Title
Metabolism disrupting chemicals and metabolic disorders

Authors
Heindel, Jerrold J
Blumberg, Bruce
Cave, Mathew
et al.

Publication Date
2017-03-01

DOI
10.1016/j.reprotox.2016.10.001

Peer reviewed

Accepted Manuscript

Title: Metabolism Disrupting Chemicals and Metabolic Disorders

Author: Jerrold J. Heindel Bruce Blumberg Mathew Cave Ronit Machtinger Alberto Mantovani Michelle A. Mendez Angel Nadal Paola Palanza Giancarlo Panzica Robert Sargis Laura N. Vandenberg Frederick vom Saal

PII: S0890-6238(16)30363-X
DOI: http://dx.doi.org/doi:10.1016/j.reprotox.2016.10.001
Reference: RTX 7405

To appear in: *Reproductive Toxicology*

Received date: 9-6-2016
Revised date: 4-9-2016
Accepted date: 13-10-2016

Please cite this article as: Heindel Jerrold J, Blumberg Bruce, Cave Mathew, Machtinger Ronit, Mantovani Alberto, Mendez Michelle A, Nadal Angel, Palanza Paola, Panzica Giancarlo, Sargis Robert, Vandenberg Laura N, Saal Frederick vom.Metabolism Disrupting Chemicals and Metabolic Disorders.*Reproductive Toxicology* http://dx.doi.org/10.1016/j.reprotox.2016.10.001

Metabolism Disrupting Chemicals and Metabolic Disorders

Jerrold J. Heindel[1], Bruce Blumberg[2], Mathew Cave[3], Ronit Machtinger[4], Alberto Mantovani[5], Michelle A. Mendez[6], Angel Nadal[7], Paola Palanza[8], Giancarlo Panzica[9], Robert Sargis[10], Laura N. Vandenberg[11], Frederick vom Saal[12]

[1]National Institute of Environmental Health Sciences, Division of Extramural Research and Training Research Triangle Park, NC**,** USA

[2]University of California, Department of Developmental and Cell Biology, Irvine CA, USA

[3]University of Louisville, Division of Gastroenterology, Hepatology and Nutrition, Louisville KY, USA

[4]Sheba Medical Center and Tel Aviv University, Tel Aviv, Israel

[5]Instituto Superiore di Sanita, Rome, Italy

[6]University of North Carolina at Chapel Hill, School of Public Health, Chapel Hill NC, USA

[7]Institute of Bioengineering and CIBERDEM, Miguel Hernandez University of Elche, Elche, Alicante, Spain

[8]University of Parma, Department of Neurosciences, Parma, Italy

[9]University of Turin, Department of Neuroscience and Neuroscience Institute Cavalieri Ottolenghi (NICO), Turin, Italy

[10]University of Chicago, Section of Endocrinology, Diabetes and Metabolism, Department of Medicine Chicago IL, USA

[11]University of Massachusetts, Department of Environmental Health Sciences, School of Public Health & Health Sciences, Amherst MA, USA

[12]University of Missouri, Department of Biological Sciences, Columbia, MO, USA

Corresponding Author: Jerrold J Heindel, PhD, Division of Extramural Research and Training, National Institute of Environmental Health Sciences, 12233 TW Alexander Drive, RTP, NC 27709

Phone: 919 541-0781, Email: heindelj@niehs.nih.gov

Key Words: endocrine disruptors, obesogens, metabolism disruptors, developmental origins of health and disease, obesity, diabetes, lipid disorders

Word count: 35,385

Abbreviations: Abbreviations are all noted in the text.

Funding: This review did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Highlights: Metabolism Disrupting Chemicals and Metabolic Disorders

- The recent epidemics of metabolic diseases, obesity, type 2 diabetes and liver lipid disorders cannot be attributed only to genetic background, and changes in diet, exercise and aging.
- Metabolic diseases, like many other diseases, have their origins during development due to altered programming that increases susceptibility to these diseases. Some effects can be transmitted across generations.
- Since metabolic diseases are controlled and regulated by hormones during development and throughout life, they are sensitive to disruption by chemicals that can interfere with hormone action: endocrine disruptors.
- We propose that there are environmental chemicals that increase the susceptibility to metabolic diseases via actions on adipose tissue, pancreas, liver, GI tract, muscle and brain homeostatic and hedonic pathways and that these chemicals should be called metabolism disrupting chemicals (MDC) or metabolism disruptors.
- MDCs can act on multiple tissues to increase susceptibility to obesity, T2D and liver lipid disorders resulting in metabolic syndrome while others may be tissue specific resulting in only one metabolic disease depending on their site and mechanism of action.
- While some MDCs can actually cause metabolic diseases per se many act via increasing the sensitivity or susceptibility to disease (e.g. alter set point for disease) and require a “second hit” later in life like high fat diet or lack of exercise. There are now data in animal models showing how MDCs can alter the set point for metabolic diseases. For example how much food it takes to gain weight and how much exercise is needed to lose weight…mimicking the human situation.
- The MDC hypothesis along with the fact that development is the most sensitive period for MDC action provide a mechanism for actually preventing metabolic diseases: reduce exposure to MDCs during development and across the lifespan.

Abstract

The recent epidemics of metabolic diseases, obesity, type 2 diabetes(T2D), liver lipid disorders and metabolic syndrome have largely been attributed to genetic background and changes in diet, exercise and aging. However, there is now considerable evidence that other environmental factors may contribute to the rapid increase in the incidence of these metabolic diseases. This review will examine changes to the incidence of obesity, T2D and non-alcoholic fatty liver disease (NAFLD), the contribution of genetics to these disorders and describe the role of the endocrine system in these metabolic disorders. It will then specifically focus on the role of endocrine disrupting chemicals (EDCs) in the etiology of obesity, T2D and NAFLD while finally integrating the information on EDCs on multiple metabolic disorders that could lead to metabolic syndrome. We will specifically examine evidence linking EDC exposures during critical periods of development with metabolic diseases that manifest later in life and across generations.

1. Introduction

Metabolic syndrome (MetS) is a complex condition characterized by insulin resistance, abdominal obesity, dyslipidemia, hypertension, and hyperglycemia; it is a risk factor for cardiovascular disease, T2D, stroke, chronic kidney disease and cancers [1, 2]. Its prevalence is increasing along with the increase in obesity, and it is reaching epidemic proportions affecting between 24% and 34% of the adult US population [3].

In the medical community, epidemics of metabolic diseases have largely been attributed to genetic background and changes in diet, exercise and aging. However, there is now considerable evidence that other environmental factors may contribute to the rapid increase in the incidence of obesity, T2D and other aspects of MetS observed over the past three decades [4]. One environmental factor that has begun to receive attention is a class of chemicals that can interfere with the action of hormones including metabolic hormones. These compounds, termed EDCs, are found in a wide variety of consumer products, and exposures are often widespread [5] Of particular concern is evidence that exposure to EDCs during critical periods when adipocytes are differentiating and the pancreas, liver, brain, etc. are developing can induce effects that manifest later in life, often as overt disease.

This review will examine changes to the incidence of obesity, T2D and NAFLD and its associated hyperlipidemia, the contribution of genetics and describe the role of the endocrine system in these metabolic disorders. It will then specifically focus on the role of EDCs in metabolic diseases, focusing on their role in the etiology of obesity, T2D and NAFLD while finally integrating the information on EDCs on multiple metabolic disorders that could lead to MetS. We will specifically examine evidence linking EDC exposures during critical periods of development with metabolic diseases that manifest later in life and across generations.

2. Metabolic Diseases

.

2.1 Obesity

Obesity is a global epidemic that affects infants, children and adults [6]. The global prevalence of obesity has nearly doubled over the past three decades and in the US it is the highest recorded in human history [7]. For the first time worldwide, the number of obese and overweight people is greater than the number of those who are underweight [8]. This dramatic increase in the rate of abdominal obesity has been observed in both developed and developing countries [9, 10].

Obesity among children and adolescents has similarly increased [6]. Approximately one third of US children are overweight or obese, and over 60% of obese children will become obese adults [11]. There is also an obesity epidemic among infants six months of age and younger; an age group where food choices and limited physical activity cannot explain this outcome [12].

The obesity epidemic is not limited to humans but has also been observed as upward trends in body weight among primates and rodents living in research colonies, as well as among feral rodents, horses and domestic dogs and cats [13].

Staggering health care costs are associated with treating the co-morbidities that typically accompany obesity [14] including cardiovascular disease, hypertension, dyslipidemia, liver and gallbladder disease, insulin resistance, hyperglycemia and T2D [9]. Obesity is also associated with neurodegenerative diseases, cancers and

obstructive sleep apnea. Thus, determining the factors that contribute to obesity has become a major public health issue.

2.2 Type 2 Diabetes

The American Diabetes Association (ADA) defines Diabetes Mellitus (DM) as: “a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both” [15]. DM can result from a deterioration in function and/or a loss of mass of pancreatic tissue [16] . T2D (formerly known as adult-onset or non-insulin-dependent diabetes or DM) accounts for 90-95% of diabetes cases and is characterized by increased insulin resistance and pancreatic beta cell dysfunction. More than 11% of individuals in the US older than 20 have diagnosed or undiagnosed T2D [7] and another 35% are estimated to be pre-diabetic. The World Health Organization (WHO) estimates that 347 million people globally suffer from diabetes (90% of which is T2D) [17]. Adolescents and even children have experienced significant increases in the prevalence of this disease over short periods [14, 18].

Obesity is the main environmental factor driving the increased incidence of T2D; 70% of the risk associated with T2D is related to weight gain. Obesity is associated with insulin resistance that promotes beta cell proliferation, leading to hyperinsulinemia typical of early stages of T2D and MetS. However, obesity is neither necessary nor sufficient to cause T2D; these conditions can occur independently. Indeed, 20% of adults with T2D were not overweight and 57% of obese individuals do not have T2D [19].

2.3 Nonalcoholic Fatty Liver Disease and Hyperlipidemia

Liver is the central organ for lipid metabolism. Nonalcoholic fatty liver disease (NAFLD), characterized by excess triglyceride accumulation within hepatocytes, or steatosis, is considered by some to be the hepatic manifestation of obesity and MetS. NAFLD is the most common liver disease, and it affects 25% of the global population [20] and almost 8% of children [21]. NAFLD and its more severe form, nonalcoholic steatohepatitis (NASH), are associated with increased liver-related and overall mortality [20], and NAFLD is a risk factor for cardiovascular disease [22]. The metabolic condition most commonly associated with NAFLD is hyperlipidemia (69%), although NAFLD is

also associated with obesity (51%), MetS (43%) and T2D (23%) [20]. NAFLD was initially thought to occur predominantly in women [23] but increasing evidence indicates that males and perhaps post-menopausal females are more susceptible to NAFLD [21, 24].

Hyperlipidemia is an elevation in blood triglycerides (hypertriglyceridemia), cholesterol (hypercholesterolemia), phospholipids, or a combination thereof. While there is an association between NAFLD and hyperlipidemia, not all patients with one disorder are affected by the other. The prevalence of hypertriglyceridemia in US adults is 25%, although it declined from 33% in 2001-2004 [25]. Total and LDL cholesterol have also been declining, and these favorable changes may be attributed to increased awareness and utilization of lipid lowering medications [26]. Among adolescents and US children, the prevalence of hyperlipidemia was 20% (1999-2012) [27].

2.4 Metabolic Syndrome

The International Diabetes Federation estimates that 20-25% of the world's adult population have MetS, which it defines as: "a cluster of the most dangerous heart attack risk factors: diabetes and prediabetes, abdominal obesity, high cholesterol and high blood pressure" (https://www.idf.org/metabolic-syndrome). The etiology of MetS is still a matter of research but insulin resistance and central obesity are significant contributors. Although there is still substantial debate, it is likely that components of MetS arise from insulin resistance. When insulin resistance occurs, there is an increase of fasting glucose and impaired glucose tolerance, often due to the abnormal expression of gluconeogenic enzymes. This metabolic state induces further insulin release, ultimately resulting in hyperinsulinemia. Hyperinsulinemia then simulates transcription factors such as Srebp-1c in the liver, which drive hypertriglyceridemia and hepatic steatosis [28]. In addition, the overproduction and secretion of insulin by pancreatic β-cells can result in their exhaustion and death, initiating the onset of T2D. The most prevalent form of insulin resistance is associated with abdominal obesity and dysfunction of adipose tissue, indicating an important central role for obesity in MetS.

2.5 Genetic Contributions to Metabolic Diseases

2.5.1 Genetic Factors in Obesity

While the hereditary origins of obesity have long been assumed, a genetic contribution to obesity became evident only in the last two decades [29]. Evidence from twins and animal studies indicates that genetic factors account for 40-70% of the variation in BMI [30-33]. Although several single genes are linked to obesity, studies have confirmed that the genetic basis of high BMI is mainly polygenic (i.e., resulting from polymorphisms in several genes that are associated with appetite and metabolism) or results from single nucleotide polymorphisms [SNPs] rather than a single gene mutation [34]. Three SNPs are significantly related to obesity: one in FTO (fat mass and the obesity-associated gene), one near *TMEM18* (transmembrane protein 18) and one near *MC4R* (melatocortin 4 receptor) [29, 34-36]. Only rare forms of obesity, usually parts of genetic syndromes, result from a single gene mutation or chromosomal abnormalities such as Prader- Willi and Bardet-Biedl syndromes [37]. Because many people who carry genetic variants linked to increased BMI are not obese, it is anticipated that other environmental factors can influence these genetic predispositions.

2.5.2 Genetic Factors in Diabetes

Genetic factors are involved in the development of both type 1 and T2D. The most prominent genetic factor known to be associated with type 1 diabetes is located in the region of chromosome 6 that contains the highly polymorphic HLA class II genes and controls immune responsiveness [38]. Recently, whole-genome investigations have detected more than 20 other genetic variants associated with type 1 diabetes [39].

Twin and family studies have provided strong evidence that T2D also has a solid genetic predisposition [40-42]. Genome wide association studies (GWAS) identified genetic variants associated with T2D; most of the loci identified are related to lipid metabolism, obesity and β-cell pathways [43, 44]. *TCF7L2* demonstrated the strongest effect of >70 loci associated with the disease [43]. Similar to the genetic basis for obesity, it is assumed that predisposition to T2D involves multiple genes and SNPs.

2.5.3 Genetic Factors in Lipid Disorder Metabolism

Genetic predisposition to several lipid metabolism disorders was demonstrated based on twin and family studies with estimates that 40% to 80% of the variance in blood lipid levels results from genetic polymorphisms [45-47]. Familial hypercholesterolemia is an autosomal dominant disease characterized by elevated

blood low-density lipoprotein levels (LDL). More than 150 mutations in the LDL receptor gene and in genes encoding the proteins apolipoprotein B (APOB), proprotein convertase subtilisin/kexin type 9 (PCSK9) and low density lipoprotein receptor adaptor protein 1 (LDLRAP1) that interact with the LDL receptor, are associated with the disease [48, 49].

High levels of very low-density lipoprotein (VLDL) and triglycerides characterize hypertriglyceridemia. The hereditary form of this disease can result from mutations in genes that regulate the metabolism of triglyceride rich lipoproteins such as apolipoprotein A5 (APOA5) LPL, apolipoprotein C2 (APOC2), lipase maturation factor-1 (LMF1) and glycosylphosphatidylinositol anchored high density lipoprotein binding protein 1 (GPIHBP1). Hypobetalipoproteinemia is an autosomal dominant disease associated with low levels of LDL cholesterol and APOB-containing lipoproteins. Mutations in APOB and PCSK9 genes are common among patients [50].

2.5.4 Genetic Factors in NAFLD

Genetics have also been shown to contribute to variability in the occurrence of NAFLD [51]. In recent years, GWAS have identified two major genetic determinants associated with NAFLD. The most significant genetic linkage identified to date is a SNP in the gene patatin-like phospholipase domain-containing 3 (PNPLA3), a gene involved in the remodeling of hepatocellular lipid droplets [52]. This variant alters the mobilization of fatty acid, inhibits the activity of lipases and can cause hepatocellular accumulation of triglycerides [53]. Carriers of this genetic variant have increased susceptibility to liver damage when exposed to environmental stressors [53]. Another SNP in transmembrane six superfamily member 2 (TM6SF2) has been linked with NAFLD. This gene variant is located on chromosome 19 and associated with increased hepatic triglyceride content and lower serum lipoproteins [54, 55].

3. Overview of Tissues and Hormones Controlling Metabolism

The endocrine system controls the tissues and organs that regulate weight and metabolism. Hormones and growth factors including estrogens, androgens, glucocorticoids, insulin and thyroid hormones (among others) regulate the pathways that control the number and content of adipocytes as well as appetite, satiety and energy

balance [56-59]. Other hormones affect metabolism via actions in the gastrointestinal tract [ghrelin, cholecystokinin (CCK), glucagon like peptide (GLP-1)], the pancreas (insulin, glucagon), muscle (insulin), liver (glucagon, insulin, FGF21), adipose tissue (leptin, adiponection, and a variety of other factors), immune system, and brain [Neuropeptide Y (NPY), agouti related protein (AgRP), pro-opiomelanocortin (POMC), alpha melanocyte-stimulating hormone (alpha MSH)] [56-60]. These and other hormones, growth factors and neurotransmitters control the hedonic pathways in the brain that regulate food reward mechanisms, food cravings and addiction [61-63]. They also control glucose and lipid levels via pancreatic, muscle and liver responses. The pancreas responds to rising blood glucose levels by releasing insulin, which then promotes glucose uptake into tissues. It also responds to falling glucose levels in the blood by releasing glucagon, which acts on the liver to stimulate glycogenolysis and gluconeogenesis to raise blood sugar. The liver also regulates glucose and lipid metabolism via a number of nuclear hormone receptors including aryl hydrocarbon receptor - AhR, pregnane x receptor - PXR, and the constitutive androstane receptor – CAR.

Below we focus on the endocrine control of adipogenesis, glucose homeostasis and liver lipids.

3.1 Neuroendocrine Control

The neuroendocrine hypothalamus, together with some structures in the brainstem, plays a key role in the regulation of energy balance through the integration of peripheral signals and onward signal transmission (Figure 1). Peripheral signals conveying information about meal processing, gastrointestinal activity, and changes in energy stores access the brain via a number of routes, crossing or by-passing the blood-brain barrier from the systemic circulation, or changing the firing rate of vagal or other sensory nerve fibers. In the medulla, the nucleus of the solitary tract and the area postrema are key sites for the integration of these peripheral signals and for sending them to other integration sites located in the hypothalamus (for reviews see [64, 65]).

The hypothalamus participates in the regulation of food intake and body weight with two neuroendocrine components: the afferent peripheral system (stimulated in response to a meal) and the efferent system (regulating the feeding behavior and energy metabolism) [66, 67]. The peripheral signals are the hormones insulin (secreted by the

endocrine pancreas in response to changes in blood sugar), leptin (secreted by adipocytes in proportion to fat mass), ghrelin and orexin-A (secreted by the stomach and the gut)[68]. These hormones link the control of peripheral energy metabolism to the feeding behavior integrating neural units by modulating short term signals that determine meal initiation and termination as well as energy balance [69]. Two neurochemically-distinct populations of hypothalamic neurons located in the arcuate nucleus (ARC) are critical for the integration of signals of nutritional status, and influence energy homeostasis [70]. One neuron group expresses the potent orexigenic neuropeptide NPY and AgRP and shows high concentrations of binding sites for many hormonal and metabolic signals such as insulin, leptin and ghrelin [71]. An increase in NPY release results in increased food intake and decreased energy expenditure. Another set of ARC neurons expresses the neuropeptide precursor POMC, which is processed to melanocortin peptides; activation of these neurons decreases food intake and increases energy expenditure [72-74]. These two populations of neurons thus exert opposite effects on energy intake and interact on several levels. The current hypothesis is that as adipose stores increase, both insulin and leptin levels increase along with POMC expression, while NPY synthesis and activity are inhibited and food intake is reduced. Conversely, when NPY synthesis and release are increased and POMC is decreased, the result is an increase in food intake [75-77]. Dysfunction of the NPY system has been implicated in obesity and T2D in humans [78, 79]

Peptidergic neurons in the ARC project to other hypothalamic nuclei such as the paraventricular nucleus (PVN), dorsomedial hypothalamus, lateral hypothalamic area (LHA), and perifornical area [80, 81]. These secondary centers process information regarding energy homeostasis. In particular, the PVN receives NPY/AgRP and POMC/METSH/CART projections and contains secondary neurons which are involved, for instance, in emotional and stress responses, which have been shown to be physiologically involved in energy homeostasis (i.e. thyrotropin releasing hormone (TRH) and corticoid releasing factor) [82]. In addition, the liver (an important integrator of nutrient metabolism) produces an endocrine satiety signal (fibroblast growth factor 21, FGF21), that suppresses the consumption of simple sugars, and reduces sweet-seeking behavior, by acting centrally at the level of the PVN [83].

Estradiol, in addition to its function as a gonadal hormone, is involved in the

regulation of metabolism through the modulation of food intake, body weight, glucose/insulin balance, body fat distribution, lipogenesis and lipolysis, and energy consumption. The central metabolic action of estradiol at the brain level occurs primarily in the ARC of the hypothalamus where it targets directly the POMC neurons and indirectly the NPY cells [84]. Estradiol represses the synthesis of NPY and AgRP and thereby has an inhibitory function on food intake [85-88]. Recent data have shown that leptin and estradiol may use a common pathway to regulate energy metabolism, namely the STAT3 pathway in POMC neurons [87, 88].

This integrated pathway between reproductive and metabolic functions is confirmed by recent findings on the role of brain kisspeptin and its receptor KISS1R (reviewed by [89]), originally identified based on their endocrine functions of regulating puberty and fertility, through actions on hypothalamic gonadotropin releasing hormone production [90]. Emerging evidence demonstrates a significant role of kisspeptin for regulating glucose homeostasis, insulin secretion, as well as food intake and body composition [91], with deficient kisspeptin signaling resulting in decreased locomotor activity and increased adiposity in a sex-dependent manner [92]. Organization and function of the kisspeptin-Kiss1R system is sex-specific, and sex steroid hormones play a crucial role in determining such sexual dimorphisms [93, 94]. The kisspeptin system is therefore a potential target of endocrine disruption; in rodent studies, exposure to EDCs altered the kisspeptin system in a region-, sex- and compound -specific manner, and induced effects on the timing of pubertal onset, estrous cycles, and socio-sexual behaviors [95-97].

3.2 Adipose Tissue

Adipose tissue is the key regulator of energy balance and nutritional homeostasis and consists of white, brown and beige fat. It is an endocrine organ with more than 20 endocrine, paracrine and autocrine secretions. The adipose tissue consists of several depots located in subcutaneous, intra-abdominal (visceral) and intra-thoracic areas. Visceral adipose tissue depots are metabolically different from subcutaneous compartments [98]. Intra-abdominal (visceral) depots are associated with T2D and cardiovascular disease while subcutaneous depots seem protective against these diseases [99].

White adipose tissue stores energy as triglyceride and also signals to other organs on the status of energy reserves via hormones, growth factors and cytokines [100]. Two major secretions of white adipose tissue are leptin and adiponectin. Leptin is secreted in proportion to fat mass; it acts on the brain to reduce food intake and increase energy expenditure. However, obese individuals typically have increased serum leptin levels due to leptin resistance [101]. Adiponectin is also secreted from adipose tissue and induces fatty acid oxidation in liver, improves pancreatic beta cell function, enhances peripheral insulin sensitivity, suppresses hepatic glucose production and reduces inflammation [102]. Adipose tissue also contains immune cells, from both the adaptive (B and T lymphocytes) or innate (macrophages) immune system thus it is an immune orgain. Obesity is considered a proinflammatory condition in which both hypertrophied adipoctyes and resident immune cells produce and release proinflammatory cytokines, including IL-6 and TNFα, which are associated with chronic low-level systemic inflammation, insulin resistance and T2D. In contrast, in non-obese individuals anti-inflammatory cytokines including adiponectin, interleukin -10, and transforming growth factor beta (TGFb) are preferentially secreted which, among other functions, improve insulin sensitivity [103].

Brown adipose tissue is present throughout life, but with highest volume in newborns. It generates body heat via non shivering thermogenesis while beige fat appears to be bifunctional, changing to either white or brown fat depending on the stimuli [104]. The sympathetic nervous system controls lipolysis in white adipose cells and stimulates the cold response in brown adipocytes.

In response to excess energy, adipocytes enlarge and/or increase in number [100]. Excess fat in these cells results in tissue dysfunction which leads to the development of other diseases and conditions including inflammation, T2D, heart disease, fatty liver, reproductive problems and some forms of cancer depending somewhat on the site of the added adipose tissue (e.g. visceral or subcutaneous) [100].

In humans, adipose tissue develops by the 14th week of gestation [105] followed by a second period of increased cellularity that continues after birth and lasts through adolescence [106]. The number of white adipocytes is usually fixed after that time [100] however adipocytes are replaced at a rate of about 10% per year in adulthood [106],

thus the tissue is not static. In mice, most subcutaneous adipogenesis occurs late in gestation and after birth; differentiation of gonadal fat only appears postnatally between birth and puberty [107]. Overall, fat mass can continue to grow due to high fat feeding which induces both hyperplasia and hypertrophy in rodents [107] with the hyperplasia occurring in the visceral tissue. Adult mice that are challenged with a high fat diet accumulate fat by hypertrophy in most adipose depots, with the exception of gonadal (visceral) fat which possesses higher capacity to expand by hyperplasia [107].

Specific genes play critical roles in fat cell development and control, including PPARγ and Runx2, often called the master regulators of fat cell differentiation [108] and sirtuins which play important roles in secretion of adipokines including leptin and adiponectin, hepatic glucose metabolism, insulin sensitivity and inflammation [109].

Adipocytes are derived from mesenchymal stem cells (MSCs), which can be neuroectodermal or mesodermal depending on where the fat body originates; differentiation of adipocytes requires a committed pre-adipocyte progenitor [110, 111]. Visceral white adipose tissue (WAT) is primarily derived from the lateral plate mesoderm [112], brown fat is largely produced by the paraxial mesoderm [113] , and cranial WAT from the neural crest [114] . Beige (a.k.a brite) fat arises from WAT (precursors or mature cells). Despite this common origin, beige fat is thermogenic, like brown fat, so it plays a different metabolic role than WAT and has a correspondingly different transcriptional program than WAT [115] [116]. Mesenchymal stem cells harvested from adipose tissue or bone marrow can be made to differentiate into fat, bone, cartilage, and other lineages in culture [117]; commitment to each of these lineages is largely mutually exclusive and irreversible [118]. Transformation of an MSC into an adipocyte requires initial commitment to the adipose lineage, followed by terminal differentiation into a mature adipocyte (reviewed in [100, 111]). Adipocyte commitment is mediated by transcription factors Zfp423 [119], Zfp467 [120], Schnurri2 [121], Tcf7l1 [111] and the mTORC1 effector S6K1 [122]. Collectively these genes function to sensitize cells to BMP2/4 signaling while inhibiting canonical Wnt signaling and promoting expression of the so-called master regulator of adipogenesis, PPARγ. Terminal differentiation is primarily controlled by PPARγ and CCAAT-enhancer-binding proteins (C/EBP) -α, -β, and -δ [123, 124] which establish a sustained feedback loop. Treatment of committed pre-adipocytes with an "adipogenic cocktail” (glucocorticoids, cAMP agonists, and

insulin) increases expression of PPARγ and C/EBP proteins and is marked by induction of metabolic genes and adipokines associated with mature adipocytes [124, 125].

3.3. Control of Glucose Homeostasis

Regulation of blood glucose within the normal range is accomplished through the concerted action of several organs: glucose absorption by the intestine, glucose-dependent secretion of insulin and glucagon from the endocrine pancreas, regulation of glucose production by the liver, and glucose uptake and metabolism by peripheral tissues. All these processes are further regulated by the neural system.

3.3.1Pancreas

The endocrine pancreas is comprised of the pancreatic islets of Langerhans, a heterogeneous population of 1000-3000 cells, where the predominant cell type is the insulin-releasing β-cell. Other cells include α-cells, responsible for glucagon secretion, and δ-cells, responsible for somatostatin release, pancreatic polypeptide-producing cells (PP-cells) and ε-cells that produce ghrelin [126, 127]. While β- and α-cell populations represent about 70-80% and 20% respectively of the total islet cell number in rodents, in humans the pancreas is comprised of 40-45% α-cells and 50% β-cells [128] and up to 10% δ-cells.

The number of β-cells rapidly expands *in utero* and in the neonatal period and then replication occurs only at very low levels in adult rodents [129] and humans [130]. β-cells replicate throughout life after physiologic challenges like high blood sugar, peripheral insulin resistance and pancreatic injury and their mass is controlled by insulin, placental lactogen and prolactin (reviewed in [131]). The liver may also control β-cell proliferation via a novel hormone, betatropin [131], which is upregulated in pregnancy and in the ob/ob and db/db diabetic mouse.

The regulation of blood glucose starts when glucose is taken up by β-cells where it undergoes intermediary metabolism. Insulin release takes place after glucose metabolism increases the ATP/ADP ratio, which closes plasma membrane ATP-sensitive K^+ (K_{ATP}) channels that are responsible for the resting membrane potential. This results in cellular depolarization and ultimately insulin release from the cell. Insulin

secreted into circulation then binds to receptors on the surface of target cells in the periphery to facilitate glucose uptake and metabolism. Impaired β-cell insulin production results in a rise in blood glucose levels that over time can lead to the development of diabetes (See figure 3). This metabolic transition can arise from frank β-cell destruction as seen in type 1 diabetes or to β-cell dysfunction arising from increased synthetic demand resulting from peripheral insulin resistance as in T2D.

Glucagon is another key glucose-regulating hormone. It is secreted by α-cells in response to falling blood glucose levels and principally stimulates the liver to increase glycogenolysis and gluconeogenesis to raise circulating blood sugar [132, 133]. When extracellular glucose concentrations rise to levels required for insulin release, glucagon release decreases [134]. Several paracrine and neural mechanisms also inhibit glucagon release [127, 135-138]. While pure hyperglucagonemia is a rare cause of diabetes, disruptions in the autoregulatory feedback loop linking insulin and glucagon secretion is thought to result in inappropriate glucagon secretion in both type 1 and T2D [139].

3.3.2 Liver

The liver is the principal location of glucose storage as glycogen, and the main source of glucose for all tissues. Because the pancreatic veins drain into the portal venous system, every hormone secreted by the pancreas must traverse the liver before entering systemic circulation. The liver is a major target for pancreatic insulin and glucagon action as well as their site of degradation. In fact, 70% of hepatic glucose output occurs via liver glycogenolysis and 30% via gluconeogenesis.

Insulin promotes glycogen synthesis and decreases its breakdown after enhancing the transcription of glucokinase and the activation of glycogen synthase through changes in its phosphorylation state. Insulin increases transcription of the glucokinase gene and other enzymes involved in glycolysis such as phosphofructokinase and pyruvate kinase, promoting glycolysis [140]. Insulin also inhibits gluconeogenesis by decreasing phosphoenolpyruvate carboxykinase (PEPCK) and fructose-1, 6-biphosphatase (FBPase) gene expression. As a result, insulin inhibits glucose production during the fed state, keeping glucose levels within the normal range. At the same time, high glucose levels inhibit glucose-6-phosphatase and decrease the

activity of glycogen phosphorylase; all together, these processes considerably reduce the conversion of glycogen to glucose.

Insulin also promotes the storage of fat by stimulating lipogenesis. It inhibits the oxidation of fatty acids by decreasing fatty acid transport into the mitochondria. Additionally, insulin stimulates fatty acid synthase (FAS). All together, these pathways promote the formation of triglycerides that can either be stored in the liver or exported as very low density-lipoproteins (VLDL).

