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What Are We Putting in Our Food That Is Making Us Fat? Food Additives, Contaminants, and Other Putative Contributors to Obesity

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Abstract

The “chemical obesogen” hypothesis conjectures that synthetic, environmental contaminants are contributing to the global epidemic of obesity. In fact, intentional food additives (e.g., artificial sweeteners and colors, emulsifiers) and unintentional compounds (e.g., bisphenol A, pesticides) are largely unstudied in regard to their effects on overall metabolic homeostasis. With that said, many of these contaminants have been found to dysregulate endocrine function, insulin signaling, and/or adipocyte function. Although momentum for the chemical obesogen hypothesis is growing, supportive, evidence-based research is lacking. In order to identify noxious synthetic compounds in the environment out of the thousands of chemicals that are currently in use, tools and models from toxicology should be adopted (e.g., functional high throughput screening methods, zebrafish-based assays). Finally, mechanistic insight into obesogen-induced effects will be helpful in elucidating their role in the obesity epidemic as well as preventing and reversing their effects.

Keywords

obesity; BPA; bisphenol A; food additives; preservatives; pesticides; plastics; pollutants; contaminants

Introduction

Since the industrial revolution, the goals of food technology have predominately been maximizing palatability, optimizing process efficiency, increasing shelf life, reducing cost, and improving food safety (free from harmful viruses, bacteria, and fungi). As such, over 4,000 novel ingredients have entered the food supply, some intentionally (such as

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Conflict of Interest

Amber L. Simmons, Jennifer J. Schlezinger, and Barbara E. Corkey declare that they have no conflict of interest.

Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

preservatives) and some inadvertently (such as bisphenol A, BPA), and there are 1,500 new compounds that enter the market every year [52]. While food processing techniques are also constantly being optimized to minimize toxic compounds and toxicants such as lead, melamine, and aflatoxin, other “non-toxic” additives are not thoroughly tested for their chronic, additive, and/or cumulative effects on human physiology.

Obesity and related chronic disorders are increasing at alarming rates and it is estimated that 86% of Americans will be overweight by 2030 [53]. This trend continues despite increases in awareness, nutritional and behavioral research, the amount of diet foods available, and even gym memberships [54]. Unfortunately, the etiology of obesity and diabetes in regard to biochemical mechanisms is still largely not understood. Treatment and prevention of obesity hinges on our ability to 1) characterize the biochemical pathways that promote obesity, 2) identify what changes in our environment are promoting obesity, and 3) avoid and reverse the effects of the offensive agents and practices. It is crucial that clinicians understand and communicate that most novel food ingredients have not been evaluated for metabolic safety. In this review, we outline what agents have been identified that may be contributing to obesity, describe current methods being used to identify offensive compounds, and identify critical gaps in our methods and body of knowledge.

The importance of identifying agents that contribute to obesity

There is an abundance of research related to obesity etiology and prevention in regard to decreasing caloric intake and increasing energy expenditure. However, “non-traditional” risk factors are under increased scrutiny for their contributions to the obesity epidemic: emotional stress, sleep deprivation, disruption of normal circadian rhythm, composition of the gut microbiome, oxidative stress, medications such as antidepressants and oral contraceptives, average home temperature, and environmental toxicants [24,36,55]. Agents in our food supply have immense potential to affect metabolism due to continuous exposure and potential interactions among multiple compounds. A recently hypothesized factor contributing to the obesity epidemic is our exposure to *obesogens*, chemicals in our environment that can disrupt metabolism and lead to accumulation of excess fat mass (coined by Grün and Blumberg in 2006 [27]). It is critical that we identify these obesogens in our food supply in order to facilitate obesity prevention and treatment [34].

