43 Environmental Chemicals and Obesity

AU 1

Amanda S. Janesick, Thaddeus T. Schug, Jerrold J. Heindel, and Bruce Blumberg

AU 2

CONTENTS

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 Heath 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[4] 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.[5] Hence, preadipocytes treated with a PPARγ activator, such as the fungicide tributyltin (TBT), would differentiate into fat cells more efficiently than controls.[6] Animals treated with the chemical became fatter as a result, despite consuming a normal diet.[6] Since this original finding, many other chemicals have been shown to activate PPARγ, increase fat cell differentiation, and make animals or humans fatter.[7,8] 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.[3] 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.[9] 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.[10] Nutrition during development also plays an important role in the obesity epidemic.[11] 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.[12] 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,[13] suggesting a common mechanism for chemical and nutritional stress that ultimately leads to long-term obesity.

AU 3

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.[14] 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.[3] Adipose tissue is generated from mesenchymal stem cells (MSCs), which are also capable of differentiating into bone, cartilage, and other tissue.[15] 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.[3]

AU 4

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.[1] 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.[16] 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.[17] Some brain mechanisms that support drug addiction in humans are also responsible for compulsive eating behaviors and development of obesity in animals.[17] 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 of 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.[18,19] 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.[20] Indeed, it is now clear that the epigenetic system is responsive to environmental stimuli, such as drugs of abuse, diet, or chemical exposures.[21] 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.[22]

Recent reports have identified epigenetic modifications in the CNS in response to altered diet, particularly in the prenatal or early postnatal time period, when brain development is particularly vulnerable to perturbations.[23] 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 nu-opioid receptor expression.[23] 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.[24]

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.[25] For example, TBT is known to be obesogenic with chronic or single-dose prenatal exposures.[6,26,27] It was recently shown that pubertal exposure to TBT yields weight gain and fatty liver.[28]

An adolescent's risk for obesity later in life is based on multifactorial inputs related to chemical exposure.[3] 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.[29] 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 ^{14}C labeling it has been shown that childhood and adolescent periods are the main time of adipose hyperplastic growth.[30] In early adulthood, the total number of fat cells stabilizes; the number only increases when existing cells have reached full capacity through hypertrophic growth.[30] Although fat tissue is less plastic in the adult,[3,30] it is a fully accepted principle that adipose depots are endocrine organs[31,32] 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.[31–36] 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.[37–40] Heavy metals such as cadmium, lead, and arsenic are linked to the prevalence of diabetes in adults.[41–46] Numerous organochlorines including certain polychlorinated biphenyls (PCBs), dichlorodiphenyl-dichloroethylene (DDE), hexachlorobenzene (HCB), TNC, dioxins, β-HCH, DDT, DDE, oxychlordane, 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.[3,7,8] 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.[5] TBT is a superior activator of PPARγ and 9-cis retinoic acid receptor (RXR)[6,47,48] compared to TFZ, which only activates PPARγ.[146] However, both stimulate adipogenesis at nanomolar doses in murine 3T3-L1 preadipocytes[6,48,146,147] and in human and mouse MSCs.[27,146,148] These effects were shown to be dependent on PPARγ, since TBT- or TFZ-induced adipogenesis was inhibited by PPARγ antagonists.[27,146,148] 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.[6] 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.[146] The MSCs derived from TBT- or TFZ-exposed offspring also exhibited a decreased capacity to differentiate into bone.[27,146]

TABLE 43.1
AU 8 **Known Obesogenic Chemicals, Exposure, and Mechanisms of Action**

Publications	Chemical	Endpoint	Exposure
		Organotins: Fungicides, House Dust, Seafood	
		Mechanisms: PPARα,β/δ,γ, RXRα, RXRγ, NURR1 Activator[6,47,48]; ER Activator[49]	
Biemann (2012)[50]	TBT	Increased adipocyte number and LA in C3H/10T1/2 cells	
Bo (2011)[158]	TBT	Hypothalamic disruption in C57/BL6 adult male mice	
Grün (2006)[6]	TBT	Increased LA in frogs, mice, 3T3-L1 cells; weight gain in mice	**PRE-GAV**
Inadera (2005)[147]	TBT	Increased LA in 3T3-L1 cells	
Janer (2007)[51]	TBT	Increased lipogenesis in the digestive gland/gonad of Ramshorn snail	
Kanayama (2005)[48]	TBT, TPT	Increased LA in 3T3-L1 cells	
Kirchner (2010)[27]	TBT	Increased LA in MSCs at the expense of bone in C57BL/6J mice	**PRE-GAV**
Li (2011)[148]	TBT	Increased LA in 3T3-L1 cells	
Penza (2011)[49]	TBT	Increased fat mass in pubertal C57BL/6J mice	
Si (2011)[52]	TBT	Decreased E2, T, and LH levels in adult Kun Ming mice	**PUB-DW**
Zuo (2011)[28]	TBT	Weight gain, insulin resistance, increased leptin, fatty liver in adult Kun Ming mice	**PUB-GAV**
		Organobromines: Flame Retardants, Poultry, Red Meat, House Dust	
		Mechanisms: General thyroid dysfunction; no specific mechanism identified	
Allgood (2009)[188]	PBDE, PBDE + HF/HS diet	Weight gain, increased adipose mass, decreased T4, impaired glucose homeostasis in male Wistar rats	
AU 9 Chao (2007)[193]	BDE-47, BDE-99, BDE-100	Low birth weight in human offspring	**BM**
Hallgren (2001)[189]	Bromkal 70-5 DE, DE-47	Decreased T4 in female Sprague–Dawley rats and C57B/l6N mice	
Herbstman (2008)[194]	BDE-100, BDE-153	Low TSH, T4, Free T4 in human neonates	**CB**
Hoppe (2007)[190]	penta-BDE	Dyslipidemia, impaired glucose homeostasis in adipocytes from Sprague–Dawley rats	
van der Ven (2006, 2008)[191,192]	HBCD	Thyroid dysfunction, increased cholesterol in female Wistar rats	
		Organochlorines: Pesticides, Herbicides, Fungicides, Food	
		Mechanisms: AhR,[53] aromatase inhibitor[54]; DDE is an antiandrogen[178]; triflumizole is a PPARγ activator[146]; tolylfluanid and endrin activate GR[204]	
Arsenescu (2008)[53]	PCB 77, TCDD	Weight gain in mice, increased LA in 3T3-L1 cells	
Calvert (1999)[186]	TCDD	Diabetes, serum glucose, free T4 in adult veterans	
Dirinck et al. (2010)[55]	β-HCH	Increased BMI, WC, fat mass, IR in human adult men and women	
Eggesbo (2009)[177]	HCB	Low birth weight in human offspring	**BM**
Elobeid (2010)[182]	OCDD, DDT, hpcdd, oxychlordane	Increased BMI, WC in adults (NHANES)	
Gladen (2000)[56]	PCBs (congeners not specified), DDE	Weight gain in females (PCB), males (DDE) at puberty	**BM, SER, CB**
Glynn (2003)[179]	PCBs 105, 118, DDE, HCB, β-HCH	Increased BMI and T2DM in human adult and elderly women	
Govarts (2012)[57]	PCB 153	Low birth weight (ENRIECO, EU OBELIX)	**CB**
Hallgren (2001)[189]	Aroclor 1254, PCB 105, Bromkal 70-5 DE and DE-47	Decreased T4 levels in Sprague–Dawley rats and C57BL/6 N mice	
Herbstman (2008)[194]	PCBs (many congeners)	Low TSH, T4, free T4 in human neonates	**CB**
Hertz-Picciotto (2005)[58]	PCBs 101, 105, 110, 118, 137, 138, 153, 156, 170, 180, and 187	Low birth weight in human male offspring	**SER**