On the other hand, glucagon signaling in the liver plays a key role during fasting, as well as in the adaptive response to hypoglycemia. After binding at its receptors, glucagon activates the cAMP/PKA pathway, which decreases glycolysis via a modulatory action on pyruvate kinase [127]. Glucagon increases gluconeogenesis after up-regulation of glucose-6-phosphatase and PEPCK through the activation of coactivators such as CREB-binding protein (CBP), P300, PGC-1 and TORC2 [134, 141-144]. In addition, glucagon also activates ketogenesis. All these effects favor hepatic release of glucose to maintain normal blood glucose levels during fasting. Glucagon also promotes the oxidation of fat in the liver, increasing the activity of the citric acid cycle and the generation of ketone bodies. Moreover, there is a glucagon-induced decrease of triglyceride, VLDL, cholesterol and fatty acid synthesis mediated by PPARα [145].

3.3.3 Skeletal muscle

Skeletal muscle is the major site of insulin-mediated glucose usage; it can clear up to 70% of the blood glucose pool. Unlike the liver, glucose transport in skeletal muscle is insulin dependent via the recruitment of the glucose transporter GLUT4 to the membrane. Insulin activation of hexokinase and glycogen synthase enhances glycogen synthesis. Activation of phosphofructokinase and pyruvate dehydrogenase enhances glucose breakdown and oxidation. The action of insulin in glucose utilization allows the muscle to store fat as triglycerides that together with glycogen can be used as sources of energy during exercise and heat generation.

3.3.4 White adipose tissue

Similar to skeletal muscle, insulin promotes recruitment of GLUT4 to the membrane and accelerates glucose transport into adipocytes. It then induces the

breakdown of glucose to generate triglycerides. These triglycerides are stored in fat together with those delivered via the circulation as chylomicrons and VLDL. In addition, insulin inhibition of triglyceride lipase decreases triglyceride breakdown. Insulin decreases lipolysis through inhibition of hormone sensitive lipase in a cAMP-dependent manner [146, 147]. Insulin promotes the synthesis of lipoprotein lipase (LPL), which is exported to the endothelial cell plasma membrane. Once anchored there, LPL cleaves triglycerides from VLDL and chylomicrons into glycerol and fatty acids that are taken up by nearby adipocytes to form triglycerides.

Although the role of glucagon in WAT is controversial, recent results point to a role in lipolysis [127]. This lipolytic action has been attributed to glucagon-induced release of fibroblast growth factor 21 (FGF21) [148] as well as to signals from the sympathetic nervous system [149].

3.3.5 Importance of Insulin Resistance

Insulin resistance is present in many cases of obesity and T2D. However, most insulin-resistant individuals do not develop hyperglycemia due to compensatory increases biosynthesis and the release of insulin as well as increases in pancreatic β-cell mass. For example, obese subjects secrete 2-5 times more insulin in response to glucose, while athletes secrete 2-5 times less insulin [150]. Insulin resistance developed during puberty and pregnancy is counteracted by adaptation of β-cell mass and function, with sex and maternal hormones playing important roles [151-155]. Insulin sensitivity, therefore, regulates β-cell function; insulin resistant subjects, whether they are obese or lean, have greater insulin response and lower insulin clearance than insulin-sensitive individuals. In order for insulin resistance to lead to T2D, β-cells adaptation must fail [156]. Regulation of β-cell mass may occur by hypertrophy of existing cells and proliferation. Glucose, non-esterified fatty acids, incretins, and neuronal signaling are involved in increasing β-cell mass and function, yet when glucose and lipids are increased for longer than normal β-cell are killed which generates the onset of T2D [157, 158].

The ability of pancreatic β-cells to integrate responses to changes in insulin sensitivity likely involves increased metabolism and metabolic signals. These include signaling molecules from adipocytes (e.g. NEFAs signaling via GPR40) as well as and

fatty acyl-CoAs that augment insulin release via the exocytotic machinery and protein kinase C (PKC). Leptin, adiponectin, and proinflammatory cytokines such as TNFα, IL-6 and monocyte chemoattractant protein (MCP-1) from macrophages and other cells infiltrating adipose tissue have a role as well [157]. Pancreatic α-cells are responsible for glucagon production and release. Thus alterations in the pancreatic α-cell function can also contribute to T2D [127]. Unlike β-cells, the mass of pancreatic α-cell does not decrease in T2D, resulting in an increased α-to-β cell ratio; this altered ratio also contributes to higher plasma levels of glucagon and therefore to hypoglycemia.

Thus, when β-cells are healthy, their adaptive responses counterbalance insulin resistance and preserve normal glucose tolerance. However, if β-cell dysfunction occurs due to genetic causes, environmental perturbations, or both, then the individual is more prone to develop impaired glucose tolerance, high fasting glucose levels, and ultimately T2D.

3.4 Liver Control of Xenobiotic and IntermediaryMetabolism

The liver is the largest and most metabolically complex organ in the human body. Hepatocytes make up over 80% of total liver mass and play a critical role in intermediary energy (lipid, carbohydrate, amino acid) and xenobiotic metabolism (Phase I-III metabolizing enzymes). Other liver-specific cell types include Kupffer cells, biliary epithelial cells, sinusoidal endothelial cells, and stellate cells. These cells have specialized functions ranging from protection against infection, bile duct flow, endocytosis and fibrosis. The liver arises from the hepatic diverticulum of the foregut during the fourth week of gestation. Hepatoblasts are bipotential progenitor cells arising from foregut endodermal cells that differentiate into hepatocytes and cholangiocytes.

The liver is the principal organ for xenobiotic detoxification. Ligand-activated xenobiotic receptors induce foreign compound metabolism by cytochrome P450s. For example, the aryl hydrocarbon receptor (AhR) induces expression of CYP1A1, the constitutive androstane receptor (CAR) induces CYP2B10, and the pregnane X receptor (PXR) induces CYP3A4. In general, chemical ligands are metabolized by the P450s that they induce. In addition to foreign compound metabolism, xenobiotic receptors play an

important role in the control of hepatic lipid and carbohydrate metabolism. It was recently proposed that activation and cross-talk of xenobiotic receptors by foreign compounds is a molecular initiating event in hepatic steatosis [159]. Likewise, interactions between environmental compounds and xenobiotic receptors regulate, in part, hepatic carbohydrate metabolism including gluconeogenesis and insulin resistance [160, 161]. These mechanisms appear to account for the wasting syndrome associated with some dioxin-like chemicals that activate the AhR [161].

Owing to its critical role in xenobiotic and intermediary metabolism, the liver is a principle target organ for chemicals resulting in the development of steatosis. Steatosis may progress to steatohepatitis (steatosis with superimposed hepatic inflammation), cirrhosis and hepatocellular carcinoma, and ultimately liver-related death if liver transplantation does not occur. In the clinic, steatohepatitis is named according to its etiology: alcohol (alcoholic steatohepatitis, ASH), cancer medications (chemotherapy associated steatohepatitis, CASH), excess dietary lipids or carbohydrates (NASH), and industrial chemicals (toxicant associated steatohepatitis, TASH) [162, 163]. While disease mechanisms vary by etiology [164], steatosis is invariable associated with an imbalance of hepatocyte lipid synthesis, oxidation, uptake, and efflux via VLDL [159].

3.5. Thyroid Control of Metabolism

The thyroid gland, located in the neck, is one of the largest endocrine glands in the body. It plays a crucial role in normal growth and development, energy homeostasis and regulation of adult metabolism. The main hormones secreted by the gland are Thyroxine (T_4), which has limited biological activity and triiodothyronine (T_3) which is more potent but with a shorter half-life. T_4 is converted to T_3 by the enzyme thyroxine 5'-deiodinase [165]. Thyroid hormones are regulated by thyroid stimulating hormone (TSH) secreted by the anterior pituitary gland, which in turn is regulated by TRH produced by the hypothalamus [166, 167].

Tight interaction exists between thyroid function, weight control, and obesity [168]. Mild differences in thyroid function can be associated with changes in body weight and fat mass [168, 169]. Even small variations in serum TSH, within the reference range of the assay, were associated with differences in body mass; higher levels of TSH were

associated with increased BMI [170-172]. There is an inverse correlation between free thyroxine (fT4) values and body mass index (BMI), even when fT4 values remain in the normal range [173, 174] .

3.6. Sexual Dimorphism and Metabolism

In humans, there are important sex differences in the incidence and health consequences of obesity; men and women differ in the patterns of fat deposition, fat mobilization, utilization of fat, and the consequences of both excess and insufficient fat stores. Gonadal hormones appear to play a crucial role in shaping such differences. Women suffer fewer obesity-related disorders than men do. In fact women are resistant to free fatty acid-induced insulin release and are therefore less prone to T2D before manopause but the prevalence of these disorders increases dramatically after menopause[175]. The prevalence of T2D is higher in men before puberty compared to reproductive age females. It is noteworthy that T1D has a male predominance as well[176]. Androgens, adiposity and disease are clearly interrelated in humans.

These asymmetries in energy balance traits probably reflect evolved adaptive differences due to differential investment and costs of reproduction in male and female mammals and are mainly shaped by gonadal hormones either during development (organizational effects) or at adulthood (activational effects) (for reviews see [177-179]). Development and maturation of brain circuits involved in the regulation of food intake and metabolism occur during the perinatal period. The current literature argues that there are multiple critical periods in which hormones organize energy balancing traits; besides the fetal and neonatal stage, the peripubertal period is also a time window when sexually dimorphic eating behaviors are established [180]. Sex differences in body fat composition and distribution, energy expenditure, orosensory physiology, taste and smell preference, food intake, binge eating, susceptibility to diet induced obesity, responses to leptin-, ghrelin,- or insulin- induced hyperphagia, POMC gene expression in the ARC nucleus, and many other traits are well documented (reviewed in: [181-183]).

The POMC, melanocortin system, is sexually dimorphic [184]. In adults, females have increased responsiveness to leptin and decreased responsiveness to insulin in comparison to males. These differences are estrogen dependent [185], and they are

perinatally organized by testosterone [186]. The NPY/AgRP circuit is also sexually dimorphic. In particular, *in situ* hybridization studies demonstrated sex differences in the distribution of NPY mRNA-containing cells in the rat ARC, and its modulation by testosterone in males [187]. Also, NPY immunoreactivity is sexually dimorphic in the ARC, the dorsomedial hypothalamus, and the PVN [188]; NPY-Y1 receptor expression is higher in females compared to males [189].

Male mice have higher levels of daily food intake, post-fast hyperphagia and leptin-induced hypophagia compared to female mice, and these behavioral differences are related to sexual dimorphisms in the ARC as far as the number of ARC cells containing NPY, AgRP, and POMC. Females perinatally treated with testosterone or DHT show male-like levels of food intake, post-fast hyperphagia and POMC gene expression and projection [186].

Estrogens play a pivotal role in regulating energy homeostasis, especially in female mammals, either by acting directly on the brain or through activation of estrogen receptors (ER) on adipocytes. Estrogens protect against increased adiposity/obesity through their effects of suppressing appetite and increasing energy expenditure; estradiol suppresses feeding by enhancing the potency of other anorectic signals (leptin, apolipoprotein, BDNF, cholecystokinin) and by decreasing the potency of orexigenic signals such as ghrelin and melanin concentrating hormone [87, 185, 190, 191]. The liver is a major target for estrogen action in female mammals and the activity of the liver ERα is strictly associated with ovarian activity [192]. In the liver, ERα regulates fertility in response to protein consumption and controls lipid and cholesterol synthesis in relation to the reproductive cycle [193] . Since the liver is the major organ for the control of energy homeostasis, the activity of hepatic ERα also influences the synthesis and secretion of the signaling molecules necessary for coordinated responses among liver, fat, muscles and brain [192].

In mammals, including humans, the liver is a sexually dimorphic organ and exhibits major differences in the profile of steroid, lipid, foreign compound metabolism [194], and gene expression. These differentially expressed genes regulate a wide range of biological processes; accordingly, many enzymes, such as steroid hydroxylases belonging to the cytochrome P450 (CYP) superfamily, are expressed in the liver in

unique, sexually biased patterns [195]. Such differences have implications for sex-related steroid metabolism, xenobiotic metabolism and pharmacokinetics, and differential susceptibility to some liver diseases [23, 196]. The sexual dimorphism of liver gene expression is established and maintained, in part, by the temporal pattern of pituitary GH secretion, which is sex specific in many species (episodic in males and more stable in females) [197]. GH secretion is affected by brain and lactotrope dopamine 2 receptors (D2Rs) [198]. A link exists between obesity, growth, and dopaminergic systems located within the central nervous system and in other tissues [199-201].

4. Environmental Contributions to Obesity, T2D, and Dyslipidemia

The global pandemic of obesity, T2D and MetS is often causally linked to marked changes in diet and lifestyle, namely increases in dietary intake of high energy diets and concomitant reduction in physical activity levels [202]. However, it is clear that the susceptibility to these diseases is not that simple. Indeed there have been multiple environmental factors that have been linked to the increase in these metabolic diseases including stress, lack of sleep, adenoviruses, childhood antibiotics [202-205] and exposure to environmental chemicals [206] . While all of these environmental stressors likely play some role in the epidemic of metabolic diseases, we focus here on exposure to environmental chemicals, especially EDCs and the role they might play in disease etiology. Indeed the current rise in metabolic diseases correlates with substantial increases in environmental chemical production and exposures over the past four decades [207-209].

4.1 Overview of Endocrine Disrupting Chemicals

In 2012, the Endocrine Society defined EDCs as “an exogenous chemical, or mixture of chemicals, that can interfere with any aspect of hormone action” [210]. This definition is a more simplified version of the one originally proposed by the US EPA, that EDCs are “an exogenous agent that interferes with the production, release, transport, metabolism, binding, action, or elimination of natural hormones in the body responsible for the maintenance of homeostasis and the regulation of developmental processes”

[211]. At the global level, the WHO/UNEP definition of EDCs is “an exogenous substance or mixture that alters the function(s) of the endocrine system and consequently causes adverse effects in intact organism, or its progeny or (sub) population [212]. Although EDCs were first identified as agonists or antagonists of estrogen, androgen and thyroid hormone receptors [213], EDCs disrupt hormonal signaling systems by interfering with a variety of hormones through numerous mechanisms. EDCs can disrupt normal hormone levels by inhibiting or stimulating the production and metabolism of hormones, or changing the way hormones are transported to target tissues.

The effects of EDCs, like those of hormones, can occur at very low levels [214-217]. Other principles of hormone action are similarly expected for EDCs including their ability to induce tissue- and time-dependent effects and strong evidence that responses to EDCs can be non-monotonic (often referred to as biphasic or U-shaped responses) [5, 210, 215, 218, 219]. Some EDCs are persistent and can bioaccumulate in tissues [220, 221]. With more than 85,000 registered chemicals in commerce, most of which are poorly studied; current estimates have identified approximately 1000 chemicals that meet the criteria of an EDC [213, 222].

Decades of work from both basic and clinical endocrinology have revealed that the disruption of hormones can have detrimental effects on a variety of diseases [223] [223-225]. A number of recent “state of science” reviews of the EDC literature, as well as large reviews of hundreds or thousands of EDC studies, draw strong conclusions about the association between EDC exposures and diseases [210, 215, 218, 223, 226-229]. These conclusions are drawn from observational human epidemiology studies and controlled laboratory animal studies, as well as additional support from wildlife studies, *in vitro* mechanistic studies, and *in silico* studies. In 2015, a review of the EDC literature by scientists in the Endocrine Society found that there was strong evidence for a role of EDCs in the etiology of metabolic diseases, although these diseases were generally examined individually [230]. Some of these conclusions were challenged, with groups contesting the strength of evidence linking EDC exposures to endocrine-related diseases [231-236]. However, whereas some useful criticisms were put forward, these challenges typically resulted from a lack of understanding of the endocrine system, as well as of endocrine disruption as an effect on a complex regulatory network of the

organism [219, 237-242]. On the contrary, the need to fully appreciate the impact of EDCs is apparent considering the health care costs associated with inaction [9, 229].

A number of relevant factors can influence whether significant effects are observed in experimental studies of EDCs and these factors can affect the strength of the evidence for an effect. First, measurement of body weight alone is now recognized to be an inadequate measure in experimental rodent studies to assess the effects of chemical exposure on adipocyte endpoints [243]. Second, the endocrine milieu of males and females is different, and thus it should be expected that sex-specific effects are often observed because of EDC exposure, particularly for compounds that interfere with sex hormones. Third, the specific type of feed used in animal experiments can affect sex hormone levels in pregnant females and fetuses, and consequently result in significant differences in phenotype, including the potential to modify effects of chemical exposures [244, 245]. Indeed, natural diet components and EDCs may interact in several ways [246] .

One relevant challenge concerns the publication of apparently “conflicting” results on EDCs. Independent replication of results is the accepted standard for assessing validity of findings in research, thus the issue of non-replication of findings in some EDC studies must take into account the issues described above (sensitivity of endpoint, sex-specific effects, influence of animal feed), as well as the appropriate use of positive controls [247-249], [249, 250], and /or negative control groups [251, 252], and the range of dose levels used [219, 253]. There also appears to be a relationship between the source of funding and the likelihood of identifying effects of EDCs [238, 249, 254]. Thus, rather than labelling results as “conflicting” the factors involved in the apparent failure to replicate certain findings should be assessed [247, 255].

4.2 EDC Exposures: Sources & Routes

As noted above, approximately 1000 chemicals have been identified that meet the criteria of an EDC [213, 222]. These compounds are used in a wide range of consumer products including food packaging, building materials, pesticides, clothing and upholstery, personal care products, detergents and other cleaning agents, thermal paper, plastics and medical equipment [210, 215, 227, 228, 256, 257]. Some chemicals used in industrial processes lead to unintended contamination of food, water and air.

Thus, routes of exposure can include oral, dermal, and inhalation, as well as subcutaneous and intravenous (via medical equipment).

The US CDC's National Health and Nutrition Examination Survey (NHANES) is a nationally representative biomonitoring program which assesses, among other things, exposures to environmental chemicals in the general population [258].The CDC has documented widespread exposures to a number of EDCs (e.g. [259-264]). Importantly, a large number of chemicals are not examined, and thus the number of exposed individuals, as well as the typical levels of exposure, remains unknown. Although the sampling of infants and young children is limited in the context of NHANES [265], other studies have revealed the presence of environmental chemicals in placenta, amniotic fluid and umbilical cord blood, documenting exposure throughout the most critical stages of development as well as across the lifespan (e.g. [266-272]).

4.3 Vulnerable Windows of Exposure and Metabolic Disorders

4.3.1 Gestation and neonatal development

The concept that adult diseases could have a fetal basis was highlighted by the work of David Barker who proposed a hypothesis, which was expanded to the Fetal Basis of Adult Disease and has now been restated as the Developmental Origins of Health and Disease (DOHaD) hypothesis [273] [274] [275]. The core DOHaD hypothesis is that there are critical windows during development, and environmental disruptions during these life stages can lead to subtle changes in gene expression, tissue organization, or other levels of biological organization that lead to permanent dysfunction leading to increased susceptibility to disease. Unlike birth defects and neonatal diseases, these dysfunctions manifest later in life mostly as increased vulnerability to common diseases including obesity [276-278]. Barker and others showed that low birth weight (LBW) babies resulting from maternal malnutrition developed increased susceptibility to diseases in adult life including coronary heart disease, obesity, stroke, T2D, osteoporosis, increased blood pressure, dyslipidemia, impaired glucose metabolism and metabolic dysfunction (reviewed in [274, 279].

Barker's focus on nutrition was preceded by the iatrogenic event involving the prescription of diethylstilbestrol (DES) to millions of women from the 1940s through the early 1970s to prevent miscarriage. Not only was DES shown to be ineffective, it

increased the incidence of a rare cervical cancer. Animal studies confirmed it is a transplacental carcinogen and the effects, including other deformities of the reproductive tract and increased incidence of mammary cancer, shown to result from developmental exposure in animal models, have now been confirmed in human studies. The DES tragedy remains one of the best examples of the long-latency adverse health outcomes associated with fetal endocrine disruption and was a clear example of DOHaD, with adverse health outcomes associated with the alteration of normal endocrine function during development [280, 281].

The observation that alternations in human development affects the risk of non-communicable diseases later in life is confirmed by epidemiology studies focusing on both nutrition and environmental chemical exposures [277, 282-284]. Developing organisms are extremely sensitive to perturbation by chemicals including EDCs because hormones and growth factors control development. Alterations of their levels during development by EDCs leads to tissues with abnormal gene expression, numbers of cells, location of cells, imbalance between cell types, as well as altered organ structure and hormonal signaling that lead to increased susceptibility to disease/dysfunctions across the life course [282, 285]. Adverse effects may be most pronounced in the developing organism and occur at concentrations of the chemical that are far below levels that would be considered harmful in the adult [286, 287]. Some of the reasons for this increased sensitivity include the fact that the protective mechanisms that are available to the adult, such as DNA repair mechanisms, a competent immune system, detoxifying enzymes, liver metabolism, and the blood/brain barrier are not fully functional in the fetus or newborn. In addition, the developing organism has an increased metabolic rate as compared to an adult, which, in some cases, may result in increased toxicity [287].

Another critically important reason for the increased sensitivity of the developmental period to EDCs (as well as nutritional deficits) is that epigenetic signaling regulates gene expression which controls development. Epigenetic changes provide biochemical evidence of the deleterious effects of adverse conditions during development and subsequent disease including metabolic diseases [288]. Some aspects of epigenetic signaling (e.g.DNA methylation, histone marks, chromatin remodeling and noncoding RNAs) are likely involved in the mechanisms responsible for

altered programming of tissue development by EDCs that lead to obesity [289-291]. Since hormones and growth factors control development, signaling errors caused by hormones expressed at the wrong time or concentration can cause alterations in gene expression in tissues, and these abnormal expression patterns become permanent due to epigenetic signaling [291-293].

There are now credible data that supporting the claim that many chronic diseases including obesity, T2D and MetS can be linked to epigenetic changes in cells and tissues during development that manifest in altered tissue development as a result of early environmental factors (stress, drugs, nutrition, environmental chemicals) [294-296]. Extensive data from animal and human studies show that developmentally induced disease outcomes often are not immediately apparent but manifest later in life [278, 297, 298].

There are now data that show that environmental factors can account for disruption of individual or multiple systems involved in metabolism depending on the timing of exposure. For example, exposure to a chemical during the fetal or perinatal period can permanently alter the functioning of mesenchymal stem cells and lead to disruption of adipocyte function [299]. Altered adipocyte function is likely to affect other organs/tissues due to hormonal and paracrine action. This brief chemical exposure might also impact differentiation of the pancreas, heart, brain, liver or any other component of the complex regulatory system impacting the various components of metabolic disease [276].

4.4 Obesogen Hypothesis Overview (historical)

In 2002, Baille-Hamilton wrote the first article relating environmental chemicals to obesity. Her article, “Chemical toxins: a hypothesis to explain the global obesity epidemic”, suggested that the current obesity epidemic was associated with the increase in production of environmental chemicals [300]. She reviewed published studies showing associations between exposure to a variety of environmental chemicals, including some pesticides, solvents, plastics, flame retardants and heavy metals, and increased weight gain; because these studies originally focused on weight loss and toxicity, their effects on weight gain had gone unnoticed. In 2006, Grun and Blumberg, published their now classic paper, in which they coined the term “obesogen” followed by a 2009 review

"Endocrine disruptors as obesogens" [301]. They noted the existence of chemicals that alter regulation of energy balance to favor weight gain and obesity and proposed that obesogens derail the homeostatic and reward mechanisms important for weight control, such that exposed individuals have increased susceptibility to weight gain despite normal diet and exercise.

The obesogen hypothesis makes two important points. First, susceptibility to obesity starts during development (*in utero* and the first few years of life). Second, susceptibility to obesity is due in part to the influence of a specific subclass of EDCs that alter developmental programming, and thus disrupt the set point for weight gain later in life.

"Obesogens" are defined functionally as chemicals that promote obesity by increasing the number of fat cells and/or the storage of fat in existing adipocytes. Obesogens can also act indirectly to promote obesity by shifting energy balance to favor calorie storage, by altering basal metabolic rate, by altering gut microbiota to promote food storage [302], and by altering hormonal control of appetite and satiety [303-307]. New obesogenic chemicals are being identified at an increasing rate. The obesogen field has recently expanded to include chemicals that cause or lead to diabetes [308] as well as altered lipid metabolism and fatty liver [309].

4.5 The Metabolism Disrupting Chemical (MDC) Hypothesis

In 2015 the Parma Consensus Statement proposed that the Obesogen hypothesis should be expanded, considering newer evidence of chemicals that increased susceptibility to T2D, liver lipid abnormalities and MetS [310]. The Parma Statement proposed a name change to 'metabolic disruptor hypothesis', which we further propose should be termed 'metabolism disrupting chemical (MDC) hypothesis' to distinguish the role of chemicals from other metabolic disruptors such as nutrition and stress. The MDC hypothesis postulates that environmental chemicals have the ability to promote metabolic changes that can result in obesity, T2D or fatty liver in animals including humans; these metabolic alterations may play an important role in the global epidemics of obesity, T2D and MetS. In the study of liver disease etiology, the MDC hypothesis provides, for the first time, a framework for the integration of different etiology of steatohepatitis (ASH, CASH, NASH, and TASH). Alcohol, chemotherapeutic

medications, fructose, dietary fatty acids, and industrial chemicals are all MDCs; while they disrupt hepatic metabolism differently the pathologic end result is the same [162, 163].

For the remainder of this manuscript we will focus on MDCs as chemicals that can alter any aspect of metabolism and describe the current state of the science.

5. MDCs and Metabolism-Relevant Diseases

5.1 Adipogenesis, Subsequent Weight Gain and Obesity

A number of MDCs have been shown to significantly alter the function (gene expression, hormone secretion) of white adipose tissue, adipose tissue mass (adipocyte number and/or volume), or body weight in animal models after developmental exposures (Figure 2). Epidemiological studies also support the identification of obesogenic MDCs [311, 312] and these studies focus mainly on weight gain and (body mass index) BMI as endpoints. This is typical for a new field, where the focus is on descriptive studies that show that a chemical can have an effect on an endpoint or disease of interest (e.g. weight gain). In many cases, effects of MDCs on adult adiposity and/or body weight are reported to be significant for only one sex, consistent with the sexually dimorphic responses that are a common feature of EDCs and thus MDCs [227].

Nicotine is an MDC where there are compelling data for its obesogenic properties from both animals and human studies [7, 313, 314]. Maternal smoking in pregnancy is a risk factor for subsequent obesity in offspring [315] even when exposure is limited only to early pregnancy [316, 317]. Although multiple mechanisms have been proposed, associations may be partly attributable to impaired fetal growth, which as Barker and colleagues noted is a risk factor for subsequent rapid growth and long-term obesity [318].

Developmental exposure in mice to DES [319] has also been shown to increase weight gain which is specific to females and does not appear until puberty [320]. In another study, prenatal exposure to DES resulted in an increase in number of adipocytes in the gonadal fat pad of male mice[321]. Two epidemiological studies also link DES exposure to obesity; prenatal exposure to DES is associated with an increased

likelihood of childhood obesity at age 7y [322] and increased risk of adult obesity in women that was most evident at lower doses [323].

Bisphenol A (BPA) [324-326], a chemical used to make polycarbonate plastic, epoxy resins that line food and beverage cans, and as a developer in cash register receipts has been shown to increase weight gain and body fat after developmental exposure in rats [327-329] and mice [321, 330-332]. Some studies have not shown effects of BPA on weight gain [333, 334] including government standardized study designs e.g. guideline studies, [335, 336]. The two guideline studies with CD-SD rats,which appear to be relatively insensitive to xenoestrogens [337], showed no significant effects for any outcome measure. Also in one mouse study reporting no significant effect of BPA on body fat[333], the control animals were obese due to the use of casein-based feed, which increases body fat in CD-1 mice [338, 339] . These studies differ with regard to several aspects including animal strain, doses, developmental windows, and diet which are likely responsible for the discordant results (reviewed in [340]). Also a distinction needs to be made between studies that only measured body weight (for example [331]) which is recognized to be a poor indicator of significant changes in body fat in rodents [7] and studies that actually measured body fat.

Human studies have shown that prenatal exposure to BPA was associated with increased body fat at age 7 [341] or BMI by age 9 [342] or accelerated postnatal growth without a change in BMI between age 2-5 [343] consistent with the DOHaD prediction that light at birth babies would experience increased rate of growth in childhood[14, 344]. Not all epidemiology studies report a positive relationship between an exposure and a health outcome [342, 343, 345-347] which is not uncommon for studies linking environmental chemicals with adverse outcomes in humans, possibly due to potential for multiple environmental “stressors” to interact with chemical exposures [345, 348, 349]. Because of considerable within-person variability [350-353] and because most studies typically have only one sample to characterize exposure, BPA exposures may have been substantially misclassified and peak exposures, which generally occur in the evening, may have been underestimated [351]; these misclassifications may have increased the likelihood of a false negative outcome. Stronger attention is also needed for potential confounding by diet, which is only one source of BPA exposure [257, 354]. Moreover, since the developing organism is more

susceptible to BPA effects, epidemiology studies must consider the lifestage when exposure is measured. The inconsistencies in the data notwithstanding, there are data from both animal and human studies that support the hypothesis that developmental exposure to BPA can lead to an increase in weight gain later in life in exposed offspring.

Phthalates are a class of chemicals that promote flexibility in plastic products such as tubing and vinyl flooring. Fragrances and a variety of household and personal care products including food packaging also contain a variety of phthalates. Phthalate metabolites have been shown to activate PPAR receptors and have antiandrogenic effects which may contribute to the development of obesity [355]. Prenatal exposure of mice to one phthalate, DEHP, results in increased body weight as well as increased body fat in male offspring; similar findings were reported in studies from different labs using different animal models [356-359]. Epidemiologic data linking prenatal phthalate exposures to obesity are limited and mixed [360-364]. Although daily exposure measurements are less variable than BPA, phthalates are also prone to exposure misclassifications. One recent study found evidence of a sex-specific effect, with high molecular weight phthalates — including DEHP — associated with reduced BMI z-scores among boys, but increased BMI z-scores among girls from Spain [362]. DEHP metabolites were associated with lower BMI z-scores in ethnically diverse boys from a US cohort [360], and in children of both sexes in another [361]. However, high molecular weight phthalates were associated with higher BMI z-scores in US children of Mexican American and African American descent, though not in Whites [365]. Phthalate exposure during pregnancy was also associated with increased triglyceride levels in cord blood and with increased body mass three months after birth in boys [366]. While more data are needed, these data support the conclusion that developmental exposure to DEHP and perhaps other phthalates, depending on their molecular weight, can lead to increased weight gain in animal and human studies.

Tributyltin (TBT) [367, 368] is an organotin used as a fungicide; it is a retinoic acid X receptor and PPARγ agonist. Several laboratories have shown that TBT stimulates adipogenesis in preadipoctyes in vitro [369-371] [372]. Prenatal exposure to TBT results in increased lipid accumulation, increased adipose tissue mass (due to both adipocyte hyperplasia and hypertrophy), and reduced muscle mass that persists into adulthood and across generations in mouse models [309, 367] and increased adiposity

in zebrafish [373]. A recent study explored organotins and weight gain in humans for the first time, finding placental TBT to be associated with a non-significant trend towards higher weight gain, but only in the first three months of life [374]. These limited data in humans warrant further investigation, whereas the animal data strongly support the notion that TBT exposure during development may play a role in the obesity epidemic.