Unfortunately, many of the obesogenic compounds in our food supply were added *deliberately* to enhance production instead of being added to enhance nutrition. For example, pesticides are added to ward off insects during farming; BPA is a strong, clear plastic that has ideal properties for making bottles and coating cans; and mono- and diglycerides are added to emulsify the fat and water in foods to achieve a favorable texture. Simple exclusion of these compounds may not be possible until alternatives are developed, but then these novel compounds must be tested. Like pharmaceuticals, thorough testing is time-consuming and expensive.

Obesogen identification and characterization is in its infancy, and much of the scientific evidence supporting the relationship between synthetic compounds and the obesity epidemic is currently weak. Strong, evidence-based scientific support is derived from randomized,

controlled trials, ideally cross-over design, that comprise four steps: 1) addition of the compound of interest, 2) observation of an effect, 3) removal of the compound of interest, and 4) disappearance of the effect. However, the bulk of evidence relating environmental contaminants and obesity is derived from epidemiological studies which are correlational by nature. While correlations are important, they are limited in that conclusions about causal relationships are impossible. Well-designed animal studies provide strong evidence within the animal model, but must be confirmed in humans. Cell studies are important for deriving mechanisms that may link certain compounds to obesity, yet provide only weak evidence for the global phenomenon (the obesity epidemic). Thus, we currently do not have any strong evidence that any contaminant, food additive, or ingredient that is “generally recognized as safe” (GRAS) causes obesity, which is essential for making confident recommendations and changes in public policy.

It is important to note that in evaluating foods for their contribution to obesity, we may identify ingredients that *prevent* obesity. For example, some hydrocolloids including guar gum and β -glucan may be able to increase satiety and reduce caloric intake with their bulking properties [56]. Also, anthocyanins (potent color compounds from grapes, purple corn, blueberries, and other plants) may reduce oxidative stress, prevent obesity, and help control diabetes in cell culture, animal models, and humans [57]. Again, not all compounds in a class are equal; for example, although the hydrocolloid guar gum may prevent obesity (mentioned above), another hydrocolloid called carrageenan, found commonly in chocolate milk and ice cream, may contribute to insulin resistance in mice [58].

What in our food is making us fat?

There are many aspects of the average Western diet that may promote obesity. The macronutrient ratio (fat:carbohydrate:protein), the characteristics of the fat (e.g., diets rich in palmitic acid vs. eicosapentaenoic acid), the characteristics of the carbohydrates (refined vs. whole grain carbohydrates) [2,59], and form of the protein [60] are major concerns and reviewed elsewhere [2,59-63]. In addition, advances in food processing have facilitated consumption of high caloric food that is low in other nutrients (e.g., edible oils, refined grains) [61] as well as increased the glycemic load of common meals [62]. Increased consumption of nutrient-poor added fat, added sugar, added salt, and refined grains may also underlie obesity and co-morbidities in ways that extend beyond energy balance [63]. Baillie-Hamilton announced a well-received hypothesis in 2002 highlighting the potential for environmental compounds in our food to contribute to the obesity epidemic [55]. While the relationship between obesity and food structure is reviewed elsewhere [59-63], herein, we will focus on potential obesogens and obesity-promoting food additives in our foods supply (Table 1).

Fat: Saturated fat and trans-fat

The negative social stigma around saturated fat stems from studies correlating high intake of saturated fat, often from meat and cheese, with elevated risk of unhealthy weight gain, cardiovascular disease, insulin resistance and type 2 diabetes [2]. However, more comprehensive studies have revealed that this nutritional advice is oversimplified and misleading; lauric acid (C12:0) and stearic acid (C18:0) may not be as harmful as myristic

acid (C14:0) and palmitic acid (C16:0) in regard to cardiovascular health [2]. Moreover, saturated medium chain fatty acids such as caproic acid (C6:0), caprylic acid (C8:0), and capric acid (C10:0) may even promote fat oxidation [64]. The science of macronutrient intake is very complex; replacement of saturated fat with other nutrient categories (e.g., monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA), high vs. low glycemic index carbohydrates,) often yields disparate results due to a variety of confounding factors (e.g., age, lifestyle factors) [2]. Thus, although we know that there are some aspects and some types of saturated fat that promote obesity, particularly in rodents, it is not appropriate to view all saturated fat as metabolically similar in humans.