Karmaus (2009)[59]	DDE	Weight and BMI in adult human female offspring	**SER**
Kern (2004)[185], Cranmer (2000)[187]	TCDD	Insulin resistance in adult veterans	
Lee (2006)[181]	PCB 153, HpCDD, OCDD, oxychlordane, DDE, TNC	Increased T2DM in adults (NHANES)	
Lee (2007)[180]	Oxychlordane, TNC	Insulin resistance, waist circumference in adult humans	
Lee (2011)[183]	Oxychlordane, TNC, p,p'-DDE, HCB	Increased BMI, triglycerides, and insulin resistance in adult humans	
Lee (2011)[60]	p,p'-DDE and dioxin	Increased abdominal obesity in elderly individuals	
Li (2012)[146]	Triflumizole	Lipid accumulation in prenatally exposed MSCs and in 3T3-L1 cells; weight gain	**PRE-DW**
Mendez (2011)[61]	DDE	Rapid growth and increased BMI in human infants	**SER**
Rayner (2005)[62]	Atrazine	Low birth weight in Long–Evans rats	**PRE-GAV**
Rönn (2011)[178]	PCBs 74, 99, 105 and 118, TNC, DDE, HCB	Increased fat mass in elderly individuals	
Roos (2012)[173]	PCBs 105, 118, 189, DDE, HCB, TNC	Increase VAT and SAT, VAT/SAT ratio in elderly individuals	
Sargis (2010)[204]	Tolylfluanid, endrin	Increased LA in 3T3-L1 cells	
Sargis (2012)[63]	Tolylfluanid	Insulin resistance in primary mice, rat, and human adipocytes	
Smink (2008)[176]	HCB	Overweight in human children offspring	**CB**
Valvi (2012)[64]	PCBs 28, 52, 101, 118, 138, 153, 180, DDE	Overweight in human children offspring	**CB**
Verhulst (2009)[175]	HCB, PCBs 118, 138, 153, 170, 180, DDE	Increased BMI in children	**CB**
Vitalone (2010)[65]	PCB-126	Weight gain in adult Wistar rats	**PERI-GEL**
	Organophosphates: Insecticides		
	Mechanisms: Mostly unknown (potential neuroendocrine disruptor)		
Lassiter (2008, 2010)[66,67]	Parathion ± HFD	Weight gain, metabolic dysfunction in adult Sprague–Dawley rats	**NEO-INJ**
Lassiter (2008)[68]	Chlorpyrifos	Weight gain in adult Long–Evans rats	**PERI-GAV**
Roegge (2008)[69]	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		
	Mechanisms: ER,[64,71] GR,[204] Akt,[72] PPAR[73]; TBBPA, TCBPA, TMPBA inhibit T3 binding[74]		
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 mice offspring	**PRE-INJ**
Carwile (2011)[77]	BPA	Increased obesity in adults (NHANES)	
Chamorro-García (2012)[172]	BADGE	Increased LA in 3T3-L1 cells and MSCs	
Huc (2012)[78]	BPA	Increased LA in HepG2 cells	
Lang (2008)[79]	BPA	Increased T2DM in adults (NHANES)	
Masuno (2002)[80]	BPA + insulin	Increased LA in 3T3-L1 cells	
Masuno (2005)[81]	BPA, BPB, BPE, BPF, BPS	Increased LA in 3T3-L1 cells	
Miyawaki (2007)[163]	BPA	Increased body weight, adipose tissue weight, and hyperlipidemia in adolescent CD-1 mice offspring	**PERI, POST-DW**
Miyawaki (2008)[82]	4-Tert-Octylphenol	Increased LA in C3H10T1/2 cells; inhibition of bone	
Ryan (2010)[83]	BPA, BPA + HFD	Increased body mass in young CD-1 mice	**NEO**
Sargis (2010)[204]	BPA	Increased LA in 3T3-L1 cells	
Shankar (2011)[84]	BPA	Increased T2DM in adults (NHANES)	

(*Continued*)

TABLE 43.1 (*Continued*)
Known Obesogenic Chemicals, Exposure, and Mechanisms of Action

Publications	Chemical	Endpoint	Exposure
Silver (2011)[85]	BPA	Increased T2DM in adults (NHANES)	
Somm (2009)[164]	BPA, BPA + HFD	Increased body weight and fat mass in young Sprague–Dawley rat offspring	**PERI-DW**
Wang (2010)[73]	BPA	Increased LA in Huh7-PPRE-Luc and 3T3-L1 cells	
Wang (2012)[86]	BPA	Increased IR and obesity in human adults	
Wei (2011)[87]	BPA ± HFD	MetS in adult Wistar rat offspring	**PERI-GAV**
Xu (2011)[165]	BPA	Weight gain, increased fat mass, sweet preference in adult Sprague–Dawley rat offspring	**PERI-DW**
	Heavy Metals: PVC Stabilizer, Seafood		
	Mechanisms: Cadmium binds ER and mimics estrogen;[207] cadmium also inhibits 11β-HSD2;[88] arsenic affects the biochemistry of glucose metabolism[89]		
Afridi (2008)[46]	Pb, Cd, and As	Increased T2DM prevalence	
Haswell-Elkins (2008)[44]	Cadmium	Increased albuminuria (associated with T2DM)	
Lai (1994)[41]	Arsenic	Increased T2DM prevalence	
Leasure (2008)[90]	Lead	Obesity in adult male C57BL/6 mice	**PRE-DW**
Rahman (1995)[91]	Arsenic	Increased T2DM prevalence	
Rahman (1998)[43]	Arsenic	Increased T2DM prevalence	
Schwartz (2003)[45]	Cadmium	Impaired glucose metabolism, increased T2DM prevalence	
Tseng (2000)[42]	Arsenic	Increased T2DM prevalence	
	Nicotine, PAH: Cigarettes, Tobacco, Smoke, Air Pollution, Charbroiled Food		
	Mechanisms: Cholinergic/catecholaminergic[92]; oxidative stress leading to apoptosis of β-cells, activation of nicotinic receptors reduces insulin secretion[93,208]		
Bergmann (2003)[94]	Nicotine (inferred)	Reduced birth weight, increased BMI in human children offspring	**MS**
Bergmann (2003)[94]	Nicotine (inferred)	Increased BMI, skinfold thickness in child offspring	**MS**
Bolton (2012)[95]	Diesel exhaust, ± HFD	Weight gain, increased insulin in C57BL/6 adult mice offspring	**PRE-INH**
Bruin (2007)[93]	Nicotine	Reduced β-cell mass and impaired glucose homeostasis in adult Wistar rat offspring	**PERI-INJ**
Friedman (2012)[96]	Nicotine (cotinine)	T2DM, obesity in adults exposed to second hand smoke	
Gao (2005)[97]	Nicotine	Increased postnatal body weight, fat pad weight, PVAT in adult Wistar rat offspring	**PRE-INJ**
Grove (2001)[98]	Nicotine	Decreased NPY, reduced leptin, increased POMC in rhesus monkey neonate offspring	**PRE-OP**
Holloway (2005)[99]	Nicotine	Dyslipidemia, impaired glucose homeostasis, weight gain in adult Wistar rat offspring	**PERI-INJ**
Irigaray (2006)[100]	BaP	Weight gain, increased fat mass in C57Bl/6J male mice	
Montgomery (2002)[101]	Nicotine (inferred)	T2DM, obesity in adult offspring	**MS**
Oken (2008)[102]	Nicotine (inferred)	Increased BMI in child offspring (meta-analysis)	**MS**
Oliveira (2009)[103]	Nicotine	Weight gain, hyperleptinemia, and hypothyroidism in adult Wistar rat offspring	**NEO-OP**
Power (2002)[104]	Nicotine (inferred)	Reduced birth weight, increased BMI in adolescent and adult offspring	**MS**
Rundle (2012)[105]	PAH	Increased BMI, % body fat in human children offspring	**MS**
Somm (2008)[106]	Nicotine	Increased WAT weight, larger adipocytes in young Sprague–Dawley rat offspring; metabolic syndrome in the adult offspring	**PRE-OP**
Syme (2009)[107]	Nicotine (inferred)	Abdominal obesity in adult adolescent human offspring	**MS**
von Kries (2002)[108]	Nicotine (inferred)	Increased BMI in children human offspring	**MS**

AU 10

Widerøe (2003)[109]	Nicotine (inferred)	Increased BMI, skinfold thickness in human children offspring	**MS**
Williams (1984)[110]	Nicotine	Increased fetal body fat in Sprague–Dawley rats	**PRE-DW**
Xu (2011)[111]	$PM_{2.5}$	Decreased adiponectin and leptin; insulin resistance in C57Bl/6J male mice	
	Phthalates: Plasticizer, PVC Tubing, PVC Flooring, Personal Care Products		
	Mechanisms: PPAR activator[73,112–114]; GR activator[204]; TR antagonist or increased SMRT recruitment to TR[115,116]; DBP is ER agonist.[115]		
Biemann (2011)[50]	DEHP	Increased adipocyte number, lipid accumulation in C3H/10T1/2 cells	
Bility (2004)[113]	MBenP, MEHA, MIHP2, MEHP, MIHP, MnOP, MINP, MIDP	Increased LA in 3T3-L1 cells	
Boas (2010)[117]	MEP, MCiOP, MBP, MBzP	Decreased T3 levels in children	
Feige (2007)[112]	MEHP	Increased LA in 3T3-L1 cells	
Hatch (2008)[38]	MEP, MBP, MBzP, MEHHP, MEOHP	Increased WC and BMI in adult males	
Hurst (2003)[114]	MEHP, MBzP, MBuP	Increased LA in 3T3-L1 cells	
James-Todd (2012)[118]	MnBP, MiBP, MBzP, MCPP, and ∑DEHP	Increased diabetes prevalence, IR in women	
Lind (2012)[40]	MMP, MiBP, MEP	Increased diabetes prevalence, IR in elderly individuals	
Lind (2012)[39]	MiBP	Increased WC, total fat mass, abdominal SAT in elderly women	
Sargis (2010)[204]	DCHP	Increased LA in 3T3-L1 cells	
Schmidt (2012)[119]	DEHP	Impaired fertility, increased body weight and larger adipocytes in C3H/N female F0 mice, F1 offspring showed increased visceral fat and body weight	**PRE-FD**
Stahlhut (2007)[37]	MBP, MBzP, MEHHP, MEOHP, MEP	Increased WC in adult males	
Wang (2010)[73]	BBP	Increased LA in Huh7-PPRE-Luc and 3T3-L1 cells	
	PFCs: Teflon and Scotchgard		
	Mechanisms: Unknown		
Halldorsson (2012)[196]	PFOA	Increased adiposity biomarkers, waist circumference, BMI	**SER**
Hines (2009)[195]	PFOA	Increased body weight, insulin, leptin in postpubertal female mice offspring	
	Medications: Antidiabetic, Atypical Antipsychotics, Synthetic Estrogens, Anti-Inflammatories		
	Mechanisms: Thiazoloadinediones activate PPARγ[120]; Cox2 inhibitors inhibit prostaglandin synthesis[121] and could potentially be PPARγ, PPARα activators[122]; olanzapine and clozapine affect TGFβ, neurotransmitters[123]; DES is a synthetic estrogen[205]		
Jin (2002)[124]	Clozapine, olanzapine, quetiapine, and risperidone	Increased T2DM (meta-analysis) in human adults	
Knight et al. (1987)[125]	Indocin	Increased LA in 3T3-L1 cells	
Newbold (2005)[205]	DES	Increased body weight in adult CD1 mice	**NEO-INJ**
Pratley (2006)[126]	Pioglitazone	Weight gain in human adults	
Shim (2006)[127]	Rosiglitazone	Increased HDL-C and body weight in human adults	
Vegiopoulos (2010)[121]	Cox2 inhibitors	Reduced brown fat production	
Williams (1997)[128]	Indocin	Increased LA in 3T3-L1 cells	