Polycyclic aromatic hydrocarbons (PAHs) are a family of environmental chemicals that are byproducts of fossil fuel burning which includes diesel exhaust, air pollution and cigarette smoke [206]. Prenatal exposure to a nebulized PAH mixture 5 days a week for three weeks led to increased weight, fat mass and higher gene expression of PPARγ, fatty acid synthase and adiponectin in mice[375]. Developmental exposure in rats to PAHs in diesel exhaust have been shown to lead to increased obesity, insulin resistance and inflammation; these effects were observed only in adults fed a high fat diet, indicating a second hit was needed, and only in males, indicating a sexually dimorphic effect [376, 377]. Specific exposure to benzo (a) pyrene during development also resulted in increased visceral adipose tissue weight in female offspring [378].The use of different model systems and exposures limits our ability to determine the importance of PAHs as an important contributor to obesity. There are limited human data on the association of childhood obesity with maternal exposure to ambient PAHs, however a study by Rundle and colleagues [379] shows children born to mothers with the highest PAH exposures during pregnancy had higher body weights both at 5 and 7 years of age. The extensive exposure of populations to air pollution necessitates a further examination of its overall effects and its specific contribution to increased risk of obesity.

The most consistent human evidence that prenatal MDC exposure is associated with obesity in offspring is for several organochlorine compounds: the in vivo metabolites of DDT (DDE), as well as hexachlorobenzene (HCB) [311, 312, 380, 381]. Persistent organic pollutants (POPs) are a class of chemicals that bioaccumulate in tissues and magnify in the food chain [382]. They include some pesticides (DDT, HCB) and some industrial chemicals such as polychlorinated biphenols (PCBs). While the use of these chemicals is banned in many countries (PCBs, HCB and DDT) exposures exist due to their persistence in the environment. In some countries like South Africa DDT is still used thus current exposure also exists. Exposure during early gestation to some

POPs, namely PCBs, HCB and DDT, can lead to the development of obesity later in life [383] [312, 381, 384-388]. In rodent studies, prenatal exposure to DDT followed by a high fat diet for 12 weeks in adulthood led to the development of glucose intolerance, hyperinsulinemia, dyslipidemia and altered bile acid metabolism as well as reduced energy expenditure and impaired thermogenesis as measured by reductions in core temperature in female offspring [389]. Six separate epidemiology studies showed that prenatal DDE exposures were associated with increased BMI in the offspring at ages 1 and 3 [390], at age 4 [381] and between ages 5-7[384] [384], as well as increased overweight at age 6.5 [386], 7 years [380], and age 9 [391]. Prenatal exposure to HCB has been associated with rapid growth in the first 6 months of life and obesity in infancy and childhood [383, 392]. Similarly, prenatal exposure to specific PCB congeners resulted in increased BMI at 14 months [387], at 1 and 3 yrs. of age [390], and age 5 and 7 [393].

Effects of several POPs on growth may be sex-specific. For example, some associations between PCBs and measures of general or central obesity are specific to girls [384, 386, 394] while the weight gain due to DDT/DDE occurred in boys or girls depending on the cohort and conditions of the study. In addition, it remains uncertain to what extent the effects of these chemicals on long-term growth may be due to indirect effects, dependent on the mismatch between a prenatal environment that can program offspring to survive in an environment that inhibits growth and the energy-dense diets available in the postnatal environment. Many POPs for which prenatal exposure is associated with obesity are also associated with smaller size at birth [385], and thus associations with obesity may be, at least in part, related to rapid postnatal growth in these children, similar to that observed in offspring of smokers and malnourished infants [316, 387, 388, 395]. In contrast to the human data, there is a paucity of animal data on the role of POPs on obesity; this area requires future study.

Data are limited, and sometimes inconsistent, for associations between obesity and a number of chemicals in humans [312] and animals [206]. For example, prenatal exposure to perfluorinated compounds, chemicals used to repel grease stains in carpets and clothing, was not associated with subsequent adiposity in childhood [396] in a recent study, though a prior study found such an association at age 20y [397]. Similarly, in animal models, one study found *in utero* exposure to perfluorooctanoic acid

(PFOA) led to weight gain in offspring in outbred CD-1 mice [398] whereas another inbred transgenic mouse model did not show any weight gain [399]. The animal [400] and epidemiological data on obesogenic effects of prenatal exposure to arsenic [401, 402] while limited are consistent across species. Cd, Pb and As exposures are associated with smaller size at birth [403-406] which is a risk factor for subsequent weight gain and greater adiposity. Prenatal exposure to toxic metals is also related to higher leptin at birth [407, 408]. Similarly, limited but consistent data suggest obesity-related effects of exposures to various flame retardants *in utero* in humans with some indication of sex-specific effects [409]. Developmental exposure of rats to Firemaster 550, a flame retardant mixture, was associated with weight gain later in life [410].

Taken together, these observations support the relevance of the MDC hypothesis with respect to weight gain in animal and human studies.

5.2 MDCs and Fat Cell Differentiation and Development

Preadipocytes such as 3T3-L1 cells are often used as models to test the ability of chemicals to induce adipogenesis. A recent study used 3T3-L1 cells and MSCs to evaluate the effects of a collection of chemicals on adipogenesis and adipogenic gene expression [411]. This study found that several pesticides with different chemical structures and modes of action, zoxamide, spirodiclofen, quinoxyfen, fludioxonil, tebupirimfos, forchlorfenuron, flusilazole, acetamaprid, and pymetrozine all induced adipogenesis and adipogenic gene expression in 3T3-L1 preadipocytes, whereas quinoxyfen and fludioxonil were also able to induce adipogenesis and adipogenic gene expression in MSCs [411, 412] (Figure 2). Dioxins and PCBs acting via the AhR alter the expression of important genes related to adipogenesis, lipid metabolism and inflammatory factors [413-417]. Activation of PPARγ via exogenous ligands such as rosiglitazone or TBT strongly promotes adipocyte differentiation and maintenance, together with the expression of genes involved in lipid droplet formation, glucose uptake, fatty acid synthesis, and adipokine secretion [418] [419]. Other studies have identified BPA [132, 420, 421], bisphenol A diglycidyl ether [422], aklylphenols [423], phthalates [356, 357, 372, 424, 425] and flame retardants [372, 424, 426, 427] as well as organochlorine [428, 429] and neonicotinoid pesticides [430] as chemicals that can promote adipocyte differentiation.

In addition to differentiation of cell lines to adipocytes, it is also possible to regulate the fate of MSC to result in increased numbers of fat cells. Because multiple signaling pathways converge to regulate MSC fate, there are numerous opportunities for extrinsic factors to disrupt or modify differentiation. For example, the pesticides chlorpyrifos and carbofuran inhibited the ability of MSCs to differentiate into bone [431] although the potential to differentiate into fat was not tested. Treatment with the organotin TBT or the pharmaceutical rosiglitazone (ROSI) led to adipogenic differentiation of 3T3-L1 preadipocytes and MSCs in vitro [432, 433] in a PPARγ-dependent manner [434]. The fungicides triflumizole [357] and tolyfluanid [434] also promoted adipocyte differentiation and gene expression in MSCs and 3T3-L1 cells. Prenatal exposure of pregnant mice to TBT or ROSI led to increased fat deposition at birth [367]. These exposures also diverted MSCs toward the adipogenic lineage at the expense of the osteogenic lineage [432]. Although adipogenesis and obesity have been the most studied outcome of exposure to obesogens and MDCs, it should be obvious that the bipotential switch between the adiopogenic and osteogenic lineages opens an entirely new field for the effects of MDCs on bone development and osteoporosis.

It is clear that chemicals can alter MSC lineage allocation in animal models; however, there are no studies that examine MSC lineage commitment in obese verses lean individuals. Nonetheless, it is worth focusing on the potential consequences of chemicals altering MSC lineage in humans. Obese individuals definitely have more fat cells than individuals of normal weight [106]. It is likely that obese individuals either were born with more fat cells because of prenatal programming or developed them early in life by mechanisms outlined above. It is probable that adipogenic stimuli (such as exposure to chemical obesogens or inappropriate diet) received perinatally or during adolescence permanently increased fat cell number. In turn, this creates an altered metabolic set-point that favors the storage of calories as fat. Once fat cell number is programmed, the number cannot be altered readily by diet, exercise, or even surgery [106]; many studies have documented the expansion of visceral fat depots in adults via increased adipocyte number [107, 435, 436] whereas permanent decreases in cell number accompanied by weight loss have not been documented. It is possible to successfully shrink the size of existing fat cells by faithful adherence to a restrictive diet and a vigorous exercise regimen. However, clinical studies repeatedly show that 83-87% of people who achieve significant weight loss regain the weight within a few years [437,

438]. These data strongly suggest that obese individuals have altered metabolic set-points that favor calorie storage over the long term.

There is no evidence that lipid-depleted fat cells automatically undergo apoptosis. Indeed, it is difficult to envision how such a scenario would be favored over evolutionary time since healthy fat cells would be required for the organism to survive periods of fasting that regularly occur in hunter-gatherer societies. Moreover, expression of the satiety hormone, leptin closely parallels fat mass and small fat cells secrete the least leptin making it likely that shrunken fat cells would "crave to be filled" [439].

5.3 MDCs and Neuroendocrine Control of Feeding and Metabolism

Only a few studies have investigated the action of potential MDCs on neural circuits/cells and on the resulting feeding behavior and energy balance output. However, the neuroendocrine control of these features could be an important target of environmental chemicals.

Prenatal exposure to low doses of BPA alters the development of the POMC system in a sexually differentiated way [440]. The differences are evident when adult are exposed to a high-fat diet; in particular, males show reduced POMC fiber innervation of the PVN and increased NPY and AGRP expression in the ARC. Females exposed to BPA show reduced POMC expression and ERα expression patterns in the ARC similar to those seen in males, suggesting a masculinizing effect of BPA. Also, fetal exposure to BPA in mice alters food intake during puberty and in adulthood as well as leptin and insulin levels, which in turn regulate the NPY system[321].

Organotin compounds such as TBT have not only peripheral effects, but also may activate elements in the brain, in particular in a crucial region for the regulation of food intake, the ARC [441] . Adult mice exposed to TBT for 4 weeks show profound alterations of the leptin-NPY-NPY-Y1 receptor system [96, 188]. Prenatal exposure to TBT also induces hypothyroidism in the progeny, while the acute treatment of pregnant females induces a dose-dependent increase of T3-independent TRH transcription levels [442] in the hypothalamus.

In summary, there are a number of important endpoints to study the effects of

MDCs on the regulation of food intake and metabolism in the central nervous system. These include expression of the leptin receptor, ERα, thyroid hormone receptor (associated also with PPARy), the POMC-CART system, the NPY-AGRP system and their receptor systems, and the dopaminergic system.

5.4 Sexually dimorphic effects

Because by definition they interfere with hormonal actions, sex specific effects are expected for many MDCs. A critical aspect regarding research on sex differences related to metabolic disease is that until recently, the majority of biomedical studies have focused only on males. With regard to the impact of MDCs on adipocity and metabolism, it is well known that females differ dramatically from males in subcutaneous fat deposition as well as in the endocrine function of adipocytes. For example, females have higher circulating concentrations of both leptin and adiponectin relative to males {Mauvais-Jarvis, 2015 #2079} Thus, while not all studies that examined a few outcomes of exposure in males and females report sex differences, one would expect on detailed examination to find sex differences. In this regard, some studies have demonstrated that MDCs can masculinize or feminize energy balancing traits depending upon type and dose of the tested chemical, the timing of exposure and the metabolic challenge. In experimental animals, sex-dependent differences in body weight in response to prenatal or early postnatal exposure to low doses of BPA or DES have been reported; both chemicals increased body weight in female rodents but decreased or did not affect it in males [328, 443]. A recent study has examined in detail the energy balance traits of mice prenatally exposed either to a low or a high dose of BPA or to DES showing that exposure to BPA but not to DES hypermasculinized male and masculinized female mice (see also [440]). In addition, exposure to MDCs can diminish, eliminate, reverse or widen sex differences in behavior, thus interfering with normal sexual differentiation of the brain [444-447] which can also affect metabolic processes. For example, numerous studies have confirmed the ability of BPA to affect the rodent developing brain in a sex-specific manner (for review see [448] even at very low doses [449, 450], indicating that the brain is a very sensitive target organ for BPA action. The cerebral cortex, hippocampus and hypothalamus are key sexually dimorphic regions in the rodent brain, and these brain areas can be affected by pre- and perinatal MDC exposure, with sex specific effects observable even before the increase in gonadal hormones during puberty. The developing hypothalamus has sex-specific vulnerability to BPA, with the preoptic area

(POA) and mediobasal hypothalamus (MBH) being the most studied and robustly affected [97, 451].

5.5 Type 2 Diabetes (T2D)

Evidence that chemicals can disrupt the function of the endocrine pancreas dates to the early 1940s when alloxan, a glucose analogue which selectively destroys insulin producing cells in the pancreas, was shown to promote type 1 diabetes in rabbits [452]. This was followed by the discovery that streptozotocin similarly induced a diabetic state through selective β-cell destruction. Although humans are not exposed to alloxan or sreptozotocin, they are used in animal research on diabetes. Initial human evidence that synthetic chemicals promote the development of diabetes came from patients accidentally or intentionally exposed to pyrinuron (Vacor) [453]. Exposure to this rodenticide resulted in β-cell destruction and the development of type 1 diabetes [454]. More recently, a patient exposed to high levels of the fungicide chlorothalonil was reported to develop diabetic ketoacidosis, a condition arising from insulin deficiency [455]. These and other studies of environmental contaminants provide mechanistic insights into the pathways by which MDCs may promote diabetes pathogenesis through defects in β-cell physiology.

5.5.1 MDCs and Beta Cell Survival and Function

5.5.1.1 Cellular Studies

A structurally diverse array of synthetic and inorganic toxicants disrupts β-cell survival and function in cell lines and isolated rodent islets. 2,3,7,8-tetrachlorodibenzodioxin (TCDD) reduces glucose-stimulated insulin secretion (GSIS) in isolated islets [415, 456, 457]. Similarly, DDT impairs both GSIS as well as insulin secretion in response to tolbutamide (a pharmacological insulin secretagogue) [458]. Among organotin compounds, triphenyltin was shown to disrupt cellular signaling in β-cells and impair insulin secretion in response to a variety of stimuli [459]. Similarly, inorganic contaminants including both inorganic and methylated arsenic [460-462], cadmium [463-465], and mercury [466] disrupt β-cell function (Figure 2).

Interestingly, several compounds disrupt β-cell signaling and function in a manner that promotes insulin release. In the RINm5F cell line, a PCB mixture (Aroclor

1254) increased insulin secretion into the culture media, an effect recapitulated by coplanar PCB congeners [467]; TCDD also promotes continuous insulin release [468]. Interestingly, the insulin secretory effect resulted in a depletion of cellular insulin content by PCBs [467] and TCDD was proposed to promote β-cell "exhaustion" [468]. This suggests that prolonged exposure to these compounds could result in insulin deficiency.

BPA has been shown to augment GSIS; unlike TCDD and PCBs, low doses of BPA augmented β-cell insulin content in an ERα dependent manner [469]. A rapid action on insulin release was shown to be dependent on ERβ expression, and was confirmed in human as well as mouse islets [470, 471]. Importantly, these effects of BPA may be representative of effects of other phenolic compounds because nonylphenol and octylphenol were also shown to augment GSIS in isolated rat islets [472].

In contrast to the extensive work examining MDC effects on β-cell physiology, less is known about the effects of environmental pollutants on α-cell biology. In early studies, cobalt was shown to be toxic to α-cells [473]. More recently, BPA has been shown to alter calcium signaling in α-cells [474]. Collectively, these data support the theory that the endocrine pancreas is an important target for the deleterious effects of MDCs on energy homeostasis.

5.5.1.2 Animal studies: Exposures During Adulthood

The strength of evidence supporting environmental toxicants altering β-cell physiology is reinforced by animal studies that examine the effects of whole-body exposure to a variety of MDCs on insulin secretion and glucose homeostasis. Although the focus of this review is on developmental exposure, in the case of MDCs exposures and T2D, it is important to also mention adult studies. These studies demonstrate a direct induction of insulin resistance without the need for an increase in weight or adiposity.

Adult mice exposed to TCDD exhibited reduced glucose-stimulated insulin release without concomitant hyperglycemia, an effect that was absent in AhR-null mice [456]. Furthermore, TCDD-exposed rats had islets depleted of insulin [415], similar to the depletion of secretory granules observed with chronic exposure to PCBs [475]. This contrasts with the effects of *in vivo* BPA exposure, which augments insulin release and increases β-cell insulin content in a murine model [469]. Oral administration of TBT was

shown to promote hyperglycemia with reduced circulating insulin levels accompanied by increased islet apoptosis and reduced cellular proliferation, suggesting a β-cell defect as a contributing lesion to TBT-induced metabolic dysfunction [476].

The use of genetic models of type 1 and T2D have also unlocked the deleterious effects of MDCs on β-cell biology. In the db/db mouse model of T2D in which a defect in the leptin receptor promotes the development of obesity and diabetes, exposure to arsenic through drinking water enhanced the development of hyperglycemia with concomitant reductions in insulin levels, suggesting an arsenic-induced impairment in β-cell function [477]. The non-obese diabetic (NOD) mouse, in contrast, is a model of type 1 diabetes as these mice develop autoimmune inflammation of the pancreatic islets (insulitis) and insulinopenic diabetes. Chronic exposure to BPA modulates insulitis in female NOD mice with complex concentration-dependent effects [478].

5.5.1.3 Epidemiological studies in adult human populations

The effects of MDCs on β-cell physiology in adult human studies are limited. In a Northern Mexican cohort, inorganic arsenic exposure was associated with a reduction in β-cell function, with the effect amplified among those with T2D [479]. Along with larger epidemiologic literature linking arsenic exposure to diabetes [480-482], other studies have also found arsenic to be associated specifically with measures of β-cell dysfunction or reduced insulin secretion, more strongly than with measures of insulin resistance [483, 484]. Epidemiological studies also suggest that BPA, phthalates, dioxins, and POPs including DDT metabolites and PCBs are associated with measures of altered glucose homeostasis including T2D [345, 485-489]. In one recent study, urinary BPA concentration in US adults was associated with an increase in β-cell function, hyperinsulinemia and insulin resistance [490] preferentially in males. These results are similar to those obtained from studies performed in mice [469].

Consistent with animal studies [491], a number of human studies —including studies among children and numerous studies in adults— suggest that DEHP is more strongly associated than are other phthalates with diabetes and other markers of impaired glucose metabolism [365, 492-495], perhaps because of greater activation of PPARs. However, several other studies [496-498] found stronger evidence of associations with butyl phthalates, which have a weaker PPARγ affinity than do DEHP metabolites [499].

Because data thus far are limited, it is uncertain to what extent the mixed results in humans may be due to factors such as differences in exposures [496], measurement errors in estimates of exposure [350], or sex-specific effects [500]. Moreover, to date very few epidemiological studies have examined the developmental or perinatal exposures thought to have the most potent diabetogenic effects [501], though recent animal studies support adverse effects of ongoing exposures including those in adulthood [502, 503]. Nonetheless, overall, these studies support the idea that MDC-induced disruptions in β-cell function may mediate some of the observed associations between environmental chemicals and diabetes in human populations.

5.5.1.4 Animal studies: Gestational and Perinatal Exposures

While disruptions in glucose homeostasis due to diminished insulin action result from developmental exposure to several chemicals, evidence specifically linking MDCs to impaired β-cell function is less common(Figure 3). In a rat model, females exposed to the phthalate DEHP throughout gestation and perinatal development exhibited hyperglycemia in the presence of reduced insulin levels [504]. Histological evaluation of pancreatic islets from weanlings revealed reductions in β-cell mass, reduced islet insulin content, and disruptions in β-cell ultrastructure [491]. In a similar model, restriction of exposure to days 9-21 of gestation, albeit to higher DEHP levels, similarly altered β-cell function and reduced insulin levels with hyperglycemia [505].

In the NOD model of type 1 diabetes, in utero and perinatal exposure to BPA increased the severity of insulitis at 11 weeks of age and increased the prevalence of diabetes at 20 weeks of age in female mice [506]. Interestingly, a recent study also demonstrated that BPA exposure during pregnancy promotes the development of glucose intolerance in later life through impairments in β-cell function and mass [507]. This suggests that exposures during pregnancy may alter the long-term metabolic trajectory of both the mother and her offspring. These studies support extending the view of ‘developmental windows’ beyond early life, as important periods of sensitivity to disruptions in β-cell function may be mediated by exposure to environmental toxicants during other critical periods, e.g. pregnancy.

Collectively, experimental evidence from cell lines to humans supports the endocrine pancreas as a target for disruption by diverse MDCs. Further work is required

to determine the exposure conditions under which α- and β-cell physiology is disrupted in humans to better characterize the threat of exposures to MDCs to metabolic health.

5.5.2 MDCs, Insulin Action and Glucose Disposal

5.5.2.1 Cellular models

In addition to data demonstrating that MDCs disrupt insulin production, an increasing body of evidence suggests that a variety of MDCs have the capacity to impair peripheral insulin action. In diverse cell line and organ culture models of insulin-responsive tissues, an array of compounds have been shown to impair insulin signal transduction or insulin-stimulated glucose disposal, including TCDD [508, 509], tolylfluanid [510], inorganic and methylated arsenic species [511, 512], DEHP [513, 514], and POPs [416]. In one model, BPA was also shown to inhibit insulin-stimulated glucose utilization in 3T3-L1 adipocytes [417] and another study showed that BPA can increase basal and insulin-stimulated glucose uptake in 3T3-F442A cells [412]. BPA also stimulated secretion of pro-inflammatory cytokines IL-6 and TNF while inhibiting the anti-inflammatory cytokine adiponectin from human adipoctyes in culture {Ben-Jonathan, 2009 #2081}. Collectively, these data suggest impairments in insulin action may result from exposure to a variety of environmental MDCs; however, dose, duration, and model system may alter the phenotypic response of some tissues to these compounds.

5.5.2.2 Adult animal studies

Evidence that MDCs disrupt cellular energy handling is supported by data from animal models in which multiple compounds have been shown to promote insulin resistance. For example, in vivo exposure to DEHP down-regulates expression of adipocyte insulin signaling intermediates [515], while rats exposed to BPA demonstrated a reduction of insulin signaling intermediates in both muscle [516] and liver [517]. Cadmium exposure has been shown to promote glucose intolerance with a specific reduction in adipose expression of Glut4 [518] and TCDD has been shown to also reduce glucose uptake in adipose and brain [519, 520]. In addition, the fungicide tolylfluanid promotes glucose intolerance with concomitant global and adipose-specific insulin resistance, with the latter resulting from a specific down-regulation of insulin receptor substrate-1 (IRS-1) [521].

While less specific, a variety of studies have also shown that exposure to various organic and inorganic toxicants promotes global insulin resistance or glucose intolerance with associated shifts in serum insulin levels. For example, in vivo exposure to inorganic arsenic promotes glucose intolerance with concordant insulin resistance [477, 522], including accentuation of the inherent insulin resistance of pregnancy [523]. Extended exposure to air pollution particular matter (PM2.5) for 24 weeks induced whole body insulin resistance in mice [524]. Acute and chronic malathion exposure resulted in increases in both glucose and insulin levels in rats [525]. Chronic exposure to POPs has also been shown to promote insulin resistance [502]. Similarly, BPA promotes insulin resistance in mice [469], and this effect can be observed with exposures as short as 8 days [526]. In addition to effects on β-cells, in vivo studies of TBT exposure in mice demonstrate hyperinsulinism [527].

While these studies emphasize the diverse array of compounds that can alter insulin action, key factors may modulate the ultimate metabolic phenotype. For example, female mice exposed to arsenic develop glucose intolerance; however, the etiology may be influenced by the background hormonal status of the animal as ovariectomized mice exhibit elevated insulin levels while those with intact ovaries have reduced insulin levels [528]. Furthermore, an animal's genetic background may also influence the phenotype. In one study, inorganic arsenic was shown to preferentially induce glucose intolerance in diabetic db/db mice but not non-diabetic mice [477]. Importantly, additional metabolic stressors such as high fat feeding may also modify MDC effects on energy homeostasis. Atrazine has been shown to promote insulin resistance, an effect exacerbated by a high fat diet [529]. BPA also promotes glucose intolerance and impair insulin action in a chronic model of exposure coupled with a high fat diet [530]. Interestingly, PCB77 and PCB126 were shown to impair glucose tolerance with the induction of systemic insulin resistance when coupled with a low fat diet; however, the effect of PCB77 on glucose tolerance was absent in the context of high fat diet but reemerged with weight loss [531]. Indeed, the evidence for diet-PCB interactions in promoting insulin resistance may be quite complex and congener-specific as exposure to the PCB mixture Aroclor 1254 induced insulin resistance in both lean and diet-induced obese states [532]. Similarly, in one epidemiology study, effects of PCBs on odds of diabetes appeared to be modified by intakes of fruits and vegetables [533]. Conversely, rats exposed to PM2.5 developed increased insulin levels and elevated HOMA-IR only in the context of a high fat diet [534]

and Aroclor 1260 administered to mice fed a high fat diet altered carbohydrate metabolism at multiple levels including glucose tolerance, insulin resistance/sensitivity, adipokines, pancreatic insulin secretion, and hepatic gluconeogenesis [535]. Taken together, this evidence suggests that the relationships between MDCs and dietary metabolic stressors are complex, with an ultimate phenotype that may be exposure-specific.

5.5.2.3 Animal studies: gestational and perinatal exposures

Various models have suggested that imbalances in insulin action can arise from MDC exposures during development. BPA enhanced the insulin resistance of pregnancy, with female offspring demonstrating higher insulin levels and males exhibiting glucose intolerance with systemic insulin resistance [536]. Insulin resistance was also observed in BPA-exposed rats [537], while another mouse model similarly demonstrated glucose intolerance with insulin resistance; however, the effect was observed only at low doses[321]. Metabolic stressors like high fat diet may be additive to the BPA-induced insulin resistance [331]. Indeed, high-fat diet potentiated GSIS impairments elicited by low doses of BPA given subcutaneously [538]. In the CD-1 mouse, however, developmental exposure to BPA did not alter glucose homeostasis in adult mice fed a normal chow or high fat diet [333]. Overall, these findings suggest that developmental BPA exposure can alter metabolism, albeit the ultimate metabolic phenotype may be modulated by genotype, diet and exposure patterns.

Additional studies have suggested that developmental exposure to other compounds can promote alterations in insulin action. For example, exposure to low doses of PFOA in midlife were shown to increase insulin levels [398], while PFOS exposure during gestation and early postnatal development resulted in glucose intolerance and insulin resistance [539]. Rats exposed to PFOS from gestation day 0 to postnatal day 21 also shown exhibited glucose intolerance with elevated insulin levels [540].

Developmental exposure to DEHP induces a complicated phenotype with the development of hyperglycemia with reduced insulin levels in female rats, while male offspring had elevated insulin levels but normal glucose tolerance [491]. In another model, DEHP exposure led to glucose intolerance with insulin resistance in the offspring, although this model also revealed central defects in β-cell function as well [505]. Sex-

specific effects of DEHP on measures of insulin resistance have been reported in some epidemiological studies [495], but not others [541].

These data suggests that both adult and developmental exposures to various MDCs have the capacity to modulate insulin action globally as well as at the cellular level. This conclusion is further supported by a number of studies, not discussed, in which MDC exposure promoted glucose intolerance without examination of insulin levels or action. However, the precise mechanism(s) by which this common phenotype occurs remains somewhat obscure. Examining the totality of the data, several molecular pathways are implicated as potential mechanisms of altered insulin action. These include increased production of proinflammatory cytokines that induce insulin resistance such as TNFα and IL-6 [508, 524, 542], increased oxidative stress [466, 477, 515, 525, 543], and mitochondrial dysfunction [529], which may also increase oxidative damage. Further work is required to fully characterize the modes by which MDCs promote impaired insulin action to devise strategies to mitigate their adverse effects on global energy homeostasis.

5.5.3 MDCs and Energy Homeostasis

In addition to the effects of MDCs on insulin production and action, specific defects in intermediary metabolism have also been described for MDCs using a variety of model systems. For example, in the 3T3-F442a cell line, TCDD reduces expression of lipoprotein lipase [509], suggesting one mechanism by which MDCs may promote hypertriglyceridemia. PBDE exposure inhibits adipose glucose oxidation while augmenting isoproterenol-induced lipolysis [544], potentially increasing circulating free fatty acid levels, which are substrates for hepatic triglyceride synthesis.

Additional lipid abnormalities may be induced by perinatal exposure to 4-nonylphenol which has been shown to increase serum total cholesterol [423]. Disruptions in hepatic metabolic function were shown with subchronic exposure to malathion, which induced hyperglycemia with evidence of increased hepatic gluconeogenesis and glycogenolysis [545]. Chronic intake of DEHP impairs glucose tolerance with an alteration in glycolytic intermediates in both liver and muscle that were suggestive of impaired lactate as well as glucose handling [546]. In utero and lactational exposure to BPA in a rat model demonstrated a reduction in hepatic glycogen content at

21 weeks of age with evidence that the promoter for hepatic glucokinase was hypermethylated, suggesting a reduction in the expression of this key enzyme [537]. In a multigenerational rat model, BPA exposure in the F0 generation promoted glucose intolerance and insulin resistance in the F2 generation with an associated reduction in hepatic glucokinase expression and concomitant hypermethylation of the gene promoter [547]. Interestingly, adult mice exposed to BPA have also been shown to exhibit reduced hepatic glucokinase activity [548]. This suggests that disruptions in hepatic glucose handling may be a common mode by which MDCs promote metabolic dysfunction.

5.6 MDCs, Hepatic Steatosis, and Hyperlipidemia

Developmental studies examining MDCs and liver health endpoints have been conducted in laboratory animals, but epidemiology studies examining the developmental basis of these diseases are lacking. This is likely due to the relatively long time to develop clinically apparent human liver disease owing to the slowly progressive nature of hepatic fibrosis. Compounding the problem, routine clinical biomarkers (e.g. alanine aminotransferase) may be insensitive for the detection of environmental liver disease[549] Novel biomarkers for fatty liver disease and fibrosis [550] are being developed for clinical use, and perhaps these could be applied to future environmental epidemiology studies. Due to the relative lack of epidemiological data on developmental MDC exposures in steatosis and hyperlipidemia, post-developmental studies (adolescent and adult) provide ‘proof of concept’ and thus are reviewed below.

5.6.1 Adult MDC Exposures, Steatosis and Hyperlipidemia

Hepatic steatosis is likely to be the most common pathologic liver responses to chemical exposures [163]. Indeed, hepatic steatosis was noted in approximately 8-10% of rodent studies warehoused in the Environmental Protection Agency’s (EPA) Integrated Risk Information System (IRIS) database and the Toxicological Reference Database (pesticide) [162, 551]. Furthermore, in the Chemical Effects in Biological Systems (CEBS) data repository of the US National Toxicology Program (NTP), 329 rodent studies of 81 unique chemicals reported hepatic steatosis [551]. Whatever its etiology, hepatic steatosis is invariably associated with insulin resistance [163]. However, this interaction is complex as fatty liver disease is both a cause and effect of insulin resistance.

While some chemicals (e.g. vinyl chloride) appear to directly cause steatosis and steatohepatitis [552], other chemicals such as non-dioxin like PCBs merely modify the hepatic response to diet-induced obesity [535]. These chemicals may be a 'second hit' in the progression of diet-induced steatosis to frank steatohepatitis, which may further progress to cirrhosis and hepatocellular carcinoma. Many non-dioxin like PCBs interact with NR1 class nuclear receptors such as PXR and CAR [553]. However, the role of MDC-nuclear receptor interactions in fatty liver disease is likely to be complex, as PPARɣ agonists (e.g. obesogens) have been proposed as treatments for non-alcoholic fatty liver disease and associated insulin resistance [554]. Nuclear receptor crosstalk especially at the liver X receptor response element is also likely to be important, but is currently understudied. Other proposed mechanisms include oxidative/carbonyl stress, endoplasmic reticulum stress, mitochondrial dysfunction, increased cytokine production, increased hepatic lipid synthesis/uptake and impaired VLDL synthesis and secretion [162, 163]. Many of the environmental chemicals associated with steatosis are organochlorines. Of the compounds in the US Environmental Protection Agency's Integrated Risk Information System (IRIS) that induced steatosis in rodents following oral (dietary) treatment, the most potent (mirex, chlordecone, chlordane) were structurally similar, highly chlorinated molecules (>8 chlorines) [162]. While these data suggest that highly halogenated environmental chemicals could be of particular interest in steatosis, more data are required.