Trans-fat, although inherent in bovine milk at about 0.85 g/kg and other natural foods, is consumed in much larger quantities from partially hydrogenated vegetable oil [3]. Partial hydrogenation of oil yields a solid (often soft and spreadable) fat at room temperature. It is a common ingredient in fried foods, high-fat bakery products (especially packaged cookies and cakes), and packaged frozen foods such as pizza and breaded chicken nuggets. Based on a meta-analysis of four prospective cohort studies, an increase of 2% energy from *trans*-fats (i.e. 5 g in a 2000 kcal diet) is associated with an increase in the risk of coronary heart disease by 23% [3]. In the same vein, there is strong evidence that *trans*-fat consumption is associated with increased adiposity in monkeys [4] yet randomized, controlled clinical trials in humans have not been performed.

Food additives and ingredients “generally recognized as safe” (GRAS)

The FDA maintains a database with “Everything added to food in the U.S.” (EAFUS) [52]. As of January 2014, the database includes 3,968 additives with varying regulatory statuses. Some of these ingredients are food additives approved by the FDA and others are GRAS (i.e. they have demonstrated safety through long-term use in the food supply and/or published studies). While many ingredients have undergone an extensive literature search for toxicology information, most of the items on this list have not been evaluated for effects on metabolic regulation. Artificial sweeteners, preservatives, monosodium glutamate (MSG), mono-oleoylglycerol (MOG) and others have demonstrated potential lipid accumulation effects (see Table 1). There are scores of other compounds that are used generously in our food but have not been evaluated for effects on key metabolic pathways (Table 2).

High intensity sweeteners are studied most often when comparing consumption of sugar-sweetened beverages to consumption of beverages with calorie-free (or low calorie) artificial sugars with the assumption that artificial sugars are inert. However, Kyriazis *et al.* demonstrated that saccharin can potentiate glucose-stimulated insulin release from isolated pancreatic β -cells via direct binding to the sweet taste receptor [65]. Additionally, aspartame, in combination with MSG, promoted fat accumulation and other pre-diabetic symptoms in C57BL/6 mice [66]. On the other hand, the high intensity sweetener stevia has the potential to treat insulin resistance in mice [67]. Recently, artificial sweeteners have been shown to resist breakdown during sewage treatment, thus persisting in the water system [68]. Formidably, irradiation of acesulfame (sold as acesulfame potassium, AceK) by sunlight can cause a persistent by-product that is greater than 500 times more toxic than

AceK *per se* [68]. Taken together, prudent analyses of the effects of artificial sweeteners in humans and in the environment are crucial in light of their wide-spread use and potential hazard to health.

Artificial colors (dyes) are used in many foods including candy, fruit-flavored drinks, many breakfast cereals marketed to children and, not as obviously, in packaged foods containing fruit (e.g., blueberries in blueberry muffins), vitamin supplements, and even white marshmallows. There are nine artificial colors approved for use in the U.S. (see Table 2), plus Citrus Red #2, permissible for citrus rinds, and Orange B, allowed in hot dogs and sausage casings. In fact, use of artificial food colors per capita has increased almost five-fold between 1950 and 2010 [69]. This may be important because research has suggested that consumption of artificial colors can reduce attention and increase hyperactivity in sensitive children [69]. However, research correlating artificial color consumption with obesity is scarcer. Amin *et al.* did not observe an increase in weight gain in rats consuming “low” (15 mg/kg body weight) or “high” (500 mg/kg) concentrations of tartrazine for 30 days [70], though they did observe alterations in the circulating redox state, which could affect weight gain later in life [71]. Axon *et al.* discovered that tartrazine and sunset yellow bind the estrogen receptor, thus exhibiting potential to disrupt endocrine function [72]. More investigation into the molecular effects of these compounds, particularly in human cells, is crucial in light of their ubiquity in the food supply, increased consumption, and potential for adverse metabolic effects.