(*Continued*)

TABLE 43.1 (*Continued*)
Known Obesogenic Chemicals, Exposure, and Mechanisms of Action

Publications	Chemical	Endpoint	Exposure
		Sugar, Trans Fat, Phytoestrogens: Food, Food Additives, Beverage, Infant Formula	
		Mechanisms: Fructose alters liver biochemistry[129–131]	
Abdel-Sayed (2008)[132]	Fructose	Impaired lipid metabolism in human adult males	
Abid (2009)[133]	Fructose	NAFLD in human adults	
Assy (2008)[134]	Fructose	NAFLD in human adults	
Dawson (1981)[135]	Excitotoxin	Increased fat mass, obesity in adult Sprague–-Dawley rats	
He (2008)[214]	Excitotoxin	Overweight in human adults	
Hermanussen (2006)[136]	Excitotoxin	Low birth weight in Wistar rats	**PRE-FD**
Le (2008)[137]	Fructose	Impaired glucose and lipid metabolism in human adult males	
Montonen (2007)[138]	Fructose	Increased T2DM in human adults	
Newbold (2005)[205]	Genistein	Increased body weight in adult CD1 mice	**NEO-INJ**
Olney (1969)[139]	Excitotoxin	Obesity in adult mice	**NEO-INJ**
Ouyang (2008)[218]	Fructose	NAFLD in human adults	
Palmer (2008)[140]	Fructose	Increased T2DM in human adult females	
Perez-Pozo (2010)[141]	Fructose	MetS in human adult men	
Stanhope (2009)[142]	Fructose	Increased visceral adiposity and IR in human adult males	
Stettler (2005)[143]	Genistein (inferred)	Overweight in human adults	**NEO-FD**
Tetri (2008)[144]	HFCS ± trans fat	NAFLD in adult C57BL/6 mice	
Yoshida (2007)[145]	Fructose	Insulin resistance	

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; PERI, perinatal exposure; PRE, prenatal exposure; PUB, pubertal exposure; SER, maternal serum; T2DM, type 2 diabetes.

AU 11

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.[149] TBT crosses the blood-brain barrier[150] 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.[151] 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[152,153] and are inhibited by leptin and insulin, but stimulated by ghrelin [154–157]. Treatment of adult mice with TBT resulted in increased c-fos expression in the arcuate nucleus[158]; 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 negligible 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 during gametogenesis that normally erase epigenetic marks acquired by the previous generation.[19,22,26] For example, F0 exposure to fungicides, pesticides, plastics, and air pollution is linked to ovarian diseases in the F3 generation.[159] Maternal exposure to BPA is linked to social behavioral changes in F4.[160] Data surrounding transgenerational inheritance of obesity is beginning to appear in the literature. Prenatal exposure of pregnant F0 mice to TBT led to increased adipose depot weight, larger adipocyte size, and biased cell fate in the MSC compartment to favor the adipocyte lineage in the F1, F2, and F3 generations.[26] Moreover, prenatal TBT exposure led to fatty liver in all three generations.[26] These results demonstrate that the effects of early life obesogen exposure are permanent and transgenerational, increasing the risk of future generations to develop obesity and related disorders.

43.5.2 Obesogens with Unconfirmed Mechanisms of Action

43.5.2.1 Bisphenol A

There has been a great deal of interest in BPA because of its high production volume and widespread commercial use. Numerous animal studies have shown a link between BPA exposure with increased body weight and adiposity and it is presumed, although, not yet demonstrated that these effects of BPA are mediated through one of the estrogen receptors (ERs).[161,162] BPA exposure during gestation and lactation accelerated adipogenesis or increased fat pad weights at the time of or soon after weaning.[163–165] A recent study in rats confirmed an increase in the expression of adipogenic genes in adipose tissue at the time of weaning in BPA-exposed animals.[164] Some evidence suggests that the increases in body weight are sex specific, but timing and dose may contribute to the complexity of these findings.[163,164,166] 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.[167] 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.[162]

Since the 1990s, several dozen studies have been dedicated to determining human exposure to BPA and its impact on human metabolic systems.[44] 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).[167,168] 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.[162] Thus, fetal exposure to BPA may be more important to the development of metabolic disorders than exposure later in life.

43.5.2.2 Bisphenol A Diglycidyl Ether

Bisphenol 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.[169] Like BPA, BADGE migrates from container linings into foods and is routinely ingested,[170,171] 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.[172] 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.[172] Therefore, BADGE is unlikely to act as a ligand for the RXR-PPARγ heterodimer at doses that could be encountered, in vivo,[172] 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,[172] which suggests that their mechanisms of action may be distinct.

43.5.2.3 Organochlorines

AU 12 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 congener number (degree of chlorination) with the risk of obesity[173]; however, this research is ongoing. HCB was once widely used as a fungicide, particularly on wheat seeds, and remains present in the population[174] despite being banned in 1966. Higher concentrations of HCB in cord blood,[175] maternal serum,[176] or breast milk[177] were associated with low birth weight[177] and increased BMI in children.[175,176] HCB concentrations in adult serum are also positively correlated with fat mass in elderly individuals[173,178] and diabetes.[179] Chlordane and its relatives were used as pesticides on crops and for termite control. Chlordane and its breakdown products, such as oxychlordane, trans-nonachlor, and cis-nonachlor, are linked to increased BMI, fat mass, triglycerides, and waist circumference in adults, and are also associated with insulin resistance and diabetes.[178,180–183] Dioxins such as 2,3,7,8-tetrachlorodibenzodioxin (TCDD) were notorious for their contamination of the defoliant Agent Orange and might provide a reason for why diabetes risk is higher for veterans who were in contact with Agent Orange compared to veterans who were not exposed.[184] TCDD serum levels are positively associated with insulin resistance and T2DM.[185–187]

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 (http://www.cdc.gov/nchs/nhanes.htm) that have been associated with various adverse health outcomes including obesity and reduced thyroid function.[188–192] Prenatal or neonatal exposure to PBDEs is associated with low birth weight and thyroid function in offspring.[193,194]

43.5.2.5 Perfluorochemicals

PFOA and PFOS, found in Teflon® and formerly Scotchgard™, AU 13 are linked to the prenatal programming of obesity. Young adult mice that were exposed in utero to PFOA[195] have increased serum insulin and leptin levels. In humans, prenatal exposure to PFOA is associated with increased BMI, adiposity biomarkers, and waist circumference.[196]

43.5.2.6 Phthalates

Phthalates and phthalate metabolites have been associated with waist circumference, insulin resistance, and obesity in humans,[37,38] and an abundance of studies show that phthalates can induce adipogenesis in cell culture models, reviewed in the work by Casals-Casas et al.,[197] 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 C3H/N 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 C57BL6/J mice carrying the human PPARα were susceptible to high-fat-induced obesity, whereas wild-type mice were not.[198] 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.[3,7,24,199,200] In addition to the mechanisms in the preceding discussion, the following mechanisms may also be relevant to obesity in humans.

43.6.1 Obseogenic 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,[3] Perissi et al.,[201] and van Beekum et al.[202] 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.[168] Glucocorticoids increase adipocyte proliferation and their differentiation from stromal cells; hence, the presence of excess glucocorticoids will undoubtedly stimulate adipogenesis locally.[203] BPA, dicyclohexyl phthalate, endrin, and tolylfluanid were all found to activate glucocorticoid receptors and increase adipogenesis in the 3T3-L1 preadipocyte model.[204] Prenatal or perinatal exposure to excess estrogen also promotes obesity in adult offspring, reviewed in the works by Rubin and Soto,[167] Newbold et al.,[205] and Vom Saal et al.[206] Cadmium binds to the ER and mimics estrogen[207] and is associated with diabetes in adults.[44,45] 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.[208]

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.[209,210] 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[211] while inhibiting it in others, thereby reducing estradiol levels.[212]

AU 14

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

AU 15

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.[213] The effects of early life exposure to soy and obesity consequences later in life have been reviewed.[200] Monosodium glutamate is associated with obesity[214] 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[215] without inducing insulin secretion.[216] For this reason, low doses of fructose are thought to help regulate glucose homeostasis, reviewed in the work by Sievenpiper et al.,[217] 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,[218] and excess fat is secreted in the form of very-low-density lipoprotein, which is highly associated with T2DM.[219] 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.

ACKNOWLEDGMENTS

Work in the Blumberg laboratory was supported by grants from the NIH (ES015849, ES015849-04S1, and ES021020). Amanda Janesick was a predoctoral trainee of NSF IGERT DGE 0549479.