Key chemical classes identified in adult steatosis studies include solvents and volatile organic chemicals; POPs and pesticides; and metals [163, 551]. Solvent exposures have historically been associated with steatosis and liver injury in the occupational health literature [552, 555]. These data were recently reviewed by the Institute of Medicine and the National Research Council which concluded that there was "…evidence of an association between chronic exposure to solvents in general and hepatic steatosis that could persist after cessation of exposure" [556, 557]. Unfortunately, it is difficult to assess biomarkers of prior solvent exposures, and epidemiological data on the impact of solvent exposures in human cohorts are lacking.

Exposure to BPA is associated with liver enzyme abnormalities reflective of liver injury in population-based studies [344, 558], although pathologic data were not provided. Regarding dyslipidemia, non-significant trends were observed for BPA in

pediatric NHANES populations [559]. However, prolonged (8-month) exposure of male mice to low BPA doses induced hypercholesterolemia with upregulation of key genes involved in cholesterol biosynthesis including sterol regulatory element-binding protein 2. Whole body *de novo* cholesterol synthesis was also increased as seen by the plasma lathosterol-to-cholesterol ratio [503]. Interestingly, the food contaminant 1,3-dichloro-2-propanol induced hyperlipidemia with increased LDL/HDL ratio in mice via the AMP-activated protein kinase (AMPK) signaling pathway [560].

Exposures to POPs and pesticides have been associated with fatty liver disease in adults. In the NHANES study, PCB exposures were associated with 'unexplained alanine aminotransferase (ALT) elevation', a surrogate marker for fatty liver [561]. The observed association between PCB exposures and ALT was subsequently confirmed in NHANES by two other independent groups using different statistical techniques; and also in the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) cohort [562-564]. Likewise, associations between organochlorine pesticides or their metabolites and liver enzymes have been seen for ALT [562] and gamma glutamyl transferase [565]. Perfluorinated chemical exposures were also positively associated with ALT in NHANES [566], and this association was more evident for PFOA exposures in obese adults [567]. Positive associations were also seen between both PFOA and PFOS exposures in adult participants of the C8 study (n=47,092 subjects) [568]. Animal studies of PCBs [160-162, 535, 551, 569], organochlorine pesticides [162], and PFOA [570] suggest that the liver enzyme abnormalities reported in these adult epidemiological studies could be due to fatty liver disease.

In population-based studies of hyperlipidemia, PCB exposures were associated with longitudinal increases in LDL cholesterol [571]. However, other studies reported nonlinear associations between PCBs and organochlorine pesticides with hyperlipidemia [572, 573]. PCB treatment has been associated with hyperlipidemia in some [574], but not all rodent studies [549]. The chlorinated insecticide, lindane, interacts with ERβ [575], and high-dose lindane exposure (12 mg/kg x 20 days) in rats increased serum total cholesterol and triglycerides while decreasing HDL cholesterol [576]. On the other hand, TCDD decreased total cholesterol, LDL, and HDL in a rodent study suggesting an AhR-mediated serum lipid clearance and decreased hepatic efflux [577].

Metals/metalloids have also been associated with abnormal liver function and hyperlipidemia. In Bangladesh, drinking from arsenic contaminated wells was associated with increased ALT [578]. Chronic arsenic exposures were also associated with increased triglycerides in a cross-sectional study [579]; in rats, arsenic increased serum cholesterol, triglycerides, free fatty acids and phospholipids in association with increased oxidative stress and hepatic mitochondrial damage [580] as well as ALT when combined with an obesogenic agent [581, 582]. Lead and mercury exposures were associated with the fatty liver surrogate biomarker, 'unexplained ALT elevation' in adult NHANES [561]; and lead, but not mercury, was associated with ALT, plasma triglycerides and LDL, in Iranian adolescents [583]. In mice, however, methylmercury markedly and specifically increased total and LDL cholesterol [584]. Cadmium exposures were also associated with ALT in adult Korean NHANES participants [585] and Iranian adolescents [586].

Animal studies suggest that the observed ALT elevations in the adult/adolescent populations following exposures to arsenic [582], mercury [587], and cadmium [588] may be due to fatty liver disease. Thus, data implicate post-developmental exposures to specific volatile organic compounds/solvents, plasticizers, POPs, and metals/metalloids in hepatic steatosis and dyslipidemia.

The herbicide, atrazine, is a chloroplast inhibitor which has also been associated with mitochondrial dysfunction and NAFLD in rodents[529, 589, 590] Respiratory routes of exposure have also been associated with the development of fatty liver disease via the lung-liver axis. For example, air pollution and particulate matter were associated with steatohepatitis in rodents [591, 592], though mechanisms including toll-like receptor activation. However, confirmation in human studies is required. While smoking has not historically been considered to be a clinically significant factor in the pathogenesis of liver disease, recent data demonstrate a link between active and secondhand smoke in the development of both adult and pediatric NAFLD[593-596].

5.6.2 Developmental MDC Exposures and Hepatic Steatosis

Given the liver's importance in toxicology, it is somewhat surprising that only scattered evidence exists to characterize pathways and patterns of its altered functional development. Nevertheless, a number of rodent studies suggest that specific

developmental perturbations to liver programming may influence the long-term predisposition to steatohepatitis and MetS. Of great interest is the multi-generational effect of maternal high-fat feeding, which may prime steatohepatitis in adult mice offspring [597-599] (Figure 4). These effects result from mechanisms similar to those observed in adult steatohepatitis studies including increased lipogenic gene expression with mitochondrial dysfunction and decreased beta oxidation, due in part, to altered PPARα/PPARɣ expression; microRNA changes; increased oxidative stress with reduction in hepatic antioxidant enzymes; and increased inflammation.

Likewise, maternal exposures to chemicals have been associated with altered hepatic metabolism and steatosis in offspring. Exposure throughout gestation and perinatal development to BPA may further exacerbate the nonalcoholic steatohepatitis-like phenotype in male rats that were fed a high-fat diet post-weaning; in particular, BPA worsened the accumulation of lipids in hepatocytes as well as liver inflammation and oxidative stress fibrosis [600]. Liver function markers were unimpaired in BPA-exposed rats kept on a standard diet; however, these animals showed effects suggestive of subtle alterations of liver programming, such as moderately increased steatosis and altered expression of insulin signaling elements.

Epigenetic changes may be a hotspot in altered liver programming: developmental BPA exposure alters gene methylation in mouse liver, in particular concerning genes relevant to metabolism and stimulus response. As observed for other molecular and cellular effects of EDCs, the effects of BPA were different at low and high dose levels (0.05 and 50 mg/kg bw, respectively) [601]. Overall, the findings suggest that the developmentally-induced altered liver methylome increased insulin resistance phenotypes in adults. Some of these effects may have been related to hepatic changes including altered nuclear receptor expression (PPARα/PPARɣ) key regulators of energy metabolism, mitochondrial dysfunction, and DNA methylation.

Gestational exposures to, DEHP, also resulted in hepatic steatosis in offspring as well as decreased glycogen storage in males, but with a delayed shift to glycogen-dependent metabolism of the mature hepatocyte [602]. This phenotype could stem from the DEHP-PPARα interactions influencing expression of lipid metabolism genes such as microsomal triglyceride transfer protein [603]. However, DEHP also interacts with other

nuclear receptors including CAR and PXR. While there is no direct evidence of the involvement of CAR and/or PXR in the DEHP-induced effects on liver metabolic programming, nevertheless, their involvement is plausible and deserves attention for potential human disease relevance. While DEHP is a less potent human than rodent PPARα activator, it more potently activates human CAR [604].

While probably best characterized for plasticizers (BPA, DEHP), developmental exposures to other toxicants including benzo[a]pyrene, TBT, PBDEs, and pesticides have also been associated with development of fatty liver disease and/or abnormal hepatic lipid metabolism in rodents [368, 378, 551, 605]. Rats perinatally exposed to polybrominated diphenyl ether 47 (PBDE-47) had increased blood cholesterol levels [606]. Altered blood cholesterol was likely a result of reduced hepatic Cyp7a1 expression, a critical enzyme for the conversion of cholesterol into bile acids [605, 606]. Exposure to BDE-47 and DE-71 (a commercial mix of PBDE) resulted in transcriptomic enrichment of genes of lipid metabolism in rat livers [605, 606], including long-term systematic activation of pathways of α, ω, and β-oxidation of fatty acids.

Overall, the available evidence indicates that liver programming may be an important target for MDCs that increase predisposition to MetS. Relevant morphological changes include increased lipid accumulation and depleted glycogen storage in hepatocytes; changes at molecular or biochemical levels may include altered methylation patterns, altered nuclear receptor cross-talk, mitochondrial dysfunction, and enhanced free radical production. However, more data are needed to define the set of chemicals that result in steatosis and dyslipidemia following developmental exposure and the mode of action of these chemicals in fatty liver disease. While the animal study data are compelling for developmental BPA exposures and steatosis, significant knowledge gaps exist for other MDCs. Epidemiological data are also very limited in this area.

5.7 MDCs and Metabolic Syndrome

As noted above there are MDCs that can result in obesity, T2D or lipid disorders. What is striking is that when multiple endpoints were examined within individual studies, in many cases an MDC caused disruptions in multiple disease pathways leading to what could be called MetS. Table 1 shows that indeed many EDCs should be characterized

as MDCs as they can cause multiple disease/dysfunctions, even when not all of the metabolic endpoints were measured in the same experiment. We highlight examples here to show that indeed there are MDCs that can affect multiple tissues leading to multiple metabolic disorders and in some cases to MetS due to their ability to induce weight gain, glucose intolerance and lipid disorders. These data indicate it is important to examine more than one endpoint and tissue to define an action of a suspected MDC.

The first example comes from developmental exposure to BPA, which can induce glucose intolerance and insulin resistance [331], and impairments β-cell function and mass [507]. Developmental exposure to BPA has also been shown to cause weight gain in offspring in some animal models and human studies (reviewed in [340]). BPA exposure throughout gestation and perinatal development exacerbates a nonalcoholic steatohepatitis-like phenotype in male rats that were fed a high-fat diet post-weaning; in particular, BPA worsened the accumulation of lipids in hepatocytes as well as liver inflammation and oxidative stress fibrosis [600].

Similarly, rats exposed to DEHP throughout gestation and perinatal development exhibited hyperglycemia in the presence of reduced insulin levels [504] along with reductions in β-cell mass, reduced islet insulin content, and disruptions in β-cell ultrastructure [491]. Sex-specific effects of DEHP on measures of insulin resistance have been reported in some epidemiological studies[495]. Gestational exposures to DEHP resulted in hepatic steatosis in offspring as well as decreased glycogen storage in males, but with a delayed shift to glycogen-dependent metabolism of the mature hepatocyte [602]. Prenatal exposure of mice to DEHP results in increased body weight as well as numbers and size of adipocytes in male offspring in several studies from different labs using different models [356-359].

DDT and its metabolites have been associated with increased risk of higher body weight, insulin resistance, T2D and dyslipidemia in human studies [573, 607]. In rodent studies, female offspring exposed prenatally to DDT followed by a high fat diet for 12 weeks in adulthood developed glucose intolerance, hyperinsulinemia, dyslipidemia and altered bile acid metabolism as well as reduced energy expenditure and impaired thermogenesis [389]. DDT effects were also transmitted across generations resulting in obesity in the F3 generation [608].

PBDEs have also been associated with development of fatty liver disease and/or abnormal hepatic lipid metabolism in rodent studies [368, 378, 551, 605]. Exposure to BDE-47 and DE-71 resulted in transcriptomic enrichment of genes of lipid metabolism in rat livers [605, 606], including long-term systematic activation of pathways of α, ω, and β-oxidation of fatty acids. Developmental exposure in a rodent model to a specific PBDE mixture, Firemaster 550, resulted in weight gain in the offspring [410].

Prenatal exposure to TBT in mice promotes adipocyte differentiation that results in increased lipid accumulation and adipose tissue while reducing muscle mass that persists into adulthood and across generations [309, 367] . It also increases adiposity in zebrafish [373] . One epidemiology study noted that prenatal TBT exposures were associated with a non-significant trend towards higher weight gain in the first three months of life [374]. In a transgenerational study, TBT resulted in hepatic steatosis through the F3 generation. Finally TBT was shown to promote hyperglycemia with reduced circulating insulin levels accompanied by increased islet apoptosis and reduced cellular proliferation, suggesting a β-cell defect as a contributing lesion to TBT-induced metabolic dysfunction [476].

Among the other chemicals summarized in table 1, developmental exposure to PAHs in a rodent model induce obesity, insulin resistance and inflammation in adults on a high fat diet [376] [377]. In a human cohort, children of mothers with the highest PAHs exposure during pregnancy had increased weight at 5 and 7 years of age [379]. Prenatal exposure to specific PCB congeners in birth cohort studies was shown to result in increased BMI in offspring [387] [390, 393]. Arsenic also deserves mention because of its specific association with insulin dysregulation and T2D and liver toxicity [477, 522, 528, 582]

5.8 MDCs and Transgenerational Metabolic Disruption

A variety of stressors including high-fat, high-sugar diets, low protein diets and environmental chemicals can induce transgenerational inheritance of metabolic diseases [609]. Several recent papers have shown that the effects of MDC exposure in pregnant F0 animals were propagated until at least the F3 generation (reviewed in [309, 610, 611]). This is significant because when exposures occur in the maternal lineage,

the F0 and F1 animals are directly exposed to the chemical and the F2 generation is exposed as germ cells within the gestating F1 animals. The F3 generation is the first generation that has not received any direct chemical exposure; therefore, effects observed in F3 and beyond are considered to be transgenerational and permanent, and are distinguished from the multigenerational effects in F1 and F2 animals [612].

Exposure of pregnant F0 animals to low, environmentally-relevant levels of TBT in their drinking water led to increased fat depot size, MSCs reprogrammed toward the adipogenic lineage and hepatic steatosis through the F3 generation [368]. Effects on fat depot size were more pronounced in F1 females than F1 males. Prenatal TBT exposure permanently alters MSC cell fate in both males and females and caused hepatic steatosis and altered hepatic gene expression in both males and females through the F3 generation. Skinner and colleagues have similarly shown that plastic components such as BPA, DEHP, dibutyl phthalate [358], a mixed hydrocarbon mixture (jet fuel JP-8) [358], and DDT [358] all lead to a transgenerational predisposition to obesity in the F3 generation. The molecular mechanisms remain unclear; however, many of the toxicants work through nuclear receptors [611] that are likely linked to epigenetic changes [613, 614] that likely play a significant role in the transgenerational effects. Imprinting, altered DNA methylation, histone modifications and copy number variants have all been implicated in transgenerational phenotype transmission as a result of exposure to chemicals or altered nutrition [610] [615-617]. Candidate sperm epimutations were also identified that could be involved in the etiology of the transgenerational obesity and other disease outcomes [618].

6. Conclusions: A Perfect storm for Metabolic Disease

Many of the studies discussed above highlight the importance of development as a sensitive time for programming all aspects of metabolism. Environmental chemicals with endocrine activity can alter programming of metabolism; this fact, along with the importance of diet during development and throughout life on metabolism, and the role for exercise in controlling weight and glucose metabolism, leads to the perfect storm for metabolic disease. *In utero*, and the first few years of life, are critical periods where the sensitivity or set point for obesity, diabetes and liver disease are established. We have herein shown that sensitivity or set points for the development of these diseases can be altered by MDCs that interfere with the normal developmental trajectories of adipose

tissue, pancreas, muscle, liver, GI tract and the brain. These set points are also influenced by diet and nutrition *in utero* and early childhood years, thus nutrition and MDC exposures during development are the key along with genetic background for setting the stage for all metabolic diseases.

These metabolic diseases may not manifest until later in life when the system is challenged by over-nutrition and/or lack of exercise. MDCs can change the expression of genes involved in the control of adipogenesis as well as glucose and lipid metabolism. Exposure to MDCs, together with excess calories and lack of exercise, would increase the susceptibility to these disease epidemics. Thus, we propose that some individuals are more prone to gain weight due to both their genetic background and the effects of developmental exposures to MDCs that are critical for setting the sensitivity or susceptibility of the tissues for metabolic disruption later in life.

Some recent publications support increased susceptibility to obesity due to environmental exposures. Developmental exposure to BPA induced weight gain due to increased food intake, changes in brain satiety neurons [619] and decreased activity and energy expenditure in females [620]. Similarly, prenatal nicotine leads to increased body weight due to a marked hypertrophy of adipocytes and fat deposition along with decreased spontaneous physical activity later in life, cold intolerance, and also increased sensitivity to the effects of high fat diet [313]. In addition, there are many examples of the effects of developmental exposures to MDCs that are exacerbated by high fat diet later in life, again indicating that developmental exposures increase the susceptibility to obesity (and other metabolic diseases) but may need a “second hit” later in life for the effects to actually become apparent as disease. For example, developmental exposure to PAH results in obesity, insulin resistance and inflammation only after a high fat diet as adults [376] [377]; the effect of atrazine on insulin resistance was exacerbated by high fat diet [529]; and BPA-induced insulin resistance may be additive with high fat diet [331]. Thus there are emerging data supporting a role for developmental exposures to MDCs in altering the set point of susceptibility for metabolic diseases later in life. The second hit of high fat diet and lack of exercise then results in onset of the metabolic diseases.

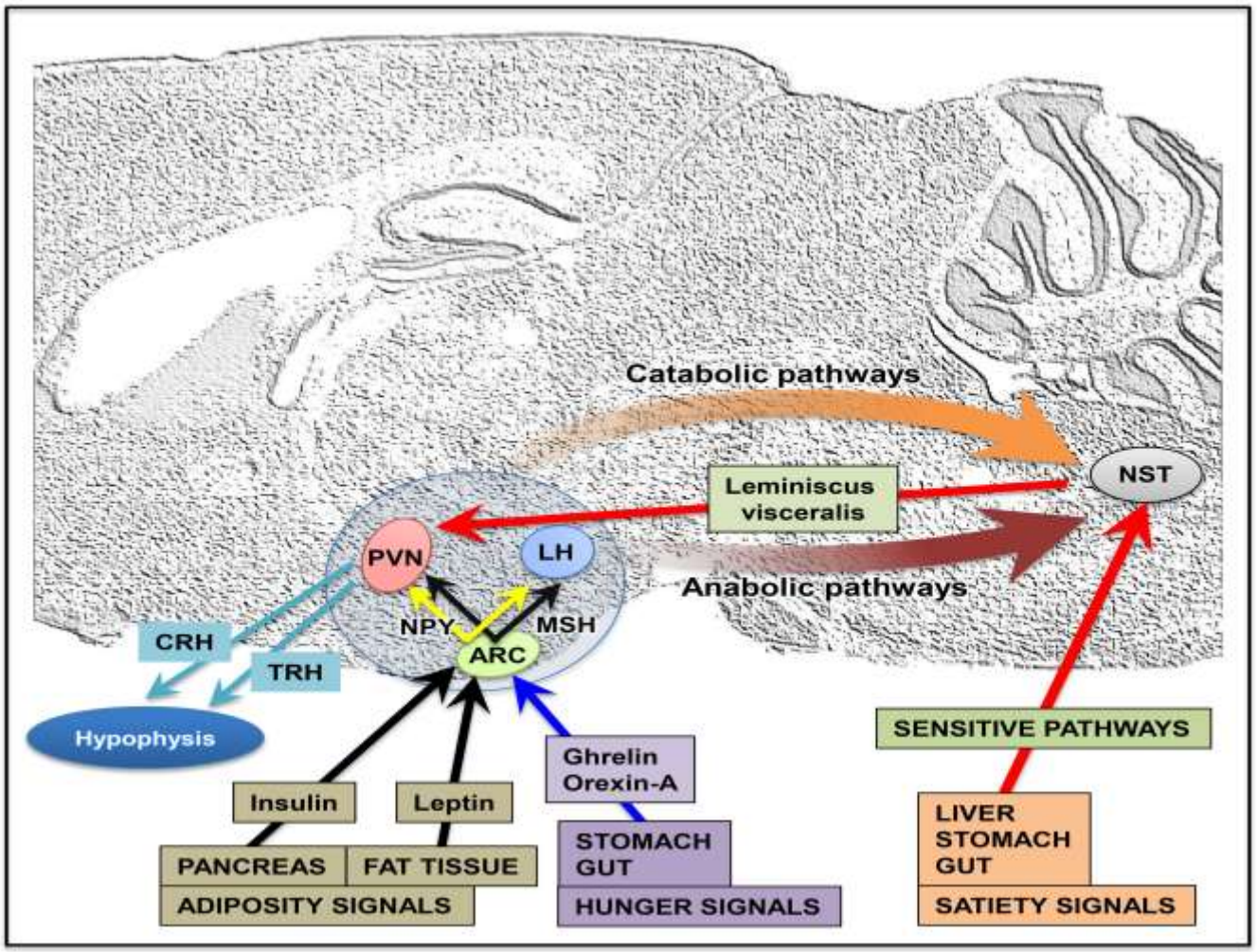
Of course, throughout life there are likely to be multiple exposures to MDCs that can also

increase sensitivity to metabolic disruption leading to weight gain, altered glucose tolerance and lipid disorders. For example, young mice exposed to BPA for 30 days showed significantly increased body weight and fat mass on a chow diet [332] but not on HFD (45%) which could be due to the overwhelming effect of the HFD. If true, then it would be difficult to control or treat metabolic disorders with pharmaceuticals later in life, as they would need to be able to offset the increased sensitivity programmed during early development. Indeed, the current state of science and medicine focuses on losing weight, and restoring glucose homeostasis and liver lipids after they are disrupted; it is clear that this approach is not working as the incidence of these diseases continues to increase. Furthermore, it is well documented that while it is possible to lose weight and keep it off for an extended time, the vast majority of people will gain the weight back, perhaps indicating they are fighting against a set point or sensitivity to develop these metabolic problems that favors calorie storage over the long term [437, 438, 621, 622].

For this reason, a consequence of the MDC hypothesis is that a focus should be on prevention instead of intervention. If indeed a set point for body weight, diabetes and/or METS is developed in early life, then a better approach would be to focus on limiting factors that can alter programming during these sensitive times; for example, addressing these metabolic epidemics will require reducing MDC exposures and improving early-life nutrition. In this way, the MDC hypothesis offers the ability to actually prevent these diseases, which is more cost effective and public health protective than the current focus on interventions after the diseases are apparent. Primary prevention measures must include up-to-date regulation of chemicals: robust tools are needed in order to identify MDCs among existing as well as new chemicals.

The MDC hypothesis proposes both a mechanism for the increased epidemic of obesity, diabetes and MetS and a solution. If indeed these diseases are due in part to developmental exposures to MDCs, as proposed, then for the first time there is a path to actually preventing them. The MDC hypothesis changes the focus from genetics to environmental exposures and from intervention to prevention.

Figure 1. Schematic illustrating the neuroendocrine control of energy balance (modified from Schwartz et al Nature 404, 661-71, 2000)



Peripheral signals reach the central nervous system through two main routes:

Adiposity Signals (leptin, insulin and others) and hunger (Ghrelin, Orexin A, and others) signals bypass the blood brain barrier and target the hypothalamus (transparent blue circle), in particular the arcuate nucleus (ARC).

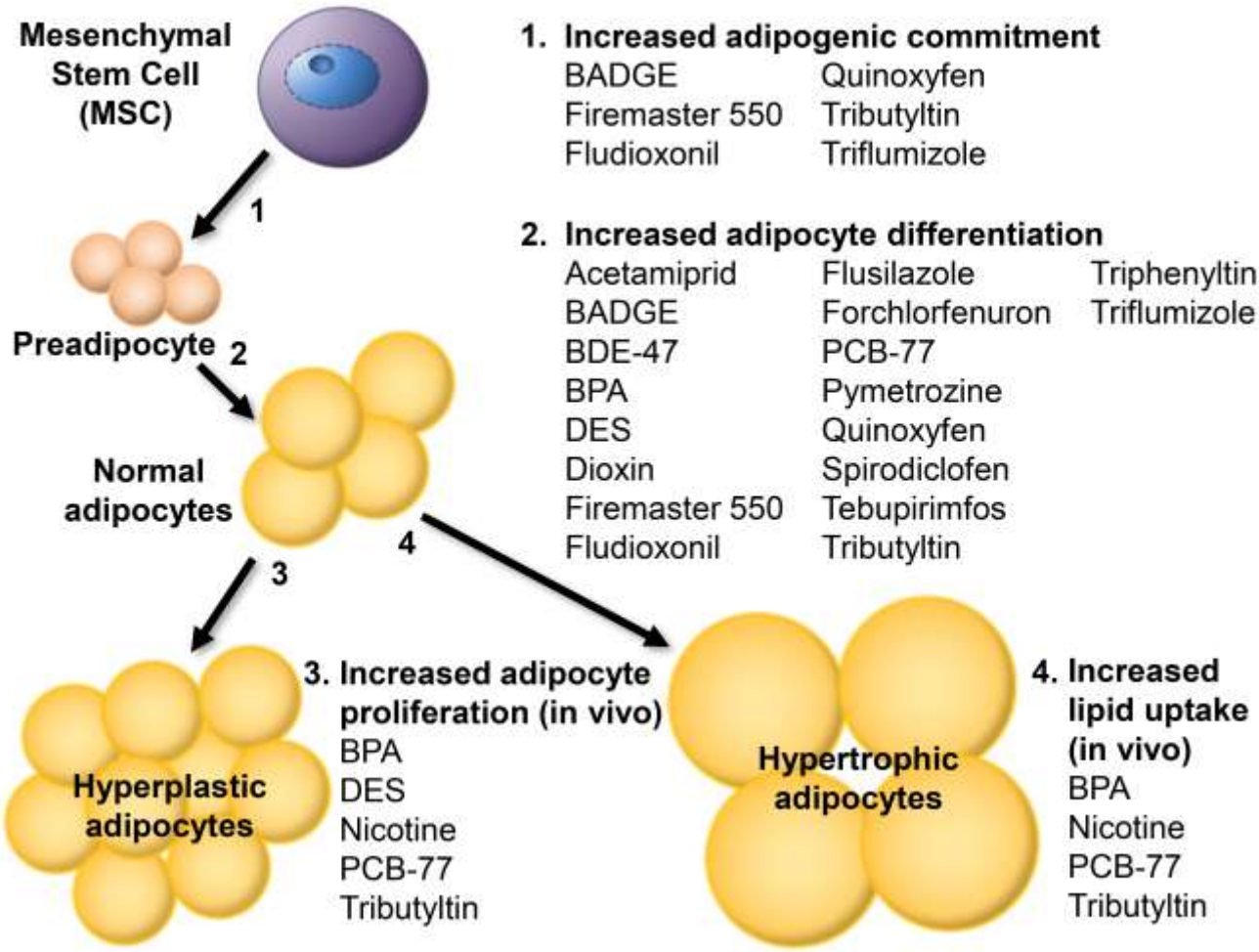
b) Peripheral hunger and satiety signals that control meal processing, gastrointestinal activity and changes in energy stores reach the brainstem (nucleus of the solitary tract, NST) through vagal and other sensory nerve fibers.

NPY and MSH neurons located within the ARC (stimulated or inhibited by adiposity and hunger signals) project to other hypothalamic nuclei (paraventricular nucleus, PVN, lateral hypothalamic nucleus, LH, and others). In particular, within the PVN they control

CRH and TRH neurons, regulating (via the adenohypophysis) the hypophysis-adrenal and hypophysis-thyroid axes.

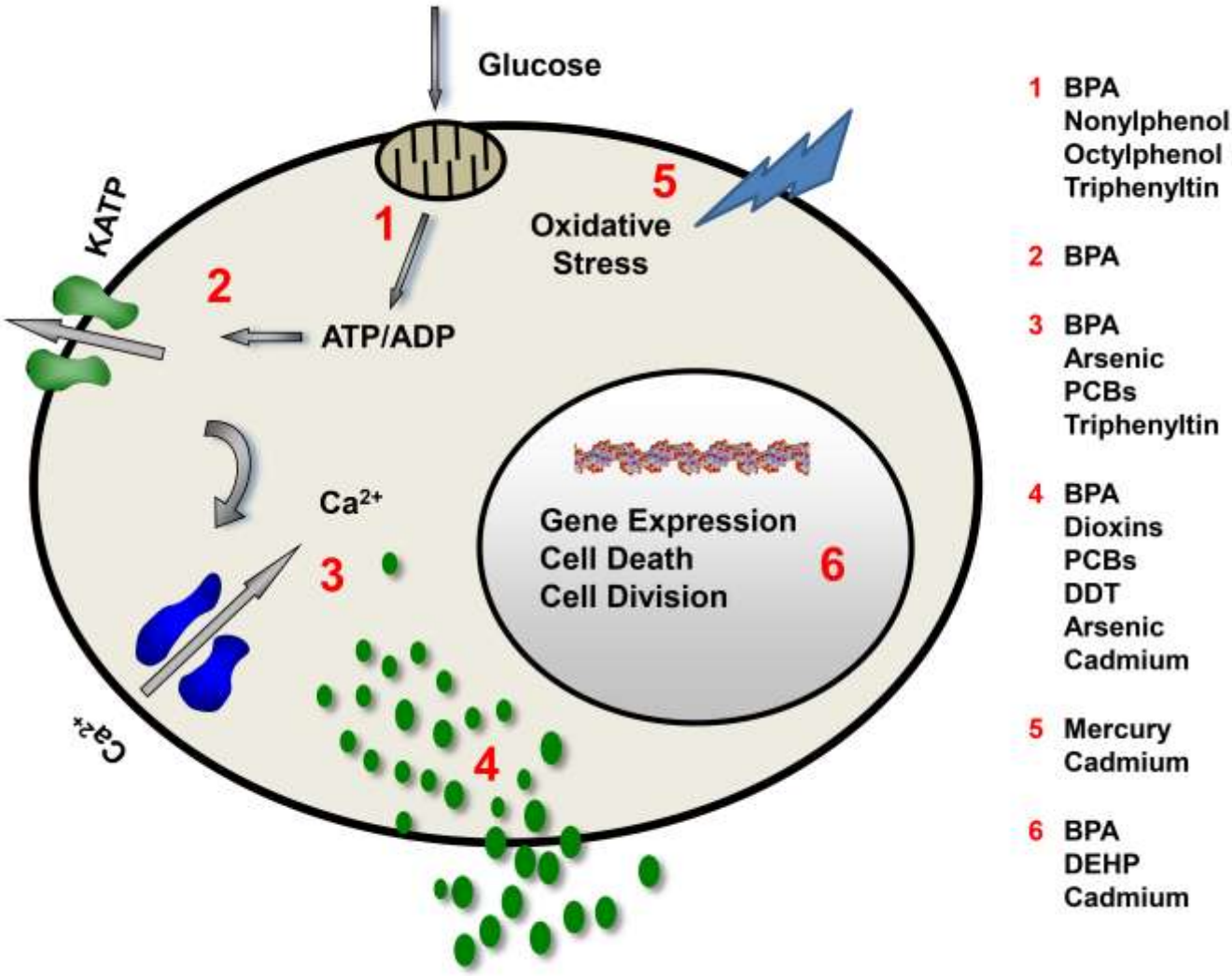
From the hypothalamus, catabolic and anabolic pathways reach the brainstem where their data are integrated with the peripheral signals carried by the sensory system. There are also ascending projections from the NST that may reach the hypothalamus, through the lemniscus visceralis, contributing to adaptative changes in food intake and energy expenditure.

