43 Environmental Chemicals and Obesity

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43.1 INTRODUCTION

It is widely agreed upon that the burgeoning obesity epidemic occurring throughout the world is the product of poor nutrition and lack of exercise. However, there has also been increasing interest in the concept that exposures to environmental chemicals may be contributing factors to the remarkable changes in body composition over the past 20 years. Recent studies have identified a subclass of endocrine disrupting chemicals (EDCs) that interfere with endocrine signaling, which can disrupt hormonally regulated metabolic processes, especially during early development.1 Certain chemicals, called “obesogens,” may predispose individuals to gain weight despite efforts to limit caloric intake and increase physical activity.2 Plausible evidence also suggests that chemical exposures early in life can predispose individuals to weight gain through changes in metabolic “set points” and enhance dysfunctional eating behaviors later in life. This chapter reviews the latest research on the obesogen concept, including discussions of windows of susceptibility and the Developmental Origins of Health and Disease (DOHaD) model. We provide examples of known obesogens, and their general mechanisms of action, as well as emerging obesogens for which the mechanisms are less clear. The relevance and reality of the research reviewed here provides a solid foundation of knowledge from which health scientists may draw from and build upon to inform their research and decision making.

43.2 ENDOCRINE DISRUPTING CHEMICALS AND OBESOGENS

EDCs are synthetic chemicals that were originally designed for a specific purpose such as a pesticide, plasticizer, or solvent. Such chemicals, when absorbed into the body, have the side effect of mimicking or blocking hormones by binding to their cognate receptors and disrupting the body’s normal functions.1 EDCs can also disrupt normal hormone levels by inhibiting or stimulating the production and metabolism of hormones or changing the way hormones travel through the body, thus affecting the functions that these hormones control. Some EDCs are obesogens that specifically promote obesity by increasing the number of fat cells or the storage of fat into existing cells.3 They can also act on fat cells indirectly by altering metabolic rate and hormonal control of appetite and satiety.3 Nicotine, air pollution, polyhalogenated flame retardants, insecticides, fungicides, plastics, plasticizers, heavy metals, fructose, food additives, and some prescription
medications have all been linked to obesity and/or the metabolic syndrome. This could be just the tip of the iceberg since there are close to 800 chemicals with reported EDC properties and only a very few of the ~80,000 chemicals in commerce have been tested for endocrine disrupting activity.

The original definition of an obesogen was founded in the observation that certain chemicals could activate peroxisome proliferator-activated receptor gamma (PPARγ), the master regulator of fat development. Hence, preadipocytes treated with a PPARγ activator, such as the fungicide tributyltin (TBT), would differentiate into fat cells more efficiently than controls. Animals treated with the chemical became fatter as a result, despite consuming a normal diet. Since this original finding, many other chemicals have been shown to activate PPARγ, increase fat cell differentiation, and make animals or humans fatter. Over the past decade, several other mechanisms for obesogen action have been identified. Although obesogens function locally by interfering with a specific biochemical process, they can act globally to affect the entire endocrine system. Their target tissue may not always be the adipocyte, but the liver, brain, pancreas, stomach, intestines, or endocrine glands. Therefore, obesogens are not solely associated with obesity but also have a strong correlation to type 2 diabetes (T2DM) and the metabolic syndrome. Other end points of interest for obesogen research include glucose homeostasis, visceral versus subcutaneous fat, brown fat versus white fat, cardiovascular health, and measures of appetite and physical activity.

43.3 DEVELOPMENTAL ORIGINS OF HEATH AND DISEASE

Early development is a highly orchestrated series of biochemical, physical, and organizational events that must be tightly coordinated to ensure proper growth. Because the developmental period is a “plastic” phase, an organism is critically sensitive to perturbations such as alterations in hormone levels that can lead to changes in gene expression and protein levels, which persist as tissues and organs develop. This increased sensitivity is also a consequence of incomplete development or partial function of protective mechanisms such as DNA repair, immunity, xenobiotic metabolism, and the blood-brain barrier in the fetus or newborn compared with older individuals. The DOHaD hypothesis was proposed to explain observations that poor in utero nutrition resulted in high rates of cardiovascular disease (CVD) manifested later in life. Nutrition during development also plays an important role in the obesity epidemic. The DOHaD concept now includes nonnutritional early life exposures that have been shown to alter the body’s physiology. Prenatal exposure to obesogenic factors can modify normal cellular and tissue development and function, especially at the level of the stem cell (discussed later). Adverse perturbations in the metabolic system of the developing organism translate to a higher risk of metabolic and hormonal disorders later in life. Thus, the DOHaD hypothesis provides a framework to assess the effect of not only early nutrition but also obesogenic chemicals on long-term health. Many disease patterns linked to poor nutrition have also been traced to maternal chemical exposure, suggesting a common mechanism for chemical and nutritional stress that ultimately leads to long-term obesity.

43.4 GENERAL MECHANISMS OF OBESOGEN EXPOSURE DURING IMPORTANT DEVELOPMENTAL WINDOWS

Obesity is currently an intractable problem—nearly 90% of those who lose a significant amount of weight regain it within a year. Therefore, it is important to understand prenatal or perinatal mechanisms that contribute to stagnant metabolic set points and the physical and emotional anguish associated with losing weight. Focusing on the fetus and/or neonate is of primary concern since, as noted earlier, developing organisms are extremely sensitive to perturbation by chemicals with hormonelike activity. EDCs can affect fetal adipose tissue by increasing adipocyte number and size, resulting in enlarged white adipose depots. Adipose tissue is generated from mesenchymal stem cells (MSCs), which are also capable of differentiating into bone, cartilage, and other tissue. Obesogenic chemicals can affect the lineage allocation of MSCs (with more of these stem cells becoming committed preadipocytes), the differentiation of preadipocytes into adipocytes, and the filling of mature adipocytes with triglycerides, reviewed in the work by Janesick and Blumberg.

