ISSN: 2357-0547 (Print)
ISSN: 2357-0539 (Online)

Review Article / JAPR / Sec. B
Jabaqji et al., 2024, 8(3), 135-149

Journal of Advanced Pharmacy Research

Section B: Pharmaceutical Analytical & Organic Chemistry, Medicinal & Biochemistry

Environmental Obesogens: What You Need to Know

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Submitted on: 24-03-2024; Revised on: 14-07-2024; Accepted on: 21-07-2024

To cite this article: Jabaqji, M.; Shaimaa Nakameh, S.; Kabeer, O.; Joujeh, D. Environmental Obesogens: What You Need to Know. *J. Adv. Pharm. Res.* **2024**, *8* (3), 135-149. DOI: 10.21608/aprh.2024.284605.1266

ABSTRACT

Background and Objective: Obesity has evolved into a present-day pandemic, impacting individuals of all ages globally. Various factors have been implicated in the worldwide increase of obesity and diseases related to it, examined from numerous viewpoints. Environmental obesogen is characterized as a chemical agent that promotes obesity in humans or animals. This review offers an up-to-date synopsis of findings from both animal and human research concerning the contribution of environmental obesogens to obesity, as well as a detailed perspective on the mechanisms by which they exert their effects. **Methods:** The review was created by searching Pubmed and Google Scholar, using many keywords, such as: “Obesity”, “Obesogens”, “obesogenic compounds”, “Endocrine-disrupting chemicals”, “mechanism of action”, “in vivo model”, “in vitro model”, “PPARγ”. **Results:** Several mechanisms have been proposed to explain the mechanism of action of obesogens, including activation of PPARγ, altering the gut microbiome, altering appetite, satiety and food preferences, DNA methylation, regulatory role of micro-RNAs, impaired thermogenesis. In vivo and in vitro studies have provided evidence of the effects of obesogenes and have proposed additional mechanisms to explain their mechanism of action. **Conclusions:** Although great progress has been made, **s**tudies about obesogens are still in the early stages, and more research is needed to discover the obesogens that are still unknown, and to understand the precise mechanisms of the previously discovered obesogens.

Keywords: *Obesity, obesogens, Endocrine-disrupting chemicals, mechanism of action, model systems.*

INTRODUCTION

Obesity has evolved into a present-day pandemic, impacting individuals of all ages globally[1]. It may be described as a persistent and extensive growth of adipose tissue, which is partly attributed to a prolonged disparity between caloric intake and energy output, with environmental and genetic factors playing contributory roles[2]. The World Health Organization states that worldwide obesity rates have almost tripled since 1975, and this prevalence is continuing to rise[1].

Obesity is not merely aesthetic issues; it also correlates with concomitant conditions like increased susceptibility to cardiovascular diseases, type 2 diabetes, various metabolic disorders, and several types of cancer. These have culminated in around 4 million deaths globally from 1980 to 2015. Comprehending the multifactorial contributors to obesity is imperative to devise treatment strategies that have, up to this point, remained challenging to pinpoint and execute[3].

Various factors have been implicated in the worldwide increase of obesity and diseases related to it, examined from numerous viewpoints. These include genetic variations, as well as the intake of too many calories paired with a lack of physical activity. This discussion was prominent. In 2002, Baillie-Hamilton presented the hypothesis that the rise in obesity over the last forty years could be connected to the increased number of new industrial chemicals. This surge in obesity rates seemed to coincide with the escalated chemical production that occurred after World War II[4]. The term "environmental obesogen" was released by Grün and Blumberg in 2006[5], environmental obesogen is characterized as a chemical agent that promotes obesity in humans or animals[4]. It has the capability to disrupt lipid homeostasis, thereby fostering adipogenesis and the accumulation of lipids[6]. Compounds known as obesogens have been demonstrated to induce metabolic disruptions that can persist later in life and may be transmitted across generations after exposure[1].

Three factors that can impact the action of obesogens which are the partition constant –which is an equilibrium constant that quantifies the distribution of a compound between two solvents that are not miscible-, half-life, and molecular weight. Low molecular weight lipophilic compounds can readily pass through cellular membranes. Moreover, substances with extended half-lives may be stored in fatty tissue for extensive periods, ranging from months to years. A number of obesogens that have been extensively studied exhibit these particular properties[7].

Obesogens originally comes from natural sources such as metals and viruses, from prescription medications, environmental agents including insecticides and plastics, or even from dietary elements like fructose and food additives. Individuals can encounter these substances through the air, water, ingestion, dermal contact, or inhalation of dust. Nowadays, everyone is exposed to a wide array of obesogenic compounds. Although such exposure is widespread, the impact of obesogens can differ greatly based on factors like genetic susceptibility, age, gender, geographic location, lifestyle, and diet[8].

