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RESEARCH ARTICLE

Obesogens in food: the role of chemical pollutants in the obesity epidemic

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Abstract

In recent decades, the issue of food contamination with chemical substances resulting from industrialization and increasing environmental pollution has become a severe challenge for global food security, carrying significant consequences for both public health and the economy. The term "obesogen" was introduced to describe environmental chemical pollutants, classified as endocrine disrupting compounds (EDCs), which can promote obesity in both humans and animals. Among these substances are commonly used chemicals such as bisphenols, phthalates, and perfluoroalkyl substances, whose main source of exposure for humans is consumed food. Studies indicate that exposure to obesogens can disrupt intestinal hormone secretion, lead to dysbiosis of the gut microbiota, and stimulate adipogenesis and fat accumulation in adipocytes, which favors the development of obesity and metabolic disorders. Understanding the mechanisms of action of obesogens is gaining particular importance in the face of the growing global obesity problem.

KEYWORDS
obesogens, endocrine disrupting compounds, gut microbiota, obesity

1. Introduction

The obesity pandemic is widely regarded as one of the major problems of the 21st century. According to the World Health Organization (WHO), in 2022, over 2.5 billion adults were overweight, and 890 million adults were obese, representing 43% and 16% of the global population, respectively [WHO 2024]. Moreover, approximately 4 million people die each year due to obesity [Sarma et al. 2021], and global trends indicate a further increase in the prevalence of obesity in long-term forecasts [Janssen et al. 2020]. Obesity leads to the development of chronic diseases such as metabolic syndrome, type 2 diabetes, cardiovascular diseases, and cancers [Amato et al. 2021]. It is widely believed that changes that have occurred over the years in developed countries, such as the increased prevalence of sedentary lifestyle, Western-style diet, and the consumption of excessive calories, are the main causes of this problem [Heindel, Blumberg 2019]. Interestingly, various species of laboratory animals (monkeys, rats, mice) have also shown significant weight gain over the past few decades. These animals have strictly controlled diets, so their weight gain indicates the involvement of factors other than increased calorie intake [Heindel, Blumberg 2019, Klimentidis et al. 2011]. Research indicates that the etiology of obesity is much more complicated than commonly thought and involves biological, psychological, and environmental factors [Kadouh, Acosta 2017, Lister et al. 2023].

Recent reports indicate that a heterogeneous group of chemical compounds, both anthropogenic and natural in origin, may be an environmental factor leading to the development of obesity in humans and animals [Heindel, Blumberg 2019, Wang et al. 2024]. These compounds are referred to as "obesogens", a term introduced by Grün and Blumberg in 2006, who described weight gain in mice induced by tributyltin (TBT) [Grün, Blumberg 2006, Heindel 2019]. Many mechanisms of obesogenic action include promoting adipogenesis and fat storage in adipocytes, disrupting control over hunger and satiety, changes in metabolism, and disturbances in the taxonomic and metabolomic structure of the gut microbiota (GM) [Amato et al. 2021, Kladnicka et al. 2022]. In vitro and in vivo tests have shown that various common chemical pollutants

in food, including bisphenol A (BPA) and its chemical analogs, organotin compounds, per- and polyfluoroalkyl substances (PFASs), phthalates, polybrominated diphenyl ethers (PBDE), and polychlorinated biphenyls (PCB) exhibit obesogenic activity [Griffin et al. 2020, Nogueiras et al. 2018, Varghese, Hall 2023, Wang et al. 2024].

Properties of obesogens

Obesogens possess diverse chemical characteristics and differ in lipophilicity, degradation/biodegradation time, and molecular weight [Griffin et al. 2020]. The chemical properties of these compounds have profound significance in the context of potential adverse actions and impact on bioaccumulation and affinity for receptors. Lipophilicity and low molecular weight facilitate passage through cell membranes and hinder biodegradation [Długoński et al. 2016]. Lipophilic compounds with a long half-life can accumulate in fat tissue over extended periods, meaning that short exposure can lead to long-lasting effects. For this reason, lipophilic compounds tend to exhibit a biphasic half-life curve, which relates to the compound being excreted simultaneously with its tissue distribution. [La Merill et al. 2013]. Some obesogens belong to the persistent organic pollutants (POPs) group, which means they are resistant to biological and chemical biodegradation, such as PCBs and PBDEs. These compounds resist environmental biodegradation and are not metabolized by liver enzymes and accumulate in fat tissue [Jackson et al. 2017]. Moreover, obesogens can be released into the blood during lipolysis that occurs during weight loss, resulting in further concentration of toxic substances in the remaining fat tissue [Jackson et al. 2017, Lee et al. 2017].