A less recognized action of EDCs occurs in the developing brain. EDC exposure can trigger changes in the hypothalamus, the region of the brain that plays a particularly important role in feeding behaviors. Improper hypothalamic programming may adjust metabolic “set points” in adolescents and adults, and these adjustments may help explain differences between the eating behavior of lean and obese individuals. Exposure to EDCs disrupts the organization and function of dopaminergic pathways throughout the brain, resulting in a wide range of behavioral effects including elevated impulsivity, anxiety, and disrupted sociality. Bisphenol A (BPA) alters both presynaptic and postsynaptic dopamine activity in brain regions associated with addiction and impulse control, suggesting that this may be a mechanism by which BPA exposure alters feeding behavior. There may be parallels between chemical exposures early in life and later life onset of obsessive eating in obese individuals and other addictive behaviors. Lean individuals eat primarily to sustain fitness and tend to stop eating when they perceive they are full, even when food is bountiful. Obese people tend to eat more high-fat and high-sugar foods and continue to eat even when they are not hungry, suggesting addiction. Some brain mechanisms that support drug addiction in humans are also responsible for compulsive eating behaviors and development of obesity in animals. While it is not entirely clear whether the psychological and physiological characteristics of the obese are a cause, or consequence, of weight gain, it appears likely that there are common underlying changes in behavioral circuitry predisposing individuals to gain weight.

It seems likely that at least part of the developmental programming of disease and metabolic dysfunction is the result of
alterations in the epigenetic control of gene expression during development. Epigenetic modifications, such as DNA methylation and histone methylation, acetylation, and ubiquitination regulate gene expression during development and are thus responsible for normal tissue and organ development. During this critical time period, the epigenome cycles through a series of precisely timed methylation changes designed to ensure proper development. The appropriate timing and extraordinary accuracy of methylation in the gametes and following fertilization makes this system particularly vulnerable to interference from environmental exposures. Indeed, it is now clear that the epigenetic system is responsive to environmental stimuli, such as drugs of abuse, diet, or chemical exposures. Many changes to our epigenetic landscape are likely to be permanent and can be manifested in multiple generations, even if the original chemical insult is no longer found in the environment.

Recent reports have identified epigenetic modifications in the CNS in response to altered diet, particularly in the prenatal or early postnatal period, when brain development is particularly vulnerable to perturbations. For example, consumption of a palatable high-fat diet increases DNA and histone methylation and decreases histone acetylation status in the promoter region of the opioid receptor mu 1 (MOR1) gene, which correlates with decreased mu-opioid receptor expression. Thus, changes in DNA methylation patterns and chromatin remodeling in response to nutritional status in utero or during early postnatal development can affect dietary preference and metabolism.

While fetal development is commonly known to be a period of increased sensitivity to chemical insult, childhood and adolescence are also marked by continued maturation of key endocrine systems, including the major metabolic organs, and are therefore susceptible to chemical exposure. For example, TBT is known to be obesogenic with chronic or single-dose prenatal exposures. It was recently shown that pubertal exposure to TBT yields weight gain and fatty liver.

An adolescent’s risk for obesity later in life is based on multifactorial inputs related to chemical exposure. First, prenatal exposure to obesogens might have already increased the risk of obesity in the adolescent. Chemical exposure during the pubertal period is linked with early menarche in females and delayed sexual maturation in males. These changes in sexual maturation are risk factors for obesity later in life. Furthermore, adolescents tend to have the worst nutrition of any age group, especially with regard to sugar consumption. Future studies that separate prenatal versus perinatal, in utero versus nursing, and prenatal versus pubertal obesogen exposures will be important in understanding the degree to which obesogens contribute to the obesity epidemic.

Using 14C labeling it has been shown that childhood and adolescent periods are the main time of adipose hyperplastic growth. In early adulthood, the total number of fat cells stabilizes; the number only increases when existing cells have reached full capacity through hypertrophic growth. Although fat tissue is less plastic in the adult, it is a fully accepted principle that adipose depots are endocrine organs and have the ability to affect the health of the entire body, given an environmental insult. Furthermore, recent data suggest that the liver, pancreas, and brain also behave as endocrine organs during adult life and are very susceptible to EDCs. An increasing number of studies have correlated the presence of persistent organic pollutants, including EDCs, in adult humans with indicators of obesity or metabolic disease. Phthalate exposure is linked to increased waist circumference, incidence of diabetes, and increased fat mass. Heavy metals such as cadmium, lead, and arsenic are linked to the prevalence of diabetes in adults. Numerous organochlorines including certain polychlorinated biphenyls (PCBs), dichlorodiphenyl-dichloroethylene (DDE), hexachlorobenzene (HCB), TNC, dioxins, β-HCH, DDT, DDE, oxychlorodane, and nonachlor are linked to increased body mass index (BMI), abdominal obesity, and insulin resistance in children, adults, and elderly (see Table 43.1).