REFERENCES

1. Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, et al. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. *Endocr Rev* 2009;30:293–342.
2. Grun F, Blumberg B. Environmental obesogens: organotins and endocrine disruption via nuclear receptor signaling. *Endocrinology* 2006;147:S50–5.
3. Janesick A, Blumberg B. Endocrine disrupting chemicals and the developmental programming of adipogenesis and obesity. *Birth Defects Res C Embryo Today* 2011;93:34–50.
4. Thayer KA, Heindel JJ, Bucher JR, et al. Role of environmental chemicals in diabetes and obesity: a national toxicology program workshop review. *Environ Health Perspect* 2012;120:779–89.
5. Tontonoz P, Spiegelman BM. Fat and beyond: the diverse biology of PPARgamma. *Annu Rev Biochem* 2008;77:289–312.
6. Grun F, Watanabe H, Zamanian Z, et al. Endocrine-disrupting organotin compounds are potent inducers of adipogenesis in vertebrates. *Mol Endocrinol* 2006;20:2141–55.
7. Heindel JJ. The obesogen hypothesis of obesity: overview and human evidence. In Lustig RH, ed. *Obesity Before Birth: Maternal and Prenatal Influences on the Offspring*. New York: Springer Verlag, 2011:355–66.
8. Tang-Peronard JL, Andersen HR, Jensen TK, et al. Endocrine-disrupting chemicals and obesity development in humans: a review. *Obes Rev* 2011;12:622–36.
9. Dolinoy DC, Weidman JR, Jirtle RL. Epigenetic gene regulation: linking early developmental environment to adult disease. *Reprod Toxicol* 2007;23:297–307.
10. Gluckman PD, Hanson MA. Living with the past: evolution, development, and patterns of disease. *Science* 2004;305:1733–6.
11. Gluckman PD, Hanson MA, Beedle AS, et al. Fetal and neonatal pathways to obesity. *Front Horm Res* 2008;36:61–72.
12. Newbold RR, Padilla-Banks E, Jefferson WN. Environmental estrogens and obesity. *Mol Cell Endocrinol* 2009;304:84–9.
13. Barouki R, Gluckman PD, Grandjean P, et al. Developmental origins of non-communicable disease: implications for research and public health. *Environ Health* 2012;11:42.
14. Sumithran P, Prendergast LA, Delbridge E, et al. Long-term persistence of hormonal adaptations to weight loss. *N Engl J Med* 2011;365:1597–604.
15. Pittenger MF, Mackay AM, Beck SC, et al. Multilineage potential of adult human mesenchymal stem cells. *Science* 1999;284:143–7.
16. Adriani W, Seta DD, Dessi-Fulgheri F, et al. Altered profiles of spontaneous novelty seeking, impulsive behavior, and response to D-amphetamine in rats perinatally exposed to bisphenol A. *Environ Health Perspect* 2003;111:395–401.
17. Corsica JA, Pelchat ML. Food addiction: true or false? *Curr Opin Gastroenterol* 2010;26:165–9.
18. Bernal AJ, Jirtle RL. Epigenomic disruption: the effects of early developmental exposures. *Birth Defects Res* 2010;88:938–44.
19. Skinner MK, Manikkam M, Guerrero-Bosagna C. Epigenetic transgenerational actions of endocrine disruptors. *Reprod Toxicol* 2011;31:337–43.
20. Murphy SK, Jirtle RL. Imprinting evolution and the price of silence. *Bioessays* 2003;25:577–88.
21. Feil R, Fraga MF. Epigenetics and the environment: emerging patterns and implications. *Nat Rev Genet* 2011;13:97–109.
22. Anway MD, Skinner MK. Epigenetic transgenerational actions of endocrine disruptors. *Endocrinology* 2006;147:S43–9.
23. Vucetic Z, Kimmel J, Totoki K, et al. Maternal high-fat diet alters methylation and gene expression of dopamine and opioid-related genes. *Endocrinology* 2010;151:4756–64.
24. Schug TT, Janesick A, Blumberg B, et al. Endocrine disrupting chemicals and disease susceptibility. *J Steroid Biochem Mol Biol* 2011;127:204–15.
25. Diamanti-Kandarakis E, Gore AC, eds. *Endocrine Disruptors and Puberty*. New York: Humana Press, 2011.
26. Chamorro-Garcia R, Sahu M, Abbey R, et al. Transgenerational inheritance of prenatal obesogen exposure *Environ Health Perspect* 2012. AU 16
27. Kirchner S, Kieu T, Chow C, et al. Prenatal exposure to the environmental obesogen tributyltin predisposes multipotent stem cells to become adipocytes. *Mol Endocrinol* 2010;24:526–39.
28. Zuo Z, Chen S, Wu T, et al. Tributyltin causes obesity and hepatic steatosis in male mice. *Environ Toxicol* 2011;26:79–85.
29. Vos MB, Kimmons JE, Gillespie C, et al. Dietary fructose consumption among US children and adults: the Third National Health and Nutrition Examination Survey. *Medscape J Med* 2008;10:160.
30. Spalding KL, Arner E, Westermark PO, et al. Dynamics of fat cell turnover in humans. *Nature* 2008;453:783–7.
31. Ahima RS. Adipose tissue as an endocrine organ. *Obesity (Silver Spring)* 2006;14 Suppl 5:242S–9S.
32. Galic S, Oakhill JS, Steinberg GR. Adipose tissue as an endocrine organ. *Mol Cell Endocrinol* 2010;316:129–39.
33. Scherer PE. Adipose tissue: from lipid storage compartment to endocrine organ. *Diabetes* 2006;55:1537–45.
34. Mastracci TL, Sussel L. The endocrine pancreas: insights into development, differentiation, and diabetes. *Wiley Interdiscip Rev Membr Transp Signal* 2012;1:609–8.
35. Ohlsson C, Mohan S, Sjogren K, et al. The role of liver-derived insulin-like growth factor-I. *Endocr Rev* 2009;30:494–535.
36. Ugrumov MV. Developing brain as an endocrine organ: a paradoxical reality. *Neurochem Res* 2010;35:837–50.
37. Stahlhut RW, van Wijgaarden E, Dye TD, et al. Concentrations of urinary phthalate metabolites are associated with increased waist circumferece and insulin resistance in adult U.S. males. *Environ Health Perspect* 2007;115:876–82.
38. Hatch EE, Nelson JW, Qureshi MM, et al. Association of urinary phthalate metabolite concentrations with body mass index and waist circumference: a cross-sectional study of NHANES data, 1999–2002. *Environ Health* 2008;7:27.
39. Lind PM, Roos V, Ronn M, et al. Serum concentrations of phthalate metabolites are related to abdominal fat distribution two years later in elderly women. *Environ Health* 2012;11:21.