Certain substances with obesogenic properties, such as phthalates, are rapidly metabolized but are commonly present in many human tissues, including fat tissue, because they are frequently used in everyday products, leading to chronic exposure in the population [Hsu et al. 2020]. Fat tissue may be considered a storage site for various xenobiotics that cannot be easily metabolized or excreted from the body [Lee et al. 2017].

The vast majority of obesogens belong to the broader group of endocrine disrupting compounds (EDCs), which are biologically active xenobiotics that affect the endocrine system in humans and animals [Lv et al. 2016]. It is known that EDCs can disrupt hormonal homeostasis through changes in hormone synthesis and transport, receptor binding, cellular metabolism, and the processes of hormone removal from the body [Vilela et al. 2018, Papalou et al. 2019]. Over 1000 chemical compounds exhibiting hormonal activity have been identified, including drugs, pesticides, compounds used in the plastics industry, detergents, and heavy metals [Lee et al. 2022, Pironti et al. 2021]. Furthermore, the biological activity of EDCs varies; some compounds, like natural hormones, are active at very low concentrations (nanomoles or even picomoles) and often exhibit a non-monotonic dose-response curve (NMDRC) [Vandenberg et al. 2012, Schug et al. 2016].

Furthermore, xenobiotics can act synergistically, leading to what is referred to as the "cocktail effect" [Djordjevic et al. 2020], meaning that mixtures of such substances can produce various effects, including stronger ones than individual substances acting at equivalent doses [Djordjevic et al. 2020]. The cocktail effect is commonly utilized in the pesticide industry, for example, to enhance the action of insecticides, the low-toxicity compound piperonyl butoxide, a cytochrome P450 inhibitor, is added to formulations. As a result, it inhibits the degradation of insecticides by insects, prolonging their period of activity, which significantly increases toxicity [Rizzati et al. 2016]. Currently, due to regulations, individual chemical substances are tested to determine their safety, but people are still exposed to many different chemical substances simultaneously [Shaw 2014]. A neglected area of research is determining the impact of mixtures of obesogens on human health, especially their potential for additive and synergistic action.

Obesogens in food

Around the world, due to industrialization, tens of thousands of anthropogenic chemical compounds have been released into the environment, and each year 2,000 new synthetic substances enter the market [Lai et al. 2018]. A significant source of human exposure to obesogens is the consumption of contaminated food and beverages. Sources of food contamination include agriculture (pesticides), food contact materials (FCMs) (BPA and its chemical analogs, phthalates, PFOA), anthropogenic pollution of soils and waters (PCBs, PBDEs, heavy metals, organotin compounds, alkylphenols), and food processing (benzo[a]pyrene) [Kladnicka et al. 2022]. On the other hand, it is worth noting that not all obesogens contaminating food have anthropogenic origins; some enter the food chain through natural processes, such as volcanic activity, weathering of rocks and soils, earthquakes, and erosion (heavy metals and metalloids) [Peivasteh-Roudsari et al. 2023]. Although environmental chemical pollutants enter the food chain unintentionally, there is a challenging debate about the potential obesogenic action concerning some food additives and ingredients with GRAS status (Generally Recognized as Safe). Although they have a long history of safe use, most have not been tested for their impact on metabolism and obesity development. In vivo and in vitro studies show that some artificial sweeteners, preservatives, monosodium glutamate (MSG), and mono-oleoylglycerol (MOG) may induce lipid accumulation [Simmons et al. 2014]. It should be noted that obesogens are a relatively new research topic, and the possible mechanisms of action and effects are still poorly understood. Most current research on food contaminants and additives is based on experiments on cell lines, laboratory animals, or epidemiological studies. Therefore, there is still a need for research to obtain a strong, scientifically evidence-based position and scientific recommendations.