### 43.5 Examples of Obesogenic Chemicals in Animal and Human Studies

Table 43.1 lists the known obesogenic chemicals, the evidence for each and the mechanisms of action through which the chemicals have been demonstrated to act in at least one system. This does not necessarily mean that the indicated mechanism has been demonstrated to cause or be associated with the particular end point. Rather we wish to highlight plausible mechanisms through which the obesogens might be expected to act. This topic has been extensively reviewed in recent years. Therefore, rather than exhaustively describing all potential obesogens and the evidence for their action, we will highlight a few notable classes of obesogens including those for which the evidence is particularly strong and others for which important new data have recently emerged.

#### 43.5.1 Tributyltin and Triflumizole: Obesogens that Act through PPARγ

Only a fraction of known obesogens have a defined mechanism of action. TBT and triflumizole (TFZ) are two fungicides known to act through PPARγ, the master regulator of adipogenesis. TBT is a superior activator of PPARs and 9-cis retinoic acid receptor (RXR), compared to TFZ, which only activates PPARγ. However, both stimulate adipogenesis at nanomolar doses in murine 3T3-L1 preadipocytes, and in human and mouse MSCs. These effects were shown to be dependent on PPARγ, since TBT- or TFZ-induced adipogenesis was inhibited by PPARγ antagonists. A single prenatal exposure to TBT resulted in strikingly elevated lipid accumulation in adipose depots, liver, and testis of neonate mice and increased adipose depot mass in adult mice. Similarly, chronic exposure to TFZ in utero, at a dose 400-fold below the established no-observed-adverse-effect level, increased fat depot size and programmed mouse MSCs to favor the adipogenic lineage. The MSCs derived from TBT- or TFZ-exposed offspring also exhibited a decreased capacity to differentiate into bone.
### TABLE 43.1
Known Obesogenic Chemicals, Exposure, and Mechanisms of Action

<table>
<thead>
<tr>
<th>Publications</th>
<th>Chemical</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Organotins: Fungicides, House Dust, Seafood</strong></td>
<td></td>
<td></td>
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<tr>
<td>Biemann (2012)</td>
<td>TBT</td>
<td>Increased adipocyte number and LA in C3H/10T1/2 cells</td>
</tr>
<tr>
<td>Bo (2011)</td>
<td>TBT</td>
<td>Hypothalamic disruption in C57/BL6 adult male mice</td>
</tr>
<tr>
<td>Grün (2006)</td>
<td>TBT</td>
<td>Increased LA in frogs, mice, 3T3-L1 cells; weight gain in mice</td>
</tr>
<tr>
<td>Inadera (2005)</td>
<td>TBT</td>
<td>Increased LA in 3T3-L1 cells</td>
</tr>
<tr>
<td>Janer (2007)</td>
<td>TBT</td>
<td>Increased lipogenesis in the digestive gland/gonad of Ramshorn snail</td>
</tr>
<tr>
<td>Kanayama (2005)</td>
<td>TBT, TPT</td>
<td>Increased LA in 3T3-L1 cells</td>
</tr>
<tr>
<td>Kirchner (2010)</td>
<td>TBT</td>
<td>Increased LA in MSCs at the expense of bone in C57BL/6J mice</td>
</tr>
<tr>
<td>Li (2011)</td>
<td>TBT</td>
<td>Increased LA in 3T3-L1 cells</td>
</tr>
<tr>
<td>Penza (2011)</td>
<td>TBT</td>
<td>Increased fat mass in pubertal C57BL/6J mice</td>
</tr>
<tr>
<td>Si (2011)</td>
<td>TBT</td>
<td>Decreased E2, T, and LH levels in adult Kun Ming mice</td>
</tr>
<tr>
<td>Zuo (2011)</td>
<td>TBT</td>
<td>Weight gain, insulin resistance, increased leptin, fatty liver in adult Kun Ming mice</td>
</tr>
</tbody>
</table>

| **Organobromines: Flame Retardants, Poultry, Red Meat, House Dust** | | |
| Allgood (2009) | PBDE, PBDE + HF/HS diet | Weight gain, increased adipose mass, decreased T4, impaired glucose homeostasis in male Wistar rats |
| Chao (2007) | BDE-47, BDE-99, BDE-100 | Low birth weight in human offspring |
| Hallgren (2001) | Bromkal 70-5 DE, DE-47 | Decreased T4 in female Sprague–Dawley rats and C57BL/6N mice |
| Herbstman (2008) | BDE-100, BDE-153 | Low TSH, T4, Free T4 in human neonates |
| Hoppe (2007) | penta-BDE | Dyslipidemia, impaired glucose homeostasis in adipocytes from Sprague–Dawley rats |
| van der Ven (2006, 2008) | HBCD | Thyroid dysfunction, increased cholesterol in female Wistar rats |

| **Organochlorines: Pesticides, Herbicides, Fungicides, Food** | | |
| Arsenescu (2008) | PCB 77, TCDD | Weight gain in mice, increased LA in 3T3-L1 cells |
| Calvert (1999) | TCDD | Diabetes, serum glucose, free T4 in adult veterans |
| Dirinck et al. (2010) | β-HCH | Increased BMI, WC, fat mass, IR in human adult men and women |
| Eggesbo (2009) | HCB | Low birth weight in human offspring |
| Elobeid (2010) | OCDD, DDT, hpcdd, oxychlordane | Increased BMI, WC in adults (NHANES) |
| Gladen (2000) | PCBs (congeners not specified), DDE | Weight gain in females (PCB), males (DDE) at puberty |
| Glynn (2003) | PCBs 105, 118, DDE, HCB, β-HCH | Increased BMI and T2DM in human adult and elderly women |
| Govarts (2012) | PCB 153 | Low birth weight (ENRIECO, EU OBELIX) |
| Hallgren (2001) | Aroclor 1254, PCB 105, Bromkal 70-5 DE and DE-47 | Decreased T4 levels in Sprague–Dawley rats and C57BL/6N mice |
| Herbstman (2008) | PCBs (many congeners) | Low TSH, T4, Free T4 in human neonates |
Environmental Chemicals and Obesity