As the synthesis, usage, and environmental release of chemical substances continue to grow, the obesogenic consequences of such activities have elicited significant concerns[5].

This review offers an up-to-date synopsis of findings from both animal and human research concerning the contribution of environmental obesogens to obesity, as well as a detailed perspective on the mechanisms by which they exert their effects.

METHODS

The review was created by searching Pubmed and Google Scholar, using many keywords, such as: “Obesity”, “Obesogens”, “obesogenic compounds”, “Endocrine-disrupting chemicals”, “mechanism of action”, “in vivo model”, “in vitro model”, “PPARγ”.

Endocrine-disrupting chemicals (EDCs)

Endocrine-disrupting chemicals (EDCs) are substances that can mimic the body's natural hormones and interrupt the normal functioning of the endocrine system by meddling with the body’s hormonal balance[1]. In 2003, Jerry Heindel was the first to draw a connection between EDCs and obesity. The theory that EDCs could affect obesity was credible considering the endocrine system plays a central role in regulating appetite, satiety feelings, metabolism, and the management of fat reserves[3].

Over the course of the 20th and 21st centuries, the widespread application of pharmaceuticals and pesticides in farming practices and the escalation of industrial byproducts have increased worries regarding the spread of EDCs into our surrounding environment[9]. Directly or indirectly, these chemicals are broadly used as major elements or additives in the production of a multitude of consumer goods. Once manufactured or implemented, EDCs are effortlessly dispersed into the environment, leading to spread and exposure of both humans and wildlife, which has now escalated into a concern of global significance[10]. EDCs can be found in substances including pesticides, herbicides, fungicides, flame retardants, surfactants, plastics, sunscreens, cosmetics, and personal care products, among others[4]. Presently, it has been reported that more than a thousand chemicals have been recognized to have an impact on the endocrine system[6]. A group of EDC known as Phthalates, these compounds build the fat cells within the body. Phthalates are found in about 40% of all consumer products utilized by humans. Over time, these chemicals seep out of the materials containing them. Consequently, they invade indoor air and dust, embedding themselves in the environments humans inhabit[11].

Nicotine functions as an endocrine disruptor. By the year 2013, there were already more than thirty distinct epidemiological studies all reporting a consistent observation; children experienced an elevation in weight gain if their mothers smoked during pregnancy. Past studies in both humans and animals have revealed that nicotine contributes to an increase in body weight and fat distribution, an enlargement of fat cell size, and an upregulation of genes associated with fat cell formation, along with a reduction in physical activity levels[12].

Acrylamide is also regarded as a potential EDC, primarily deriving from fried, baked, and roasted foods, which are consumed extensively by children, adolescents, and adults globally[13]. Acrylamide has the potential to promote fat cell development through pathways such as the mitogen-activated protein kinase, as well as the AMPK/acetyl-CoA carboxylase signaling pathways. Studies have uncovered that acrylamide negatively impacts the metabolism of fat tissue, adipogenesis, and obesity, acting like environmental hormones and endocrine disruptors that are commonly recognized as obesogens[14].

Phytoestrogens function as endocrine disruptors through pathways mediated by estrogen receptors[15]. in both in vitro studies and obesity-related animal models, phytoestrogens have demonstrated effects similar to estrogen on the formation and metabolism of fat cells. Yet, the impact of consuming phytoestrogens on the development of obesity in humans remains somewhat uncertain. Findings from randomized controlled trials indicate that phytoestrogens' effects on body weight are specific to the compound and vary depending on the metabolic state[16].

Obesogens: mechanisms of action

Obesogenic substances can act either directly on adipocytes or indirectly. Direct action involves increasing the number of adipocytes, stimulating fat storage in the existing adipocyte, or producing dysfunctional adipocyte. On the other hand, indirect action occurs through multiple mechanisms, such as disrupting metabolism and appetite control, altering metabolic setpoints, inducing unfavorable changes in microbiome composition, and increasing the proportion of calories that are stored as fat[17]. (Figure 1)

Activation of PPARγ

The PPARγ (peroxisome proliferator-activated receptor gamma) is a receptor that, upon activation by certain ligands, functions as a transcription factor critical in regulating gene expression associated with multiple physiological functions. PPARγ has been initially identified as a pivotal regulator in the formation and development of adipose tissue[18]. Activation of this receptor induces the differentiation of mesenchymal stem cells (MSCs) into fat cells and triggers the commencement of fat production[19].

Tributyltin (TBT) acts as a highly effective ligand for PPARγ, prompting the differentiation of both bone marrow and adipose-derived multipotent stromal cells (MSCs) into adipocytes. TBT functions not just as a PPARγ agonist but also as an agonist for retinoid X receptors (RXR) α and β. This dual-acting capacity of organotins suggests that RXR might play a role in the effects of TBT on MSC differentiation, separately from PPARγ[20].