40. Lind PM, Zethelius B, Lind L. Circulating levels of phthalate metabolites are associated with prevalent diabetes in the elderly. *Diabetes Care* 2012;35:1519–24.
41. Lai MS, Hsueh YM, Chen CJ, et al. Ingested inorganic arsenic and prevalence of diabetes mellitus. *Am J Epidemiol* 1994;139:484–92.
42. Tseng CH, Tai TY, Chong CK, et al. Long-term arsenic exposure and incidence of non-insulin-dependent diabetes mellitus: a cohort study in arseniasis-hyperendemic villages in Taiwan. *Environ Health Perspect* 2000;108:847–51.
43. Rahman M, Tondel M, Ahmad SA, et al. Diabetes mellitus associated with arsenic exposure in Bangladesh. *Am J Epidemiol* 1998;148:198–203.
44. Haswell-Elkins M, Satarug S, O'Rourke P, et al. Striking association between urinary cadmium level and albuminuria among Torres Strait Islander people with diabetes. *Environ Res* 2008;106:379–83.
45. Schwartz GG, Il'yasova D, Ivanova A. Urinary cadmium, impaired fasting glucose, and diabetes in the NHANES III. *Diabetes Care* 2003;26:468–70.
46. Afridi HI, Kazi TG, Kazi N, et al. Evaluation of status of toxic metals in biological samples of diabetes mellitus patients. *Diabetes Res Clin Pract* 2008;80:280–8.
47. le Maire A, Grimaldi M, Roecklin D, et al. Activation of RXR-PPAR heterodimers by organotin environmental endocrine disruptors. *EMBO Rep* 2009;10:367–73.
48. Kanayama T, Kobayashi N, Mamiya S, et al. Organotin compounds promote adipocyte differentiation as agonists of the peroxisome proliferator-activated receptor gamma/retinoid X receptor pathway. *Mol Pharmacol* 2005;67:766–74.
49. Penza M, Jeremic M, Marrazzo E, et al. The environmental chemical tributyltin chloride (TBT) shows both estrogenic and adipogenic activities in mice which might depend on the exposure dose. *Toxicol Appl Pharmacol* 2011;255:65–75.
50. Biemann R, Navarrete Santos A, Riemann D, et al. Endocrine disrupting chemicals affect the adipogenic differentiation of mesenchymal stem cells in distinct ontogenetic windows. *Biochem Biophys Res Comm* 2012;417:747–52.
51. Janer G, Navarro JC, Porte C. Exposure to TBT increases accumulation of lipids and alters fatty acid homeostasis in the ramshorn snail *Marisa cornuarietis*. *Comp Biochem Physiol C Toxicol Pharmacol* 2007;146:368–74.
52. Si J, Wu X, Wan C, et al. Peripubertal exposure to low doses of tributyltin chloride affects the homeostasis of serum T, E2, LH, and body weight of male mice. *Environ Toxicol* 2011;26:307–14.
53. Arsenescu V, Arsenescu RI, King V, et al. Polychlorinated biphenyl-77 induces adipocyte differentiation and proinflammatory adipokines and promotes obesity and atherosclerosis. *Environ Health Perspect* 2008;116:761–8.
54. Woodhouse AJ, Cooke GM. Suppression of aromatase activity in vitro by PCBs 28 and 105 and Aroclor 1221. *Toxicol Lett* 2004;152:91–100.
55. Dirinck E, Jorens PG, Covaci A, et al. Obesity and persistent organic pollutants: possible obesogenic effect of organochlorine pesticides and polychlorinated biphenyls. *Obesity (Silver Spring)* 2011;19:709–14.
56. Gladen BC, Ragan NB, Rogan WJ. Pubertal growth and development and prenatal and lactational exposure to polychlorinated biphenyls and dichlorodiphenyl dichloroethene. *J Pediatr* 2000;136:490–6.
57. Govarts E, Nieuwenhuijsen M, Schoeters G, et al. Birth weight and prenatal exposure to polychlorinated biphenyls (PCBs) and dichlorodiphenyldichloroethylene (DDE): a meta-analysis within 12 European Birth Cohorts. *Environ Health Perspect* 2012;120:162–70.
58. Hertz-Picciotto I, Charles MJ, James RA, et al. In utero polychlorinated biphenyl exposures in relation to fetal and early childhood growth. *Epidemiology* 2005;16:648–56.
59. Karmaus W, Osuch JR, Eneli I, et al. Maternal levels of dichlorodiphenyl-dichloroethylene (DDE) may increase weight and body mass index in adult female offspring. *Occup Environ Med* 2009;66:143–9.
60. Lee DH, Lind PM, Jacobs DR, Jr., et al. Polychlorinated biphenyls and organochlorine pesticides in plasma predict development of type 2 diabetes in the elderly: the prospective investigation of the vasculature in Uppsala Seniors (PIVUS) study. *Diabetes Care* 2011;34:1778–84.
61. Mendez MA, Garcia-Esteban R, Guxens M, et al. Prenatal organochlorine compound exposure, rapid weight gain, and overweight in infancy. *Environ Health Perspect* 2011;119:272–8.
62. Rayner JL, Enoch RR, Fenton SE. Adverse effects of prenatal exposure to atrazine during a critical period of mammary gland growth. *Toxicol Sci* 2005;87:255–66.
63. Sargis RM, Neel BA, Brock CO, et al. The novel endocrine disruptor tolylfluanid impairs insulin signaling in primary rodent and human adipocytes through a reduction in insulin receptor substrate-1 levels. *Biochim Biophys Acta* 2012;1822:952–60.
64. Valvi D, Mendez MA, Martinez D, et al. Prenatal concentrations of polychlorinated biphenyls, DDE, and DDT and overweight in children: a prospective birth cohort study. *Environ Health Perspect* 2012;120:451–7.
65. Vitalone A, Catalani A, Cinque C, et al. Long-term effects of developmental exposure to low doses of PCB 126 and methylmercury. *Toxicol Lett* 2010;197:38–45.
66. Lassiter TL, Ryde IT, Mackillop EA, et al. Exposure of neonatal rats to parathion elicits sex-selective reprogramming of metabolism and alters the response to a high-fat diet in adulthood. *Environ Health Perspect* 2008;116:1456–62.
67. Lassiter TL, Ryde IT, Levin ED, et al. Neonatal exposure to parathion alters lipid metabolism in adulthood: interactions with dietary fat intake and implications for neurodevelopmental deficits. *Brain Res Bull* 2010;81:85–91.
68. Lassiter TL, Brimijoin S. Rats gain excess weight after developmental exposure to the organophosphorothionate pesticide, chlorpyrifos. *Neurotoxicol Teratol* 2008;30:125–30.
69. Roegge CS, Timofeeva OA, Seidler FJ, et al. Developmental diazinon neurotoxicity in rats: later effects on emotional response. *Brain Res Bull* 2008;75:166–72.
70. Slotkin TA, Brown KK, Seidler FJ. Developmental exposure of rats to chlorpyrifos elicits sex-selective hyperlipidemia and hyperinsulinemia in adulthood. *Environ Health Perspect* 2005;113:1291–4.
71. Alonso-Magdalena P, Laribi O, Ropero AB, et al. Low doses of bisphenol A and diethylstilbestrol impair Ca2+ signals in pancreatic alpha-cells through a nonclassical membrane estrogen receptor within intact islets of Langerhans. *Environ Health Perspect* 2005;113:969–77.
72. Kidani T, Kamei S, Miyawaki J, et al. Bisphenol A downregulates Akt signaling and inhibits adiponectin production and secretion in 3T3-L1 adipocytes. *J Atheroscler Thromb* 2010;17:834–43.
73. Wang YF, Chao HR, Wu CH, et al. A recombinant peroxisome proliferator response element-driven luciferase assay for evaluation of potential environmental obesogens. *Biotechnol Lett* 2010;32:1789–96.
74. Decherf S, Seugnet I, Fini JB, et al. Disruption of thyroid hormone-dependent hypothalamic set-points by environmental contaminants. *Mol Cell Endocrinol* 2010;323:172–82.

75. Alonso-Magdalena P, Vieira E, Soriano S, et al. Bisphenol A exposure during pregnancy disrupts glucose homeostasis in mothers and adult male offspring. *Environ Health Perspect* 2010;118:1243–50.
76. Cagampang F, Anthony F, Hanson M. P2-14 Developmental exposure to bisphenol-A leads to obesity and cardiovascular dysfunction in adult mouse offspring. *Early Hum Dev* 2007;83:S132–3.
77. Carwile JL, Michels KB. Urinary bisphenol A and obesity: NHANES 2003–2006. *Environ Res* 2011;111:825–30.
78. Huc L, Lemarie A, Gueraud F, et al. Low concentrations of bisphenol A induce lipid accumulation mediated by the production of reactive oxygen species in the mitochondria of HepG2 cells. *Toxicol In Vitro* 2012;26:709–17.
79. Lang IA, Galloway TS, Scarlett A, et al. Association of urinary bisphenol A concentration with medical disorders and laboratory abnormalities in adults. *JAMA* 2008;300:1303–10.
80. Masuno H, Kidani T, Sekiya K, et al. Bisphenol A in combination with insulin can accelerate the conversion of 3T3-L1 fibroblasts to adipocytes. *J Lipid Res* 2002;43:676–84.
81. Masuno H, Iwanami J, Kidani T, et al. Bisphenol A accelerates terminal differentiation of 3T3-L1 cells into adipocytes through the phosphatidylinositol 3-kinase pathway. *Toxicol Sci* 2005;84:319–27.
82. Miyawaki J, Kamei S, Sakayama K, et al. 4-tert-octylphenol regulates the differentiation of C3H10T1/2 cells into osteoblast and adipocyte lineages. *Toxicol Sci* 2008;102:82–8.
83. Ryan KK, Haller AM, Sorrell JE, et al. Perinatal exposure to bisphenol A and the development of metabolic syndrome in CD-1 mice. *Endocrinology* 2010;151:2603–12.
84. Shankar A, Teppala S. Relationship between urinary bisphenol A levels and diabetes mellitus. *J Clin Endocrinol Metab* 2011;96:3822–6.
85. Silver MK, O'Neill MS, Sowers MR, et al. Urinary bisphenol A and type-2 diabetes in U.S. adults: data from NHANES 2003–2008. *PLoS One* 2011;6:e26868.
86. Wang T, Li M, Chen B, et al. Urinary bisphenol A (BPA) concentration associates with obesity and insulin resistance. *J Clin Endocrinol Metab* 2012;97:E223–7.
87. Wei J, Lin Y, Li Y, et al. Perinatal exposure to bisphenol A at reference dose predisposes offspring to metabolic syndrome in adult rats on a high-fat diet. *Endocrinology* 2011;152:3049–61.
88. Yang K, Julan L, Rubio F, et al. Cadmium reduces 11 beta-hydroxysteroid dehydrogenase type 2 activity and expression in human placental trophoblast cells. *Am J Physiol Endocrinol Metab* 2006;290:E135–42.
89. Tseng CH. The potential biological mechanisms of arsenic-induced diabetes mellitus. *Toxicol Appl Pharmacol* 2004;197:67–83.
90. Leasure JL, Giddabasappa A, Chaney S, et al. Low-level human equivalent gestational lead exposure produces sex-specific motor and coordination abnormalities and late-onset obesity in year-old mice. *Environ Health Perspect* 2008;116:355–61.
91. Rahman M, Axelson O. Diabetes mellitus and arsenic exposure: a second look at case-control data from a Swedish copper smelter. *Occup Environ Med* 1995;52:773–4.
92. Abreu-Villaca Y, Seidler FJ, Tate CA, et al. Prenatal nicotine exposure alters the response to nicotine administration in adolescence: effects on cholinergic systems during exposure and withdrawal. *Neuropsychopharmacology* 2004;29:879–90.
93. Bruin JE, Kellenberger LD, Gerstein HC, et al. Fetal and neonatal nicotine exposure and postnatal glucose homeostasis: identifying critical windows of exposure. *J Endocrinol* 2007;194:171–8.
94. Bergmann KE, Bergmann RL, Von Kries R, et al. Early determinants of childhood overweight and adiposity in a birth cohort study: role of breast-feeding. *Int J Obes Relat Metab Disord* 2003;27:162–72.
95. Bolton JL, Smith SH, Huff NC, et al. Prenatal air pollution exposure induces neuroinflammation and predisposes offspring to weight gain in adulthood in a sex-specific manner. *FASEB J* 2012;26:4734–54.
96. Friedman EA. Optimizing care in diabetes: a quixotic challenge. *Diabetes Care* 2012;35:1204–5.
97. Gao YJ, Holloway AC, Zeng ZH, et al. Prenatal exposure to nicotine causes postnatal obesity and altered perivascular adipose tissue function. *Obes Res* 2005;13:687–92.
98. Grove KL, Sekhon HS, Brogan RS, et al. Chronic maternal nicotine exposure alters neuronal systems in the arcuate nucleus that regulate feeding behavior in the newborn rhesus macaque. *J Clin Endocrinol Metab* 2001;86:5420–6.
99. Holloway AC, Lim GE, Petrik JJ, et al. Fetal and neonatal exposure to nicotine in Wistar rats results in increased beta cell apoptosis at birth and postnatal endocrine and metabolic changes associated with type 2 diabetes. *Diabetologia* 2005;48:2661–6.
100. Irigaray P, Ogier V, Jacquenet S, et al. Benzo[a]pyrene impairs beta-adrenergic stimulation of adipose tissue lipolysis and causes weight gain in mice. A novel molecular mechanism of toxicity for a common food pollutant. *FEBS J* 2006;273:1362–72.
101. Montgomery SM, Ekbom A. Smoking during pregnancy and diabetes mellitus in a British longitudinal birth cohort. *BMJ* 2002;324:26–7.
102. Oken E, Levitan EB, Gillman MW. Maternal smoking during pregnancy and child overweight: systematic review and meta-analysis. *Int J Obes (Lond)* 2008;32:201–10.
103. Oliveira E, Moura EG, Santos-Silva AP, et al. Short- and long-term effects of maternal nicotine exposure during lactation on body adiposity, lipid profile, and thyroid function of rat offspring. *J Endocrinol* 2009;202:397–405.
104. Power C, Jefferis BJ. Fetal environment and subsequent obesity: a study of maternal smoking. *Int J Epidemiol* 2002;31:413–9.
105. Rundle A, Richards C, Neslund-Dudas C, et al. Neighborhood socioeconomic status modifies the association between individual smoking status and PAH-DNA adduct levels in prostate tissue. *Environ Mol Mutagen* 2012;53:384–91.
106. Somm E, Schwitzgebel VM, Vauthay DM, et al. Prenatal nicotine exposure alters early pancreatic islet and adipose tissue development with consequences on the control of body weight and glucose metabolism later in life. *Endocrinology* 2008;149:6289–99.
107. Syme C, Abrahamowicz M, Mahboubi A, et al. Prenatal exposure to maternal cigarette smoking and accumulation of intra-abdominal fat during adolescence. *Obesity (Silver Spring)* 2010;18:1021–5.
108. von Kries R, Toschke AM, Koletzko B, et al. Maternal smoking during pregnancy and childhood obesity. *Am J Epidemiol* 2002;156:954–61.
109. Wideroe M, Vik T, Jacobsen G, et al. Does maternal smoking during pregnancy cause childhood overweight? *Paediatr Perinat Epidemiol* 2003;17:171–9.
110. Williams CM, Kanagasabai T. Maternal adipose tissue response to nicotine administration in the pregnant rat: effects on fetal body fat and cellularity. *Br J Nutr* 1984;51:7–13.
111. Xu X, Liu C, Xu Z, et al. Long-term exposure to ambient fine particulate pollution induces insulin resistance and mitochondrial alteration in adipose tissue. *Toxicol Sci* 2011;124:88–98.