Karmaus (2009)59 DDE Weight and BMI in adult human female offspring SER
Lee (2007)180 Oxychlordane, TNC, p,p’-DDE, HCB Insulin resistance, waist circumference in adult humans PRE-DW
Lee (2011)60 Oxychlordane, TNC, p,p’-DDE and dioxin Increased BMI, triglycerides, and insulin resistance in adults (NHANES) PRE-DW
Li (2012)146 Triflumizole Lipid accumulation in prenatally exposed MSCs and in 3T3-L1 cells; weight gain PRE-DW
Mendez (2011)181 DDE Rapid growth and increased BMI in human infants PRE-DW
Rayner (2005)57 Atrazine Low birth weight in Long–Evans rats PRE-DW
Rönn (2011)178 PCBs 74, 99, 105 and 118, TNC, DDE, HCB Increased fat mass in elderly individuals CB
Roos (2012)179 PC5bs 105, 118, 189, DDE, HCB, TNC Increase VAT and SAT, VAT/SAT ratio in elderly individuals CB
Sargis (2010)204 Tolylfluanid, endrin Increased LA in 3T3-L1 cells CB
Sargis (2012)63 Tolylfluanid Insulin resistance in primary mice, rat, and human adipocytes CB
Vitalone (2010)65 PCB-126 Weight gain in adult Wistar rats CB

Organophosphates: Insecticides

Lassiter (2008)66 Chlorpyrifos Weight gain in adult Long–Evans rats NEO-INJ
Roegge (2008)89 Diazinon + HFD Weight gain in adult Sprague–Dawley rats NEO-INJ
Slotkin (2005)70 Chlorpyrifos Increased serum triglycerides; hyper-insulinemia in adult Sprague–Dawley rats NEO-INJ

Phenols: Paints, Adhesives, Pesticides, Adhesives, Plastics, Rubbers, Cosmetics, Herbs, Flame Retardants

Alonso-Magdalena (2010)75 BPA Impaired glucose homeostasis in adult OF-1 mice and their offspring PRE-INJ
Cagampang (2007)76 BPA Increased fat mass, low birth weight, catch-up growth, MetS in MF-1 mouse offspring PRE-INJ
Carwile (2011)77 BADGE Increased obesity in adults (NHANES) PRE-INJ
Chamorro-García (2012)172 Huc (2012)76 BPA Increased LA in 3T3-L1 cells and MSCs PRE-INJ
Lang (2008)89 BPA Increased LA in adult Sprague–Dawley rats PRE-INJ
Masuno (2002)90 BPA + insulin Increased LA in 3T3-L1 cells PRE-INJ
Masuno (2005)81 BPA, BFB, BPE, BPB, BPS Increased LA in 3T3-L1 cells PRE-INJ
Miyawaki (2007)65 BPA Increased body weight, adipose tissue weight, and hyperlipidemia in adolescent CD-1 mice offspring POST-DW
Miyawaki (2008)82 4-Tert-Octylphenol Increased LA in C3H10T1/2 cells; inhibition of bone NEO-INJ
Ryan (2010)83 BPA, BPA + HFD Increased body mass in young CD-1 mice NEO-INJ
Sargis (2010)84 BPA Increased LA in 3T3-L1 cells NEO-INJ
Shankar (2011)94 BPA Increased T2DM in adults (NHANES) NEO-INJ
(Continued)
# Known Obesogenic Chemicals, Exposure, and Mechanisms of Action

<table>
<thead>
<tr>
<th>Publications</th>
<th>Chemical</th>
<th>Endpoint</th>
<th>Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silver (2011)</td>
<td>BPA</td>
<td>Increased T2DM in adults (NHANES)</td>
<td>PERI-DW</td>
</tr>
<tr>
<td>Somm (2009)</td>
<td>BPA, BPA + HFD</td>
<td>Increased body weight and fat mass in young Sprague-Dawley rat offspring</td>
<td>PERI-DW</td>
</tr>
<tr>
<td>Wang (2010)</td>
<td>BPA</td>
<td>Increased LA in Huh7-PPRE-Luc and 3T3-L1 cells</td>
<td>PRE-DW</td>
</tr>
<tr>
<td>Wang (2012)</td>
<td>BPA</td>
<td>Increased IR and obesity in human adults</td>
<td>PRE-INH</td>
</tr>
<tr>
<td>Wei (2011)</td>
<td>BPA ± HFD</td>
<td>MetS in adult Wistar rat offspring</td>
<td>PRE-INJ</td>
</tr>
<tr>
<td>Xu (2011)</td>
<td>BPA</td>
<td>Weight gain, increased fat mass, sweet preference in adult Sprague-Dawley rat offspring</td>
<td>PRE-OP</td>
</tr>
</tbody>
</table>

**Heavy Metals: PVC Stabilizer, Seafood**

Mechanisms: Cadmium binds ER and mimics estrogen;207 cadmium also inhibits 11β-HSD2;89 arsenic affects the biochemistry of glucose metabolism89