In addition to TBT, a variety of other obesogens target PPARγ, either by increasing its expression or through direct binding which initiates subsequent processes resulting in increased adipogenesis. These compounds include, dichlorodiphenyltrichloroethane (DDT) and its derivative DDE, nonylphenol (NP), octylphenol (OP), bisphenol A (BPA), di-(2-ethylhexyl)phthalate (DEHP), dibutyl phthalate (DBP), benzyl butyl phthalate (BBP), and mono-benzyl phthalate (MBzP)[19].

Acrylamide which can promote fat cell development through several pathways-as noted above-is also capable of initiating the differentiation of 3T3-L1 preadipocytes into fat cells by promoting the expression of adipogenesis-related transcription factors, including PPAR-γ and CCAAT/enhancer-binding protein α[14].

A growing array of natural compounds known to activate PPARγ has been discovered. Several among these not only activate PPARγ but also stimulate adipocyte formation in cellular models like 3T3-L1 cells, including substances such as flavanone, bixin, and emodin[21].

Altering the gut microbiome

The gut microbiome is the collection of microbes that reside in the human gut. Obesogen exposure could lead to obesity by altering the gut microbiome, a relatively novel mechanism which leads to obesity. It is evident from several experimental data that many obesogens induce the gut microbiome dysbiosis in zebrafish, mice and human.

In a study investigating the relationship between Atrazine, a widely used pesticide in the US known to be an obesogen, and microbiota, zebrafish were subjected to Atrazine concentrations of 25 ng/L and 0.50 ng/L for a duration of two weeks. After exposure, bacterial DNA was extracted using real-time PCR and analyzed. The findings revealed a rise in the levels of Bifidobacterium, it is a phylum linked to carbohydrate metabolism, in the zebrafish treated with Atrazine. This suggests that obesogens may alter the host's microbiota in a way that promotes increased fat storage[22]. It has been determined that adding diethylhexyl phthalate (DEHP) into the diet contributes to worsening microbial imbalances in zebrafish, which could partially explain its function as an obesogen[23].

Exposure to Tributyltin (TBT) has also been observed to cause dysbiosis in the gut microbiome of mice. It reduced the diversity of gut microbial species, altered the composition of the microbiome, and led to an increase in body weight, greater accumulation of visceral fat, and dyslipidemia in male mice[24]. Another study found that exposure to Tributyltin leads to an imbalance in the gut microbiome, which is associated with increased weight gain, disrupted glucose and insulin regulation, and endocrine disruption in mice[25].

The "Western dietary pattern" has a significant correlation with obesity, and numerous recent research found that elements of the Western diet, such as ultra-processed foods, food additives, and artificial sweeteners, have the potential to disturb the balance of

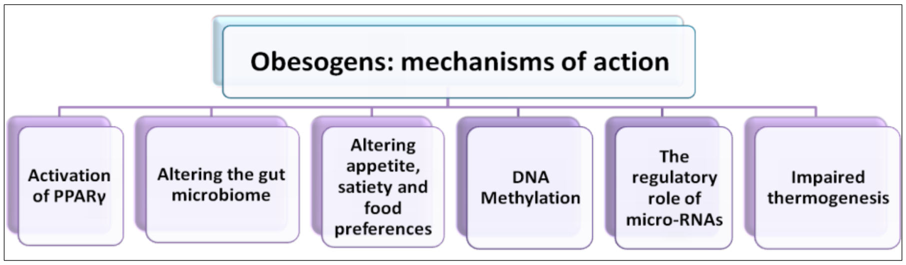

Figure 1. Obesogens: mechanisms of action

the gut microbiome[26], Recent studies have revealed that two prevalent dietary emulsifiers, carboxymethylcellulose and polysorbate-80, can cause inflammation in the intestines and an imbalance in the gut microbiome. This disruption is linked to the development of metabolic syndrome in mice, along with an increase in body weight and white adipose tissue (WAT) depot weight[27].

Altering appetite, satiety and food preferences

Leptin, a 16-kDa peptide hormone that promotes the feeling of fullness, is produced by the gene associated with obesity. It helps maintain energy equilibrium by reducing the sensation of hunger[28].

The set and control of appetite regulation occurs early on in the hypothalamus during a person's life. Signaling molecules such as leptin and ghrelin are crucial in programming the appetite control centers within the hypothalamus. Environmental chemicals can have direct impacts by attaching to neurons in the developing brain and by modifying the expression of essential appetite-regulating factors[29]. A recent study supports this by demonstrating that in a 3T3-L1 adipocyte model, there was a noticeable increase in the production of leptin mRNA after three weeks of exposure to 1 nM of BPA[30]. Exposure to methylparaben after weaning has been shown to raise the levels of leptin in the serum of a mouse model[31].