Bisphenols

BPA is an organic compound widely used in the plastics industry for the production of polycarbonate and epoxy resins. Polymers based on BPA are used to manufacture bottles, containers, and inner coatings of food cans, and reports indicate that BPA can leach from packaging into food products [Almeida et al. 2018]. BPA interacts with estrogen receptors because its chemical structure is similar to that of 17β-estradiol, a natural estrogen hormone. Due to this similarity, BPA can competitively bind to estrogen receptors, but its binding and activation of these receptors are significantly weaker than that of 17β-estradiol. This means that BPA can act to some extent as an estrogen mimic, but its effect is limited due to its weaker interaction with estrogen receptors [Della Rocca et al. 2023].

Nevertheless, numerous in vitro studies indicate that BPA affects both genomic and non-genomic mechanisms of estrogen response, while simultaneously disrupting cellular functions [Vilarinho et al. 2019]. Numerous scientific studies reporting the harmful health effects of BPA have led to stricter regulations concerning the content of this compound in materials intended for contact with food and infant products [Liu et al. 2019]. As a re-

sult of the need for BPA substitutes, production has increased for bisphenol analogs such as Bisphenol S (BPS), Bisphenol F (BPF), Bisphenol AF (BPAF), Bisphenol AP (BPAP), and Bisphenol B (BPB), which possess similar properties and impacts on biological systems. In vitro and in vivo studies on BPA analogs have confirmed their estrogenic activity [Gálvez-Ontiveros et al. 2020, Vilarinho et al. 2019]. The primary source of BPA in the diet is migration from FCMs. Additionally, factors significantly increasing BPA migration include high temperatures, such as during the sterilization of food cans and heating food in plastic containers in microwave ovens, or contact with acid and base solutions [Peivasteh-Roudsari et al. 2023].

Phthalates

Phthalates are esters of phthalic acid commonly used in the plastics industry and added to polyvinyl chloride (PVC), polyethylene terephthalate (PET), polyvinyl acetate (PVA), and polyethylene (PE) to enhance their physical properties such as flexibility and resilience [Kladnicka et al. 2022]. Phthalates are widely used in the production of numerous household plastic products, such as cables, wall coverings, furniture, flooring, but also food packaging, pesticides, and cosmetics. Due to their broad industrial use, they are common contaminants of air, water, and soil [Wang et al. 2021]. Phthalates are considered high-risk pollutants and exert a negative, multidirectional impact on the endocrine system, interfering with various molecular signaling pathways. Moreover, studies indicate that primary and secondary metabolites of phthalates also act as EDCs [Eales et al. 2022]. The main route of human exposure to phthalates is through the consumption of contaminated food, beverages, and water. Due to their lipophilic properties, phthalates are often present in high-fat food products, such as dairy, meat, edible oils, and fats. Furthermore, alcoholic beverages may contain higher amounts of phthalates, as ethanol can act as an extractor. Phthalates can easily migrate into food products during storage, transport, and meal preparation from FCMs [Giuliani et al. 2020].

Phthalates can disrupt the release of hormones at the level of the hypothalamus, and pituitary gland, as well as peripheral hormones (estradiol, progesterone, testosterone, and pregnenolone). Additionally, at the intracellular level, they affect nuclear and membrane receptors, signaling pathways, and the expression of genes related to reproductive functions [Hlisníková et al. 2020]. Exposure to phthalates has been linked to harmful effects on the hormonal system and the functioning of various organs, as confirmed by both experimental and epidemiological studies. Moreover, they can negatively impact the cardiovascular, respiratory, neurological, and immune systems. There is particular concern regarding the relationship between phthalate exposure and the risk of insulin resistance and obesity in children [Basso et al. 2022].

Organotin compounds

Organotin compounds (OTs) are chemical compounds consisting of a tin atom covalently bonded to one or more carbon atoms with an organic substituent [Tinkov et al. 2019]. These compounds are used as PVC stabilizers, biocides, antifouling paints, and catalysts for the production of polyurethanes and silicones. Possible exposure pathways to organotins include consuming contaminated food, as well as absorption through the skin and inhalation [Gupta et al. 2020, Rosenberg 2013]. Sources of organotins in food include migration from FCMs (dibutyltin - DBT, dioctyltin - DOT), bioaccumulation in seafood from antifouling paints containing organotins (tributyltin - TBT), and use as pesticides in agriculture (triphenyltin chloride - TPT) [Gupta et al. 2020, Sousa et al. 2017, Tinkov et al. 2019]. Organotins, especially TBT, have been widely used since 1970 as an antifouling agent in ship paints to prevent the growth of algae, and the settling of mollusks, and other marine organisms on ship hulls. Organotins leached from paints, entered the marine environment, and accumulated in sediments. In 2008, due to their persistence, bioaccumulative properties, and endocrine disrupting action, the use of organotins in antifouling paints was globally banned [Rosenberg 2013]. Sousa et al. [2017] assessed the levels of OTs in diet samples and demonstrated the presence of these compounds in 32% of the analyzed diets at low levels. 89% of samples did not exceed the estimated daily intake (EDI) and had significantly lower levels than the established tolerable daily intake (TDI) [Sousa et al. 2017].