<table>
<thead>
<tr>
<th>Publications</th>
<th>Chemical</th>
<th>Endpoint</th>
<th>Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afridi (2008)</td>
<td>Pb, Cd, and As</td>
<td>Increased T2DM prevalence</td>
<td>PRE-OP</td>
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<td>Lai (1994)</td>
<td>Arsenic</td>
<td>Increased T2DM prevalence</td>
<td>MS</td>
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<tr>
<td>Leasure (2008)</td>
<td>Lead</td>
<td>Obesity in adult male C57BL/6 mice</td>
<td>MS</td>
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<tr>
<td>Rahman (1995)</td>
<td>Arsenic</td>
<td>Increased T2DM prevalence</td>
<td>PRE-DW</td>
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<tr>
<td>Rahman (1998)</td>
<td>Arsenic</td>
<td>Increased T2DM prevalence</td>
<td>PRE-DW</td>
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<tr>
<td>Schwartz (2003)</td>
<td>Cadmium</td>
<td>Impaired glucose metabolism, increased T2DM prevalence</td>
<td>PRE-DW</td>
</tr>
<tr>
<td>Tseng (2000)</td>
<td>Arsenic</td>
<td>Increased T2DM prevalence</td>
<td>PRE-DW</td>
</tr>
</tbody>
</table>

**Nicotine, PAH: Cigarettes, Tobacco, Smoke, Air Pollution, Charbroiled Food**

Mechanisms: Cholinergic/catecholaminergic93; oxidative stress leading to apoptosis of β-cells, activation of nicotinic receptors reduces insulin secretion93,208

<table>
<thead>
<tr>
<th>Publications</th>
<th>Chemical</th>
<th>Endpoint</th>
<th>Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bergmann (2003)</td>
<td>Nicotine (inferred)</td>
<td>Reduced birth weight, increased BMI in human children offspring</td>
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<tr>
<td>Bergmann (2003)</td>
<td>Nicotine (inferred)</td>
<td>Increased BMI, skinfold thickness in child offspring</td>
<td>MS</td>
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<tr>
<td>Bolton (2012)</td>
<td>Diesel exhaust, ± HFD</td>
<td>Weight gain, increased insulin in C57BL/6 adult mice offspring</td>
<td>MS</td>
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<td>Bruin (2007)</td>
<td>Nicotine</td>
<td>Reduced β-cell mass and impaired glucose homeostasis in adult Wistar rat offspring</td>
<td>MS</td>
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<td>Friedman (2012)</td>
<td>Nicotine (cotinine)</td>
<td>T2DM, obesity in adults exposed to second hand smoke</td>
<td>MS</td>
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<tr>
<td>Gao (2005)</td>
<td>Nicotine</td>
<td>Increased postnatal body weight, fat pad weight, PVAT in adult Wistar rat offspring</td>
<td>MS</td>
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<tr>
<td>Grove (2001)</td>
<td>Nicotine</td>
<td>Decreased NPY, reduced leptin, increased POMC in rhesus monkey neonate offspring</td>
<td>MS</td>
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<tr>
<td>Holloway (2005)</td>
<td>Nicotine</td>
<td>Dyslipidemia, impaired glucose homeostasis, weight gain in adult Wistar rat offspring</td>
<td>MS</td>
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<tr>
<td>Irigaray (2006)</td>
<td>BaP</td>
<td>Weight gain, increased fat mass in C57Bl/6J male mice</td>
<td>MS</td>
</tr>
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<td>Montgomery (2002)</td>
<td>Nicotine (inferred)</td>
<td>T2DM, obesity in adult offspring</td>
<td>MS</td>
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<td>Oken (2008)</td>
<td>Nicotine (inferred)</td>
<td>Increased BMI in child offspring (meta-analysis)</td>
<td>MS</td>
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<td>Oliveira (2009)</td>
<td>Nicotine</td>
<td>Weight gain, hyperleptinemia, and hypothyroidism in adult Wistar rat offspring</td>
<td>MS</td>
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<td>Power (2002)</td>
<td>Nicotine (inferred)</td>
<td>Reduced birth weight, increased BMI in adolescent and adult offspring</td>
<td>MS</td>
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<td>Rundle (2012)</td>
<td>PAH</td>
<td>Increased BMI, % body fat in human children offspring</td>
<td>MS</td>
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<td>Somm (2008)</td>
<td>Nicotine</td>
<td>Increased VAT weight, larger adipocytes in young Sprague-Dawley rat offspring; metabolic syndrome in the adult offspring</td>
<td>MS</td>
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<tr>
<td>Syme (2009)</td>
<td>Nicotine (inferred)</td>
<td>Abdominal obesity in adult adolescent human offspring</td>
<td>MS</td>
</tr>
</tbody>
</table>
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Xu (2011) PM2.5 Decreased adiponectin and leptin; insulin resistance in C57Bl/6J male mice

Phthalates: Plasticizer, PVC Tubing, PVC Flooring, Personal Care Products

Biemann (2011) DEHP Increased adipocyte number, lipid accumulation in C3H/10T1/2 cells


Boas (2010) MEP, MCiOP, MBP, MBzP Decreased T3 levels in children

Feige (2007) MEHP Increased LA in 3T3-L1 cells

Hatch (2008) MEP, MBP, MBzP, MEHHP, MEOP Increased WC and BMI in adult males

Hurst (2003) MEHP, MBzP, MBuP Increased LA in 3T3-L1 cells

James-Todd (2012) MnBP, MIBP, MBzP, MCOP, and ∑DEHP Increased diabetes prevalence, IR in women