Figure 2. Mechanisms of Adipocyte Formation and Sites of Action of Metabolism Disruptors



1. Mesenchymal stem cells commit to the adipogenic lineage and become preadipocytes. Commitment to the adipocyte lineage is mediated by transcription factors Zfp423, Zfp467, Schnurri2, Tcf7l1 and the mTORC1 effector S6K1. 2. Adipocyte differentiation is primarily controlled by PPARγ and CCAAT-enchancer binding proteins (C/EBP)α, β and δ which establish a sustained feedback loop. Numerous chemicals are capable of differentiating pre-adipocytes into mature adipocytes. Adipocyte number and size can be increased in vivo under hormonal control and can also be influenced by chemical exposure. 3. Adipocyte hyperplasia has been shown in rodents to be caused by perinatal exposure to a variety of chemicals. 4. Adipocyte hypertrophy in rodents due to permanent upregulation of genes involved in lipid uptake is also caused by exposure during perinatal life to a number of chemicals.

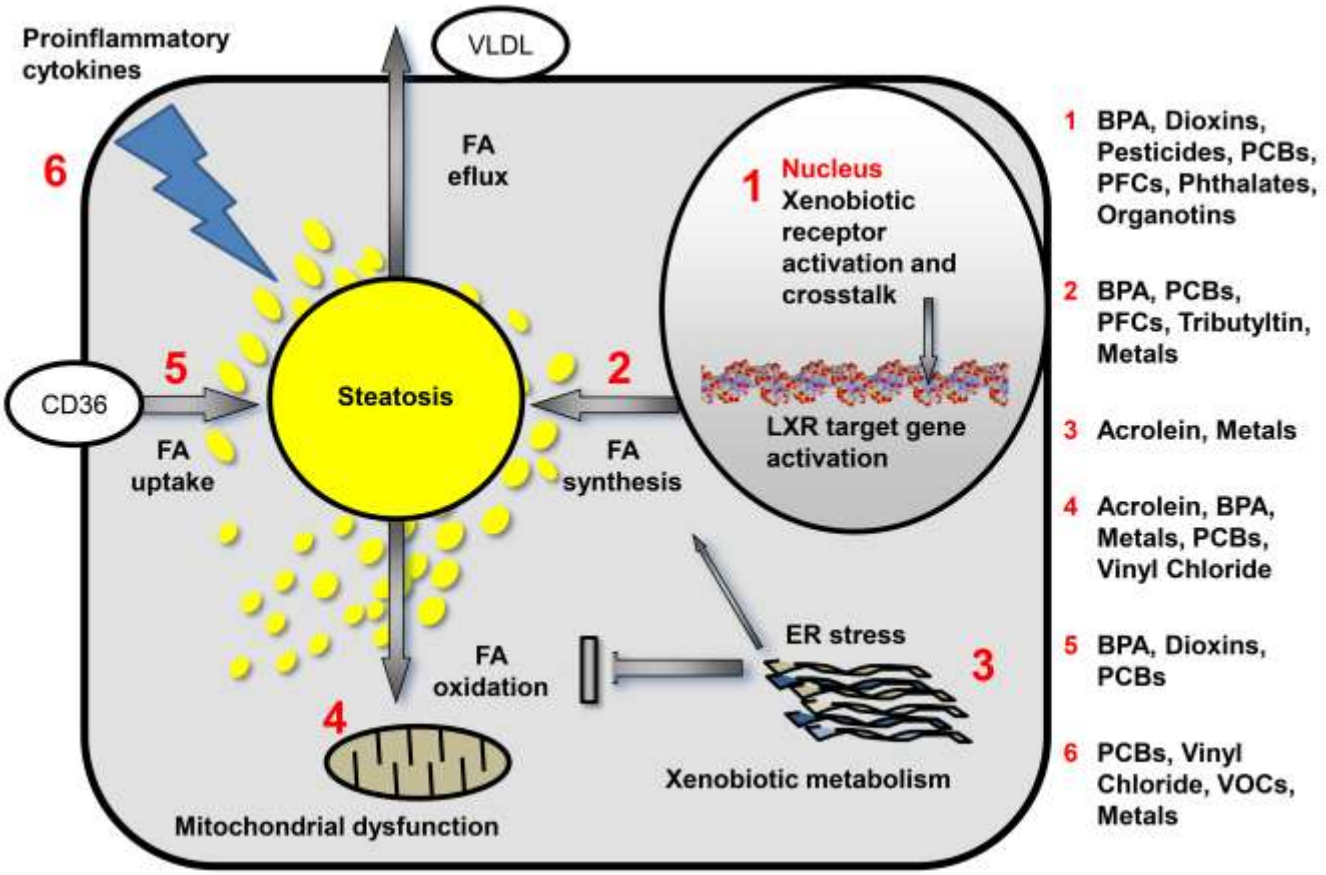
Figure 3. Regulation of pancreas beta cell control of blood glucose and sites of action of metabolism disruptors.



Glucose enters pancreatic beta-cells through glucose transporters (GLUT2 in mice and GLUT1 in humans) where it is metabolized in mitochondria resulting in an increase in the ATP/ADP ratio; this results in closure of membrane ATP-sensitive K^+ channels (K_{ATP}) that are responsible for the resting membrane potential. K_{ATP} channel closure results in cellular depolarization that opens voltage-gated calcium channels, triggering Ca^{2+} signals that induce insulin granule exocytosis and a subsequent rise in circulating insulin levels. This secretory pathway is disrupted by EDCs at different points: 1) Bisphenol-A, nonylphenol, octylphenol and triphenyltin impair mitochondrial function. 2) Bisphenol-A blocks K_{ATP} channels after binding ERbeta. 3) Calcium signaling is altered by Bisphenol-A, Arsenic, PCBs and Triphenyltin. 4) disruption of insulin secretion has been described for Bisphenol-A, dioxins, PCBs, DDT, Arsenic, and Cadmium . Beta-cells have a low antioxidant capacity and are

very sensitive to oxidative stress mediated by reactive oxygen and nitrogen species that impair their function by altering metabolism and/or K_{ATP} activity while inducing apoptosis. Mercury and Cadmium (5) are EDCs that produce oxidative stress in beta-cells. 6) Insulin gene expression is regulated by BPA via ERα, while DEHP and Cadmium provoke cell death and decrease in beta-cell mass.

Figure 4. Regulation of hepatic lipid metabolism and sites of action of metabolism disruptors



Hepatic steatosis occurs due to a combination of increased fatty acid (FA) synthesis or uptake and decrease FA oxidation or efflux. FA synthesis occurs as a consequence of liver X receptor (LXR) target gene activation which may occur following receptor activation by myriad environmental chemicals or via nuclear receptor cross talk. FA synthesis is upregulated by BPA, metals, PFCs, POPs, and tributyltin. BPA and POPs also upregulate scavenger receptors (e.g. CD36) to increase FA uptake into hepatocytes. Decreased FA oxidation is a consequence of mitochondrial dysfunction which may be mediated by BPA, chlorinated solvents POPs and metals. Liver also

mediates xenobiotic metabolism which may increase oxidative stress. Endoplasmic reticulum (ER) stress is a consequence of exposures to aldehydes and metals. ER stress, in turn, impacts FA metabolism. Steatohepatitis occurs due to increased hepatic inflammation and cytokines. Proinflammatory cytokines are induced by many exposures including POPs, vinyl chloride, VOCs, and metals. More data are needed on the impact of MDCs on FA efflux in hepatic steatosis.

Literature Cited

1. Grundy, S.M., et al., *Definition of Metabolic Syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association Conference on Scientific Issues Related to Definition.* Circulation, 2004. **109**(3): p. 433-438.
2. Alberti, K.G., et al., *Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity.* Circulation, 2009. **120**(16): p. 1640-5.
3. Aguilar, M., et al., *Prevalence of the metabolic syndrome in the United States, 2003-2012.* Jama, 2015. **313**(19): p. 1973-4.
4. Heindel, J.J., et al., *Developmental Origins of Health and Disease: Integrating Environmental Influences.* Endocrinology, 2015: p. En20151394.
5. Vandenberg, L.N., et al., *Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses.* Endocr Rev, 2012. **33**.
6. Ogden, C.L., et al., *Prevalence of Obesity Among Adults and Youth: United States, 2011-2014.* NCHS Data Brief, 2015(219): p. 1-8.
7. Thayer, K.A., et al., *Role of Environmental Chemicals in Diabetes and Obesity: A National Toxicology Program Workshop Report.* Environ Health Perspect, 2012.
8. Speakman, R.J. and S. O'Rahilly, *Fat: an evolving issue.* Dis. Model. Mech., 2012. **5**: p. 569-573.
9. Legler, J., et al., *Obesity, diabetes, and associated costs of exposure to endocrine-disrupting chemicals in the European Union.* J Clin Endocrinol Metab, 2015. **100**(4): p. 1278-88.
10. Seuring, T., O. Archangelidi, and M. Suhrcke, *The Economic Costs of Type 2 Diabetes: A Global Systematic Review.* Pharmacoeconomics, 2015. **33**(8): p. 811-31.
11. Herman, K.M., et al., *Tracking of obesity and physical activity from childhood to adulthood: the Physical Activity Longitudinal Study.* Int J Pediatr Obes, 2009. **4**(4): p. 281-8.
12. Kim, J., et al., *Trends in overweight from 1980 through 2001 among preschool-aged children enrolled in a health maintenance organization.* Obesity (Silver Spring), 2006. **14**(7): p. 1107-12.
13. Klimentidis, Y.C., et al., *Canaries in the coal mine: a cross-species analysis of the plurality of obesity epidemics.* Proceedings of the Royal Society B: Biological Sciences, 2010.
14. Trasande, L., T.M. Attina, and J. Blustein, *Association between urinary bisphenol A concentration and obesity prevalence in children and adolescents.* JAMA, 2012. **308**: p. 1113-1121.
15. Association, A.D., *Diagnosis and classification of diabetes mellitus.* Diabetes Care, 2004. **27 Suppl 1**: p. S5-S10.

16. Muoio, D.M. and C.B. Newgard, *Mechanisms of disease:Molecular and metabolic mechanisms of insulin resistance and beta-cell failure in type 2 diabetes.* Nat Rev Mol Cell Biol, 2008. **9**(3): p. 193-205.
17. Wild, S., et al., *Global prevalence of diabetes: estimates for the year 2000 and projections for 2030.* Diabetes Care, 2004. **27**(5): p. 1047-53.
18. Dabelea, D. and E.J. Mayer-Davis, *Diabetes prevalence among youth--reply.* Jama, 2014. **312**(11): p. 1153-4.
19. Nguyen, N.T., et al., *Relationship between obesity and diabetes in a US adult population: findings from the National Health and Nutrition Examination Survey, 1999-2006.* Obes Surg, 2011. **21**(3): p. 351-5.
20. Younossi, Z.M., et al., *Global Epidemiology of Non-Alcoholic Fatty Liver Disease-Meta-Analytic Assessment of Prevalence, Incidence and Outcomes.* Hepatology, 2015.
21. Anderson, E.L., et al., *The Prevalence of Non-Alcoholic Fatty Liver Disease in Children and Adolescents: A Systematic Review and Meta-Analysis.* PLoS One, 2015. **10**(10): p. e0140908.
22. Bhatia, L.S., et al., *Non-alcoholic fatty liver disease: a new and important cardiovascular risk factor?* Eur Heart J, 2012. **33**(10): p. 1190-200.
23. Durazzo, M., et al., *Gender specific medicine in liver diseases: a point of view.* World J Gastroenterol, 2014. **20**(9): p. 2127-35.
24. Souza, M.R., et al., *Metabolic syndrome and risk factors for non-alcoholic fatty liver disease.* Arq Gastroenterol, 2012. **49**(1): p. 89-96.
25. Carroll, M., B. Kit, and D. Lacher, *Trends in elevated triglyceride in adults: United States, 2001-2012.* NCHS Data Brief, 2015(198): p. 198.
26. Carroll, M.D., et al., *Trends in lipids and lipoproteins in US adults, 1988-2010.* Jama, 2012. **308**(15): p. 1545-54.
27. Kit, B.K., et al., *Prevalence of and trends in dyslipidemia and blood pressure among US children and adolescents, 1999-2012.* JAMA Pediatr, 2015. **169**(3): p. 272-9.
28. Haas, J.T. and S.B. Biddinger, *Dissecting the role of insulin resistance in the metabolic syndrome.* Curr Opin Lipidol, 2009. **20**(3): p. 206-10.
29. Waalen, J., *The genetics of human obesity.* Transl Res, 2014. **164**(4): p. 293-301.
30. Locke, A.E., et al., *Genetic studies of body mass index yield new insights for obesity biology.* Nature, 2015. **518**(7538): p. 197-206.
31. Maes, H.H., M.C. Neale, and L.J. Eaves, *Genetic and environmental factors in relative body weight and human adiposity.* Behav Genet, 1997. **27**(4): p. 325-51.
32. Stunkard, A.J., T.T. Foch, and Z. Hrubec, *A twin study of human obesity.* JAMA, 1986. **256**(1): p. 51-4.
33. Choquet, H. and D. Meyre, *Genetics of Obesity: What have we Learned?* Curr Genomics, 2011. **12**(3): p. 169-79.
34. Speliotes, E.K., et al., *Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index.* Nat Genet, 2010. **42**(11): p. 937-48.
35. Peters, T., K. Ausmeier, and U. Ruther, *Cloning of Fatso (Fto), a novel gene deleted by the Fused toes (Ft) mouse mutation.* Mamm Genome, 1999. **10**(10): p. 983-6.
36. Willer, C.J., et al., *Six new loci associated with body mass index highlight a neuronal influence on body weight regulation.* Nat Genet, 2009. **41**(1): p. 25-34.
37. Goldstone, A.P. and P.L. Beales, *Genetic obesity syndromes.* Front Horm Res, 2008. **36**: p. 37-60.
38. Todd, J.A., J.I. Bell, and H.O. McDevitt, *HLA-DQ beta gene contributes to susceptibility and resistance to insulin-dependent diabetes mellitus.* Nature, 1987. **329**(6140): p. 599-604.

39. Vehik, K., et al., *The changing landscape of type 1 diabetes: recent developments and future frontiers.* Curr Diab Rep, 2013. **13**(5): p. 642-50.
40. Groop, L., et al., *Metabolic consequences of a family history of NIDDM (the Botnia study): evidence for sex-specific parental effects.* Diabetes, 1996. **45**(11): p. 1585-93.
41. Kaprio, J., et al., *Concordance for type 1 (insulin-dependent) and type 2 (non-insulin-dependent) diabetes mellitus in a population-based cohort of twins in Finland.* Diabetologia, 1992. **35**(11): p. 1060-7.
42. Lyssenko, V. and M. Laakso, *Genetic screening for the risk of type 2 diabetes: worthless or valuable?* Diabetes Care, 2013. **36 Suppl 2**: p. S120-6.
43. Norris, J.M. and S.S. Rich, *Genetics of glucose homeostasis: implications for insulin resistance and metabolic syndrome.* Arterioscler Thromb Vasc Biol, 2012. **32**(9): p. 2091-6.
44. Hara, K., et al., *Genetic architecture of type 2 diabetes.* Biochem Biophys Res Commun, 2014. **452**(2): p. 213-20.
45. Chang, M.H., et al., *Genetic variants associated with fasting blood lipids in the U.S. population: Third National Health and Nutrition Examination Survey.* BMC Med Genet, 2010. **11**: p. 62.
46. Heller, D.A., et al., *Genetic and environmental influences on serum lipid levels in twins.* N Engl J Med, 1993. **328**(16): p. 1150-6.
47. Spielmann, N., et al., *CETP genotypes and HDL-cholesterol phenotypes in the HERITAGE Family Study.* Physiol Genomics, 2007. **31**(1): p. 25-31.
48. Garuti, R., et al., *The modular adaptor protein autosomal recessive hypercholesterolemia (ARH) promotes low density lipoprotein receptor clustering into clathrin-coated pits.* J Biol Chem, 2005. **280**(49): p. 40996-1004.
49. Ramasamy, I., *Update on the molecular biology of dyslipidemias.* Clin Chim Acta, 2015.
50. Gutierrez-Cirlos, C., et al., *Familial hypobetalipoproteinemia in a hospital survey: genetics, metabolism and non-alcoholic fatty liver disease.* Ann Hepatol, 2011. **10**(2): p. 155-64.
51. Dongiovanni, P. and L. Valenti, *Genetics of nonalcoholic fatty liver disease.* Metabolism, 2015.
52. Romeo, S., et al., *Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease.* Nat Genet, 2008. **40**(12): p. 1461-5.
53. Dongiovanni, P., S. Romeo, and L. Valenti, *Genetic Factors in the Pathogenesis of Nonalcoholic Fatty Liver and Steatohepatitis.* Biomed Res Int, 2015. **2015**: p. 460190.
54. Kozlitina, J., et al., *Exome-wide association study identifies a TM6SF2 variant that confers susceptibility to nonalcoholic fatty liver disease.* Nat Genet, 2014. **46**(4): p. 352-6.
55. Liu, Y.L., et al., *TM6SF2 rs58542926 influences hepatic fibrosis progression in patients with non-alcoholic fatty liver disease.* Nat Commun, 2014. **5**: p. 4309.
56. Das, U.N., *Obesity: genes, brain, gut, and environment.* Nutrition, 2010. **26**(5): p. 459-73.
57. Maric, G., et al., *The role of gut hormones in appetite regulation (review).* Acta Physiol Hung, 2014. **101**(4): p. 395-407.
58. Exley, M.A., et al., *Interplay between the immune system and adipose tissue in obesity.* J Endocrinol, 2014. **223**(2): p. R41-8.
59. Lanthier, N. and I.A. Leclercq, *Adipose tissues as endocrine target organs.* Best Practice & Research Clinical Gastroenterology, 2014. **28**(4): p. 545-558.
60. Sohn, J.W., *Network of Hypothalamic Neurons that Control Appetite.* BMB Rep, 2015.
61. Volkow, N.D., et al., *Obesity and addiction: neurobiological overlaps.* Obes Rev, 2013. **14**(1): p. 2-18.

62. Jager, G. and R.F. Witkamp, *The endocannabinoid system and appetite: relevance for food reward.* Nutr Res Rev, 2014. **27**(1): p. 172-85.
63. Schellekens, H., et al., *Ghrelin signalling and obesity: at the interface of stress, mood and food reward.* Pharmacol Ther, 2012. **135**(3): p. 316-26.
64. Broberger, C., *Brain regulation of food intake and appetite: molecules and networks.* J Intern Med, 2005. **258**(4): p. 301-27.
65. Mercer, J.G. and Z.A. Archer, *Putting the diet back into diet-induced obesity: diet-induced hypothalamic gene expression.* Eur J Pharmacol, 2008. **585**(1): p. 31-7.
66. Field, B.C., *Neuroendocrinology of obesity.* Br Med Bull, 2014. **109**: p. 73-82.
67. Lustig, R.H., *The neuroendocrinology of obesity.* Endocrinol Metab Clin North Am, 2001. **30**(3): p. 765-85.
68. Somogyi, V., et al., *Endocrine factors in the hypothalamic regulation of food intake in females: a review of the physiological roles and interactions of ghrelin, leptin, thyroid hormones, oestrogen and insulin.* Nutr Res Rev, 2011. **24**(1): p. 132-54.
69. Schwartz, M.W., et al., *Central nervous system control of food intake.* Nature, 2000. **404**(6778): p. 661-671.
70. Cone, R.D., et al., *The arcuate nucleus as a conduit for diverse signals relevant to energy homeostasis.* Int J Obes Relat Metab Disord, 2001. **25 Suppl 5**: p. S63-7.
71. Beck, B., *Neuropeptide Y in normal eating and in genetic and dietary-induced obesity.* Philos Trans R Soc Lond B Biol Sci, 2006. **361**(1471): p. 1159-85.
72. Bertolini, A., R. Tacchi, and A.V. Vergoni, *Brain effects of melanocortins.* Pharmacol Res, 2009. **59**(1): p. 13-47.
73. Coll, A.P. and Y.C. Loraine Tung, *Pro-opiomelanocortin (POMC)-derived peptides and the regulation of energy homeostasis.* Mol Cell Endocrinol, 2009. **300**(1-2): p. 147-51.
74. Harrold, J.A. and G. Williams, *Melanocortin-4 receptors, beta-MSH and leptin: key elements in the satiety pathway.* Peptides, 2006. **27**(2): p. 365-71.
75. Inui, A., *Transgenic study of energy homeostasis equation: implications and confounding influences.* Faseb j, 2000. **14**(14): p. 2158-70.
76. Eva, C., et al., *Physiology and gene regulation of the brain NPY Y1 receptor.* Frontiers in Neuroendocrinology, 2006. **27**: p. 308-339.
77. Bertocchi, I., et al., *Regulatory functions of limbic Y1 receptors in body weight and anxiety uncovered by conditional knockout and maternal care.* Proc Natl Acad Sci U S A, 2011. **108**(48): p. 19395-400.
78. Ding, B., et al., *Human neuropeptide Y signal peptide gain-of-function polymorphism is associated with increased body mass index: possible mode of function.* Regul Pept, 2005. **127**(1-3): p. 45-53.
79. Ukkola, O. and Y.A. Kesaniemi, *Leu7Pro polymorphism of PreproNPY associated with an increased risk for type II diabetes in middle-aged subjects.* Eur J Clin Nutr, 2007. **61**(9): p. 1102-5.
80. Elmquist, J.K., C.F. Elias, and C.B. Saper, *From Lesions to Leptin: Hypothalamic Control of Food Intake and Body Weight.* Neuron, 1999. **22**: p. 221–232.
81. Kalra, S.P., et al., *Interacting appetite-regulating pathways in the hypothalamic regulation of body weight.* Endocr Rev, 1999. **20**(1): p. 68-100.
82. Aréchiga-Ceballos, F., et al., *Pro-TRH and pro-CRF expression in paraventricular nucleus of small litter-reared fasted adult rats.* The Journal of endocrinology, 2014. **221**(1): p. 77-88.
83. von Holstein-Rathlou, S., et al., *FGF21 Mediates Endocrine Control of Simple Sugar Intake and Sweet Taste Preference by the Liver.* Cell Metab, 2016. **23**(2): p. 335-43.

84. Olofsson, L.E., A.A. Pierce, and A.W. Xu, *Functional requirement of AgRP and NPY neurons in ovarian cycle-dependent regulation of food intake.* Proc Natl Acad Sci U S A, 2009. **106**(37): p. 15932-7.
85. Asarian, L., et al., *Estradiol increases body weight loss and gut-peptide satiation after Roux-en-Y gastric bypass in ovariectomized rats.* Gastroenterology, 2012. **143**(2): p. 325-7 e2.
86. Asarian, L. and N. Geary, *Modulation of appetite by gonadal steroid hormones.* Philos Trans R Soc Lond B Biol Sci, 2006. **361**(1471): p. 1251-63.
87. Clegg, D.J., *Minireview: the year in review of estrogen regulation of metabolism.* Mol Endocrinol, 2012. **26**(12): p. 1957-60.
88. Gao, Q. and T.L. Horvath, *Neuronal control of energy homeostasis.* FEBS Lett, 2008. **582**(1): p. 132-41.
89. Hussain, M.A., W.J. Song, and A. Wolfe, *There is Kisspeptin - And Then There is Kisspeptin.* Trends Endocrinol Metab, 2015. **26**(10): p. 564-72.
90. Oakley, A.E., D.K. Clifton, and R.A. Steiner, *Kisspeptin signaling in the brain.* Endocr Rev, 2009. **30**(6): p. 713-43.
91. Song, W.J., et al., *Glucagon regulates hepatic kisspeptin to impair insulin secretion.* Cell Metab, 2014. **19**(4): p. 667-81.
92. Tolson, K.P., et al., *Impaired kisspeptin signaling decreases metabolism and promotes glucose intolerance and obesity.* J Clin Invest, 2014. **124**(7): p. 3075-9.
93. Navarro, V.M., et al., *Developmental and hormonally regulated messenger ribonucleic acid expression of KiSS-1 and its putative receptor, GPR54, in rat hypothalamus and potent luteinizing hormone-releasing activity of KiSS-1 peptide.* Endocrinology, 2004. **145**(10): p. 4565-74.
94. Smith, J.T., D.K. Clifton, and R.A. Steiner, *Regulation of the neuroendocrine reproductive axis by kisspeptin-GPR54 signaling.* Reproduction, 2006. **131**: p. 623-630.
95. Mueller, J.K. and S. Heger, *Endocrine disrupting chemicals affect the gonadotropin releasing hormone neuronal network.* Reproductive toxicology, 2014. **44**: p. 73-84.
96. Panzica, G.C., et al., *Neuropeptides and Enzymes are Targets for the Action of Endocrine Disrupting Chemicals in the Vertebrate Brain.* J Toxicol Environ Health B Crit Rev, 2011. **14**(5-7): p. 449-72.
97. Patisaul, H.B. and E.K. Polston, *Influence of endocrine active compounds on the developing rodent brain.* Brain Res Rev, 2008. **57**(2): p. 352-62.
98. Rosen, E.D., *Two paths to fat.* Nat Cell Biol, 2015. **17**(4): p. 360-361.
99. Lafontan, M. and J. Girard, *Impact of visceral adipose tissue on liver metabolism. Part I: heterogeneity of adipose tissue and functional properties of visceral adipose tissue.* Diabetes Metab, 2008. **34**(4 Pt 1): p. 317-27.
100. Rosen, E.D. and B.M. Spiegelman, *What we talk about when we talk about fat.* Cell, 2014. **156**(1-2): p. 20-44.
101. Santoro, A., G. Mattace Raso, and R. Meli, *Drug targeting of leptin resistance.* Life Sci, 2015. **140**: p. 64-74.
102. Chakraborti, C.K., *Role of adiponectin and some other factors linking type 2 diabetes mellitus and obesity.* World J Diabetes, 2015. **6**(15): p. 1296-308.
103. Yang, X. and H.B. Ruan, *Neuronal Control of Adaptive Thermogenesis.* Front Endocrinol (Lausanne), 2015. **6**: p. 149.
104. Poissonnet, C.M., A.R. Burdi, and S.M. Garn, *The chronology of adipose tissue appearance and distribution in the human fetus.* Early Hum Dev, 1984. **10**(1-2): p. 1-11.

105. Spalding, K.L., et al., *Dynamics of fat cell turnover in humans.* Nature, 2008. **453**(7196): p. 783-7.
106. Wang, Q.A., et al., *Tracking adipogenesis during white adipose tissue development, expansion and regeneration.* Nat Med, 2013. **19**(10): p. 1338-44.
107. James, A.W., *Review of Signaling Pathways Governing MSC Osteogenic and Adipogenic Differentiation.* Scientifica (Cairo), 2013. **2013**: p. 684736.
108. Quiñones, M., et al., *Cross-talk between SIRT1 and endocrine factors: effects on energy homeostasis.* Molecular and Cellular Endocrinology, 2014. **397**(1–2): p. 42-50.
109. Rosen, E.D. and O.A. MacDougald, *Adipocyte differentiation from the inside out.* Nat Rev Mol Cell Biol, 2006. **7**(12): p. 885-96.
110. Cristancho, A.G. and M.A. Lazar, *Forming functional fat: a growing understanding of adipocyte differentiation.* Nat Rev Mol Cell Biol, 2011. **12**(11): p. 722-34.
111. Chau, Y.Y., et al., *Visceral and subcutaneous fat have different origins and evidence supports a mesothelial source.* Nat Cell Biol, 2014. **16**(4): p. 367-75.
112. Atit, R., et al., *Beta-catenin activation is necessary and sufficient to specify the dorsal dermal fate in the mouse.* Dev Biol, 2006. **296**(1): p. 164-76.
113. Billon, N. and C. Dani, *Developmental origins of the adipocyte lineage: new insights from genetics and genomics studies.* Stem Cell Rev, 2012. **8**(1): p. 55-66.
114. Harms, M. and P. Seale, *Brown and beige fat: development, function and therapeutic potential.* Nat Med, 2013. **19**(10): p. 1252-63.
115. Wang, Q.A., et al., *Distinct regulatory mechanisms governing embryonic versus adult adipocyte maturation.* Nat Cell Biol, 2015. **17**(9): p. 1099-111.
116. Pittenger, M.F., et al., *Multilineage potential of adult human mesenchymal stem cells.* Science, 1999. **284**(5411): p. 143-7.
117. Nimmo, R.A., G.E. May, and T. Enver, *Primed and ready: understanding lineage commitment through single cell analysis.* Trends Cell Biol, 2015. **25**(8): p. 459-67.
118. Gupta, R.K., et al., *Transcriptional control of preadipocyte determination by Zfp423.* Nature, 2010. **464**(7288): p. 619-23.
119. Quach, J.M., et al., *Zinc finger protein 467 is a novel regulator of osteoblast and adipocyte commitment.* J Biol Chem, 2011. **286**(6): p. 4186-98.
120. Jin, W., et al., *Schnurri-2 controls BMP-dependent adipogenesis via interaction with Smad proteins.* Dev Cell, 2006. **10**(4): p. 461-71.
121. Carnevalli, L.S., et al., *S6K1 plays a critical role in early adipocyte differentiation.* Dev Cell, 2010. **18**(5): p. 763-74.
122. Siersbaek, R. and S. Mandrup, *Transcriptional networks controlling adipocyte differentiation.* Cold Spring Harb Symp Quant Biol, 2011. **76**: p. 247-55.
123. Tontonoz, P. and B.M. Spiegelman, *Fat and beyond: the diverse biology of PPARgamma.* Annu Rev Biochem, 2008. **77**: p. 289-312.
124. Lefterova, M.I., et al., *PPARgamma and C/EBP factors orchestrate adipocyte biology via adjacent binding on a genome-wide scale.* Genes Dev, 2008. **22**(21): p. 2941-52.
125. Brissova, M., et al., *Assessment of human pancreatic islet architecture and composition by laser scanning confocal microscopy.* J Histochem Cytochem, 2005. **53**(9): p. 1087-97.
126. Marroqui, L., et al., *Nutrient regulation of glucagon secretion: involvement in metabolism and diabetes.* Nutr Res Rev, 2014. **27**(1): p. 48-62.
127. Cabrera, O., et al., *The unique cytoarchitecture of human pancreatic islets has implications for islet cell function.* Proc Natl Acad Sci U S A, 2006. **103**(7): p. 2334-9.
128. Teta, M., et al., *Very slow turnover of beta-cells in aged adult mice.* Diabetes, 2005. **54**(9): p. 2557-67.