Organotin compounds can cause a range of health issues in humans, such as hormonal disturbances, reproductive problems, metabolic disorders, and neurotoxicity. Exposure to these compounds can lead to congenital defects in newborns and reproductive disorders. In animals exposed to OTs, phenotypic abnormalities, hormonal changes, and fertility issues have been observed [Santos et al. 2018]. OTs induce both morphological and functional changes in various tissues involved in the regulation of hormonal functions and metabolism in mammals, such as the hypothalamus, pituitary gland, pancreas, gonads, adipose tissue, adrenal glands, and thyroid [Beg et al. 2023].

Perfluoroalkyl substances

PFASs are a class of synthetic organofluorine compounds widely used as protective coatings for FCMs, textiles, and furniture due to their unique physicochemical properties [Knutsen et al. 2018]. Many of them are characterized by high thermal and acid resistance, hydrophobicity, lipophobicity, and low chemical reactivity [Inoue et al. 2020]. The main sources of food contamination by PFASs are bioaccumulation in marine and terrestrial food chains, and migration from FCMs [Knutsen et al. 2018]. The most studied PFASs are perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS), but due to their negative impact on human health, their production has been restricted in the EU and the USA since 2007 [Sajid, Ilyas 2017]. Nevertheless, PFOS and PFOA are still prevalent in the environment due to their extreme resistance to biodegradation and long half-lives [Panieri et al. 2022]. PFOA was used in the production process of Teflon, a non-stick coating for pots and other kitchenware, but due to concerns about toxicity, it has been replaced by other substances, including polytetrafluoroethylene (PTFE) and perfluoro-2-propoxypropanoic acid (PFPrOPrA, trade name: GenX). However, although the new substances are less prone to accumulation in organisms, they are suspected to have similar toxic effects to PFOA [Sajid, Ilyas 2017, U.S. EPA 2018].

Evidence from both animal models and epidemiological studies suggests that PFAS can have a detrimental effect on both animals and humans. PFAS may negatively impact the metabolism of endogenous hormones and the production of steroid hormones, such as estradiol (E2), progesterone, testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) [Rickard et al. 2023]. Additionally, PFAS can disrupt thyroid function by affecting the levels of thyroid-stimulating hormone (TSH), triiodothyronine (T3), and/or thyroxine (T4) [Panieri et al. 2022]. Exposure to PFAS can also affect breast tissue and the placenta, altering levels of

prolactin and human chorionic gonadotropin (hCG) [Rickard et al. 2023]. Exposure to PFAS can lead to adverse health effects in both men and women including fertility issues, hormonal system function, pancreatic dysfunction and type 2 diabetes risk, lipid metabolism and obesity risk in children, neurological functions, and an increased risk of breast cancer [Espartero et al. 2022].

Polychlorinated biphenyls

PCBs are synthetic chemicals consisting of a biphenyl molecule substituted with 2 to 10 chlorine atoms [Kladnicka et al. 2022]. Due to their good thermal conductivity and chemical inertness, they were used in the industry as dielectric fluids, coolants, lubricants, fire retardants, and plasticizers. However, due to their high toxicity, environmental persistence, and ability to bioaccumulate, the Stockholm Convention in 2001 globally banned their production [Perkins et al. 2016]. Until the production ban, they were sold as mixtures of 50-100 congeners known as Aroclors. Despite this, PCBs may still be used in devices manufactured before the ban and are also by-products of certain industrial processes, including the production of paints and dyes [Saktrakulkla et al. 2020]. Numerous studies have indicated that the endocrine properties of PCBs are associated with an increased risk of metabolic diseases, including type II diabetes, thyroid dysfunctions, fertility disorders, and developmental toxicity [Djordjevic et al. 2020]. Furthermore, PCBs are classified as a Group 1 "carcinogenic to humans" by the International Agency for Research on Cancer (IARC). Additionally, due to their lipophilic properties, they easily accumulate in fatty tissue and can be detectable in the lipid compartment of serum [Yang et al. 2017]. The main source of human exposure to PCBs is food. Saktrakulkla et al. [2020] reported that the highest levels of PCBs were found in marine fish, including salmon (380 pg/g) and tuna (330 pg/g), while slightly lower levels were present in beef steak (290 pg/g), butter (270 pg/g), and fried chicken (210 pg/g).