Lind (2012) MMP, MIBP, MEP Increased diabetes prevalence, IR in elderly individuals

Lind (2012) MIBP Increased WC, total fat mass, abdominal SAT in elderly women

Sargis (2010) DCHP Increased LA in 3T3-L1 cells

Schmidt (2012) DEHP Impaired fertility, increased body weight and larger adipocytes in C3H/N female F0 mice, Fl offspring showed increased visceral fat and body weight

Stahlhut (2007) MBP, MBzP, MEHHP, MEOHP, MEP Increased WC in adult males

Wang (2010) BBP Increased LA in Hub7-PPRE-Luc and 3T3-L1 cells

PFCs: Teflon and Scotchgard

Halldorsson (2012) PFOA Increased adiposity biomarkers, waist circumference, BMI

Hines (2009) PFOA Increased body weight, insulin, leptin in postpubertal female mice offspring

Medications: Antidiabetic, Atypical Antipsychotics, Synthetic Estrogens, Anti-Inflammatories

Jin (2002) Clozapine, olanzapine, quetiapine, and risperidone Increased T2DM (meta-analysis) in human adults

Knight et al. (1987) Indocin Increased LA in 3T3-L1 cells

Newbold (2005) DES Increased body weight in adult CD1 mice


Vegiopoulos (2010) Cox2 inhibitors Reduced brown fat production

Williams (1997) Indocin Increased LA in 3T3-L1 cells

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**Notes:** BM, breast milk; CB, cord blood; DW, drinking water; FD, food; GAV, gavage; GEL, Transgel; INH, inhalation; INJ, injection; IR, insulin resistance; LA, lipid accumulation; MetS, metabolic syndrome; MS, maternal smoking; NEO, neonatal exposure; OP, osmotic pump; PERL, perinatal exposure; PRE, prenatal exposure; PUB, pubertal exposure; SER, maternal serum; T2DM, type 2 diabetes.
TBT continues to be a model obesogen and new research has expanded its role in contributing to obesity. Recently, it was shown that TBT can also act through mechanisms not related to adipocyte differentiation. PPARγ is expressed in the brain, and knocking down neuronal-specific PPARγ reduces food intake and weight gain on a high-fat diet. TBT crosses the blood-brain barrier and could potentially activate PPARγ in the brain. The TBT–PPARγ interaction in the brain has not been shown directly; however, rosiglitazone activates PPARγ in the CNS and increases c-fos expression in the arcuate nucleus. c-fos expression is indicative of activated neurons, some of which express neuropeptide Y (NPY) and agouti-related protein (AgRP). NPY and AgRP promote feeding behavior and are inhibited by leptin and insulin, but stimulated by ghrelin. Treatment of adult mice with TBT resulted in increased c-fos expression in the arcuate nucleus; however, it is unknown whether this effect is mediated by PPARγ. These results demonstrate that obesogenic chemicals need not affect adipocytes directly, but can give an animal an increased drive to eat.

Many chemicals administered during precise temporal windows during fetal development have been shown to generate phenotypes not just in the first generation, but in the second or third generation. Such phenotypes are nongenetically determined since low-dose chemical exposures do not produce damage to DNA and multiple independently exposed animals produce the same phenotypes. Transgenerational effects occur when genes are epigenetically patterned to create a permanent change in the germ line. Certain diseases or gene expression changes can be found in the F3 generation (and beyond), i.e., F4, F5, F6) as a result of chemical exposure that has affected DNA loci, which have escaped reprogramming mechanisms in adipose tissue at the time of weaning in BPA-exposed animals. Some evidence suggests that the increases in body weight are sex specific, but timing and dose may contribute to the complexity of these findings. Thus far, changes in body weight have been reported in animals exposed to BPA during gestation, or gestation and lactation, and in one study BPA exposure continued through postnatal day 30 when animals were sacrificed. To date, no studies have continued BPA exposure throughout life, and few have followed measurements of body weight and adiposity through adulthood and to later ages. Far more investigation is needed to understand the effects of BPA exposure on body weight and adiposity prepubertally and later in life and the mechanisms through which BPA may be acting.

Since the 1990s, several dozen studies have been dedicated to determining human exposure to BPA and its impact on human metabolic systems. The correlation between urinary BPA concentrations and metabolic disorders was investigated in a nationally representative cross-sectional sample of U.S. adults from the National Health and Nutrition Examination Survey (NHANES). Among 2948 adults participating in two cycles of the NHANES (2003/2004 and 2005/2006), urinary BPA concentrations were associated with increased prevalence odds of self-reported CVD and diabetes. However, associations between BPA and CVD and diabetes were stronger in the 2003/2004 cycle, when geometric mean BPA concentrations were higher (2.5 vs. 1.8 μg/L). Positive correlations between urinary BPA and serum liver enzyme concentrations were also observed. The interpretation of these results is limited by the cross-sectional design. CVD and metabolic disorders have long latency periods, and contemporaneous urinary BPA concentrations may not reflect the relevant etiologic window for the development of cardiovascular and metabolic diseases, which is known to be years or decades earlier. In addition, time-dependent confounding (i.e., reverse causality) may be responsible for observed associations since obese individuals are at increased risk for CVD and metabolic disorders and may consume more packaged and processed foods that contain BPA. Even in the face of these caveats, animal studies show that prenatal BPA exposure may influence the development of metabolic disorders. Thus, fetal exposure to BPA may be more important to the development of metabolic disorders than exposure later in life.

