts through is unknown but the action may be via its metabolite monoethylhexylphthalate on PPAR $\gamma$ .

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 PPAR $\gamma$ . 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<sup>me3</sup>) 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 quinoxifen 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 PPAR $\gamma$  [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 PPAR $\gamma$  activator, troglitazone on the differentiation and function of 3T3-L1 preadipocytes, *in vitro* [94]. TBT-induced adipocytes produced lower levels of adiponectin and CEBP $\alpha$  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  $\beta$ -oxidation of fatty acids in the liver [97]. Pharmaceutical PPAR $\gamma$  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 PPAR $\gamma$  activator rosiglitazone (ROSI), the RXR activator IRX4204 or the dual RXR/PPAR $\gamma$  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 signaling 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  $\gamma$  coactivator 1 $\alpha$  (Ppargc1 $\alpha$  or PGC-1 $\alpha$ ) and iodothyronine deiodinase 2 (Dio2, which converts thyroxine, T4, to the more thermogenic triiodothyronine, T3). Second, 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 Union 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 phenotype 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 underly transgenerational 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 noncoding 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 U.S. 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 existence 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 disease [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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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]
	Quinoxifen	+			Induce adipogenesis and adipogenic gene expression in 3T3-L1 cells	[90]
	Forchlorfenuron	+			Induce adipogenesis and adipogenic gene expression in 3T3-L1 cells	[90]
	Flusilazole	+			Induce adipogenesis and adipogenic gene expression in 3T3-L1 cells	[90]
	Fludioxonil	+			Induce adipogenesis and adipogenic gene expression in 3T3-L1 cells and MSCs	[90]
	acetamiprid	+			Induce adipogenesis and adipogenic gene expression in 3T3-L1 cells	[90]
	tebupirimfos	+			Induce adipogenesis and adipogenic gene expression in 3T3-L1 cells	[90]
	Triflumizole	+	+		Induce adipogenesis and adipogenic gene expression in 3T3-L1 cells, MSCs and in mice	[79, 90]
	spirodiclofen	+			Induce adipogenesis and adipogenic gene expression in 3T3-L1 cells	[90]
	pymetrozine	+			Induce adipogenesis and adipogenic gene expression in 3T3-L1 cells	[90]
	DDE	+	+	+	Adipogenesis in 3T3-L1 cells, increased weight gain <i>in vivo</i>	[143-146]
	DDT	+	+	*	Adipogenesis in 3T3-L1 cells, increased weight gain, <i>in vivo</i> , transgenerational obesity	[110, 143-146], reviewed in [147]

	Diazinon	+			Induces adipogenesis in 3T3-L1 cells	[148]
	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]
<b>drugs</b>	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]
<b>Metals</b>	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]
<b>Food/packaging</b>	acrylamide	+	+		Increased lipid accumulation in 3T3-L1 cells, increased fat mass in mice	[159]
	fructose	+	+	+	Induces adipogenesis 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]



<b>Personal care products</b>	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]
<b>organotins</b>	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]
<b>persistent organic pollutants</b>	Alpha naphthoflavone	+			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]
<b>Surfactant/emulsifiers</b>	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]



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