129. Meier, J.J., et al., *Beta-cell replication is the primary mechanism subserving the postnatal expansion of beta-cell mass in humans.* Diabetes, 2008. **57**(6): p. 1584-94.
130. Yi, P., J.-S. Park, and Douglas A. Melton, *Betatrophin: A Hormone that Controls Pancreatic ² Cell Proliferation.* Cell, 2013.
131. Ohlstein, J.F., et al., *Bisphenol A enhances adipogenic differentiation of human adipose stromal/stem cells.* J Mol Endocrinol, 2014. **53**(3): p. 345-53.
132. Unger, R.H., et al., *Studies of pancreatic alpha cell function in normal and diabetic subjects.* J Clin Invest, 1970. **49**(4): p. 837-48.
133. Quesada, I., et al., *Physiology of the pancreatic alpha-cell and glucagon secretion: role in glucose homeostasis and diabetes.* J Endocrinol, 2008. **199**(1): p. 5-19.
134. Ishihara, H., et al., *Islet beta-cell secretion determines glucagon release from neighbouring alpha-cells.* Nat Cell Biol, 2003. **5**(4): p. 330-5.
135. Ravier, M.A. and G.A. Rutter, *Glucose or insulin, but not zinc ions, inhibit glucagon secretion from mouse pancreatic alpha-cells.* Diabetes, 2005. **54**(6): p. 1789-97.
136. Wendt, A., et al., *Glucose inhibition of glucagon secretion from rat alpha-cells is mediated by GABA released from neighboring beta-cells.* Diabetes, 2004. **53**(4): p. 1038-45.
137. Thorens, B., *Brain glucose sensing and neural regulation of insulin and glucagon secretion.* Diabetes Obes Metab, 2011. **13 Suppl 1**: p. 82-8.
138. Campbell, J.E. and D.J. Drucker, *Islet alpha cells and glucagon-critical regulators of energy homeostasis.* Nat Rev Endocrinol, 2015.
139. Saltiel, A.R. and C.R. Kahn, *Insulin signalling and the regulation of glucose and lipid metabolism.* Nature, 2001. **414**(6865): p. 799-806.
140. Yoon, J.C., et al., *Control of hepatic gluconeogenesis through the transcriptional coactivator PGC-1.* Nature, 2001. **413**(6852): p. 131-8.
141. Herzig, S., et al., *CREB regulates hepatic gluconeogenesis through the coactivator PGC-1.* Nature, 2001. **413**(6852): p. 179-83.
142. Vidal-Puig, A. and S. O'Rahilly, *Metabolism. Controlling the glucose factory.* Nature, 2001. **413**(6852): p. 125-6.
143. Koo, S.H., et al., *The CREB coactivator TORC2 is a key regulator of fasting glucose metabolism.* Nature, 2005. **437**(7062): p. 1109-11.
144. Longuet, C., et al., *The glucagon receptor is required for the adaptive metabolic response to fasting.* Cell Metab, 2008. **8**(5): p. 359-71.
145. Anthonsen, M.W., et al., *Identification of novel phosphorylation sites in hormone-sensitive lipase that are phosphorylated in response to isoproterenol and govern activation properties in vitro.* J Biol Chem, 1998. **273**(1): p. 215-21.
146. Kitamura, T., et al., *Insulin-induced phosphorylation and activation of cyclic nucleotide phosphodiesterase 3B by the serine-threonine kinase Akt.* Mol Cell Biol, 1999. **19**(9): p. 6286-96.
147. Habegger, K.M., et al., *Fibroblast growth factor 21 mediates specific glucagon actions.* Diabetes, 2013. **62**(5): p. 1453-63.
148. Lefebvre, P., A. Luyckx, and Z.M. Bacq, *Effects of denervation on the metabolism and the response to glucagon of white adipose tissue of rats.* Horm Metab Res, 1973. **5**(4): p. 245-50.
149. In't Veld, P. and M. Marichal, *Microscopic anatomy of the human islet of Langerhans.* Adv Exp Med Biol, 2010. **654**: p. 1-19.
150. Moran, A., et al., *Insulin resistance during puberty: results from clamp studies in 357 children.* Diabetes, 1999. **48**(10): p. 2039-44.

151. Buchanan, T.A., et al., *Insulin sensitivity and B-cell responsiveness to glucose during late pregnancy in lean and moderately obese women with normal glucose tolerance or mild gestational diabetes.* Am J Obstet Gynecol, 1990. **162**(4): p. 1008-14.
152. Amaral, M.E., et al., *Participation of prolactin receptors and phosphatidylinositol 3-kinase and MAP kinase pathways in the increase in pancreatic islet mass and sensitivity to glucose during pregnancy.* J Endocrinol, 2004. **183**(3): p. 469-76.
153. Nadal, A., et al., *The role of oestrogens in the adaptation of islets to insulin resistance.* J Physiol, 2009. **587**(Pt 21): p. 5031-7.
154. Mauvais-Jarvis, F., D.J. Clegg, and A.L. Hevener, *The role of estrogens in control of energy balance and glucose homeostasis.* Endocr Rev, 2013. **34**(3): p. 309-38.
155. Kahn, S.E., et al., *Importance of early phase insulin secretion to intravenous glucose tolerance in subjects with type 2 diabetes mellitus.* J Clin Endocrinol Metab, 2001. **86**(12): p. 5824-9.
156. Dunmore, S.J. and J.E. Brown, *The role of adipokines in beta-cell failure of type 2 diabetes.* J Endocrinol, 2013. **216**(1): p. T37-45.
157. Holst, J.J., *Incretin hormones and the satiation signal.* Int J Obes (Lond), 2013. **37**(9): p. 1161-8.
158. Angrish, M.M., et al., *Tipping the Balance: Hepatotoxicity and the Four Apical Key Events of Hepatic Steatosis.* Toxicological Sciences, 2016. **[in press]**.
159. Wahlang, B., et al., *Polychlorinated Biphenyl-Xenobiotic Nuclear Receptor Interactions Regulate Energy Metabolism, Behavior, and Inflammation in Nonalcoholic-Steatohepatitis.* Toxicological Sciences, 2015.
160. Gadupudi, G.S., et al., *PCB126-Induced Disruption in Gluconeogenesis and Fatty Acid Oxidation Precedes Fatty Liver in Male Rats.* Toxicol Sci, 2016. **149**(1): p. 98-110.
161. Kaiser, J.P., J.C. Lipscomb, and S.C. Wesselkamper, *Putative mechanisms of environmental chemical-induced steatosis.* Int J Toxicol, 2012. **31**(6): p. 551-63.
162. Wahlang, B., et al., *Toxicant-associated steatohepatitis.* Toxicol Pathol, 2013. **41**(2): p. 343-60.
163. Joshi-Barve, S., et al., *Alcoholic, Non-alcoholic and Toxicant-Associated Steatohepatitis: Mechanistic Similarities and Differences. .* Cellular and Molecular Gastroenterology and Hepatology, 2015. **1**(4): p. 356-367.
164. Brent, G.A., *The molecular basis of thyroid hormone action.* N Engl J Med, 1994. **331**(13): p. 847-53.
165. Marsili, A., et al., *Physiological role and regulation of iodothyronine deiodinases: a 2011 update.* J Endocrinol Invest, 2011. **34**(5): p. 395-407.
166. Costa-e-Sousa, R.H. and A.N. Hollenberg, *Minireview: The neural regulation of the hypothalamic-pituitary-thyroid axis.* Endocrinology, 2012. **153**(9): p. 4128-35.
167. Laurberg, P., et al., *Thyroid function and obesity.* Eur Thyroid J, 2012. **1**(3): p. 159-67.
168. Biondi, B., *Thyroid and obesity: an intriguing relationship.* J Clin Endocrinol Metab, 2010. **95**(8): p. 3614-7.
169. Laurberg, P., et al., *The Danish investigation on iodine intake and thyroid disease, DanThyr: status and perspectives.* Eur J Endocrinol, 2006. **155**(2): p. 219-28.
170. Taylor, P.N., et al., *Clinical review: A review of the clinical consequences of variation in thyroid function within the reference range.* J Clin Endocrinol Metab, 2013. **98**(9): p. 3562-71.
171. Santini, F., et al., *Mechanisms in endocrinology: the crosstalk between thyroid gland and adipose tissue: signal integration in health and disease.* Eur J Endocrinol, 2014. **171**(4): p. R137-52.

172. Kristiansson, K., et al., *Genome-wide screen for metabolic syndrome susceptibility Loci reveals strong lipid gene contribution but no evidence for common genetic basis for clustering of metabolic syndrome traits.* Circ Cardiovasc Genet, 2012. **5**(2): p. 242-9.
173. Longhi, S. and G. Radetti, *Thyroid function and obesity.* J Clin Res Pediatr Endocrinol, 2013. **5 Suppl 1**: p. 40-4.
174. Ford, E.S., *Prevalence of the metabolic syndrome defined by the International Diabetes Federation among adults in the U.S.* Diabetes Care, 2005. **28**: p. 2745-9.
175. Breedlove, S.M., B.M. Cooke, and C.L. Jordan, *The orthodox view of brain sexual differentiation.* Brain, Behavior and Evolution, 1999. **54**: p. 8-14.
176. Melcangi, R.C. and G.C. Panzica, *Neuroactive steroids: old players in a new game.* Neuroscience, 2006. **138**: p. 733-739.
177. Panzica, G.C., et al., *Structural sex differences in the brain: influence of gonadal steroids and behavioral correlates.* Journal of Endocrinological Investigation, 1995. **18**(3): p. 232-52.
178. Swithers, S.E., et al., *Influence of ovarian hormones on development of ingestive responding to alterations in fatty acid oxidation in female rats.* Horm Behav, 2008. **54**(3): p. 471-7.
179. Asarian, L. and N. Geary, *Sex differences in the physiology of eating.* Am J Physiol Regul Integr Comp Physiol, 2013. **305**(11): p. R1215-67.
180. Palmer, B.F. and D.J. Clegg, *The sexual dimorphism of obesity.* Mol Cell Endocrinol, 2015. **402**: p. 113-9.
181. Shi, H., R.J. Seeley, and D.J. Clegg, *Sexual differences in the control of energy homeostasis.* Front Neuroendocrinol, 2009. **30**(3): p. 396-404.
182. Shi, H., et al., *Sexually different actions of leptin in proopiomelanocortin neurons to regulate glucose homeostasis.* Am J Physiol Endocrinol Metab, 2008. **294**(3): p. E630-9.
183. Clegg, D.J., et al., *Gonadal hormones determine sensitivity to central leptin and insulin.* Diabetes, 2006. **55**(4): p. 978-87.
184. Nohara, K., et al., *Early-life exposure to testosterone programs the hypothalamic melanocortin system.* Endocrinology, 2011. **152**(4): p. 1661-9.
185. Urban, J.H., A.C. Bauer-Dantoin, and J.E. Levine, *Neuropeptide Y gene expression in the arcuate nucleus: sexual dimorphism and modulation by testosterone.* Endocrinology, 1993. **132**: p. 139-145.
186. Bo, E., et al., *Adult exposure to tributyltin affects hypothalamic neuropeptide Y, Y1 receptor distribution, and circulating leptin in mice.* Andrology, 2016. **Submitted**.
187. Martini, M., et al., *Effects of estrous cycle and sex on the expression of neuropeptide Y Y1 receptor in discrete hypothalamic and limbic nuclei of transgenic mice.* Peptides, 2011. **32**(6): p. 1330-4.
188. Zhu, Z., et al., *Central expression and anorectic effect of brain-derived neurotrophic factor are regulated by circulating estradiol levels.* Horm Behav, 2013. **63**(3): p. 533-42.
189. Geary, N., *Estradiol, CCK and satiation.* Peptides, 2001. **22**(8): p. 1251-63.
190. Della Torre, S., et al., *Energy metabolism and fertility: a balance preserved for female health.* Nature reviews. Endocrinology, 2014. **10**(1): p. 13-23.
191. Della Torre, S., et al., *An Essential Role for Liver ERalpha in Coupling Hepatic Metabolism to the Reproductive Cycle.* Cell Rep, 2016. **15**(2): p. 360-71.
192. Roy, A.K. and B. Chatterjee, *Sexual dimorphism in the liver.* Annu Rev Physiol, 1983. **45**: p. 37-50.
193. Waxman, D.J. and M.G. Holloway, *Sex differences in the expression of hepatic drug metabolizing enzymes.* Mol Pharmacol, 2009. **76**(2): p. 215-28.

194. Meibohm, B., I. Beierle, and H. Derendorf, *How important are gender differences in pharmacokinetics?* Clin Pharmacokinet, 2002. **41**(5): p. 329-42.
195. Waxman, D.J. and C. O'Connor, *Growth hormone regulation of sex-dependent liver gene expression.* Mol Endocrinol, 2006. **20**(11): p. 2613-29.
196. Ramirez, M.C., et al., *Pituitary and brain dopamine D2 receptors regulate liver gene sexual dimorphism.* Endocrinology, 2015. **156**(3): p. 1040-51.
197. Geiger, B.M., et al., *Deficits of mesolimbic dopamine neurotransmission in rat dietary obesity.* Neuroscience, 2009. **159**(4): p. 1193-9.
198. Noain, D., et al., *Central dopamine D2 receptors regulate growth-hormone-dependent body growth and pheromone signaling to conspecific males.* J Neurosci, 2013. **33**(13): p. 5834-42.
199. Wang, G.J., et al., *Brain dopamine and obesity.* Lancet, 2001. **357**(9253): p. 354-7.
200. McAllister, E.J., et al., *Ten Putative Contributors to the Obesity Epidemic.* Critical reviews in food science and nutrition, 2009. **49**(10): p. 868-913.
201. Eisenmann, J.C., *Insight into the causes of the recent secular trend in pediatric obesity: Common sense does not always prevail for complex, multi-factorial phenotypes.* Prev Med, 2006. **42**(5): p. 329-35.
202. Principi, N. and S. Esposito, *Antibiotic administration and the development of obesity in children.* Int J Antimicrob Agents, 2016.
203. Voss, J.D., R.L. Atkinson, and N.V. Dhurandhar, *Role of adenoviruses in obesity.* Rev Med Virol, 2015. **25**(6): p. 379-87.
204. Heindel, J.J., R. Newbold, and T.T. Schug, *Endocrine disruptors and obesity.* Nat Rev Endocrinol, 2015. **11**(11): p. 653-61.
205. Casals-Casas, C. and B. Desvergne, *Endocrine disruptors: from endocrine to metabolic disruption.* Annu Rev Physiol, 2011. **73**: p. 135-62.
206. PF, B.-H., - *Chemical toxins: a hypothesis to explain the global obesity epidemic.* J Altern Complement Med, 2002. **8**(2): p. 185-92.
207. Neel, B.A. and R.M. Sargis, *The paradox of progress: environmental disruption of metabolism and the diabetes epidemic.* Diabetes, 2011. **60**(7): p. 1838-48.
208. Zoeller, R.T., et al., *Endocrine-disrupting chemicals and public health protection: a statement of principles from The Endocrine Society.* Endocrinology, 2012. **153**(9): p. 4097-110.
209. Kavlock, R.J., et al., *Research needs for the risk assessment of health and environmental effects of endocrine disruptors: a report of the U.S. EPA-sponsored workshop.* Environ Health Perspect, 1996. **104**(Supp 4): p. 715-740.
210. Bergman, A., et al., *The impact of endocrine disruption: a consensus statement on the state of the science.* Environ Health Perspect, 2013. **121**(4): p. A104-6.
211. FDA, U.S. *Endocrine Disruptor Knowledge Base*. 2010 August 20, 2012]; Available from: http://www.fda.gov/ScienceResearch/BioinformaticsTools/EndocrineDisruptorKnowledgebase/default.htm.
212. Beausoleil, C., et al., *Low dose effects and non-monotonic dose responses for endocrine active chemicals: science to practice workshop: workshop summary.* Chemosphere, 2013. **93**(6): p. 847-56.
213. Vandenberg, L.N., et al., *Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses.* Endocr Rev, 2012. **33**(3): p. 378-455.
214. Vandenberg, L.N., *Low-dose effects of hormones and endocrine disruptors.* Vitam Horm, 2014. **94**: p. 129-65.
215. Birnbaum, L.S., *Environmental chemicals: evaluating low-dose effects.* Environ Health Perspect, 2012. **120**(4): p. A143-4.

216. Bergman Å, H.J., Jobling S, Kidd KA, Zoeller RT, eds, *The State-of-the-Science of Endocrine Disrupting Chemicals – 2012*. WHO (World Health Organization)/UNEP (United Nations Environment Programme). Vol. Geneva:UNEP/WHO. 2013.
217. Vandenberg, L.N., et al., *Regulatory decisions on endocrine disrupting chemicals should be based on the principles of endocrinology.* Reprod Toxicol, 2013. **38C**: p. 1-15.
218. Cho, M.-R., et al., *Associations of fat mass and lean mass with bone mineral density differ by levels of persistent organic pollutants: National Health and Nutrition Examination Survey 1999-2004.* Chemosphere, 2011. **82**: p. 1268-76.
219. Lee, D.H., et al., *Chlorinated persistent organic pollutants, obesity, and type 2 diabetes.* Endocr Rev, 2014. **35**(4): p. 557-601.
220. TEDX. *TEDX list of potential endocrine disruptors*. 2015 21 November 2015]; Available from: http://endocrinedisruption.org/endocrine-disruption/tedx-list-of-potential-endocrine-disruptors/overview.
221. Diamanti-Kandarakis, E., et al., *Endocrine-disrupting chemicals: an Endocrine Society scientific statement.* Endocr Rev, 2009. **30**(4): p. 293-342.
222. Gore, A.C., J.J. Heindel, and R.T. Zoeller, *Endocrine disruption for endocrinologists (and others).* Endocrinology, 2006. **147**(Suppl 6): p. S1-3.
223. Diamanti-Kandarakis, E., Endocr. Rev., 2009. **30**(4): p. 293.
224. Kortenkamp, A., et al., *State of the Art Assessment of Endocrine Disruptors Final Report*. 2011, European Commission: Brussels. p. 442 pages.
225. Gore, A.C., et al., *EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals.* Endocr Rev, 2015: p. er20151010.
226. Diamanti-Kandarakis, E., et al., *Endocrine-disrupting chemical: an Endocrine Society scientific statement.* Endocr Rev, 2009. **30**: p. 293-342.
227. Trasande, L., et al., *Estimating burden and disease costs of exposure to endocrine-disrupting chemicals in the European union.* J Clin Endocrinol Metab, 2015. **100**(4): p. 1245-55.
228. Gore, A.C., et al., *Executive Summary to EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals.* Endocr Rev, 2015: p. er20151093.
229. Rhomberg, L.R. and J.E. Goodman, *Low-dose effects and nonmonotonic dose-responses of endocrine disrupting chemicals: Has the case been made?* Regul Toxicol Pharmacol, 2012. **64**(1): p. 130-133.
230. Rhomberg, L.R., et al., *A critique of the European Commission document, "State of the Art Assessment of Endocrine Disrupters".* Crit Rev Toxicol, 2012. **42**(6): p. 465-73.
231. Dietrich, D.R., et al., *Scientifically unfounded precaution drives European Commission's recommendations on EDC regulation, while defying common sense, well-established science and risk assessment principles.* Chem Biol Interact, 2013. **205**(1): p. A1-5.
232. Nohynek, G.J., et al., *Endocrine disruption: fact or urban legend?* Toxicology Letters, 2013. **223**(3): p. 295-305.
233. Lamb, J.C.t., et al., *Critical Comments on the WHO-UNEP State of the Science of Endocrine Disrupting Chemicals - 2012.* Regulatory toxicology and pharmacology : RTP, 2014.
234. Lamb, J.C.t., et al., *Comments on the Opinions Published by Bergman et al. (2015) on Critical Comments on the WHO-UNEP State of the Science of Endocrine Disrupting Chemicals (Lamb et al. 2014).* Regul Toxicol Pharmacol, 2015.
235. Bergman, A., et al., *Science and policy on endocrine disrupters must not be mixed: a reply to a "common sense" intervention by toxicology journal editors.* Environ Health, 2013. **12**: p. 69.

236. Bergman, A., et al., *Manufacturing doubt about endocrine disrupter science - A rebuttal of industry-sponsored critical comments on the UNEP/WHO report "State of the Science of Endocrine Disrupting Chemicals 2012".* Regul Toxicol Pharmacol, 2015.
237. Kortenkamp, A., et al., *Response to A critique of the European Commission Document, "State of the Art Assessment of Endocrine Disrupters" by Rhomberg and colleagues--letter to the editor.* Critical reviews in toxicology, 2012. **42**(9): p. 787-9; author reply 790-1.
238. Zoeller, R.T., et al., *A path forward in the debate over health impacts of endocrine disrupting chemicals.* Environ Health, 2014. **13**(1): p. 118.
239. Gore, A.C., *Editorial: an international riposte to naysayers of endocrine-disrupting chemicals.* Endocrinology, 2013. **154**(11): p. 3955-6.
240. Gore, A.C., et al., *Policy decisions on endocrine disruptors should be based on science across disciplines: a response to Dietrich et al.* Endocrinology, 2013. **154**(11): p. 3957-60.
241. Kuzawa, C.W. and Z.M. Thayer, *Timescales of human adaptation: the role of epigenetic processes.* Epigenomics, 2011. **3**(2): p. 221-234.
242. Heindel, J.J. and F.S. vom Saal, *Meeting report: batch-to-batch variability in estrogenic activity in commercial animal diets- importance and approaches for laboratory animal research.* Environ Health Perspect, 2008. **116**(3): p. 389-393.
243. Ruhlen, R.L., et al., *Choice of animal feed can alter fetal steroid levels and mask developmental effects of endocrine disrupting chemicals.* J Develop Origins Health Disease, 2011: p. 1-13.
244. Baldi, F. and A. Mantovani, *A new database for food safety: EDID (Endocrine disrupting chemicals - Diet Interaction Database).* Ann Ist Super Sanita, 2008. **44**(1): p. 57-63.
245. Myers, J.P., et al., *Why public health agencies cannot depend upon 'Good Laboratory Practices' as a criterion for selecting data: the case of bisphenol-A.* Environ Health Perspect, 2009. **117**(3): p. 309-15.
246. vom Saal, F.S., et al., *Flawed experimental design reveals the need for guidelines requiring appropriate positive controls in endocrine disruption research.* Toxicol Sci, 2010. **115**(2): p. 612-3.
247. vom Saal, F.S. and W.V. Welshons, *Large effects from small exposures. II. The importance of positive controls in low-dose research on bisphenol A.* Environmental Research, 2006. **100**: p. 50-76.
248. vom Saal, F.S., et al., *The importance of appropriate controls, animal feed, and animal models in interpreting results from low-dose studies of bisphenol A.* Birth Defects Res (Part A), 2005. **73**: p. 140-145.
249. Hayes, T.B., et al., *The cause of global amphibian declines: a developmental endocrinologist's perspective.* J Exp Biol, 2010. **213**(6): p. 921-33.
250. Hunt, P.A., et al., *Invalid controls undermine conclusions of FDA studies.* Toxicol Sci, 2014. **pii: kfu100. [Epub ahead of print]**.
251. Vandenberg, L.N., *Non-monotonic dose responses in studies of endocrine disrupting chemicals: bisphenol A as a case study.* Dose Response, 2013. **12**(2): p. 259-76.
252. vom Saal, F.S. and C. Hughes, *An extensive new literature concerning low-dose effects of bisphenol A shows the need for a new risk assessment.* Environ Health Perspect, 2005. **113**: p. 926-933.
253. Myers, J.P., R.T. Zoeller, and F.S. vom Saal, *A clash of old and new scientific concepts in toxicity, with important implications for public health.* Environ Health Perspect, 2009. **117**(11): p. 1652-5.

254. Bergman, A., et al., *State of the Science of Endocrine Disrupting Chemicals 2012. Summary for Decision Makers*. 2013, United National Environment Programme and World Health Organization.
255. Hormann, A.M., et al., *Holding thermal receipt paper and eating food after using hand sanitizer results in high serum bioactive and urine total levels of bisphenol A (BPA).* PLoS One, 2014. **9**(10): p. e110509.
256. Needham, L.L., A.M. Calafat, and D.B. Barr, *Assessing developmental toxicant exposures via biomonitoring.* Basic and Clinical Pharmacology and Toxicology, 2008. **102**: p. 100-8.
257. Calafat, A.M., et al., *Urinary concentrations of bisphenol A and 4-nonylphenol in a human reference population.* Environ Health Perspect, 2005. **113**(4): p. 391-5.
258. Calafat, A.M., et al., *Serum concentrations of 11 polyfluoroalkyl compounds in the u.s. population: data from the national health and nutrition examination survey (NHANES).* Environ Sci Technol, 2007. **41**(7): p. 2237-42.
259. Calafat, A.M., et al., *Concentrations of the sunscreen agent benzophenone-3 in residents of the United States: National Health and Nutrition Examination Survey 2003--2004.* Environ Health Perspect, 2008. **116**(7): p. 893-7.
260. Calafat, A.M., et al., *Urinary concentrations of four parabens in the U.S. population: NHANES 2005-2006.* Environ Health Perspect, 2010. **118**(5): p. 679-85.
261. Calafat, A.M., et al., *Exposure of the U.S. population to bisphenol A and 4-tertiary-octylphenol: 2003-2004.* Environ Health Perspect, 2008. **116**(1): p. 39-44.
262. Calafat, A.M., et al., *Urinary concentrations of triclosan in the U.S. population: 2003-2004.* Environ Health Perspect, 2008. **116**(3): p. 303-7.
263. Needham, L.L., D.B. Barr, and A.M. Calafat, *Characterizing children's exposures: beyond NHANES.* NeuroToxicology, 2005. **26**: p. 547-53.
264. Engel, S.M., et al., *Xenobiotic phenols in early pregnancy amniotic fluid.* Reprod Toxicol, 2006. **21**: p. 110-2.
265. Yamada, H., et al., *Maternal serum and amniotic fluid bisphenol A concentrations in the early second trimester.* Reprod Toxicol, 2002. **16**: p. 735-739.
266. Leino, O., et al., *Pollutant concentrations in placenta.* Food Chem Toxicol, 2013. **54**: p. 59-69.
267. Cao, X.L., et al., *Bisphenol A in human placental and fetal liver tissues collected from Greater Montreal area (Quebec) during 1998-2008.* Chemosphere, 2012. **89**(5): p. 505-11.
268. Vizcaino, E., et al., *Transport of persistent organic pollutants across the human placenta.* Environ Int, 2014. **65**: p. 107-15.
269. Wan, Y., et al., *Hydroxylated polybrominated diphenyl ethers and bisphenol A in pregnant women and their matching fetuses: placental transfer and potential risks.* Environ Sci Technol, 2010. **44**(13): p. 5233-9.
270. Gerona, R.R., et al., *BPA, BPA glucuronide, and BPA sulfate in mid-gestation umbilical cord serum in a northern California cohort.* Environ Sci Technol, 2013. **47**(21): p. 12477-85.
271. Barker, D.J., *The origins of the developmental origins theory.* J Intern Med, 2007. **261**(5): p. 412-7.
272. Hanson, M.A. and P.D. Gluckman, *Developmental origins of health and disease--global public health implications.* Best Pract Res Clin Obstet Gynaecol, 2015. **29**(1): p. 24-31.
273. Vickers, M.H., *Developmental programming and transgenerational transmission of obesity.* Ann Nutr Metab, 2014. **64 Suppl 1**: p. 26-34.

274. Sarr, O., K. Yang, and T.R. Regnault, *In utero programming of later adiposity: the role of fetal growth restriction.* J Pregnancy, 2012. **2012**: p. 134758.
275. Barouki, R., et al., *Developmental origins of non-communicable disease: implications for research and public health.* Environ Health, 2012. **11**: p. 42.
276. Padmanabhan, V., R.C. Cardoso, and M. Puttabyatappa, *Developmental Programming, a Pathway to Disease.* Endocrinology, 2016. **157**(4): p. 1328-40.
277. Inadera, H., *Developmental origins of obesity and type 2 diabetes: molecular aspects and role of chemicals.* Environmental Health and Preventive Medicine, 2013: p. 1-13.
278. Newbold, R.R., *Lessons learned from perinatal exposure to diethylstilbestrol.* Toxicology and Applied Pharmacology, 2004. **199**(2): p. 142-150.
279. McLachlan, J.A. and R.R. Newbold, *Estrogens and development.* Environmental Health Perspectives, 1987. **75**: p. 25-27.
280. Heindel, J.J., et al., *Developmental Origins of Health and Disease: Integrating Environmental Influences.* Endocrinology, 2015. **156**(10): p. 3416-21.
281. Balbus, J.M., et al., *Early-life prevention of non-communicable diseases.* The Lancet. **381**(9860): p. 3-4.
282. Haugen, A.C., et al., *Evolution of DOHaD: the impact of environmental health sciences.* Journal of developmental origins of health and disease, 2015. **6**(2): p. 55-64.
283. Iughetti, L., L. Lucaccioni, and B. Predieri, *Childhood obesity and environmental pollutants: a dual relationship.* Acta Biomed, 2015. **86**(1): p. 5-16.
284. Newbold, R.R., E. Padilla-Banks, and W.N. Jefferson, *Adverse effects of the model environmental estrogen diethylstilbestrol are transmitted to subsequent generations.* Endocrinology, 2006. **147**(6 Suppl): p. S11-7.
285. Newbold, R.R., et al., *Developmental exposure to endocrine disruptors and the obesity epidemic.* Reprod Toxicol, 2007. **23**(3): p. 290-6.
286. Smith, C.J. and K.K. Ryckman, *Epigenetic and developmental influences on the risk of obesity, diabetes, and metabolic syndrome.* Diabetes Metab Syndr Obes, 2015. **8**: p. 295-302.
287. Stel, J. and J. Legler, *The Role of Epigenetics in the Latent Effects of Early Life Exposure to Obesogenic Endocrine Disrupting Chemicals.* Endocrinology, 2015. **156**(10): p. 3466-72.
288. Trevino, L.S., Q. Wang, and C.L. Walker, *Phosphorylation of epigenetic "readers, writers and erasers": Implications for developmental reprogramming and the epigenetic basis for health and disease.* Prog Biophys Mol Biol, 2015. **118**(1-2): p. 8-13.
289. Holbrook, J.D., *An epigenetic escape route.* Trends in Genetics, 2015. **31**(1): p. 2-4.
290. Simeoni, U., et al., *Epigenetics and neonatal nutrition.* Early Hum Dev, 2014. **90 Suppl 2**: p. S23-4.
291. Martínez, J.A., et al., *Epigenetics in Adipose Tissue, Obesity, Weight Loss, and Diabetes.* Advances in Nutrition, 2014. **5**(1): p. 71-81.
292. Wadhwa, P.D., et al., *Developmental Origins of Health and Disease: Brief History of the Approach and Current Focus on Epigenetic Mechanisms.* Seminars in reproductive medicine, 2009. **27**(5): p. 358-368.
293. Ho, S.M., et al., *Environmental factors, epigenetics, and developmental origin of reproductive disorders.* Reprod Toxicol, 2016.
294. Lopomo, A., E. Burgio, and L. Migliore, *Epigenetics of Obesity.* Prog Mol Biol Transl Sci, 2016. **140**: p. 151-84.
295. Trevino, L.S., Q. Wang, and C.L. Walker, *Hypothesis: Activation of rapid signaling by environmental estrogens and epigenetic reprogramming in breast cancer.* Reprod Toxicol, 2015. **54**: p. 136-40.

296. Heindel, J.J. and F.S. vom Saal, *Role of nutrition and environmental endocrine disrupting chemicals during the perinatal period on the aetiology of obesity.* Mol Cell Endocrinol, 2009. **304**(1-2): p. 90-6.
297. Blumberg, B., *Obesogens, stem cells and the maternal programming of obesity.* J. Dev. Orig. Health Dis., 2011. **2**: p. 3-8.
298. Baillie-Hamilton, P.F., *Chemical toxins: a hypothesis to explain the global obesity epidemic.* J Altern Complement Med, 2002. **8**(2): p. 185-92.
299. Grun, F. and B. Blumberg, *Environmental obesogens: organotins and endocrine disruption via nuclear receptor signaling.* Endocrinology, 2006. **147**(6 Suppl): p. S50-5.
300. Snedeker, S.M. and A.G. Hay, *Do interactions between gut ecology and environmental chemicals contribute to obesity and diabetes?* Environ Health Perspect, 2012. **120**(3): p. 332-9.
301. Blumberg, B., *Obesogens, stem cells and the maternal programming of obesity.* Journal of Developmental Origins of Health and Disease, 2011. **2**(1): p. 3-8.
302. Janesick, A. and B. Blumberg, *Endocrine disrupting chemicals and the developmental programming of adipogenesis and obesity.* Birth Defects Res C Embryo Today, 2011. **93**(1): p. 34-50.
303. La Merrill, M. and L.S. Birnbaum, *Childhood obesity and environmental chemicals.* Mt Sinai J Med, 2011. **78**(1): p. 22-48.
304. Heindel, J.J., *The Obesogen Hypothesis of Obesity: Overview and Human Evidence*, in *Obesity Before Birth*, R.H. Lustig, Editor. 2011, Springer US. p. 355-366.
305. Newbold, R.R., *Perinatal Exposure to Endocrine Disrupting Chemicals with Estrogenic Activity and the Development of Obesity*, in *Obesity Before Birth*, R.H. Lustig, Editor. 2011, Springer US. p. 367-382.
306. Kirkley, A.G. and R.M. Sargis, *Environmental Endocrine Disruption of Energy Metabolism and Cardiovascular Risk.* Current diabetes reports, 2014. **14**(6): p. 494-494.
307. Chamorro-García, R. and B. Blumberg, *Transgenerational effects of obesogens and the obesity epidemic.* Current Opinion in Pharmacology, 2014. **19**(0): p. 153-158.
308. Heindel, J.J., et al., *Parma consensus statement on metabolic disruptors.* Environmental Health, 2015. **14**: p. 54.
309. Tang-Peronard, J.L., et al., *Endocrine-disrupting chemicals and obesity development in humans: A review.* Obes Rev, 2011. **12**(8): p. 622-636.
310. Liu, Y. and K.E. Peterson, *Maternal Exposure to Synthetic Chemicals and Obesity in the Offspring: Recent Findings.* Curr Environ Health Rep, 2015. **2**(4): p. 339-47.
311. Somm, E., 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**(12): p. 6289-99.
312. Oken, E., E.B. Levitan, and M.W. Gillman, *Maternal smoking during pregnancy and child overweight: systematic review and meta-analysis.* Int J Obes, 2007. **32**(2): p. 201-210.
313. Behl, M., et al., *Evaluation of the association between maternal smoking, childhood obesity, and metabolic disorders: a national toxicology program workshop review.* Environ Health Perspect, 2013. **121**(2): p. 170-80.
314. Mendez, M.A., et al., *Maternal smoking very early in pregnancy is related to child overweight at age 5-7 y.* Am J Clin Nutr, 2008. **87**(6): p. 1906-13.
315. Grzeskowiak, L.E., et al., *Association of early and late maternal smoking during pregnancy with offspring body mass index at 4 to 5 years of age.* J Dev Orig Health Dis, 2015. **6**(6): p. 485-92.