DNA Methylation

DNA methylation represents an epigenetic process that is linked to the suppression of gene activity, particularly when this methylation takes place on the CpG sites within promoter sequences[32], DNA methylation is the most extensively investigated process hypothesized to be responsible for the heritable consequences of exposure to obesogens[33].

Bisphenol A (BPA), is considered as xenoestrogen, it is prevalent in plastic food containers, and it is one of the components that leads to obesity[34], Analogues of BPA, known as bisphenols (BPs), possess similar chemical compositions and exhibit similar behaviors[35].

Research has demonstrated that exposure to a low dose of Bisphenol S (BPS) at 1.5 µg/kg body weight per day significantly affects gene expression, with 374 genes showing substantial deregulation, and alters the hepatic methylome in male mice, leading to hypomethylation in 58.5% of the differentially methylated regions (DMR)[36].

There was a notable association identified between the concentration of phthalates in urine and metabolic abnormalities including obesity and insulin resistance. Regarding epigenetics, phthalates have been found to modify the methylation of metabolic-related genes, namely PPARG, Insulin Growth Factor 2 (IGF2), and Sterol Regulatory Element-Binding Proteins (SREBPs)[37].

Studies have also demonstrated that when F0-generation mice are exposed to the obesogenic compound tributyltin (TBT) during pregnancy, it can predispose male descendants in the F4 generation to obesity in the event of a high-fat diet. Furthermore, TBT is capable of causing widespread alterations in DNA methylation and modifying the expression of genes that are important for metabolism[38].

The regulatory role of micro-RNAs

MicroRNAs, small RNA molecules approximately 22 nucleotides in length, function by regulating gene expression at the post-transcriptional level. Various miRNAs play a role in adipogenesis, including miR-30, miR-26b, miR-199a, and miR-148a. Higher levels of these miRNAs have been observed in both obese humans and mice that have been maintained on a high-fat diet[39], The levels of miR-17-5p and miR-132 were found to be higher in the visceral fat tissues of obese adults, with a significant correlation to body mass index, glycosylated hemoglobin, and disrupted glucose and lipid metabolism[40]. Studies have demonstrated that Tetrabromobisphenol-A (TBBPA) stimulates the expression of miR-103 and miR-107. It has been revealed that miR-103 targets Thy1, a key regulator of adipogenesis and obesity, leading to a decrease in its expression[41]. Exposure to genistein (GEN) and Bisphenol A (BPA) during development can alter expression patterns of miR/small RNA in the hypothalamus. These alterations are associated with behavioral and metabolic changes induced by EDCs[42]. Research has indicated that Benzyl Phthalate enhances adipogenesis in 3T3-L1 cells through the signaling pathway of miRNA-34a-5p[43].

Obesogens and Impaired Thermogenesis

Placental mammals possess three types of adipose tissue —white, beige, and brown—distributed in distinct fat stores across the body. White adipocytes primarily function in the storage and release of fats, whereas beige and brown fat cells are specialized for thermogenesis, the process of burning calories to generate heat[44].

Recent publications suggest that certain obesogens may interfere with the creation or activity of thermogenic adipocytes, affecting some of their functions [45].

Studies have linked heightened risk of developing insulin resistance and obesity with the exposure to the pesticide dichlorodiphenyltrichloroethane (DDT) and its derivative dichlorodiphenyldichloroethylene (DDE). These adverse effects seem to stem from a downregulation of thermogenesis in brown adipose tissue (BAT), which is under the control of the sympathetic nervous system. Early life exposure to DDT or p,p'-DDE disrupts thermogenesis by altering the sympathetic neural connectivity that governs BAT regulation[46].

La Merrill *et al.* demonstrated that DDT exposure during the perinatal period hampers thermogenic processes as well as carbohydrate and lipid metabolism, potentially raising the vulnerability to metabolic syndrome in adult female progeny[47].

This particular manifestation of impaired brown adipose tissue (BAT) functionality can be attributed, in part, to a reduction in the expression of a critical regulator of BAT activity, namely the peroxisome proliferator-activated receptor γ coactivator 1α (Ppargc1α, or PGC-1α). Additionally, there is a decrease in the expression of iodothyronine deiodinase 2 (Dio2), the enzyme that is responsible for converting thyroxine (T4) into the more thermogenically active hormone, triiodothyronine (T3)[48].

Brown adipose tissue (BAT) has also been indicated as a potential target for the toxic effects of Arsenic, mediating the metalloid's influence on body fat composition[49-50].

Prior research has shown that chlorpyrifos (CPF) not only stimulates appetite but also impedes thermogenesis in brown adipose tissue (BAT) stimulated by diet. This interference exacerbates the progression of obesity, non-alcoholic fatty liver disease (NAFLD), and insulin resistance, even in low quantities[51].