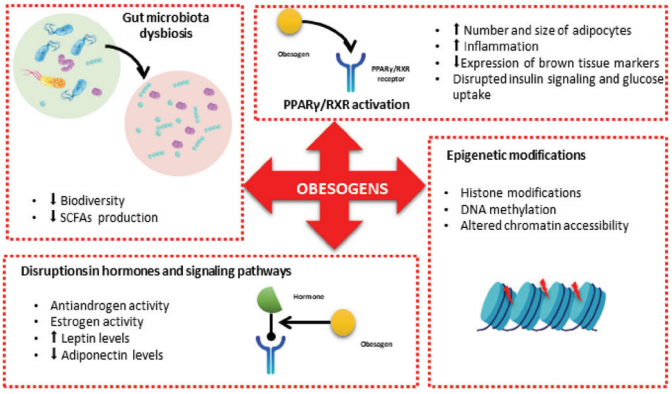
Polybrominated diphenyl ethers

PBDEs are organic aromatic compounds containing bromine, commonly used in the industry as flame retardants in the production of furniture, textiles, electronics, and building materials [Li et al. 2018, Allen et al. 2016]. PBDEs are hormonally active compounds that disrupt thyroid function by mimicking thyroid hormones (T3, T4) [Allen et al. 2016]. PBDEs exhibit low acute toxicity upon oral administration, but due to their half-lives ranging from 15 days to 11.7 years and accumulation in food chains, they can cause chronic effects. Furthermore, many studies indicate chronic toxicity to the central nervous system and reproductive system [Cai et al. 2020]. Significant amounts of these substances are found in electronics and electronic waste, and their production has been banned or restricted in many countries [Allen et al. 2016]. Despite this fact, PBDEs are detected in environmental samples, food, and also in human serum and milk [Scoville et al. 2019]. Food contamination by PBDEs results from the uncontrolled burning of plastics, the use of municipal sewage sludge in agriculture, and the release from existing products containing PBDEs throughout their lifecycle [Pietroń, Małagocki 2017]. Foods most contaminated with PBDEs are high-fat fish due to the lipophilic properties of these compounds [Kladnicka et al. 2022].

Multidirectional mechanisms of action

The molecular mechanisms of action of obesogens are still in the early stages of research; however, so far, we can distinguish mechanisms directly involved in adipogenesis, such as the activation of peroxisome proliferator-activated receptors gamma (PPARγ) and retinoid X receptors (RXR), as well as indirect mechanisms like epigenetic modifications, disruption of hormonal signaling pathways (estrogen, mitogen-activated protein kinases), changes in the composition of gut microbiota (GM) and disruptions in the secretion of appetite and satiety hormones (Figure 1) [Egusquiza, Blumberg 2020, Wang et al. 2024].

Figure 1. Mechanisms of action of obesogens.