43.5.2 BIPSCHENOL A DIGLYCIDYL ETHER

Bipschanol A diglycidyl ether (BADGE), produced by reacting BPA and epichlorhydrin, is used as an intermediate in the manufacture of epoxy resins and paints and also as a coating on food cans and food storage vessels. Like BPA, BADGE migrates from container linings into foods and is routinely ingested, raising questions concerning its
potential adverse effects on human health. BADGE induces adipogenesis and the expression of adipocyte marker genes in MSCs; however, unlike TBT or TFZ, this effect is PPARγ-independent. BADGE does not activate or antagonize PPARγ at up to 10 μM, and BADGE-induced adipogenesis is not inhibited by treatment with high-affinity PPARγ antagonists GW0662 or T0070907. Therefore, BADGE is unlikely to act as a ligand for the RXR-PPARγ heterodimer at doses that could be encountered, in vivo, and probably acts independently, or downstream of PPARγ. Since BADGE is closely related to BPA, one might suppose that it has a similar mechanism of action. However, BADGE can induce differentiation in MSCs whereas BPA cannot, which suggests that their mechanisms of action may be distinct.

43.5.2.3 Organochlorines

Although TFZ and DDE (discussed later) are obesogenic organochlorine chemicals for which the mechanism of action is known, most other organochlorines that are linked to obesity or adipogenicity have no known mechanism. The five broad categories of obesogenic organochlorines include PCBs, DDE, HCB, chlordane-based, and dioxin-based chemicals (see Table 43.1). PCBs were commonly produced in North America for over half a century. Upon the discovery that they negatively affect the health of humans and other animals, use of these chemicals was banned in the United States, yet they remain persistent environmental contaminants. Most associations of obesity, diabetes, and visceral obesity in humans have occurred with increased plasma levels of PCBs 74, 99, 105, 118, 138, 153, 170, 180, and 189 (see Table 43.1). There have been attempts to link congenomer number (degree of chlorination) with the risk of obesity; however, this research is ongoing. HCB was once widely used as a fungicide, particularly on wheat seeds, and remains present in the population despite being banned in 1966. Higher concentrations of HCB in cord blood, maternal serum, or breast milk were associated with low birth weight and increased BMI in children. HCB concentrations in adult serum are also positively correlated with waist circumference, insulin resistance, and obesity in humans, and an abundance of studies show that phthalates can induce adipogenesis in cell culture models, reviewed in the works by Janesick et al. and van Beekum et al. The reader is directed toward more extensive reviews for a thorough description of potential mechanisms for obesogen action. In addition to the mechanisms in the preceding discussion, the following mechanisms may also be relevant to obesity in humans.

43.5.2.4 Organobromine Flame Retardants

Polybrominated biphenyls and polybrominated diphenylethers (PBDEs) are widely used as flame retardants. Although a subset of these are now banned, the majority of the population has significant blood levels that have been associated with various adverse health outcomes including obesity and reduced thyroid function. Prenatal or neonatal exposure to PBDEs is associated with low birth weight and thyroid function in offspring.

43.5.2.5 Perfluorochemicals

PFOA and PFOS, found in Teflon® and formerly Scotchgard®, are linked to the prenatal programming of obesity. Young adult mice that were exposed in utero to PFOA have increased serum insulin and leptin levels. In humans, prenatal exposure to PFOA is associated with increased BMI, adiposity biomarkers, and waist circumference. Phthalates and phthalate metabolites have been associated with waist circumference, insulin resistance, and obesity in humans, and an abundance of studies show that phthalates can induce adipogenesis in cell culture models, reviewed in the works by Casals-Casas et al. but until recently, there was no strong evidence from animal studies linking phthalates with obesity. Two recent studies have linked exposure to diethylhexylphthalate (DEHP) with obesity in animal models. Schmidt and colleagues showed that prenatal exposure of C57BL/6J female mice led to increased body weight, visceral fat, and adipocyte size in F0 females and in F1 offspring. Feige and colleagues showed that DEHP-exposed C57BL/6J mice carrying the human PPARα were susceptible to high-fat-induced obesity, whereas wild-type mice were not. Apparently, the mouse PPARα protects against high-fat-diet-induced obesity, whereas its human counterpart does not. These results have important implications for interpreting negative results of chemicals that can activate PPARs on obesity.

43.6 ADDITIONAL MECHANISMS THROUGH WHICH OBESOGENS MIGHT ACT

The reader is directed toward more extensive reviews for a thorough description of potential mechanisms for obesogen action. In addition to the mechanisms in the preceding discussion, the following mechanisms may also be relevant to obesity in humans.

43.6.1 Obesogenic Chemical Influences PPARγ in a Nonligand-Dependent Fashion

While ligand activation of nuclear receptors (such as TBT activation of PPARγ) has been a prominent mechanism of action for EDCs and obesogens, nuclear receptors can also be derepressed or activated through various posttranslational modifications causing active release of co-repressors in the absence of PPARγ ligands, reviewed in the works by Janesick and Blumberg, Perissi et al., and van Beekum et al. The presence or absence of posttranslational modifications on PPARγ could be obesogenic by causing allosteric hindrance of corepressor release, protecting PPARγ against ubiquitination
and subsequent degradation, by encouraging heterodimerization with RXR, or by preventing PPARγ from recruiting methyltransferases to its promoter. All of these mechanisms would increase the steady-state levels of PPARγ protein and target genes. Whether obesogens exist that target, one of these mechanisms remains to be seen, but we consider this possibility quite plausible.