Model systems

Obesogens act through various complex mechanisms and follow multiple pathways to impact the living body. Currently, model systems are used to test mechanisms of obesogenic action including in vitro and in vivo systems.

In Vitro Assays for Obesogens

Research conducted in laboratories lends credence to the theory that exposure to chemicals plays a role in causing endocrine disorders in both humans and animals in the wild[52]. Models used in a lab setting are crucial for pinpointing environmental obesogens, and comprehending the mechanisms that lead to obesity[53].

In vitro models offer multiple advantages compared to different model systems. They can employ human cells, enhancing physiological relevance. Additionally, they tend to be more straightforward, quicker, suitable for parallel processing (enabling medium to high throughput analyses), and are more cost-effective[1].

Furthermore, in vitro models offer a swift method for exploring the risks associated with exposure to EDCs and their toxic effects, thereby diminishing or completely obviating the necessity for animal experimentation[53]. Numerous in vitro research efforts have demonstrated that certain xenobiotic substances, including tributyltin chloride and bisphenol A, have the capability to encourage the differentiation of adipocytes[54].

A widely used method for detecting chemicals that induce adipogenesis involves conducting tests using the 3T3-L1 preadipocyte model[55]. The 3T3-L1 cells are characterized as a complete, stable, and reproducible cell system[56]. However, since they are fully committed to the adipocyte lineage, the suitability of the 3T3-L1 cell line for assessing adipogenic responses remains uncertain. Furthermore, the species-specific nature of this murine-derived cell line could limit the extrapolation of findings to human health risk evaluations[7]. A list of in vitro model systems and obesogens identified using these models is presented in **Table 1**.

In Vivo Assays for Obesogens

Various in vivo models have demonstrated that specific environmental contaminants induce adipogenesis. Although animal models are not always suitable to evaluate the obesogenic effect of certain chemicals, as they do not mimic the human physiological systems, in vivo models do provide certain benefits. They permit the study of whole-body dynamics and systematic impacts which are not possible with in vitro systems[75].

Research using lab animals suggests that exposure to (EDCs) can produce effects associated with numerous diseases[52]. Human epidemiological studies have established a connection between exposure to

Table 1. ***In vitro*** **models for studying obesogens**

Model system (in vitro)	Chemical	Use	Proposed Mechanism	Effects	References
AML12 mouse hepatocytes and THP-1 human macrophages	ATBC	ATBC is a plasticizer used in medical devices, food packaging, children's toys, and personal care products etc.	ATBC exposure affected the expression of lipogenesis and lipid uptake genes	ATBC increased the lipid accumulation in both human macrophages and mouse hepatocytes	57
murine adipocytes (3T3-L1)	TPA and DMT	Used in the Manufacture of Polyethylene terephthalate food packaging	Modulating of early events in preadipocytes' differentiation	During 3T3-L1 differentiation, TPA and DMT exposure increased the lipid content, induced the adipogenic markers, impacted adipocytes' thermogenic program, reduced pAMPK and PGC-1α levels, and stimulated the NF-κB proinflammatory pathway	58
Murine adipocytes (3T3-L1)	PFAS	Used in commercial applications such as coatings for fabrics, insecticide formulations, fire-fighting foams, paper products for food packaging	PFAS are the activators of PPARγ. They may induce lipid content within undifferentiated and differentiated 3T3-L1 preadipocytes	PFAS showed potential to induce the differentiation of3T3-L1 to adipocytes	59
The murine fibroblast 3T3-L1 cell line	Quizalofop-p-Ethyl	a selective post-emergence herbicide	It exerts its effect -in part-via a pathway mediated by PPARγ	It may have a hitherto unsuspected obesogenic effect	54
3T3-L1 preadipocytes	NP	NP is a major degradation product of alkylphenol ethoxylates, which are a class of nonionic surfactants widely used in the manufacturing of detergents, pesticides paints, cosmetics, and plastics	Exposure to NP can interfere with the expression of mRNAs and/or proteins of the regulators related to lipid metabolism (FAS, PPARγ, CEBPα, SREBP1)	Exposure to NP induced the differentiation and proliferation of adipocytes and the accumulation of lipids, and ultimately results in blood lipid diseases and obesity	60
Mouse embryo 3T3-L1 fibroblasts and mouse RAW264.7 macrophages	β-CYP	β-CYP is a pyrethroid pesticide (type-II). Human may be exposed to it through diet and breathing	Increasing the level of intracellular ROS through binding to the mitochondrial respiratory chain complex I	β-CYP stimulates the adipogenesis of 3T3-L1 cells through inducing adipogenesis	61