PPARγ is the most extensively studied transcription factor in terms of fat tissue development and is essential for adipogenesis. Its activation stimulates mesenchymal stem cells to differentiate into adipocytes and is responsible for initiating lipogenesis. PPARs bind with RXR receptors to form heterodimers, which modulate the expression of target genes. Examples of substances that activate PPARγ include BPA, phthalates, and TBT. It is likely that TBT activates the PPARγ/RXR complex by binding the RXR domain [Table 1]. A study by Ahmed and Atlas [2016] found that BPA and BPS promote adipocyte differentiation in a dose-dependent manner through the activation of PPARγ, with BPS showing stronger adipogenic properties than BPA. It has also been shown that BPS promotes lipid storage and differentiation of primary human preadipocytes [Boucher et al. 2016]. Halogenated BPA analogs, as well as BPS, were found to be stronger activators of PPARγ and more effectively stimulated adipogenesis in 3T3-L1 preadipocytes than BPA [Ahmed et al. 2016]. These findings are consistent with in vivo studies, where BPS enhanced obesity in the offspring of male mice fed a high-fat diet by inducing lipid storage [Ivry Del Moral et al. 2016]. Additionally, studies have shown that exposure to BPA may be associated with obesity in children and adults [Lehmler et al. 2018, Liu et al. 2019]. Tung et al. [2014] demonstrated the obesogenic effects of PBDE in a preadipocyte model (3T3-L1). The congener BDE-47, as well as a mixture of various PBDEs, induced adipocyte differentiation and lipid accumulation. Animal studies have shown that low concentrations of PCB-77 promote adipocyte differentiation and hypertrophy. Mice administered PCB-77 exhibited higher body weight, serum dyslipidemia, and increased atherosclerosis [Arsenescu et al. 2008].

Another isoform of PPAR is PPARα, which influences fatty acid metabolism and may be associated with the obesogenic effects of certain substances, such as MSG or bis(2-ethylhexyl) phthalate (DEHP). PPARα improves insulin sensitivity, and its deficiency leads to increased adiponectin expression in mice. The role of PPARα in the development of obesity has not been as extensively studied as PPARγ, but the current literature suggests such a connection [Griffin et al. 2020, Wang et al. 2024].

Table 1. Obesogenic effects of various xenobiotic groups

Group	Obesogen	Obesogenic action	Reference
Bisphenols	BPA	• ↑ Adipogenesis	[Varghese, Hall 2023]
		• ↑ Neuropeptide Y and AgRP peptide levels, leading to ↑ appetite	[Dalamaga i in. 2024]
		• ↓ GM richness and diversity	
		• ↓ SCFA production by GM	
		• ↑ Lipopolysaccharide levels, leading to ↑ inflammation in the body	
	BPS	• ↑ Lipid accumulation	[Varghese, Hall. 2023]
		• ↑ mRNA and protein levels of adipogenic markers	
		• ↑ PPAR*γ* transcriptional activity	
		• ↑ PPAR*γ*-cofactor-1alpha expression	
	BPF	• ↓ Adiponectin/leptin ratio in children	[Lee i in. 2024]
		• ↓ Adiponectin/leptin ratio in children	[Lee i in. 2024]
		• ↑ Intracellular lipid accumulation	[Reina-Pérez i in. 2021]
		• ↑ Expression of key adipogenic genes	
	TMBPF	• ↑ Adipogenesis	[Singh i in. 2024]
		• ↑ Lipid accumulation	
		• ↑ Expression levels of adipogenic markers	
		• Likely acts as a PPARγ agonist	
Phthalates	DEHP	• Disruption of glucose homeostasis in offspring	[Xiaoyun i in. 2024]
		• Disruption of insulin signaling in adipose tissue	
		• ↑ PPAR*γ* expression	[Zhang i in. 2023]
		• ↓ GM richness and diversity in combination with a high-fat diet	
		• ↓ SCFA production by GM in combination with a high-fat diet	
	MEHP	• ↑ Adipogenesis	[Xiaoyun i in. 2024]
		• ↑ Regulation of PPAR*α* and PPAR*γ*	
OTs	TBT	• Agonist of PPAR*γ* and RXR	[Mascarenhas i in. 2023]
		• ↑ Leptin levels	
		• ↑ Adipogenesis	[Ticiani i in. 2023]
	DBT	• ↑ Adipogenesis	[Ticiani i in. 2023]
		• ↑ Lipid accumulation	
PFASs	PFOA	• Interactions with PPARα receptor, estrogen receptor *α*, and PPAR*γ*	[Frangione i in 2024]
		• ↑ Adipocyte differentiation	[Yang i in. 2017]
		• ↑ Adipogenesis markers	[Modaresi i in 2022]
	PFOS	• ↑ Adipocyte differentiation	[Yang i in. 2017]
		• ↑ Adipogenesis markers	[Modaresi i in 2022]
		• Activates PPAR*γ*	[Modaresi i in 2022]
PCB	PCB 180, PCB 153, PCB 138	• ↑ Adipogenesis	[Yu i in. 2021]
	PCB 126	• ↓ Leptin expression	[El Amine i in. 2023]
		• ↓ ATP content	
		• ↓ Glucose uptake	
PBDE	BDE 99	• ↑ Adipogenesis	[Wen i in. 2019]
		• ↓ Methylation status of the PPARγ promoter during adipogenesis	
	BDE-153	• Disruption of glucose and lipid metabolism	[Liu i in. 2023]
		• Accumulation of lipid droplets in liver cells	
		• Disruption of PPAR*γ*, AMPK*α*, and adipokine expression	