112. Feige JN, Gelman L, Rossi D, et al. The endocrine disruptor monoethyl-hexyl-phthalate is a selective peroxisome proliferator-activated receptor gamma modulator that promotes adipogenesis. *J Biol Chem* 2007;282:19152–66.
113. Bility MT, Thompson JT, McKee RH, et al. Activation of mouse and human peroxisome proliferator-activated receptors (PPARs) by phthalate monoesters. *Toxicol Sci* 2004;82: 170–82.
114. Hurst CH, Waxman DJ. Activation of PPARalpha and PPARgamma by environmental phthalate monoesters. *Toxicol Sci* 2003;74:297–308.
115. Shen O, Du G, Sun H, et al. Comparison of in vitro hormone activities of selected phthalates using reporter gene assays. *Toxicol Lett* 2009;191:9–14.
116. Shen O, Wu W, Du G, et al. Thyroid disruption by Di-n-butyl phthalate (DBP) and mono-n-butyl phthalate (MBP) in *Xenopus laevis*. *PLoS One* 2011;6:e19159.
117. Boas M, Frederiksen H, Feldt-Rasmussen U, et al. Childhood exposure to phthalates: associations with thyroid function, insulin-like growth factor I, and growth. *Environ Health Perspect* 2010;118:1458–64.
118. James-Todd T, Stahlhut R, Meeker JD, et al. Urinary phthalate metabolite concentrations and diabetes among women in the National Health and Nutrition Examination Survey (NHANES) 2001–2008. *Environ Health Perspect* 2012;120:1307–13.
119. Schmidt JS, Schaedlich K, Fiandanese N, et al. Effects of di(2-ethylhexyl) phthalate (DEHP) on female fertility and adipogenesis in C3H/N mice. *Environ Health Perspect* 2012;120:1123–9.
120. Lehmann JM, Moore LB, Smith-Oliver TA, et al. An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor gamma (PPAR gamma). *J Biol Chem* 1995;270:12953–6.
121. Vegiopoulos A, Muller-Decker K, Strzoda D, et al. Cyclooxygenase-2 controls energy homeostasis in mice by de novo recruitment of brown adipocytes. *Science* 2010;328:1158–61.
122. Lehmann JM, Lenhard JM, Oliver BB, et al. Peroxisome proliferator-activated receptors alpha and gamma are activated by indomethacin and other non-steroidal anti-inflammatory drugs. *J Biol Chem* 1997;272:3406–10.
123. Coccurello R, Moles A. Potential mechanisms of atypical antipsychotic-induced metabolic derangement: clues for understanding obesity and novel drug design. *Pharmacol Ther* 2010;127:210–51.
124. Jin H, Meyer JM, Jeste DV. Phenomenology of and risk factors for new-onset diabetes mellitus and diabetic ketoacidosis associated with atypical antipsychotics: an analysis of 45 published cases. *Ann Clin Psychiatry* 2002;14:59–64.
125. Knight DM, Chapman AB, Navre M, et al. Requirements for triggering of adipocyte differentiation by glucocorticoids and indomethacin. *Mol Endocrinol* 1987;1:36–43.
126. Pratley RE. The PROactive study: pioglitazone in the secondary prevention of macrovascular events in patients with type 2 diabetes. *Curr Diab Rep* 2006;6:45–6.
127. Shim WS, Do MY, Kim SK, et al. The long-term effects of rosiglitazone on serum lipid concentrations and body weight. *Clin Endocrinol (Oxf)* 2006;65:453–9.
128. Williams SK, Berman SS, Kleinert LB. Differential healing and neovascularization of ePTFE implants in subcutaneous versus adipose tissue. *J Biomed Mater Res* 1997;35:473–81.
129. Bremer AA, Mietus-Snyder M, Lustig RH. Toward a unifying hypothesis of metabolic syndrome. *Pediatrics* 2012;129: 557–70.
130. Lim JS, Mietus-Snyder M, Valente A, et al. The role of fructose in the pathogenesis of NAFLD and the metabolic syndrome. *Nat Rev Gastroenterol Hepatol* 2010;7:251–64.
131. Lustig RH. Fructose: metabolic, hedonic, and societal parallels with ethanol. *J Am Diet Assoc* 2010;110:1307–21.
132. Abdel-Sayed A, Binnert C, Le KA, et al. A high-fructose diet impairs basal and stress-mediated lipid metabolism in healthy male subjects. *Br J Nutr* 2008;100:393–9.
133. Abid A, Taha O, Nseir W, et al. Soft drink consumption is associated with fatty liver disease independent of metabolic syndrome. *J Hepatol* 2009;51:918–24.
134. Assy N, Nasser G, Kamayse I, et al. Soft drink consumption linked with fatty liver in the absence of traditional risk factors. *Can J Gastroenterol* 2008;22:811–6.
135. Dawson R, Jr., Lorden JF. Behavioral and neurochemical effects of neonatal administration of monosodium L-glutamate in mice. *J Comp Physiol Psychol* 1981;95:71–84.
136. Hermanussen M, Garcia AP, Sunder M, et al. Obesity, voracity, and short stature: the impact of glutamate on the regulation of appetite. *Eur J Clin Nutr* 2006;60:25–31.
137. Le KA, Faeh D, Stettler R, et al. Effects of four-week high-fructose diet on gene expression in skeletal muscle of healthy men. *Diabetes Metab* 2008;34:82–5.
138. Montonen J, Jarvinen R, Knekt P, et al. Consumption of sweetened beverages and intakes of fructose and glucose predict type 2 diabetes occurrence. *J Nutr* 2007;137:1447–54.
139. Olney JW. Brain lesions, obesity, and other disturbances in mice treated with monosodium glutamate. *Science* 1969;164:719–21.
140. Palmer JR, Boggs DA, Krishnan S, et al. Sugar-sweetened beverages and incidence of type 2 diabetes mellitus in African American women. *Arch Intern Med* 2008;168:1487–92.
141. Perez-Pozo SE, Schold J, Nakagawa T, et al. Excessive fructose intake induces the features of metabolic syndrome in healthy adult men: role of uric acid in the hypertensive response. *Int J Obes (Lond)* 2010;34:454–61.
142. 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.
143. Stettler N, Stallings VA, Troxel AB, et al. Weight gain in the first week of life and overweight in adulthood: a cohort study of European American subjects fed infant formula. *Circulation* 2005;111:1897–903.
144. Tetri LH, Basaranoglu M, Brunt EM, et al. Severe NAFLD with hepatic necroinflammatory changes in mice fed trans fats and a high-fructose corn syrup equivalent. *Am J Physiol Gastrointest Liver Physiol* 2008;295:G987–95.
145. Yoshida M, McKeown NM, Rogers G, et al. Surrogate markers of insulin resistance are associated with consumption of sugar-sweetened drinks and fruit juice in middle and older-aged adults. *J Nutr* 2007;137:2121–7.
146. Li X, Pham HT, Janesick AS, et al. Triflumizole is an environmental obesogen that acts through peroxisome proliferator activated receptor gamma (PPAR-gamma). *Environ Health Perspect* 2012;120:1720–6.
147. Inadera H, Shimomura A. Environmental chemical tributyltin augments adipocyte differentiation. *Toxicol Lett* 2005;159:226–34.
148. Li X, Ycaza J, Blumberg B. The environmental obesogen tributyltin chloride acts via peroxisome proliferator activated receptor gamma to induce adipogenesis in murine 3T3-L1 preadipocytes. *J Steroid Biochem Mol Biol* 2011; 127:9–15.