Plastics

Plastics interact with our food supply via numerous points of production, packaging, or transporting. Plastic components (e.g., BPA, phthalates, organotins) leach into food and beverages, especially at high temperatures. Plastic components, along with many pesticides and other persistent organic pollutants (POPs), share a similar mode of action in the etiology of obesity in that they disrupt endocrine communication. Endocrine disrupting compounds (EDCs), by definition, mimic hormones and/or interfere with the production, release, metabolism, or elimination of endogenous hormones. Because many EDCs are lipid soluble, they can accumulate in tissue and thus biomagnify as they traverse the food chain (e.g., humans consume and accumulate compounds that were consumed and accumulated by fish), thereby having enduring effects. Moreover, because of their liberal use, understanding interactions among EDCs is of vital importance in assessing their physiological effects. A recent discussion by Elobeid & Allison concluded that although there is not yet strong evidence in humans that EDCs are contributing to the overweight phenotype, studies in cell culture, animal models, and wildlife as well as epidemiological studies are highly suggestive [19].

Organotins, organic derivatives of tin, are used liberally for stabilization of plastics [27]. Due to its strong biological effects, the organotin tributyltin inspired the coining of the term “environmental obesogen” [27]. Butyltin compounds have been detected in food containers and parchment paper and are transferred to foods baked in/on these products [73]. Assessment of human exposure to organotins is limited, but significant human exposure is indicated by the presence of organotins in liver, blood, and breast milk ([27,73,74] and

references within). Tributyltin, triphenyltin, and, to a lesser extent, dibutyltin, are PPAR γ ligands that can induce adipocyte differentiation ([27] (review) and more recent primary literature [28,75-77]). Prenatal exposure to tributyltin induces increased adiposity in adulthood in mice [27] that results from reprogramming of the differentiation capacity of multipotent mesenchymal stromal cells (MSCs) [79]. The enhanced propensity of MSCs to differentiate into adipocytes induced by tributyltin is inherited transgenerationally in a mouse model [80].

BPA is one of the highest produced chemicals by volume ([18,21] and references within) and is used to make plastic water bottles, line tin cans, and coat production pipes. In humans, it was detected in 95% of adult urine samples at greater than 0.1 g/L from an American population ([19] and references within). Strong positive correlations were revealed between urine BPA concentration and BMI, waist circumference, and high density lipoprotein cholesterol [21]. *In vitro* and *in vivo* studies have shown that BPA accelerates adipocyte differentiation and promotes lipid accumulation via alteration of glucose homeostasis as well as by activating the glucocorticoid receptor (review: [19] and publications since then: [81-85]). However, not all studies agree that BPA promotes weight gain and adiposity. For example, mouse studies have shown no effect of BPA on weight gain or reduced weight gain following perinatal exposure [19,84,86,87]. Discrepancies among studies may be attributable to differences in sex, estrogen status, species/strain of mouse, dosing timing/regime, and diet. BPA is known to induce non-monotonic dose responses, thus low dose exposures may be the most relevant to obesogenic endpoints [84].