hMSCs	Bisphenols (BPA, BPAF, BPB, BPC, BPF, BPS, TBBPA and TCBPA)	plastic items, metal coatings, and flame retardants	increasing the number of adipocytes	All tested bisphenols can induce adipogenesi. TBBPA and TCBPA (Flame retardants), can increase both the number and the size of adipocytes	62
hMSCs	BPA, PFOA, TBT, TPP, DDE, and TCS	BPA: a plasticizer PFOA: a surfactant TBT: organotin used in boat paint TPP: flame retardant DDE: a metabolite of the insecticide TCS: an antimicrobial	Increasing the mRNA expression of adipocyte differentiation markers, the adiponectin expression, and the positive control PPARγ agonist	The chemicals altered the extracellular lipids of mature white adipocytes. Triclosan can also affect the energy balance, and the adipocytes' endocrine function	63
hMSCs	OBS, PFOS	oil production and fire-fighting foam	PFOS and OBS mixtures induce adipogenesis via activation of PPARγ	PFOS/OBS co-exposure resulted in the synergistic activation of PPARγ, eventually leading to enhanced adipogenesis	64
SGBS preadipocytes	DEHP	DEHP can accumulate in lipophilic product such as cosmetics, and binds to dust particles	DEHP can alter the secretion of leptin and adiponectin during adipogenesis	DEHP altered the level of adipokines, without affecting the intrinsic endocannabinoid system	65
human female adipose-derived stem cells (hASCs)	BPA, BPAF, and TMBPF	food-contact coating of food and beverage metal container, water supply pipes, cosmetic products packaging, storage containers, and etc.	BPA, BPAF, and TMBPF can alter the human stem cell ability to differentiates into fat cell and produces lipids	low-dose BPA and BPAF had obesogenic properties, and increased adipogenesis. TMBPF, and higher doses of BPA and BPAF decreased adipogenesis	66
HepG2 cell line	PBDEs: BDE-47, -99, -209	Man-made chemicals that have flame-retardant properties. They are added to commercial products	They had an effect on the lipid metabolism and signaling hallmarks regulating metabolism as mTORC1 and PI3K/AKT/MTOR	The treatment affected several pathways, increased the lipid accumulation in the cell, and modulated the expression of some relevant markers	67
HepaRG and HepG2 cells	TBT	a common constituent of antifouling paints, applied in shipping industry	TBT can bind and activate PPARγ and RXRA	TBT can induce lipid accumulation in the liver, and de novo lipogenesis	68-69

DEHP, DINCH, ATBC, and DEHA	Phthalate plasticizer, DEHP, and non-phthalate origin plasticizers DINCH, ATBC, and DEHA	childcare articles, toys, furniture, and etc.,	disrupting thyroid signaling, resulting in altered thyroid hormone homeostasis	It leads to adverse health effects related to the thyroid gland	70
hBM-MSCs	2,4-DTBP	It is mainly used as UV stabilizers for hydrocarbon-based products and plastics. It has been detected in wastewater, indoor dust, and etc. It's also a toxic metabolite produced by animals, plants, bacteria, and fungi. Human can be exposed through ingestion of dust, and packaged food intake	Activating the PPARγ- RXR heterodimer	Exposure to 2,4-DTBP increased lipid accumulation and the expression of adipogenic marker genes	71
C57BL/J6	BDE47	BDE-47 is used as commercial flame retardants. Human can be exposed through the food chain	BDE-47 up-regulated triglyceride synthesis, but inhibited lipid export and β oxidation, exasperating the hepatic lipid accumulation in HFD fed mice	Exposure to BDE-47 caused elevation in the body weight, and worsening of hepatic steatosis, and increased inflammation in HFD fed mice.	72-73
3T3-L1	DEHP	DEHP is the most widely used PVC plasticizer. It leaches out easily during production, use, and disposal	adipogenesis and gluconeogenesis in human adipocytes, murine 3T3-L1 pre-adipocytes, and MSCs	Low-dose long-term DEHP caused acceleration of HFD induced weight gain, and adipopexis, decreased energy metabolism in female mice, PPARγ phosphorylation at Ser273 in mice, and also caused gut microbiota remodeling	74