Table abbreviations: AgRP – Agouti-related protein; AMPK*α* – AMP-activated protein kinase; BPA – bisphenol A; BPF – bisphenol F; BPS – bisphenol S; DBT – dibutyltin; DEHP – bis(2-ethylhexyl) phthalate; GM – gut microbiota; MEHP – mono-2-ethylhexyl phthalate; OTs – organotins; PBDE – polybrominated diphenyl ethers; PCB – polychlorinated biphenyls; PFASs – per- and polyfluoroalkyl substances; PFOA – perfluorooctanoic acid; PFOS – perfluorooctanesulfonic acid; PPAR*α* – Peroxisome proliferator-activated receptor alpha; PPAR*γ* – Peroxisome proliferator-activated receptor gamma; RXR – retinoid X receptor; SCFAs – short chain fatty acids; TBT – tributyltin; TMBPF – tetramethyl bisphenol F

One of the less studied potential mechanisms of action of obesogens is the disruption of gut hormone production related to the regulation of appetite/satiety signals. Appetite and food intake are controlled not only by the central nervous system but also by gut hormones, which are secreted by enteroendocrine cells (EECs) scattered throughout the entire mucosa of the gastrointestinal tract in the crypts and villi, constituting 1% of the total population of intestinal epithelial cells [Goldspink et al. 2018]. The secretion of gut hormones is stimulated by food intake, as well as by metabolites produced by the GM. GM metabolites regulate food intake, glucose levels, gastric juice secretion, gut motility, and energy expenditure [Cani, Knauf 2016]. Disruptions in the synthesis and secretion of gut hormones may be one of the risk factors for the development of obesity, for example, by reducing the feeling of satiety and increasing the amount of food consumed. EECs have recently gained increasing interest due to their role in controlling metabolism by regulating insulin secretion and controlling appetite [Spreckley, Murphy 2015]. Obesogens may also influence appetite regulation by affecting the secretion of leptin and ghrelin. In vitro studies on the 3T3L1 cell line have shown that BPA increases leptin mRNA levels [Ariemma et al. 2016]. Epidemiological studies have found a correlation between BPA levels in blood serum and levels of leptin, ghrelin, and body weight [Rönn et al. 2014].

The secretion of gut hormones by EECs is directly related to metabolites produced by the GM. Fermentation of carbohydrates by bacteria leads to the production of short-chain fatty acids (SCFAs), such as propionic, butyric, and acetic acids, which can bind to receptors on the surface of EECs and regulate the release of gut hormones [Spreckley, Murphy 2015]. SCFAs can regulate host metabolism and affect various signaling pathways related to energy metabolism (e.g., insulin sensitivity through the activation of gluconeogenesis in the intestines). SCFAs play a beneficial role in regulating appetite and lipid and glucose metabolism. In host EECs (L-cells), SCFAs bind to and activate G-protein-coupled receptors, such as FFA2, FFA3, GPR109a, and OR51E1, stimulating the release of anorexigenic gut hormones, regulating metabolic functions, and inducing satiety [Ricardo-Silgado et al. 2021, Priyadarshini et al. 2018]. A study in mice showed that activation of FFA2 via SCFAs inhibits fat accumulation in adipose tissue and supports glucose metabolism in the liver and muscles [Kimura et al. 2013]. A study by Larraufie et al. [2018] demonstrated a strong increase in PYY gene expression and a corresponding elevated level of PYY hormone secretion in EEC cell lines after treatment with SCFAs (acetate, propionate, butyrate). Other GM-derived metabolites involved in appetite control include indole derivatives, secondary bile acids, GABA, and tryptamine [Han et al. 2021].