316. Stettler, N. and V. Iotova, *Early growth patterns and long-term obesity risk.* Curr Opin Clin Nutr Metab Care, 2010. **13**(3): p. 294-9.
317. Newbold, R.R., E. Padilla-Banks, and W.N. Jefferson, *Environmental estrogens and obesity.* Mol Cell Endocrinol, 2009. **304**(1-2): p. 84-9.
318. Newbold, R.R., et al., *Effects of endocrine disruptors on obesity.* Int. J. Androl., 2008. **31**: p. 201-208.
319. Angle, B.M., et al., *Metabolic disruption in male mice due to fetal exposure to low but not high doses of bisphenol A (BPA): Evidence for effects on body weight, food intake, adipocytes, leptin, adiponectin, insulin and glucose regulation.* Reproductive Toxicology, 2013. **42**: p. 256-268.
320. Jensen, E.T. and M.P. Longnecker, *Pharmacologic sex hormones in pregnancy in relation to offspring obesity.* Obesity (Silver Spring), 2014. **22**(11): p. 2406-12.
321. Hatch, E.E., et al., *Prenatal diethylstilbestrol exposure and risk of obesity in adult women.* J Dev Orig Health Dis, 2015. **6**(3): p. 201-7.
322. Rubin, B.S., 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**(7): p. 675-80.
323. Rubin, B.S., *Bisphenol A: an endocrine disruptor with widespread exposure and multiple effects.* J Steroid Biochem Mol Biol, 2011. **127**(1-2): p. 27-34.
324. Vandenberg, L.N., *Non-monotonic dose responses in studies of endocrine disrupting chemicals: bisphenol a as a case study.* Dose Response, 2014. **12**(2): p. 259-76.
325. Somm, E., et al., *Perinatal exposure to bisphenol a alters early adipogenesis in the rat.* Environ Health Perspect, 2009. **117**(10): p. 1549-55.
326. Rubin, B.S. and A.M. Soto, *Bisphenol A: Perinatal exposure and body weight.* Mol Cell Endocrinol, 2009. **304**(1-2): p. 55-62.
327. Rubin, B.S., 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**: p. 675-80.
328. Miyawaki, J., et al., *Perinatal and postnatal exposure to bisphenol A increase adipose tissue mass and serum cholesterol level in mice.* Journal of Atherosclerosis and Thrombosis, 2007. **14**(5): p. 245-252.
329. Wei, J., 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**(8): p. 3049-3061.
330. Yang, M., et al., *Bisphenol A promotes adiposity and inflammation in a nonmonotonic dose-response way in five-week old male and female C57BL/6J mice fed a low-calorie diet.* Endocrinology, 2016: p. en20151926.
331. Ryan, K.K., et al., *Perinatal exposure to bisphenol-A and the development of metabolic syndrome in CD-1 mice.* Endocrinology, 2010. **151**(6): p. 2603-2612.
332. Anderson, O.S., et al., *Perinatal bisphenol a exposure promotes hyperactivity, lean body composition, and hormonal responses across the murine life course.* FASEB Journal, 2013. **27**(4): p. 1784-1792.
333. Delclos, K.B., et al., *Toxicity evaluation of bisphenol A administered by gavage to Sprague Dawley rats from gestation day 6 through postnatal day 90.* Toxicol Sci, 2014. **139**(1): p. 174-97.
334. Tyl, R.W., et al., *Three-Generation Reproductive Toxicity Study of Dietary Bisphenol A in CD Sprague-Dawley Rats.* Toxicological Sciences, 2002. **68**(1): p. 121-146.
335. vom Saal, F.S. and C. Hughes, *An extensive new literature concerning low-dose effects of bisphenol A shows the need for a new risk assessment.* Environ Health Perspect, 2005. **113**(8): p. 926-33.

336. Ruhlen, R.L., et al., *Low phytoestrogen levels in feed increase fetal serum estradiol resulting in the "fetal estrogenization syndrome" and obesity in CD-1 mice.* Environ Health Perspect, 2008. **116**(3): p. 322-8.
337. Cederroth, C.R., et al., *A phytoestrogen-rich diet increases energy expenditure and decreases adiposity in mice.* Environ Health Perspect, 2007. **115**(10): p. 1467-73.
338. van Esterik, J.C., et al., *Programming of metabolic effects in C57BL/6JxFVB mice by exposure to bisphenol A during gestation and lactation.* Toxicology, 2014. **321**: p. 40-52.
339. Hoepner, L.A., et al., *Bisphenol A and Adiposity in an Inner-City Birth Cohort.* Environ Health Perspect, 2016.
340. Valvi, D., et al., *Prenatal bisphenol a urine concentrations and early rapid growth and overweight risk in the offspring.* Epidemiology, 2013. **24**(6): p. 791-9.
341. Braun, J.M., et al., *Early-life bisphenol a exposure and child body mass index: a prospective cohort study.* Environ Health Perspect, 2014. **122**(11): p. 1239-45.
342. Lang, I.A., et al., *Association of urinary bisphenol A concentration with medical disorders and laboratory abnormalities in adults.* Jama, 2008. **300**(11): p. 1303-10.
343. Ranciere, F., et al., *Bisphenol A and the risk of cardiometabolic disorders: a systematic review with meta-analysis of the epidemiological evidence.* Environ Health, 2015. **14**: p. 46.
344. Harley, K.G., et al., *Prenatal and postnatal bisphenol A exposure and body mass index in childhood in the CHAMACOS cohort.* Environ Health Perspect, 2013. **121**(4): p. 514-20, 520e1-6.
345. Volberg, V., et al., *Maternal bisphenol a exposure during pregnancy and its association with adipokines in Mexican-American children.* Environ Mol Mutagen, 2013. **54**(8): p. 621-8.
346. Lakind, J.S., M. Goodman, and D.R. Mattison, *Bisphenol A and indicators of obesity, glucose metabolism/type 2 diabetes and cardiovascular disease: a systematic review of epidemiologic research.* Crit Rev Toxicol, 2014. **44**(2): p. 121-50.
347. Chavarro, J.E., et al., *Soy Intake Modifies the Relation Between Urinary Bisphenol A Concentrations and Pregnancy Outcomes Among Women Undergoing Assisted Reproduction.* J Clin Endocrinol Metab, 2016. **101**(3): p. 1082-90.
348. Braun, J.M., et al., *Variability of urinary phthalate metabolite and bisphenol A concentrations before and during pregnancy.* Environ Health Perspect, 2012. **120**(5): p. 739-45.
349. Ye, X., et al., *Variability of urinary concentrations of bisphenol A in spot samples, first morning voids, and 24-hour collections.* Environ Health Perspect, 2011. **119**(7): p. 983-8.
350. Lassen, T.H., et al., *Temporal variability in urinary excretion of bisphenol A and seven other phenols in spot, morning, and 24-h urine samples.* Environ Res, 2013. **126**: p. 164-70.
351. Jusko, T.A., et al., *Reproducibility of urinary bisphenol A concentrations measured during pregnancy in the Generation R Study.* J Expo Sci Environ Epidemiol, 2014. **24**(5): p. 532-6.
352. Stahlhut, R.W., W.V. Welshons, and S.H. Swan, *Bisphenol A data in NHANES suggest longer than expected half-life, substantial nonfood exposure, or both.* Environ Health Perspect, 2009. **117**(5): p. 784-9.
353. Kim, S.H. and M.J. Park, *Phthalate exposure and childhood obesity.* Ann Pediatr Endocrinol Metab, 2014. **19**(2): p. 69-75.
354. Hao, C., et al., *Perinatal exposure to diethyl-hexyl-phthalate induces obesity in mice.* Front Biosci (Elite Ed), 2013. **5**: p. 725-33.

355. Hao, C., et al., *The endocrine disruptor mono-(2-ethylhexyl) phthalate promotes adipocyte differentiation and induces obesity in mice.* Biosci Rep, 2012. **32**(6): p. 619-29.
356. Manikkam, M., et al., *Plastics derived endocrine disruptors (BPA, DEHP and DBP) induce epigenetic transgenerational inheritance of obesity, reproductive disease and sperm epimutations.* PLoS ONE, 2013. **8**(1): p. e55387.
357. Schmidt, J.-S., et al., *Di(2-ethylhexyl) Phthalate (DEHP) Impairs Female Fertility and Promotes Adipogenesis in C3H/N Mice.* Environ Health Perspect, 2012.
358. Maresca, M.M., et al., *Prenatal Exposure to Phthalates and Childhood Body Size in an Urban Cohort.* Environ Health Perspect, 2015.
359. Buckley, J.P., et al., *Prenatal Phthalate Exposures and Childhood Fat Mass in a New York City Cohort.* Environ Health Perspect, 2015.
360. Valvi, D., et al., *Prenatal Phthalate Exposure and Childhood Growth and Blood Pressure: Evidence from the Spanish INMA-Sabadell Birth Cohort Study.* Environ Health Perspect, 2015. **123**(10): p. 1022-9.
361. de Cock, M., et al., *Prenatal exposure to endocrine disrupting chemicals and birth weight-A prospective cohort study.* J Environ Sci Health A Tox Hazard Subst Environ Eng, 2016. **51**(2): p. 178-185.
362. Buckley, J.P., et al., *Prenatal phthalate exposures and body mass index among 4 to 7 year old children: A pooled analysis.* Epidemiology, 2016.
363. Trasande, L., et al., *Race/ethnicity-specific associations of urinary phthalates with childhood body mass in a nationally representative sample.* Environ Health Perspect, 2013. **121**(4): p. 501-6.
364. Kim, J.H., et al., *Association of diethylhexyl phthalate with obesity-related markers and body mass change from birth to 3 months of age.* J Epidemiol Community Health, 2016.
365. Grun, F., et al., *Endocrine-disrupting organotin compounds are potent inducers of adipogenesis in vertebrates.* Mol Endocrinol, 2006. **20**(9): p. 2141-55.
366. Chamorro-Garcia, R., et al., *Transgenerational inheritance of increased fat depot size, stem cell reprogramming, and hepatic steatosis elicited by prenatal exposure to the obesogen tributyltin in mice.* Environ Health Perspect, 2013. **121**(3): p. 359-66.
367. Grun, F., *Endocrine-disrupting organotin compounds are potent inducers of adipogenesis in vertebrates.* Mol. Endocrinol., 2006. **20**: p. 2141-2155.
368. Kanayama, T., et al., *Organotin compounds promote adipocyte differentiation as agonists of the peroxisome proliferator-activated receptor [gamma]/retinoid X receptor pathway.* Mol. Pharmacol., 2005. **67**: p. 766-774.
369. Pereira-Fernandes, A., et al., *Toxicogenomics in the 3T3-L1 cell line, a new approach for screening of obesogenic compounds.* Toxicol Sci, 2014. **140**(2): p. 352-63.
370. Watt, J. and J.J. Schlezinger, *Structurally-diverse, PPARgamma-activating environmental toxicants induce adipogenesis and suppress osteogenesis in bone marrow mesenchymal stromal cells.* Toxicology, 2015. **331**: p. 66-77.
371. Ouadah-Boussouf, N. and P.J. Babin, *Pharmacological evaluation of the mechanisms involved in increased adiposity in zebrafish triggered by the environmental contaminant tributyltin.* Toxicol Appl Pharmacol, 2016. **294**: p. 32-42.
372. Rantakokko, P., et al., *Association of placenta organotin concentrations with growth and ponderal index in 110 newborn boys from Finland during the first 18 months of life: a cohort study.* Environ Health, 2014. **13**(1): p. 45.
373. Yan, Z., et al., *Prenatal polycyclic aromatic hydrocarbon, adiposity, peroxisome proliferator-activated receptor (PPAR) gamma methylation in offspring, grand-offspring mice.* PLoS One, 2014. **9**(10): p. e110706.

374. Bolton, J.L., R.L. Auten, and S.D. Bilbo, *Prenatal air pollution exposure induces sexually dimorphic fetal programming of metabolic and neuroinflammatory outcomes in adult offspring.* Brain Behav Immun, 2014. **37**: p. 30-44.
375. Strakovsky, R.S., et al., *In utero growth restriction and catch-up adipogenesis after developmental di (2-ethylhexyl) phthalate exposure cause glucose intolerance in adult male rats following a high-fat dietary challenge.* J Nutr Biochem, 2015. **26**(11): p. 1208-20.
376. Ortiz, L., et al., *In utero exposure to benzo[a]pyrene increases adiposity and causes hepatic steatosis in female mice, and glutathione deficiency is protective.* Toxicol Lett, 2013. **223**(2): p. 260-7.
377. Rundle, A., et al., *Association of childhood obesity with maternal exposure to ambient air polycyclic aromatic hydrocarbons during pregnancy.* Am J Epidemiol, 2012. **175**(11): p. 1163-72.
378. Agay-Shay, K., et al., *Exposure to Endocrine-Disrupting Chemicals during Pregnancy and Weight at 7 Years of Age: A Multi-pollutant Approach.* Environ Health Perspect, 2015. **123**(10): p. 1030-7.
379. Vafeiadi, M., et al., *Association of Prenatal Exposure to Persistent Organic Pollutants with Obesity and Cardiometabolic Traits in Early Childhood: The Rhea Mother-Child Cohort (Crete, Greece).* Environ Health Perspect, 2015. **123**(10): p. 1015-21.
380. Ghosh, S., et al., *Biomarkers Linking PCB Exposure and Obesity().* Current pharmaceutical biotechnology, 2014. **15**(11): p. 1058-1068.
381. Valvi, D., et al., *Prenatal exposure to persistent organic pollutants and rapid weight gain and overweight in infancy.* Obesity (Silver Spring), 2014. **22**(2): p. 488-96.
382. Tang-Péronard, J.L., et al., *Association between prenatal polychlorinated biphenyl exposure and obesity development at ages 5 and 7 y: a prospective cohort study of 656 children from the Faroe Islands.* The American Journal of Clinical Nutrition, 2014. **99**(1): p. 5-13.
383. Casas, M., et al., *Prenatal exposure to PCB-153, p,p'-DDE and birth outcomes in 9000 mother-child pairs: exposure-response relationship and effect modifiers.* Environ Int, 2015. **74**: p. 23-31.
384. Valvi, 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**(3): p. 451-7.
385. Mendez, M.A., et al., *Prenatal organochlorine compound exposure, rapid weight gain, and overweight in infancy.* Environ Health Perspect, 2011. **119**(2): p. 272-8.
386. Iszatt, N., et al., *Prenatal and Postnatal Exposure to Persistent Organic Pollutants and Infant Growth: A Pooled Analysis of Seven European Birth Cohorts.* Environ Health Perspect, 2015. **123**(7): p. 730-6.
387. La Merrill, M., et al., *Perinatal exposure of mice to the pesticide DDT impairs energy expenditure and metabolism in adult female offspring.* PLoS One, 2014. **9**(7): p. e103337.
388. Verhulst, S.L., et al., *Intrauterine exposure to environmental pollutants and body mass index during the first 3 years of life.* Environ Health Perspect, 2009. **117**(1): p. 122-6.
389. Warner, M., et al., *Prenatal exposure to dichlorodiphenyltrichloroethane and obesity at 9 years of age in the CHAMACOS study cohort.* Am J Epidemiol, 2014. **179**(11): p. 1312-22.
390. Smink, A., et al., *Exposure to hexachlorobenzene during pregnancy increases the risk of overweight in children aged 6 years.* Acta Paediatr, 2008. **97**(10): p. 1465-9.

391. Cupul-Uicab, L.A., et al., *Prenatal exposure to persistent organochlorines and childhood obesity in the US collaborative perinatal project.* Environ Health Perspect, 2013. **121**(9): p. 1103-9.
392. Tang-Peronard, J.L., et al., *Association between prenatal polychlorinated biphenyl exposure and obesity development at ages 5 and 7 y: a prospective cohort study of 656 children from the Faroe Islands.* Am J Clin Nutr, 2014. **99**(1): p. 5-13.
393. Valvi, D., et al., *Prenatal exposure to persistent organic pollutants and rapid weight gain and overweight in infancy.* Obesity (Silver Spring), 2013.
394. Timmermann, C.A., et al., *Adiposity and glycemic control in children exposed to perfluorinated compounds.* J Clin Endocrinol Metab, 2014. **99**(4): p. E608-14.
395. Halldorsson, T.I., et al., *Prenatal exposure to perfluorooctanoate and risk of overweight at 20 years of age: a prospective cohort study.* Environ Health Perspect, 2012. **120**(5): p. 668-73.
396. Hines, E.P., 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**(1-2): p. 97-105.
397. Ngo, H.T., et al., *In utero exposure to perfluorooctanoate (PFOA) or perfluorooctane sulfonate (PFOS) did not increase body weight or intestinal tumorigenesis in multiple intestinal neoplasia (Min/+) mice.* Environ Res, 2014. **132**: p. 251-63.
398. Rodriguez, K.F., et al., *Effects of in Utero Exposure to Arsenic during the Second Half of Gestation on Reproductive End Points and Metabolic Parameters in Female CD-1 Mice.* Environ Health Perspect, 2016. **124**(3): p. 336-43.
399. Faulk, C., et al., *Perinatal lead (Pb) exposure results in sex-specific effects on food intake, fat, weight, and insulin response across the murine life-course.* PLoS One, 2014. **9**(8): p. e104273.
400. Rodriguez, K.F., et al., *Effects of Exposure to Arsenic during the Second Half of Gestation on Reproductive End Points and Metabolic Parameters in Female CD-1 Mice.* Environ Health Perspect, 2015.
401. Nishijo, M., et al., *Effects of maternal exposure to cadmium on pregnancy outcome and breast milk.* Occup Environ Med, 2002. **59**(6): p. 394-6; discussion 397.
402. Nishijo, M., et al., *Relationship between newborn size and mother's blood cadmium levels, Toyama, Japan.* Arch Environ Health, 2004. **59**(1): p. 22-5.
403. Salpietro, C.D., et al., *Cadmium concentration in maternal and cord blood and infant birth weight: a study on healthy non-smoking women.* J Perinat Med, 2002. **30**(5): p. 395-9.
404. Ronco, A.M., et al., *Metals content in placentas from moderate cigarette consumers: correlation with newborn birth weight.* Biometals, 2005. **18**(3): p. 233-41.
405. Gossai, A., et al., *Association between maternal urinary arsenic species and infant cord blood leptin levels in a New Hampshire Pregnancy Cohort.* Environ Res, 2015. **136**: p. 180-6.
406. Ashley-Martin, J., et al., *Maternal blood metal levels and fetal markers of metabolic function.* Environ Res, 2014. **136C**: p. 27-34.
407. Erkin-Cakmak, A., et al., *In utero and childhood polybrominated diphenyl ether exposures and body mass at age 7 years: the CHAMACOS study.* Environ Health Perspect, 2015. **123**(6): p. 636-42.
408. Patisaul, H.B., et al., *Accumulation and endocrine disrupting effects of the flame retardant mixture Firemaster(R) 550 in rats: an exploratory assessment.* J Biochem Mol Toxicol, 2013. **27**(2): p. 124-36.

409. Janesick, A.S. and B. Blumberg, *Obesogens: an emerging threat to public health.* Am J Obstet Gynecol, 2016.
410. Sakurai, K., et al., *Bisphenol A affects glucose transport in mouse 3T3-F442A adipocytes.* Br J Pharmacol, 2004. **141**(2): p. 209-14.
411. Hugo, E.R., et al., *Bisphenol A at environmentally relevant doses inhibits adiponectin release from human adipose tissue explants and adipocytes.* Environ Health Perspect, 2008. **116**(12): p. 1642-7.
412. Enan, E., P.C. Liu, and F. Matsumura, *TCDD (2,3,7,8-tetrachlorodibenzo-P-dioxin) causes reduction in glucose uptake through glucose transporters on the plasma membrane of the guinea pig adipocyte.* J Environ Sci Health B, 1992. **27**(5): p. 495-510.
413. Novelli, M., S. Piaggi, and V. De Tata, *2,3,7,8-Tetrachlorodibenzo-p-dioxin-induced impairment of glucose-stimulated insulin secretion in isolated rat pancreatic islets.* Toxicol Lett, 2005. **156**(2): p. 307-14.
414. Ruzzin, J., et al., *Persistent organic pollutant exposure leads to insulin resistance syndrome.* Environ Health Perspect, 2010. **118**(4): p. 465-71.
415. Valentino, R., et al., *Bisphenol-A impairs insulin action and up-regulates inflammatory pathways in human subcutaneous adipocytes and 3T3-L1 cells.* PLoS One, 2013. **8**(12): p. e82099.
416. Chamorro-Garcia, R., *Transgenerational inheritance of increased fat depot size, stem cell reprogramming, and hepatic steatosis elicited by prenatal obesogen tributyltin in mice.* Environ. Health Perspect., 2013. **121**: p. 359-366.
417. Lehmann, J.M., et al., *An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor gamma (PPAR gamma).* J Biol Chem, 1995. **270**(22): p. 12953-6.
418. Pereira-Fernandes, A., et al., *Evaluation of a screening system for obesogenic compounds: screening of endocrine disrupting compounds and evaluation of the PPAR dependency of the effect.* PLoS One, 2013. **8**(10): p. e77481.
419. Wadia, P.R., et al., *Low-dose BPA exposure alters the mesenchymal and epithelial transcriptomes of the mouse fetal mammary gland.* PLoS One, 2013. **8**(5): p. e63902.
420. Chamorro-Garcia, R., 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**(7): p. 984-9.
421. Hao, C.J., et al., *The endocrine disruptor 4-nonylphenol promotes adipocyte differentiation and induces obesity in mice.* Cell Physiol Biochem, 2012. **30**(2): p. 382-94.
422. Fang, M., et al., *Characterizing the peroxisome proliferator-activated receptor (PPARgamma) ligand binding potential of several major flame retardants, their metabolites, and chemical mixtures in house dust.* Environ Health Perspect, 2015. **123**(2): p. 166-72.
423. Yin, L., et al., *Benzyl butyl phthalate promotes adipogenesis in 3T3-L1 preadipocytes: A High Content Cellomics and metabolomic analysis.* Toxicol In Vitro, 2016. **32**: p. 297-309.
424. Kamstra, J.H., et al., *Transcriptional and epigenetic mechanisms underlying enhanced in vitro adipocyte differentiation by the brominated flame retardant BDE-47.* Environ Sci Technol, 2014. **48**(7): p. 4110-9.
425. Pillai, H.K., et al., *Ligand binding and activation of PPARgamma by Firemaster(R) 550: effects on adipogenesis and osteogenesis in vitro.* Environ Health Perspect, 2014. **122**(11): p. 1225-32.

426. Howell, G., 3rd and L. Mangum, *Exposure to bioaccumulative organochlorine compounds alters adipogenesis, fatty acid uptake, and adipokine production in NIH3T3-L1 cells.* Toxicol In Vitro, 2011. **25**(1): p. 394-402.
427. Mangum, L.H., G.E. Howell, 3rd, and J.E. Chambers, *Exposure to p,p'-DDE enhances differentiation of 3T3-L1 preadipocytes in a model of sub-optimal differentiation.* Toxicol Lett, 2015. **238**(2): p. 65-71.
428. Park, Y., et al., *Imidacloprid, a neonicotinoid insecticide, potentiates adipogenesis in 3T3-L1 adipocytes.* J Agric Food Chem, 2013. **61**(1): p. 255-9.
429. Hoogduijn, M.J., Z. Rakonczay, and P.G. Genever, *The effects of anticholinergic insecticides on human mesenchymal stem cells.* Toxicol Sci, 2006. **94**(2): p. 342-50.
430. Kirchner, S., et al., *Prenatal exposure to the environmental obesogen tributyltin predisposes multipotent stem cells to become adipocytes.* Mol Endocrinol, 2010. **24**(3): p. 526-39.
431. Bianco, P., *Back to the future: moving beyond "mesenchymal stem cells".* J Cell Biochem, 2011. **112**(7): p. 1713-21.
432. Neel, B.A., M.J. Brady, and R.M. Sargis, *The endocrine disrupting chemical tolylfluanid alters adipocyte metabolism via glucocorticoid receptor activation.* Mol Endocrinol, 2013. **27**(3): p. 394-406.
433. Kim, S.M., et al., *Loss of white adipose hyperplastic potential is associated with enhanced susceptibility to insulin resistance.* Cell Metab, 2014. **20**(6): p. 1049-58.
434. Jeffery, E., et al., *Rapid depot-specific activation of adipocyte precursor cells at the onset of obesity.* Nat Cell Biol, 2015. **17**(4): p. 376-85.
435. Fildes, A., et al., *Probability of an Obese Person Attaining Normal Body Weight: Cohort Study Using Electronic Health Records.* Am J Public Health, 2015: p. e1-e6.
436. Kraschnewski, J.L., et al., *Long-term weight loss maintenance in the United States.* Int J Obes (Lond), 2010. **34**(11): p. 1644-54.
437. Skurk, T., et al., *Relationship between adipocyte size and adipokine expression and secretion.* J Clin Endocrinol Metab, 2007. **92**(3): p. 1023-33.
438. Mackay, H., et al., *Organizational effects of perinatal exposure to bisphenol-A and diethylstilbestrol on arcuate nucleus circuitry controlling food intake and energy expenditure in male and female CD-1 mice.* Endocrinology, 2013. **154**(4): p. 1465-1475.
439. Bo, E., C. Viglietti-Panzica, and G.C. Panzica, *Acute exposure to tributyltin induces c-fos activation in the hypothalamic arcuate nucleus of adult male mice.* Neurotoxicology, 2011. **32**(2): p. 277-80.
440. Decherf, S., et al., *Disruption of thyroid hormone-dependent hypothalamic set-points by environmental contaminants.* Mol Cell Endocrinol, 2010. **323**(2): p. 172-82.
441. Palanza, P., et al., *Effects of developmental exposure to bisphenol A on brain and behavior in mice.* Environ Res, 2008. **108**(2): p. 150-7.
442. Palanza, P., et al., *Perinatal exposure to endocrine disruptors: sex, timing and behavioral endpoints.* Current Opinion in Behavioral Science, 2016. **7**: p. 69-75.
443. Panzica, G.C., et al., *Effects of xenoestrogens on the differentiation of behaviorally-relevant neural circuits in higher vertebrates*, in *Trends in Comparative Endocrinology and Neurobiology*, H. Vaudry, et al., Editors. 2009, New York Academy of Sciences: New York, NY. p. 271-278.
444. Panzica, G.C., et al., *Effects of xenoestrogens on the differentiation of behaviorally relevant neural circuits.* Frontiers in Neuroendocrinology, 2007. **28**: p. 179-200.
445. Richter, C.A., et al., *In vivo effects of bisphenol A in laboratory rodent studies.* Reprod Toxicol, 2007. **24**(2): p. 199-224.

446. Rubin, B.S., et al., *Evidence of altered brain sexual differentiation in mice exposed perinatally to low, environmentally relevant levels of bisphenol a.* Endocrinology, 2006. **147**(8): p. 3681-3691.
447. Zsarnovszky, A., et al., *Ontogeny of rapid estrogen-mediated extracellular signal-regulated kinase signaling in the rat cerebellar cortex: potent non-genomic agonist and endocrine disrupting activity of the xenoestrogen bisphenol A.* Endocrinology, 2005. **146**: p. 5388-5396.
448. Martini, M., et al., *Effects of perinatal administration of bisphenol A on the neuronal nitric oxide synthase expressing system in the hypothalamus and limbic system of CD1 mice.* J Neuroendocrinol, 2010. **22**: p. 1004-1012.
449. Newbold, R.R., et al., *Effects of endocrine disruptors on obesity.* Int J Androl, 2008. **31**(2): p. 201-8.
450. Dunn, J.S., H.L. Sheehan, and N.G.B. McLetchie, *Necrosis of Islets of Langerhans Produced Experimentally.* The Lancet, 1943. **241**(6242): p. 484-487.
451. Pont, A., et al., *Diabetes mellitus and neuropathy following Vacor ingestion in man.* Arch Intern Med, 1979. **139**(2): p. 185-7.
452. Karam, J.H., et al., *Insulinopenic diabetes after rodenticide (Vacor) ingestion: a unique model of acquired diabetes in man.* Diabetes, 1980. **29**(12): p. 971-8.
453. Fernandez-Garcia, J.C., et al., *Diabetic ketoacidosis following chlorothalonil poisoning.* Occup Environ Med, 2014.
454. Kurita, H., et al., *Aryl hydrocarbon receptor-mediated effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin on glucose-stimulated insulin secretion in mice.* J Appl Toxicol, 2009. **29**(8): p. 689-94.
455. Piaggi, S., et al., *Cell death and impairment of glucose-stimulated insulin secretion induced by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in the beta-cell line INS-1E.* Toxicol Appl Pharmacol, 2007. **220**(3): p. 333-40.
456. Yau, D.T. and J.H. Mennear, *The inhibitory effect of DDT on insulin secretion in mice.* Toxicol Appl Pharmacol, 1977. **39**(1): p. 81-8.
457. Miura, Y. and H. Matsui, *Triphenyltin impairs a protein kinase A (PKA)-dependent increase of cytosolic Na+ and Ca2+ and PKA-independent increase of cytosolic Ca2+ associated with insulin secretion in hamster pancreatic beta-cells.* Toxicol Appl Pharmacol, 2006. **216**(3): p. 363-72.
458. Douillet, C., et al., *Methylated trivalent arsenicals are potent inhibitors of glucose stimulated insulin secretion by murine pancreatic islets.* Toxicol Appl Pharmacol, 2013. **267**(1): p. 11-5.
459. Fu, J., et al., *Low-level arsenic impairs glucose-stimulated insulin secretion in pancreatic beta cells: involvement of cellular adaptive response to oxidative stress.* Environ Health Perspect, 2010. **118**(6): p. 864-70.
460. Diaz-Villasenor, A., et al., *Arsenite reduces insulin secretion in rat pancreatic beta-cells by decreasing the calcium-dependent calpain-10 proteolysis of SNAP-25.* Toxicol Appl Pharmacol, 2008. **231**(3): p. 291-9.
461. El Muayed, M., et al., *Accumulation of cadmium in insulin-producing beta cells.* Islets, 2012. **4**(6): p. 405-16.
462. Chang, K.C., et al., *Cadmium induces apoptosis in pancreatic beta-cells through a mitochondria-dependent pathway: the role of oxidative stress-mediated c-Jun N-terminal kinase activation.* PLoS One, 2013. **8**(2): p. e54374.
463. Chen, Y.W., et al., *Heavy metals, islet function and diabetes development.* Islets, 2009. **1**(3): p. 169-76.