ATBC: Acetyl tributyl citrate, BDE47: Tetrabromodiphenyl ether, BPA: Bisphenol A, BPAF: bisphenol AF, β-CYP: β-Cypermethrin, DDE: Dichlorodiphenyldichloroethylene, DEHA: di-(2-ethylhexyl) adipate, DEHP: di-(2-ethylhexyl)-phthalate, DINCH: diisononyl hexahydrophthalate, DMT: dimethyl terephthalate, 2,4-DTBP: 2,4-Di-tert butylphenol, hBM-MSCs: Human bone marrow mesenchymal stem cells, hMSCs: human mesenchymal stem cells, HFD: high fat diet, NP: Nonylphenol, OBS: Sodium p-perfluorous nonenoxybenzenesulfonate, PBDEs: Polybrominated diphenyl ethers, PPARγ: Peroxisome proliferator activated receptor gamma, PFAS: polyfluoroalkyl substances, PFOS: perfluorooctane sulfonate, PPARγ: peroxisome proliferator-activated receptor gamma, PFOA: Perfluorooctanoic acid, PVC: polyvinyl chloride, RXRA: Retinoid X receptor alpha, TBT: Tributyltin, TCS: Triclosan, TMBPF: tetramethyl bisphenol F, TPP: Triphenylphosphate, TPA: p-phthalates terephthalic acid, TRα: thyroid hormone receptor.

Table 2. *In vivo* models for studying obesogens

Model system (in vivo)	Chemical	Source/Use	Proposed Mechanism	Effects	References
Children (442)	Neonicotinoids	Insecticides: Human may be exposed to neonicotinoids through food, air, and drinking water	Disturbances of neurological function, insulin function, endocrine homeostasis, or gut microbiota	Urinary neonicotinoids and metabolites had been determined to be differently related to obesity-associated indexes	78
US adults (NHANES 2015-2016 data)	neonicotinoids	Nicotine-containing insecticides are often used to protect agricultural crops from damage by pests	disruption of thyroid hormone and increase of oxidative stress	Inverse association was shown between Acetamiprid and measures of adiposity. On the other hand, 5-hydroxy-imidacloprid showed a positive association with being overweight/obesity, and with lean mass index	79
CHDS mothers and children	DDT	pesticide	DDT has a role in impaired metabolism that results in reduced energy expenditure and increased obesity	Maternal DDT was associated with increased obesity risk	80
Caenorhabditis elegans	MeHg	Humans can be exposed to MeHg through seafood consumption	Increasesd adipogenic miRNA expression and decreased anti-adipogenic miRNA expression	Lipid storage levels in the mir-124 and let-7 mutant worms were statistically different from the lipid storage levels in the wild type, indicating that these sequences could be potential mediators of lipid dysregulation induced by MeHg	81
C57BL/6J mice	DBP	DBP is widely used in plastics manufacturing	DBP may be related to the activation of endoplasmic reticulum stress in the mice adipose tissue, which inhibits the UCP1 expression, thus reducing the brown adipose tissue's energy consumption	Intra-uterine exposure to low-dose DBP **have an effect on** lipids and sugars metabolism, ultimately leading to obesity in the offspring	82
C57BL/6 mice	BPA and BPS	They are used in consumer products manufactureing such as polycarbonate plastics and epoxy resins. They are able to leach from these products into drinking water	PPARγ activation.	Subchronic exposure to BPA and BPS disturbed metabolism in liver tissue	83
C57BL/6	BPA and PFOA	(BPA): A plasticizing agent used in epoxy resins, polycarbonate plastics, and in many consumer products (POFA): man-made chemical used in the manufacture of several products with water- and dirt-repellent properties	modulating the functions of nuclear receptors involved in regulating metabolism	PCN and PFOA induced hepatic expression of PXR and PPARα target genes. BPA exposure caused limited changes in gene expression	84-85
offspring mice	PBEB	It is commonly used to thermoset polyester resins and fabrics. It has been found in the indoor dust, watershed, soil, and sediment	PBEB disrupts the pathways that control adipogenesis	the male offspring showed increased weight gain and adipocyte hypertrophy in the epididymal white adipose tissue	86
C57BL/6J mice	Benzene	Benzene is widely used in the petrochemical, rubber, and interior decoration industries	Exposure to benzene can lead to lipodystrophy and disturb the endocrine function of WAT	Exposure to benzene caused Dyslipidemia and decreased the content of total body fat. It also reduced the adipocytes' size, altered lipometabolism genes in WAT and affected the endocrine function of WAT	87