149. Lu M, Sarruf DA, Talukdar S, et al. Brain PPAR-gamma promotes obesity and is required for the insulin-sensitizing effect of thiazolidinediones. *Nat Med* 2011;17:618–22.
150. Hara K, Yoshizuka M, Doi Y, et al. Effect of bis (tributyl tin) oxide on permeability of the blood-brain barrier: a transient increase. *Occup Environ Med* 1994;51:735–8.
151. Ryan KK, Li B, Grayson BE, et al. A role for central nervous system PPAR-gamma in the regulation of energy balance. *Nat Med* 2011;17:623–6.
152. Luquet S, Perez FA, Hnasko TS, et al. NPY/AgRP neurons are essential for feeding in adult mice but can be ablated in neonates. *Science* 2005;310:683–5.
153. Gropp E, Shanabrough M, Borok E, et al. Agouti-related peptide-expressing neurons are mandatory for feeding. *Nat Neurosci* 2005;8:1289–91.
154. Kamegai J, Tamura H, Shimizu T, et al. Chronic central infusion of ghrelin increases hypothalamic neuropeptide Y and Agouti-related protein mRNA levels and body weight in rats. *Diabetes* 2001;50:2438–43.
155. Erickson JC, Hollopeter G, Palmiter RD. Attenuation of the obesity syndrome of ob/ob mice by the loss of neuropeptide Y. *Science* 1996;274:1704–7.
156. Stephens TW, Basinski M, Bristow PK, et al. The role of neuropeptide Y in the antiobesity action of the obese gene product. *Nature* 1995;377:530–2.
157. Schwartz MW, Sipols AJ, Marks JL, et al. Inhibition of hypothalamic neuropeptide Y gene expression by insulin. *Endocrinology* 1992;130:3608–16.
158. Bo E, Viglietti-Panzica C, Panzica GC. Acute exposure to tributyltin induces c-fos activation in the hypothalamic arcuate nucleus of adult male mice. *Neurotoxicology* 2011;32:277–80.
159. Nilsson E, Larsen G, Manikkam M, et al. Environmentally induced epigenetic transgenerational inheritance of ovarian disease. *PLoS One* 2012;7:e36129.
160. Wolstenholme JT, Edwards M, Shetty SR, et al. Gestational exposure to bisphenol A produces transgenerational changes in behaviors and gene expression. *Endocrinology* 2012; 153:3828–38.
161. Olea N, Pulgar R, Perez P, et al. Estrogenicity of resin-based composites and sealants used in dentistry. *Environ Health Perspect* 1996;104:298–305.
162. Rubin BS. Bisphenol A: an endocrine disruptor with widespread exposure and multiple effects. *J Steroid Biochem Mol Biol* 2011;127:27–34.
163. Miyawaki J, Sakayama K, Kato H, et al. Perinatal and postnatal exposure to bisphenol a increases adipose tissue mass and serum cholesterol level in mice. *J Atheroscler Thromb* 2007; 14:245–52.
164. Somm E, Schwitzgebel VM, Toulotte A, et al. Perinatal exposure to bisphenol a alters early adipogenesis in the rat. *Environ Health Perspect* 2009;117:1549–55.
165. Xu X, Tan L, Himi T, et al. Changed preference for sweet taste in adulthood induced by perinatal exposure to bisphenol A-A probable link to overweight and obesity. *Neurotoxicol Teratol* 2011;33:458–63.
166. Rubin BS, Murray MK, Damassa DA, et al. Perinatal exposure to low doses of bisphenol A affects body weight, patterns of estrous cyclicity, and plasma LH levels. *Environ Health Perspect* 2001;109:675–80.
167. Rubin BS, Soto AM. Bisphenol A: perinatal exposure and body weight. *Mol Cell Endocrinol* 2009;304:55–62.
168. Rask E, Olsson T, Soderberg S, et al. Tissue-specific dysregulation of cortisol metabolism in human obesity. *J Clin Endocrinol Metab* 2001;86:1418–21.
169. Poole A, van Herwijnen P, Weideli H, et al. Review of the toxicology, human exposure and safety assessment for bisphenol A diglycidylether (BADGE). *Food Addit Contam* 2004; 21:905–19.
170. Cabado AG, Aldea S, Porro C, et al. Migration of BADGE (bisphenol A diglycidyl-ether) and BFDGE (bisphenol F diglycidyl-ether) in canned seafood. *Food Chem Toxicol* 2008; 46:1674–80.
171. Cao XL, Corriveau J, Popovic S. Levels of bisphenol A in canned soft drink products in Canadian markets. *J Agric Food Chem* 2009;57:1307–11.
172. Chamorro-Garcia R, Kirchner S, Li X, et al. Bisphenol A diglycidyl ether induces adipogenic differentiation of multipotent stromal stem cells through a peroxisome proliferator-activated receptor gamma-independent mechanism. *Environ Health Perspect* 2012;120:984–9.
173. Roos V, Ronn M, Salihovic S, et al. Circulating levels of persistent organic pollutants in relation to visceral and subcutaneous adipose tissue by abdominal MRI. *Obesity (Silver Spring)* 2013;21:413–8.
174. Crinnion WJ. The CDC fourth national report on human exposure to environmental chemicals: what it tells us about our toxic burden and how it assist environmental medicine physicians. *Altern Med Rev* 2010;15:101–9.
175. Verhulst SL, Nelen V, Hond ED, et al. Intrauterine exposure to environmental pollutants and body mass index during the first 3 years of life. *Environ Health Perspect* 2009;117:122–6.
176. Smink A, Ribas-Fito N, Garcia R, et al. Exposure to hexachlorobenzene during pregnancy increases the risk of overweight in children aged 6 years. *Acta Paediatr* 2008;97:1465–9.
177. Eggesbo M, Stigum H, Longnecker MP, et al. Levels of hexachlorobenzene (HCB) in breast milk in relation to birth weight in a Norwegian cohort. *Environ Res* 2009;109:559–66.
178. Ronn M, Lind L, van Bavel B, et al. Circulating levels of persistent organic pollutants associate in divergent ways to fat mass measured by DXA in humans. *Chemosphere* 2011; 85:335–43.
179. Glynn AW, Granath F, Aune M, et al. Organochlorines in Swedish women: determinants of serum concentrations. *Environ Health Perspect* 2003;111:349–55.
180. Lee DH, Lee IK, Jin SH, et al. Association between serum concentrations of persistent organic pollutants and insulin resistance among nondiabetic adults: results from the National Health and Nutrition Examination Survey 1999–2002. *Diabetes Care* 2007;30:622–8.
181. Lee DH, Lee IK, Song K, et al. A strong dose-response relation between serum concentrations of persistent organic pollutants and diabetes: results from the National Health and Examination Survey 1999–2002. *Diabetes Care* 2006;29:1638–44.
182. Elobeid MA, Padilla MA, Brock DW, et al. Endocrine disruptors and obesity: an examination of selected persistent organic pollutants in the NHANES 1999–2002 data. *Int J Environ Res Public Health* 2010;7:2988–3005.
183. Lee DH, Steffes MW, Sjodin A, et al. Low dose organochlorine pesticides and polychlorinated biphenyls predict obesity, dyslipidemia, and insulin resistance among people free of diabetes. *PLoS One* 2011;6:e15977.
184. Henriksen GL, Ketchum NS, Michalek JE, et al. Serum dioxin and diabetes mellitus in veterans of Operation Ranch Hand. *Epidemiology* 1997;8:252–8.
185. Kern PA, Said S, Jackson WG, Jr., et al. Insulin sensitivity following agent orange exposure in Vietnam veterans with high blood levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin. *J Clin Endocrinol Metab* 2004;89:4665–72.