464. Chen, Y.W., et al., *Inorganic mercury causes pancreatic beta-cell death via the oxidative stress-induced apoptotic and necrotic pathways.* Toxicol Appl Pharmacol, 2010. **243**(3): p. 323-31.
465. Fischer, L.J., H.R. Zhou, and M.A. Wagner, *Polychlorinated biphenyls release insulin from RINm5F cells.* Life Sci, 1996. **59**(24): p. 2041-9.
466. Kim, Y.H., et al., *2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) induces calcium influx through T-type calcium channel and enhances lysosomal exocytosis and insulin secretion in INS-1 cells.* Int J Toxicol, 2009. **28**(3): p. 151-61.
467. Alonso-Magdalena, P., et al., *The estrogenic effect of bisphenol A disrupts pancreatic beta-cell function in vivo and induces insulin resistance.* Environ Health Perspect, 2006. **114**(1): p. 106-12.
468. Soriano, S., et al., *Rapid insulinotropic action of low doses of bisphenol-A on mouse and human islets of Langerhans: role of estrogen receptor beta.* PLoS One, 2012. **7**(2): p. e31109.
469. Nadal, A., et al., *Nongenomic actions of estrogens and xenoestrogens by binding at a plasma membrane receptor unrelated to estrogen receptor alpha and estrogen receptor beta.* Proc Natl Acad Sci U S A, 2000. **97**(21): p. 11603-8.
470. Song, L., et al., *Low-level phenolic estrogen pollutants impair islet morphology and beta-cell function in isolated rat islets.* J Endocrinol, 2012. **215**(2): p. 303-11.
471. Longnecker, D.S., *Environmental factors and diseases of the pancreas.* Environ Health Perspect, 1977. **20**: p. 105-12.
472. Alonso-Magdalena, P., 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**(8): p. 969-77.
473. Wassermann, D., M. Wassermann, and C. Lemesch, *Ultrastructure of beta-cells of the endocrine pancreas in rats receiving polychlorinated biphenyls.* Environ Physiol Biochem, 1975. **5**(5): p. 322-40.
474. Zuo, Z., et al., *Chronic exposure to tributyltin chloride induces pancreatic islet cell apoptosis and disrupts glucose homeostasis in male mice.* Environ Sci Technol, 2014. **48**(9): p. 5179-86.
475. Liu, S., et al., *Arsenic induces diabetic effects through beta-cell dysfunction and increased gluconeogenesis in mice.* Sci Rep, 2014. **4**: p. 6894.
476. Bodin, J., et al., *Long-term bisphenol A exposure accelerates insulitis development in diabetes-prone NOD mice.* Immunopharmacol Immunotoxicol, 2013. **35**(3): p. 349-58.
477. Diaz-Villasenor, A., et al., *Arsenic exposure and calpain-10 polymorphisms impair the function of pancreatic beta-cells in humans: a pilot study of risk factors for T2DM.* PLoS One, 2013. **8**(1): p. e51642.
478. Maull, E.A., et al., *Evaluation of the association between arsenic and diabetes: a National Toxicology Program workshop review.* Environ Health Perspect, 2012. **120**(12): p. 1658-1670.
479. Sung, T.C., J.W. Huang, and H.R. Guo, *Association between Arsenic Exposure and Diabetes: A Meta-Analysis.* Biomed Res Int, 2015. **2015**: p. 368087.
480. Wang, W., et al., *Association of inorganic arsenic exposure with type 2 diabetes mellitus: a meta-analysis.* J Epidemiol Community Health, 2014. **68**(2): p. 176-84.
481. Rhee, S.Y., et al., *Arsenic exposure and prevalence of diabetes mellitus in Korean adults.* J Korean Med Sci, 2013. **28**(6): p. 861-8.

482. Del Razo, L.M., et al., *Exposure to arsenic in drinking water is associated with increased prevalence of diabetes: a cross-sectional study in the Zimapan and Lagunera regions in Mexico.* Environ Health, 2011. **10**: p. 73-73.
483. Song, Y., et al., *Endocrine-Disrupting Chemicals, Risk of Type 2 Diabetes, and Diabetes-Related Metabolic Traits: A Systematic Review and Meta-analysis.* J Diabetes, 2015.
484. Jensen, T.K., et al., *Polychlorinated biphenyl exposure and glucose metabolism in 9-year-old Danish children.* J Clin Endocrinol Metab, 2014. **99**(12): p. E2643-51.
485. Suarez-Lopez, J.R., et al., *Persistent organic pollutants in young adults and changes in glucose related metabolism over a 23-year follow-up.* Environ Res, 2015. **137**: p. 485-94.
486. Tang, M., et al., *Exposure to organochlorine pollutants and type 2 diabetes: a systematic review and meta-analysis.* PLoS One, 2014. **9**(10): p. e85556.
487. Taylor, K.W., et al., *Evaluation of the association between persistent organic pollutants (POPs) and diabetes in epidemiological studies: a national toxicology program workshop review.* Environ Health Perspect, 2013. **121**(7): p. 774-83.
488. Beydoun, H.A., et al., *Sex differences in the association of urinary bisphenol-A concentration with selected indices of glucose homeostasis among U.S. adults.* Ann Epidemiol, 2014. **24**(2): p. 90-7.
489. Lin, Y., et al., *Developmental exposure to di(2-ethylhexyl) phthalate impairs endocrine pancreas and leads to long-term adverse effects on glucose homeostasis in the rat.* Am J Physiol Endocrinol Metab, 2011. **301**(3): p. E527-38.
490. Trasande, L., et al., *Urinary phthalates and increased insulin resistance in adolescents.* Pediatrics, 2013. **132**(3): p. e646-55.
491. Svensson, K., et al., *Phthalate exposure associated with self-reported diabetes among Mexican women.* Environ Res, 2011. **111**(6): p. 792-6.
492. Kim, J.H., et al., *Diethylhexyl phthalates is associated with insulin resistance via oxidative stress in the elderly: a panel study.* PLoS One, 2013. **8**(8): p. e71392.
493. Huang, T., et al., *Gender and racial/ethnic differences in the associations of urinary phthalate metabolites with markers of diabetes risk: National Health and Nutrition Examination Survey 2001-2008.* Environ Health, 2014. **13**(1): p. 6.
494. Sun, Q., et al., *Association of Urinary Concentrations of Bisphenol A and Phthalate Metabolites with Risk of Type 2 Diabetes: A Prospective Investigation in the Nurses' Health Study (NHS) and NHSII Cohorts.* Environ Health Perspect, 2014. **122**(6): p. 616-23.
495. Lind, P.M., B. Zethelius, and L. Lind, *Circulating levels of phthalate metabolites are associated with prevalent diabetes in the elderly.* Diabetes Care, 2012. **35**(7): p. 1519-24.
496. James-Todd, T., 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**(9): p. 1307-13.
497. Sarath Josh, M.K., et al., *Phthalates efficiently bind to human peroxisome proliferator activated receptor and retinoid X receptor alpha, beta, gamma subtypes: an in silico approach.* J Appl Toxicol, 2014. **34**(7): p. 754-65.
498. Naville, D., et al., *Low-dose food contaminants trigger sex-specific, hepatic metabolic changes in the progeny of obese mice.* Faseb j, 2013. **27**(9): p. 3860-70.
499. Liu, J., et al., *Perinatal bisphenol A exposure and adult glucose homeostasis: identifying critical windows of exposure.* PLoS One, 2013. **8**(5): p. e64143.
500. Ibrahim, M.M., et al., *Chronic consumption of farmed salmon containing persistent organic pollutants causes insulin resistance and obesity in mice.* PLoS One, 2011. **6**(9): p. e25170.

501. Marmugi, A., et al., *Adverse effects of long-term exposure to bisphenol A during adulthood leading to hyperglycaemia and hypercholesterolemia in mice.* Toxicology, 2014. **325**: p. 133-43.
502. *Economic costs of diabetes in the U.S. In 2007.* Diabetes Care, 2008. **31**(3): p. 596-615.
503. Rajesh, P. and K. Balasubramanian, *Gestational exposure to di(2-ethylhexyl) phthalate (DEHP) impairs pancreatic beta-cell function in F rat offspring.* Toxicol Lett, 2014. **232**(1): p. 46-57.
504. Bodin, J., et al., *Transmaternal bisphenol A exposure accelerates diabetes type 1 development in NOD mice.* Toxicol Sci, 2014. **137**(2): p. 311-23.
505. Alonso-Magdalena, P., et al., *Bisphenol-A treatment during pregnancy in mice: a new window of susceptibility for the development of diabetes in mothers later in life.* Endocrinology, 2015. **156**(5): p. 1659-70.
506. Nishiumi, S., et al., *2,3,7,8-tetrachlorodibenzo-p-dioxin impairs an insulin signaling pathway through the induction of tumor necrosis factor-alpha in adipocytes.* Toxicol Sci, 2010. **115**(2): p. 482-91.
507. Kern, P.A., et al., *The stimulation of tumor necrosis factor and inhibition of glucose transport and lipoprotein lipase in adipose cells by 2,3,7,8-tetrachlorodibenzo-p-dioxin.* Metabolism, 2002. **51**(1): p. 65-8.
508. Sargis, R.M., 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**: p. 952-960.
509. Paul, D.S., et al., *Molecular mechanisms of the diabetogenic effects of arsenic: inhibition of insulin signaling by arsenite and methylarsonous acid.* Environ Health Perspect, 2007. **115**(5): p. 734-42.
510. Xue, P., et al., *Prolonged inorganic arsenite exposure suppresses insulin-stimulated AKT S473 phosphorylation and glucose uptake in 3T3-L1 adipocytes: involvement of the adaptive antioxidant response.* Biochem Biophys Res Commun, 2011. **407**(2): p. 360-5.
511. Rengarajan, S., et al., *Diethylhexyl phthalate impairs insulin binding and glucose oxidation in Chang liver cells.* Toxicol In Vitro, 2007. **21**(1): p. 99-102.
512. Rajesh, P. and K. Balasubramanian, *Di(2-ethylhexyl)phthalate exposure impairs insulin receptor and glucose transporter 4 gene expression in L6 myotubes.* Hum Exp Toxicol, 2014. **33**(7): p. 685-700.
513. Rajesh, P., et al., *Phthalate is associated with insulin resistance in adipose tissue of male rat: role of antioxidant vitamins.* J Cell Biochem, 2013. **114**(3): p. 558-69.
514. Indumathi, D., et al., *Effect of bisphenol-A on insulin signal transduction and glucose oxidation in skeletal muscle of adult male albino rat.* Hum Exp Toxicol, 2013. **32**(9): p. 960-71.
515. Jayashree, S., et al., *Effect of Bisphenol-A on insulin signal transduction and glucose oxidation in liver of adult male albino rat.* Environ Toxicol Pharmacol, 2013. **35**(2): p. 300-10.
516. Han, J.C., et al., *Cadmium induces impaired glucose tolerance in rat by down-regulating GLUT4 expression in adipocytes.* Arch Biochem Biophys, 2003. **413**(2): p. 213-20.
517. Liu, P.C. and F. Matsumura, *Differential effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin on the "adipose- type" and "brain-type" glucose transporters in mice.* Mol Pharmacol, 1995. **47**(1): p. 65-73.
518. Enan, E. and F. Matsumura, *2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)-induced changes in glucose transporting activity in guinea pigs, mice, and rats in vivo and in vitro.* J Biochem Toxicol, 1994. **9**(2): p. 97-106.

519. Regnier, S.M., et al., *Dietary exposure to the endocrine disruptor tolylfluanid promotes global metabolic dysfunction in male mice.* Endocrinology, 2015. **156**(3): p. 896-910.
520. Paul, D.S., et al., *Characterization of the impaired glucose homeostasis produced in C57BL/6 mice by chronic exposure to arsenic and high-fat diet.* Environ Health Perspect, 2011. **119**(8): p. 1104-9.
521. Hill, D.S., et al., *Arsenate-induced maternal glucose intolerance and neural tube defects in a mouse model.* Toxicol Appl Pharmacol, 2009. **239**(1): p. 29-36.
522. Sun, Q., et al., *Ambient air pollution exaggerates adipose inflammation and insulin resistance in a mouse model of diet-induced obesity.* Circulation, 2009. **119**(4): p. 538-46.
523. Panahi, P., et al., *Stimulatory effects of malathion on the key enzymes activities of insulin secretion in langerhans islets, glutamate dehydrogenase and glucokinase.* Toxicol Mech Methods, 2006. **16**(4): p. 161-7.
524. Batista, T.M., et al., *Short-Term Treatment with Bisphenol-A Leads to Metabolic Abnormalities in Adult Male Mice.* PLoS One, 2012. **7**(3): p. e33814.
525. Zuo, Z., et al., *Tributyltin causes obesity and hepatic steatosis in male mice.* Environ Toxicol, 2011. **26**(1): p. 79-85.
526. Huang, C.F., et al., *Arsenic Exposure and Glucose Intolerance/Insulin Resistance in Estrogen-Deficient Female Mice.* Environ Health Perspect, 2015. **123**(11): p. 1138-44.
527. Lim, S., et al., *Chronic exposure to the herbicide, atrazine, causes mitochondrial dysfunction and insulin resistance.* PLoS One, 2009. **4**(4): p. e5186.
528. Moon, M.K., et al., *Long-term oral exposure to bisphenol A induces glucose intolerance and insulin resistance.* J Endocrinol, 2015. **226**(1): p. 35-42.
529. Baker, N.A., et al., *Coplanar polychlorinated biphenyls impair glucose homeostasis in lean C57BL/6 mice and mitigate beneficial effects of weight loss on glucose homeostasis in obese mice.* Environ Health Perspect, 2013. **121**(1): p. 105-10.
530. Gray, S.L., et al., *Chronic Exposure to PCBs (Aroclor 1254) Exacerbates Obesity-Induced Insulin Resistance and Hyperinsulinemia in Mice.* J Toxicol Environ Health A, 2013. **76**(12): p. 701-15.
531. Hofe, C.R., et al., *Fruit and vegetable intake, as reflected by serum carotenoid concentrations, predicts reduced probability of polychlorinated biphenyl-associated risk for type 2 diabetes: National Health and Nutrition Examination Survey 2003-2004.* Nutr Res, 2014. **34**(4): p. 285-93.
532. Yan, Y.H., et al., *Enhanced insulin resistance in diet-induced obese rats exposed to fine particles by instillation.* Inhal Toxicol, 2011. **23**(9): p. 507-19.
533. Wahlang, B., et al., *Evaluation of Aroclor 1260 exposure in a mouse model of diet-induced obesity and non-alcoholic fatty liver disease.* Toxicol Appl Pharmacol, 2014. **279**(3): p. 380-90.
534. Alonso-Magdalena, P., et al., *Bisphenol A exposure during pregnancy disrupts glucose homeostasis in mothers and adult male offspring.* Environ Health Perspect, 2010. **118**(9): p. 1243-50.
535. Ma, Y., et al., *Hepatic DNA methylation modifications in early development of rats resulting from perinatal BPA exposure contribute to insulin resistance in adulthood.* Diabetologia, 2013. **56**(9): p. 2059-67.
536. Garcia-Arevalo, M., et al., *Exposure to bisphenol-A during pregnancy partially mimics the effects of a high-fat diet altering glucose homeostasis and gene expression in adult male mice.* PLoS One, 2014. **9**(6): p. e100214.
537. Wan, H.T., et al., *Perinatal exposure to perfluorooctane sulfonate affects glucose metabolism in adult offspring.* PLoS One, 2014. **9**(1): p. e87137.

538. Lv, Z., et al., *Glucose and lipid homeostasis in adult rat is impaired by early-life exposure to perfluorooctane sulfonate.* Environ Toxicol, 2013. **28**(9): p. 532-42.
539. Attina, T.M. and L. Trasande, *Association of Exposure to Di-2-Ethylhexylphthalate Replacements With Increased Insulin Resistance in Adolescents From NHANES 2009-2012.* J Clin Endocrinol Metab, 2015. **100**(7): p. 2640-50.
540. Wang, J., X. Lv, and Y. Du, *Inflammatory response and insulin signaling alteration induced by PCB77.* J Environ Sci (China), 2010. **22**(7): p. 1086-90.
541. Kamath, V. and P.S. Rajini, *Altered glucose homeostasis and oxidative impairment in pancreas of rats subjected to dimethoate intoxication.* Toxicology, 2007. **231**(2-3): p. 137-46.
542. Hoppe, A.A. and G.B. Carey, *Polybrominated diphenyl ethers as endocrine disruptors of adipocyte metabolism.* Obesity (Silver Spring), 2007. **15**(12): p. 2942-50.
543. Abdollahi, M., et al., *Hyperglycemia associated with increased hepatic glycogen phosphorylase and phosphoenolpyruvate carboxykinase in rats following subchronic exposure to malathion.* Comp Biochem Physiol C Toxicol Pharmacol, 2004. **137**(4): p. 343-7.
544. Martinelli, M.I., N.O. Mocchiutti, and C.A. Bernal, *Dietary di(2-ethylhexyl)phthalate-impaired glucose metabolism in experimental animals.* Hum Exp Toxicol, 2006. **25**(9): p. 531-8.
545. Turner, N., et al., *Fatty acid metabolism, energy expenditure and insulin resistance in muscle.* Journal of Endocrinology, 2014. **220**(2): p. T61-T79.
546. Perreault, L., et al., *Bisphenol A impairs hepatic glucose sensing in C57BL/6 male mice.* PLoS One, 2013. **8**(7): p. e69991.
547. Al-Eryani, L., et al., *Identification of Environmental Chemicals Associated with the Development of Toxicant-associated Fatty Liver Disease in Rodents.* Toxicol Pathol, 2014.
548. Cave, M., et al., *Toxicant-associated steatohepatitis in vinyl chloride workers.* Hepatology, 2010. **51**(2): p. 474-81.
549. Wahlang, B., et al., *Human receptor activation by aroclor 1260, a polychlorinated biphenyl mixture.* Toxicol Sci, 2014. **140**(2): p. 283-97.
550. Sanyal, A.J., et al., *Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis.* N Engl J Med, 2010. **362**(18): p. 1675-85.
551. Brautbar, N. and J. Williams, 2nd, *Industrial solvents and liver toxicity: risk assessment, risk factors and mechanisms.* Int J Hyg Environ Health, 2002. **205**(6): p. 479-91.
552. Medicine, I.o., *Gulf War and Health Insecticides and Solvents*. Vol. 2. 2003, Washington DC: The National Academies Press
553. Lejeune, N.R.C.a.t.C.o.C.D.W.a.C., *Contaminated Water Supplies at Camp Lejeune: Assessing Potential Health Effects*. 2009, Washington DC: The National Academies Press.
554. Lee, M.R., et al., *Urinary bisphenol A concentrations are associated with abnormal liver function in the elderly: a repeated panel study.* J Epidemiol Community Health, 2014. **68**(4): p. 312-7.
555. Eng, D.S., et al., *Bisphenol A and chronic disease risk factors in US children.* Pediatrics, 2013. **132**(3): p. e637-45.
556. Lu, J., et al., *1,3-Dichloro-2-propanol induced hyperlipidemia in C57BL/6J mice via AMPK signaling pathway.* Food Chem Toxicol, 2014. **64**: p. 403-9.
557. Cave, M., et al., *Polychlorinated biphenyls, lead, and mercury are associated with liver disease in American adults: NHANES 2003-2004.* Environ Health Perspect, 2010. **118**(12): p. 1735-42.

558. Serdar, B., et al., *Potential effects of polychlorinated biphenyls (PCBs) and selected organochlorine pesticides (OCPs) on immune cells and blood biochemistry measures: a cross-sectional assessment of the NHANES 2003-2004 data.* Environ Health, 2014. **13**: p. 114.
559. Kumar, J., et al., *Persistent organic pollutants and liver dysfunction biomarkers in a population-based human sample of men and women.* Environ Res, 2014. **134**: p. 251-6.
560. Yorita Christensen, K.L., et al., *Multiple classes of environmental chemicals are associated with liver disease: NHANES 2003-2004.* Int J Hyg Environ Health, 2013.
561. Lee, D.H. and D.R. Jacobs, Jr., *Association between serum concentrations of persistent organic pollutants and gamma glutamyltransferase: results from the National Health and Examination Survey 1999-2002.* Clin Chem, 2006. **52**(9): p. 1825-7.
562. Gleason, J.A., G.B. Post, and J.A. Fagliano, *Associations of perfluorinated chemical serum concentrations and biomarkers of liver function and uric acid in the US population (NHANES), 2007-2010.* Environ Res, 2015. **136**: p. 8-14.
563. Lin, C.Y., et al., *Investigation of the associations between low-dose serum perfluorinated chemicals and liver enzymes in US adults.* Am J Gastroenterol, 2010. **105**(6): p. 1354-63.
564. Gallo, V., et al., *Serum perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS) concentrations and liver function biomarkers in a population with elevated PFOA exposure.* Environ Health Perspect, 2012. **120**(5): p. 655-60.
565. Wahlang, B., et al., *Polychlorinated biphenyl 153 is a diet-dependent obesogen that worsens nonalcoholic fatty liver disease in male C57BL6/J mice.* J Nutr Biochem, 2013. **24**(9): p. 1587-95.
566. Tan, X., et al., *High fat diet feeding exaggerates perfluorooctanoic acid-induced liver injury in mice via modulating multiple metabolic pathways.* PLoS One, 2013. **8**(4): p. e61409.
567. Penell, J., et al., *Persistent organic pollutants are related to the change in circulating lipid levels during a 5 year follow-up.* Environ Res, 2014. **134**: p. 190-7.
568. Arrebola, J.P., et al., *Associations of accumulated exposure to persistent organic pollutants with serum lipids and obesity in an adult cohort from Southern Spain.* Environ Pollut, 2014. **195**: p. 9-15.
569. Lee, D.H., et al., *Low dose organochlorine pesticides and polychlorinated biphenyls predict obesity, dyslipidemia, and insulin resistance among people free of diabetes.* PLoS One, 2011. **6**(1): p. e15977.
570. Yamamoto, K., et al., *Ameliorative effect of dietary probucol on polychlorinated biphenyls-induced hypercholesterolemia and lipid peroxidation in the rat.* Life Sci, 1994. **54**(14): p. 1019-26.
571. Wahlang, B., et al., *Polychlorinated biphenyl 153 is a diet-dependent obesogen that worsens nonalcoholic fatty liver disease in male C57BL6/J mice.* The Journal of Nutritional Biochemistry, 2013. **24**(9): p. 1587-1595.
572. Maranghi, F., et al., *Lindane may modulate the female reproductive development through the interaction with ER-beta: an in vivo-in vitro approach.* Chem Biol Interact, 2007. **169**(1): p. 1-14.
573. Attia, A.M., et al., *Lindane-induced biochemical perturbations in rat serum and attenuation by omega-3 and Nigella sativa seed oil.* Indian J Biochem Biophys, 2011. **48**(3): p. 184-90.
574. Angrish, M.M., C.Y. Dominici, and T.R. Zacharewski, *TCDD-elicited effects on liver, serum, and adipose lipid composition in C57BL/6 mice.* Toxicol Sci, 2013. **131**(1): p. 108-15.

575. Islam, K., et al., *Dose-response relationship between arsenic exposure and the serum enzymes for liver function tests in the individuals exposed to arsenic: a cross sectional study in Bangladesh.* Environ Health, 2011. **10**: p. 64.
576. Mendez, M.A., et al., *Chronic Exposure to Arsenic and Markers of Cardiometabolic Risk-A Cross-Sectional Study in Chihuahua, Mexico.* Environ Health Perspect, 2015.
577. Muthumani, M. and S. Miltonprabu, *Ameliorative efficacy of tetrahydrocurcumin against arsenic induced oxidative damage, dyslipidemia and hepatic mitochondrial toxicity in rats.* Chem Biol Interact, 2015. **235**: p. 95-105.
578. Arteel, G.E., et al., *Subhepatotoxic exposure to arsenic enhances lipopolysaccharide-induced liver injury in mice.* Toxicol Appl Pharmacol, 2008. **226**(2): p. 128-39.
579. Tan, M., et al., *Chronic subhepatotoxic exposure to arsenic enhances hepatic injury caused by high fat diet in mice.* Toxicol Appl Pharmacol, 2011. **257**(3): p. 356-64.
580. Poursafa, P., et al., *Association of serum lead and mercury level with cardiometabolic risk factors and liver enzymes in a nationally representative sample of adolescents: the CASPIAN-III study.* Environ Sci Pollut Res Int, 2014. **21**(23): p. 13496-502.
581. Moreira, E.L., et al., *Does methylmercury-induced hypercholesterolemia play a causal role in its neurotoxicity and cardiovascular disease?* Toxicol Sci, 2012. **130**(2): p. 373-82.
582. Kang, M.Y., et al., *Effects of environmental cadmium exposure on liver function in adults.* Occup Environ Med, 2013. **70**(4): p. 268-73.
583. Kelishadi, R., et al., *Association of blood cadmium level with cardiometabolic risk factors and liver enzymes in a nationally representative sample of adolescents: the CASPIAN-III study.* J Environ Public Health, 2013. **2013**: p. 142856.
584. Chang, L.W. and S. Yamaguchi, *Ultrastructural Changes of the Liver After Long-Term Diet of Mercury-Contaminated Tuna.* Environ Res, 1974. **7**: p. 16.
585. Go, Y.M., et al., *Low-Dose Cadmium Causes Metabolic and Genetic Dysregulation Associated With Fatty Liver Disease in Mice.* Toxicol Sci, 2015. **147**(2): p. 524-34.
586. Bruce, K.D., et al., *Maternal high-fat feeding primes steatohepatitis in adult mice offspring, involving mitochondrial dysfunction and altered lipogenesis gene expression.* Hepatology, 2009. **50**(6): p. 1796-808.
587. Benatti, R.O., et al., *Maternal high-fat diet consumption modulates hepatic lipid metabolism and microRNA-122 (miR-122) and microRNA-370 (miR-370) expression in offspring.* Br J Nutr, 2014. **111**(12): p. 2112-22.
588. Bringhenti, I., et al., *Early hepatic insult in the offspring of obese maternal mice.* Nutr Res, 2015. **35**(2): p. 136-45.
589. Wei, J., et al., *Perinatal exposure to bisphenol A exacerbates nonalcoholic steatohepatitis-like phenotype in male rat offspring fed on a high-fat diet.* J Endocrinol, 2014. **222**(3): p. 313-25.
590. Kim, J.H., et al., *Perinatal bisphenol A exposure promotes dose-dependent alterations of the mouse methylome.* BMC Genomics, 2014. **15**: p. 30.
591. Maranghi, F., et al., *In utero exposure to di-(2-ethylhexyl) phthalate affects liver morphology and metabolism in post-natal CD-1 mice.* Reprod Toxicol, 2010. **29**(4): p. 427-32.
592. Hayashi, Y., et al., *Hepatic peroxisome proliferator-activated receptor alpha may have an important role in the toxic effects of di(2-ethylhexyl)phthalate on offspring of mice.* Toxicology, 2011. **289**(1): p. 1-10.
593. Ito, Y., et al., *Plasticizers May Activate Human Hepatic Peroxisome Proliferator-Activated Receptor alpha Less Than That of a Mouse but May Activate Constitutive Androstane Receptor in Liver.* PPAR Res, 2012. **2012**: p. 201284.

594. Dunnick, J.K., et al., *Characterization of polybrominated diphenyl ether toxicity in Wistar Han rats and use of liver microarray data for predicting disease susceptibilities.* Toxicol Pathol, 2012. **40**(1): p. 93-106.
595. Suvorov, A. and L. Takser, *Global gene expression analysis in the livers of rat offspring perinatally exposed to low doses of 2,2',4,4'-tetrabromodiphenyl ether.* Environ Health Perspect, 2010. **118**(1): p. 97-102.
596. Karmaus, W., et al., *Maternal levels of dichlorodiphenyl-dichloroethylene (DDE) may increase weight and body mass index in adult female offspring.* Occupational and Environmental Medicine, 2009. **66**(3): p. 143-149.
597. Skinner, M.K., et al., *Ancestral dichlorodiphenyltrichloroethane (DDT) exposure promotes epigenetic transgenerational inheritance of obesity.* BMC Med, 2013. **11**: p. 228.
598. Stegemann, R. and D.A. Buchner, *Transgenerational inheritance of metabolic disease.* Semin Cell Dev Biol, 2015.
599. Skinner, M.K., C. Guerrero-Bosagna, and M.M. Haque, *Environmentally induced epigenetic transgenerational inheritance of sperm epimutations promote genetic mutations.* Epigenetics, 2015. **10**(8): p. 762-71.
600. Ozgyin, L., et al., *Nuclear receptors in transgenerational epigenetic inheritance.* Prog Biophys Mol Biol, 2015. **118**(1-2): p. 34-43.
601. Skinner, M.K., *What is an epigenetic transgenerational phenotype? F3 or F2.* Reprod Toxicol, 2008. **25**(1): p. 2-6.
602. Walker, C.L. and S.-m. Ho, *Developmental reprogramming of cancer susceptibility.* Nat Rev Cancer, 2012. **12**(7): p. 479-486.
603. Szyf, M., *Nongenetic inheritance and transgenerational epigenetics.* Trends in Molecular Medicine, 2015. **21**(2): p. 134-144.
604. Radford, E.J., et al., *In utero effects. In utero undernourishment perturbs the adult sperm methylome and intergenerational metabolism.* Science, 2014. **345**(6198): p. 1255903.
605. Ho, D.H. and W.W. Burggren, *Epigenetics and transgenerational transfer: a physiological perspective.* J Exp Biol, 2010. **213**(1): p. 3-16.
606. Ost, A. and J.A. Pospisilik, *Epigenetic modulation of metabolic decisions.* Curr Opin Cell Biol, 2015. **33**: p. 88-94.
607. Guerrero-Bosagna, C., S. Weeks, and M.K. Skinner, *Identification of genomic features in environmentally induced epigenetic transgenerational inherited sperm epimutations.* PLoS One, 2014. **9**(6): p. e100194.
608. Desai, M., et al., *Programmed hyperphagia secondary to increased hypothalamic SIRT1.* Brain Res, 2014. **1589**: p. 26-36.
609. Johnson, S.A., et al., *Sex-dependent effects of developmental exposure to bisphenol A and ethinyl estradiol on metabolic parameters and voluntary physical activity.* J Dev Orig Health Dis, 2015. **6**(6): p. 539-52.
610. Wing, R.R. and S. Phelan, *Long-term weight loss maintenance.* The American Journal of Clinical Nutrition, 2005. **82**(1): p. 222S-225S.
611. Fothergill, E., et al., *Persistent metabolic adaptation 6 years after "The Biggest Loser" competition.* Obesity, 2016: p. n/a-n/a.

Chemical	Obesity	T2D	Lipid Disorders
Chemical	Obesity	T2D	Fatty Liver
Bisphenol A	***	***	***
DEHP	***	***	***
DDT/DDE	***	**	*
PBDE			*
PFOA	**		***
PFOS		*	***
TBT	***	***	***
Air Pollution	**	***	***
PAHs			
PCBs	*	***	***
TCDD		**	***
Cadmium		*	**
Atrazine		*	**
Arsenic	**	***	***

HCB	*		
Trifumizole	*		
Benzo(a) pyrene	*		**
Tolyfuanid	*	*	
Smoking/nicotine	***	**	***

Table 1: Metabolism Disruptors and Metabolic Disruption

This table has been developed from the literature cited in this review. The number of *** indicates the strength of the evidence . * indicates one manuscript animal or human, ** indicates one manuscript in animal and human or more than one manuscript in either animal or human and *** indicates more than one manuscript in both animal and human studies, or multiple manuscripts in animal studies.