C57BL/6	Dioctyl sodium sulfosuccinate (DOSS)	DOSS is a lipid emulsifier, commonly used in processed foods, cosmetics. It is also used as stool softener medicines	Treatment with DOSS produces altered DNA promoter methylation	DOSS exposure during development caused impaired glucose tolerance, increased adiposity, and alteration in gene expression, circulating levels of phospholipids adipokines and cytokines	88
Zebrafish	NPEOs	NPEOs are used in pesticide formulations, surface cleaners, paints, textile production, and other products. They are also reported in sediment samples, indoor dust samples, municipal wastewater and drinking water	Activation of the estrogen receptor	NPEOs promoted adipose deposition in zebrafish	76
Zebrafish	BSA	It is added to the plastic material to harden the plastics. It is also used as dental fillers, baby bottles, food containers, and dye powders	Disruption of glucose tolerance, oxidant–antioxidant homeostasis, and modulation of fibroblast growth factor and inflammatory cytokines	Exposure to BPA caused increase in the body weight, and the expression of dnmt3a, il1ß, lepa, tnfα, il6, and fgf21, impairment of glucose tolerance, and oxidant–antioxidant homeostasis. It also caused degeneration of hepatocytes, vasocongestion, and lipid vacuolization	89
zebrafish (Danio rerio)	PFOS	PFOS is used in the manufacture of surfactants as well as in aqueous film forming foam	exposure to PFOS affected gene expression in the processes associated with in adipogenesis and lipid homeostasis	PFOS caused increase in embryonic saturated fatty acids and decrease in the expression of PPAR gene	90
male C57BL/6J mice	ATBC	ATBC is a plasticizer used in medical devices, food packaging, children's toys, and personal care products etc.	ATBC exposure affected the expression of lipogenesis and lipid uptake genes	Exposure to low doses of ATBC caused obesity and liver steatosis	57
Female mice C57BL/6	TCDD	TCDD is an environment pollutant, produced as a byproduct of industrial and chemical processes	-	Exposure to low doses of TCDD in caused impairment of the ability to metabolically adapt to high-fats diet feeding	91-92
Rodents	Atrazine	Atrazine is a herbicide frequently detected in drinking water, and waterways	Atrazine may disrupt metabolic activity by interfering with the function of the mitochondria	Exposure to Atrazine, starting in the prenatal period, caused adverse metabolic and reproductive effects	93
Male C57BL/6 mice	PVC-MPs	Used as raw material for industrial and chemical production	dysfunction of gut barrier and dysbiosis of microbiota	PVC-MPs exposure resulted in intestinal injury and altered gut microbiome composition and metabolome profile	94
Male C57BL/6J mice	BDE-47 (PBDE family)	used as flame retardants in many products	increased inflammation and dysfunction of lipid metabolism	continuous exposure to BDE-47 resulted in dysfunction of lipid metabolism and increase of inflammatory infiltration into WAT in HFD -fed mice	95

ATBC: Acetyl tributyl citrate, BDE-47: 2,2',4,4'-Tetrabromodiphenyl ether, BPA: bisphenol A, BPS: bisphenol S, CHDS: Childhood Health and Development Studies, DBP: Dibutyl phthalate, DDT: dichlorodiphenyltrichloroethane, DOSS: Dioctyl sodium sulfosuccinate, NHANES: National health and nutrition examination survey, NPEOs: Nonylphenol ethoxylates, MeHg: Methylmercury, PBDE: polybrominated diphenyl ether, PBEB: pentabromoethylbenzene, PCN: Pregnenolone-16α-carbonitrile, PFOA: perfluorooctanoic acid, PFOS: perfluorooctanesulfonic acid, PPAR: peroxisome proliferator-activated receptor, PVC-MPs: Polyvinyl chloride microplastics, PXR: pregnane X receptor, TCDD: 2,3,7,8-tetrachlorodibenzo-p-dioxin, WAT: white adipose tissue.

specific chemicals and a rise in fat accumulation, which subsequently leads to an increase in body weight[54].

Zebrafish have become an important model organism for studies on metabolic health due to their rapid development and adipose tissue that is morphologically similar to that of humans. Like mammals, zebrafish accumulate neutral triglycerides in lipid droplets within their white adipocytes, and demonstrate similar gene expression patterns that are involved in adipocyte differentiation, lipolysis, and hormonal actions[76]. The genomes of both mammals and zebrafish exhibit a considerable degree of homology, with more than 70% overall conservation, and it is estimated that zebrafish express about 80% of genes that found in humans. Moreover, the transparent nature of zebrafish embryos, coupled with the progression of sophisticated imaging technologies, enables the non-invasive observation of internal structures and in vivo biological processes, encompassing the development of the nervous system and the distribution and fate of suspected EDCs[77]. In table 2, several in vivo models for studying obesogens have been reviewed.

CONCLUSION

Evidence is mounting about the role of environmental obesogens in the global obesity epidemic. Despite increasing knowledge about the number, nature, and properties of these substances, how they spread in the environment, and the many mechanisms that have been proposed so far to explain their mechanism of action, much is still unknown about these chemicals. Therefore, further studies are required to to understand the precise mechanisms of action, and discover the obesogens that are still unknown. We aim for this review to serve as a valuable resource for researchers, healthcare professionals and policy makers striving to address the complex challenges posed by the obesity epidemic, and help reduce the exposure of future generations to these harmful substances, and take preventative measures by advocating for stricter regulations and safer alternatives for chemicals of concern, promoting consumer awareness, and adopting healthier lifestyle practices to reduce overall chemical exposures.

Acknowledgments

No external funding was received.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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