186. Calvert GM, Sweeney MH, Deddens J, et al. Evaluation of diabetes mellitus, serum glucose, and thyroid function among United States workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Occup Environ Med* 1999;56:270–6.
187. Cranmer M, Louie S, Kennedy RH, et al. Exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is associated with hyperinsulinemia and insulin resistance. *Toxicol Sci* 2000; 56:431–6.
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.
AU 17
189. Hallgren S, Sinjari T, Hakansson H, et al. Effects of polybrominated diphenyl ethers (PBDEs) and polychlorinated biphenyls (PCBs) on thyroid hormone and vitamin A levels in rats and mice. *Arch Toxicol* 2001;75:200–8.
190. Hoppe AA, Carey GB. Polybrominated diphenyl ethers as endocrine disruptors of adipocyte metabolism. *Obesity (Silver Spring)* 2007;15:2942–50.
191. van der Ven LT, Verhoef A, van de Kuil T, et al. A 28-day oral dose toxicity study enhanced to detect endocrine effects of hexabromocyclododecane in Wistar rats. *Toxicol Sci* 2006; 94:281–92.
192. van der Ven LT, van de Kuil T, Verhoef A, et al. A 28-day oral dose toxicity study enhanced to detect endocrine effects of a purified technical pentabromodiphenyl ether (pentaBDE) mixture in Wistar rats. *Toxicology* 2008;245:109–22.
193. Chao HR, Wang SL, Lee WJ, et al. Levels of polybrominated diphenyl ethers (PBDEs) in breast milk from central Taiwan and their relation to infant birth outcome and maternal menstruation effects. *Environ Int* 2007;33:239–45.
194. Herbstman JB, Sjodin A, Apelberg BJ, et al. Birth delivery mode modifies the associations between prenatal polychlorinated biphenyl (PCB) and polybrominated diphenyl ether (PBDE) and neonatal thyroid hormone levels. *Environ Health Perspect* 2008;116:1376–82.
195. Hines EP, White SS, Stanko JP, et al. Phenotypic dichotomy following developmental exposure to perfluorooctanoic acid (PFOA) in female CD-1 mice: low doses induce elevated serum leptin and insulin, and overweight in mid-life. *Mol Cell Endocrinol* 2009;304:97–105.
196. Halldorsson TI, Rytter D, Haug LS, et al. Prenatal exposure to perfluorooctanoate and risk of overweight at 20 years of age: a prospective cohort study. *Environ Health Perspect* 2012; 120:668–73.
197. Casals-Casas C, Feige JN, Desvergne B. Interference of pollutants with PPARs: endocrine disruption meets metabolism. *Int J Obes (Lond)* 2008;32 Suppl 6:S53–61.
198. Feige JN, Gerber A, Casals-Casas C, et al. The pollutant diethylhexyl phthalate regulates hepatic energy metabolism via species-specific PPARalpha-dependent mechanisms. *Environ Health Perspect* 2010;118:234–41.
199. La Merrill M, Birnbaum LS. Childhood obesity and environmental chemicals. *Mt Sinai J Med* 2011;78:22–48.
200. Newbold RR. Developmental exposure to endocrine-disrupting chemicals programs for reproductive tract alterations and obesity later in life. *Am J Clin Nutr* 2011;94:1939S–42S.
201. Perissi V, Jepsen K, Glass CK, et al. Deconstructing repression: evolving models of co-repressor action. *Nat Rev Genet* 2010;11:109–23.
202. van Beekum O, Fleskens V, Kalkhoven E. Posttranslational modifications of PPAR-gamma: fine-tuning the metabolic master regulator. *Obesity (Silver Spring)* 2009;17:213–9.
203. Hauner H, Entenmann G, Wabitsch M, et al. Promoting effect of glucocorticoids on the differentiation of human adipocyte precursor cells cultured in a chemically defined medium. *J Clin Invest* 1989;84:1663–70.
204. Sargis RM, Johnson DN, Choudhury RA, et al. Environmental endocrine disruptors promote adipogenesis in the 3T3-L1 cell line through glucocorticoid receptor activation. *Obesity (Silver Spring)* 2010;18:1283–8.
205. Newbold RR, Padilla-Banks E, Snyder RJ, et al. Developmental exposure to estrogenic compounds and obesity. *Birth Defects Res A Clin Mol Teratol* 2005;73:478–80.
206. Vom Saal FS, Nagel SC, Coe BL, et al. The estrogenic endocrine disrupting chemical bisphenol A (BPA) and obesity. *Mol Cell Endocrinol* 2012;354:74–84.
207. Johnson MD, Kenney N, Stoica A, et al. Cadmium mimics the in vivo effects of estrogen in the uterus and mammary gland. *Nat Med* 2003;9:1081–4.
208. Yildiz D. Nicotine, its metabolism and an overview of its biological effects. *Toxicon* 2004;43:619–32.
209. Atanasov AG, Nashev LG, Tam S, et al. Organotins disrupt the 11beta-hydroxysteroid dehydrogenase type 2-dependent local inactivation of glucocorticoids. *Environ Health Perspect* 2005;113:1600–6.
210. Atanasov AG, Tam S, Rocken JM, et al. Inhibition of 11beta-hydroxysteroid dehydrogenase type 2 by dithiocarbamates. *Biochem Biophys Res Comm* 2003;308:257–62.
211. Nakanishi T, Kohroki J, Suzuki S, et al. Trialkyltin compounds enhance human CG secretion and aromatase activity in human placental choriocarcinoma cells. *J Clin Endocrinol Metab* 2002;87:2830–7.
212. Saitoh M, Yanase T, Morinaga H, et al. Tributyltin or triphenyltin inhibits aromatase activity in the human granulosa-like tumor cell line KGN. *Biochem Biophys Res Comm* 2001;289:198–204.
213. Badger TM, Ronis MJ, Hakkak R, et al. The health consequences of early soy consumption. *J Nutr* 2002;132: 559S–65S.
214. He K, Zhao L, Daviglus ML, et al. Association of monosodium glutamate intake with overweight in Chinese adults: the INTERMAP Study. *Obesity (Silver Spring)* 2008;16: 1875–80.
215. Bjorkman O, Crump M, Phillips RW. Intestinal metabolism of orally administered glucose and fructose in Yucatan miniature swine. *J Nutr* 1984;114:1413–20.
216. Bruckdorfer KR, Kang SS, Yudkin J. Plasma concentrations of insulin, corticosterone, lipids and sugars in rats fed on meals with glucose and fructose. *Proc Nutr Soc* 1973;32: 12A–3A.
217. Sievenpiper JL, Chiavaroli L, de Souza RJ, et al. 'Catalytic' doses of fructose may benefit glycaemic control without harming cardiometabolic risk factors: a small meta-analysis of randomised controlled feeding trials. *Br J Nutr* 2012;108: 418–23.
218. Ouyang X, Cirillo P, Sautin Y, et al. Fructose consumption as a risk factor for non-alcoholic fatty liver disease. *J Hepatol* 2008;48:993–9.
219. Adiels M, Olofsson SO, Taskinen MR, et al. Overproduction of very low-density lipoproteins is the hallmark of the dyslipidemia in the metabolic syndrome. *Arterioscler Thromb Vasc Biol* 2008;28:1225–36.

AUTHOR QUERIES

AU 1: Page No 471 Please confirm the correct chapter title. Whether it should be 'Environmental Pollutants and Obesity' or 'Environmental Chemicals and Obesity'.

AU 2: Page No 471 Please confirm the correct order of the author group. Whether it should be 'Bruce Blumberg, Amanda Janesick, Jerrold Heindel, and Thaddeus Schug' or 'Amanda S. Janesick, Thaddeus T. Schug, Jerrold J. Heindel, Bruce Blumberg'.

AU 3: Page No 472 Please specify the section number.

AU 4: Page No 472 Please specify the section number.

AU 5: Page No 473 Should it be in italics? Please check.

AU 6: Page No 473 Should this be 'mu'? Please check.

AU 7: Page No 473 Please define 'TNC, β-HCH, DDT'.

AU 8: Page No 474 Please provide the significant of the boldface used in the text in 'Exposure' column in Table 43.1

AU 9: Page No 474 Should it be 'Bromkal DE-70–5;? please check.

AU 10: Page No 476 Please provide either symbol or spelled out from for chemical names.

AU 11: Page No 478 Please define 'HFCS, NAFLD, DES, PFC, DCHP, MMP, MnBP, MiBP, MCPP, MBuP, MEHHP, MEOHP, MEP, MCiOP, MBP, MBzP, MBenP, MEHA, MIHP2, MEHP, MIHP, MnOP, MINP, MIDP, TR, SMRT, DBP, BaP, POMC, PAH, PVC, Akt, TBBPA, TCBPA, TMPBA, HFD, VAT, SAT, HpCDD, OCDD, hpcdd, AhR, GR, HBCD, TSH, BDE, HF/HS, LH, LA, NURR1' given in Table 43.1.

AU 12: Page No 480 Please specify the section number.

AU 13: Page No 480 Please define 'PFOA' and 'PFOS'.

AU 14: Page No 481 Please confirm if the underscore symbol given is OK.

AU 15: Page No 481 Please shorten the section heading, if possible.

AU 16: Page No 482 Please provide the volume number and page range in reference 26.

AU 17: Page No 487 Please provide the publisher's location in reference 188.