Obesogens can influence the composition and metabolic activity of the GM, contributing to obesity through potential mechanisms such as altering energy balance, disrupting appetite/satiety signaling pathways, and promoting inflammation [Egusquiza et al. 2020]. Numerous studies indicate the impact of BPA on the composition and metabolome of the GM [Malaise et al. 2017, Reddivari et al. 2017, Wang et al. 2018], though the amount of research on BPA analogs is limited [Reddivari et al. 2017]. Consumption of low doses of BPA by mice caused changes in the microbial community structure similar to those induced by a high-fat diet (HFD) and a high-sucrose diet (HSD). Moreover, a comparative analysis of microbial communities showed that both BPA and HFD favored the growth of bacteria from the Proteobacteria phylum, which are markers of dysbiosis [Lai et al. 2016]. Studies by Wang et al. [2018] demonstrated that exposure to low doses of BPA resulted in reduced richness of the gut microbial community, whereas high doses increased biodiversity. Additionally, BPA exposure increased the expression of genes related to oxidative stress and altered the expression of estrogen receptors [Wang et al. 2018]. Sequencing of the 16S rRNA gene revealed significant, concentration-dependent disturbances in the microbial community structure associated with exposure to BPS, BPA, or BPF, but not BPB or BPAF [Carton et al. 2019]. BPA consumption led to an altered colonic metabolome in rabbits and reduced the abundance of the taxa Bacteroidetes, Ruminococcaceae, and Oscillospira, while inducing colonic inflammation [Reddivari et al. 2017].

The mechanisms by which GM may contribute to the development of obesity are not yet fully understood, but there is some evidence supporting the link between GM activity and energy extraction from food digestion. Additionally, GM modulates metabolism, appetite, bile acid metabolism, and the endocrine and immune systems [Van Hul et al. 2023]. Disruptions in GM composition lead to dysbiosis, which can be a significant factor in the development of obesity [Muscogiuri et al. 2019]. A detailed taxonomic profile of GM associated with obesity has not yet been identified. However, common findings regarding GM composition include a decrease in butyrate-producing microorganisms, an increase in opportunistic pathogens, a decrease in overall diversity and richness of microorganisms, a reduction in microbial gene counts, a decrease in the abundance of Oscillospira, Rikenellaceae, Bifidobacterium, Christensenellaceae, and Akkermansia, and an increase in Roseburia, Prevotellaceae, Coriobacteriaceae, Erysipelotrichaceae, and Alcaligenaceae [Cunningham et al. 2021]. Studies indicate that the pathogenesis of obesity is closely related to GM disturbances, particularly the ratio between bacteria belonging to the Firmicutes and Bacteroidetes phyla [Riva et al. 2017, Spreckley, Murphy 2015]. Exposure to TBT resulted in a reduction in microbial species diversity in the gut and disrupted the GM composition in mice. Additionally, a significant negative correlation was found between body weight and GM diversity. These findings suggest that exposure to TBT may lead to GM dysbiosis in mice, potentially contributing to the development of obesity [Guo et al. 2018].

An alternative potential mechanism of action for obesogens is their impact on hypothalamic function, an area of the brain responsible for regulating feeding behaviors. Studies conducted on rats indicate that early-life exposure to BPA causes changes in both presynaptic and postsynaptic signaling pathways. These changes promote addictive and compulsive behaviors, leading to increased food intake, which can consequently contribute to the development of obesity [MacKay et al. 2017].

SUMMARY

Humans are chronically exposed to low doses of obesogens through the consumption of food contaminated with these substances. The primary mechanism of action for obesogens is the activation of PPARγ and the induction of adipogenesis. However, alternative mechanisms of action include the activation of other nuclear receptors, GM dysbiosis, and disruption of appetite/satiety regulation. A significant challenge in obesogen research is understanding the effects of mixtures of these substances. The classical toxicological approach and regulations focus on assessing the safety of individual substances, almost entirely neglecting mixtures, which may exhibit synergistic effects. Additionally,

when assessing the risk associated with food contamination, it is crucial to consider that some chemical compounds may undergo changes during food processing, such as boiling, frying, or baking. Some may degrade while others remain stable. Moreover, some substances classified as obesogens may biomagnify in the food chain, meaning their concentrations may increase as they move through different trophic levels. This phenomenon can lead to the accumulation of obesogens in the bodies of predators or animals higher up the food chain, posing potential health risks to organisms at these trophic levels, including humans.

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