### 43.6.2 Obesogenic Chemical Serves as a Ligand for a Different Receptor

Obesity is linked to a general increase of positive feedback within the hypothalamic-pituitary-adrenocortical axis, characterized by the impaired ability to clear or inactivate cortisol in adipose tissue, particularly visceral adipose tissue. Glucocorticoids increase adipocyte proliferation and their differentiation from stromal cells; hence, the presence of excess glucocorticoids will undoubtedly stimulate adipogenesis locally. BPA, dicyclohexyl phthalate, endrin, and tolylfluoride were all found to activate glucocorticoid receptors and increase adipogenesis in 3T3-L1 preadipocyte model. Prenatal or perinatal exposure to excess estrogen also promotes obesity in adult offspring, reviewed in the works by Rubin and Soto, Newbold et al., and Vom Saal et al. Cadmium binds to the ER and mimics estrogen and is associated with diabetes in adults. Other chemicals can activate receptors in the brain. For example, maternal smoking activates nicotinic acetylcholine receptor, which induces oxidative stress and pancreatic β-cell death and reduces insulin secretion in offspring.

### 43.6.3 Chemical Interferes with an Enzyme–Substrate Interaction

EDCs can act independently of a hormone receptor. For example, an EDC could alter the synthesis of a hormone or modulate its breakdown. Dibutyltin and dithiocarbamate pesticides inhibit 11-β-hydroxysteroid dehydrogenase-2, thereby interfering with glucocorticoid breakdown and upregulating glucocorticoid levels. TBT is a low-affinity competitive inhibitor of cytochrome P450 (CYP19) (aka P450 aromatase), which normally converts testosterone to estradiol. TBT increases the expression of CYP19 mRNA and protein in some cell types, which will lead to higher levels of estradiol while inhibiting it in others, thereby reducing estradiol levels.

### 43.6.4. Chemical is a Nutrient Required for Development and Survival, but Has the Capacity to be Overconsumed, and Thus Adversely Affect Adipogenic Pathways, much as an EDC Does

Obesogens are most commonly viewed as industrial chemicals; however, they can also be the chemicals that we ingest purposely in our diet. Soy has been found in the diets of Asian populations for centuries; however, soy formula and soy milk are mostly phenomena in the United States. In particular, infant exposure levels are much higher in the United States compared to Asia. The effects of early life exposure to soy and obesity consequences later in life have been reviewed. Monosodium glutamate is associated with obesity and permeates American diets.

Sugars, particularly fructose, have been increasingly linked with obesity (albeit not without controversy). The glycemic index of fructose is significantly lower than glucose. However, the majority of fructose is quickly metabolized in the liver without inducing insulin secretion. For this reason, low doses of fructose are thought to help regulate glucose homeostasis, reviewed in the work by Sievenpiper et al., but at the high doses ingested by most Americans, fructose has pathological consequences. Unlike glucose, which is stored as glycogen, fructose metabolites are stored as triglycerides in the liver and excess fat is secreted in the form of very-low-density lipoprotein, which is highly associated with T2DM. Fructose creates de novo lipogenesis in the liver and thus is a unique obesogen by directly stimulating inappropriate storage of fat in the liver, as opposed to the adipocyte. Table 43.1 provides many examples of the correlative link between fructose and fatty liver.

### 43.7 Perfect Storm for Obesity

We propose that the confluence of developmental programming of metabolic set points by obesogens in association with continued obesogen exposures, overconsumption of processed foods containing added sugars and EDCs from the packaging materials, together with decreased physical activity throughout life create “The Perfect Storm” that is driving the obesity epidemic. There are now nearly 20 chemicals shown to cause long-term weight gain and metabolic dysfunction in humans or animals and there is no systematic effort yet underway to identify obesogens or to determine whether they promote weight gain and obesity in animal models or humans. Obesogen exposure during critical periods of development can disrupt normal hormone and neuronal signaling pathways that are being established, leading to an increased vulnerability during early life. It is undoubtedly true that adults have the self-preservation instinct to entertain the idea of detoxifying themselves, avoiding chemical exposure, and increasing activity. However, emerging data from animal studies suggest that the effects of prenatal or early life obesogen exposure may be permanent and be transmitted to subsequent generations. It will be important to understand how prenatal obesogen exposure elicits transgenerational effects on fat depot size, adipocyte size, adipocyte number, and fatty livers. It will be particularly interesting to elucidate how obesogen exposure alters stem cell fate and lineage allocation in the stem cell compartment to favor adipogenesis at the expense of osteogenesis. Once outside of the womb, children and adults must further contend with the ubiquitous presence of dietary and chemical obesogens, which confound their ability to fight obesity. Determining how diet interacts with prenatal and
early life obesogen exposure to influence obesity will harmonize nutritional, toxicological, endocrinological, and developmental studies that will make important contributions to our understanding of the degree to which obesogen exposure contributes to the obesity epidemic. In turn, these studies will provide important new tools for policymakers in the ongoing debate about what should be done about EDC and obesogen exposure.

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REFERENCES


Environmental Chemicals and Obesity


139. Stanhope KL, Havel PJ. Fructose consumption: considerations for future research on its effects on adipose distribution, lipid metabolism, and insulin sensitivity in humans. J Nutr 2009;139:1236S–41S.


188. Allgood EL. The effect of diet and polybrominated diphenyl ether (PBDE) exposure on adipocyte and whole body metabolism in male Wistar rats. University of New Hampshire; 2009.


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