Phthalates are used in the pharmaceutical industry, in food production, and in packaging as plasticizing agents. They can be found in the enteric coatings of nutritional and pharmaceutical capsules; polyvinylchloride (PVC) tubing used in food production; packaging of plastic milk cartons, cheese, and meat; and PVC-based plastic wrap [88]. Phthalates, unlike BPA, are not covalently bound to the plastic and thus can readily diffuse into food, especially foods high in fat such as meat due to their high lipophilicity. Urine samples from the 2009-2010 U.S. National Health and Nutrition Examination Study (NHANES) from 2,749 Americans presented an average of 64.4 g/L of mono-(2-ethylhexyl) phthalate, a metabolite of di-(2-ethylhexyl) phthalate [89•]. Monoester metabolites of phthalates are ligands of PPAR α and PPAR γ and can induce adipocyte differentiation, yet at concentrations 100-1000 times greater than what is present in urine (M concentrations vs. nM concentrations) [90,91]. Phthalates have been associated with dysregulated sex hormones, obesity, and insulin resistance at a large range of concentrations [23,24••]. Analysis of data from males in the NHANES study from 1999-2002 revealed significant correlations between four phthalate metabolites and waist circumference and three phthalate metabolites and insulin resistance (review [25]). Additionally, Trasande *et al.* reported an association between low molecular weight metabolites of phthalates and increases in being overweight or obese in non-Hispanic black children between the ages of 6-19 years who participated in the NHANES study between 2002-2008 [92].

Persistent organic pollutants (POPs) and pesticides

POPs are a category of compounds that resist typical chemical, biological, or photolytic degradation. POPs, some of which are used as pesticides, introduce danger because of their stability in the environment; they tend to be hydrophobic and bioaccumulate in the food chain. Some also undergo transformation by natural sunlight irradiation, increasing their toxicity [68]. The 12 POPs of greatest concern, all organochlorides, were addressed in the Stockholm Convention in 2001 and included aldrin, chlordane, dichlorodiphenyltrichloroethane (DDT), dieldrin, dioxins, endrin, furans, heptachlor, hexachlorobenzene, mirex, polychlorinated biphenyls (PCBs), and toxaphene. More recently, chemicals such as perfluorooctanoic acid, organobromines, polybrominated diphenyl ethers, and organotins have been considered POPs as well. Systematic review of the epidemiological data supports an association between POP exposure and type 2 diabetes [20••,34••]. Also, animal studies with PCBs support the role of these chemicals in modulating glucose/insulin homeostasis. PCB exposure has been shown to impair glucose homeostasis, exacerbate high fat diet-induced insulin resistance, and disrupt lipid metabolism in mice (36 mg Aroclor-1254/kg/wk for 20 wks [30], 4 × 50 mg PCB-153/kg over 10 wks [32], 50 mg PCB-77/kg/wk for 2 wks [33], or 1.6 mg PCB-126/kg/wk for 2 wks [33]). These few studies likely mark the beginning of a large initiative to document the effects of man-made compounds on the environment and on human health.

Heavy metals

Inorganic arsenic from natural mineral deposits contaminates drinking water worldwide [93]. As many as 25 million Americans are exposed to concentrations of arsenic in drinking water greater than the Environmental Protection Agency (EPA) drinking water standard of 100 ppb [94], while people in parts of Bangladesh and Taiwan are exposed to arsenic concentrations >150 ppm [34]. In addition, because rice is grown in arsenic-contaminated fields, people can be exposed to levels greater than the recommended intake of arsenic by consuming only about 1/2 cup of rice per day [40]. Inorganic arsenic has been shown to elevate basal glucose and insulin concentrations in rats (1.7 mg arsenite/kg for 90 days), reduce insulin sensitivity in insulin-sensitive cells in cell culture, and, *in vitro*, interfere with insulin signaling pathways ([93,95] and references within). Furthermore, 25 and 50 ppm inorganic arsenic in drinking water for 20 weeks has been shown to exacerbate high-fat, diet-induced glucose intolerance in mice [96]. While arsenic exposure has not been linked with accretion of fat mass *per se*, arsenic indeed impairs adipocyte metabolism *in vivo* [97] and total arsenic concentration in the urine has been associated with metabolic complications such as type 2 diabetes [34••,93].

Cadmium is found in high concentrations in shellfish since it biomagnifies in the aquatic food chain, as well as in the livers of other meat animals. Cadmium can accumulate in other foods, too, as it is present in industrial processes for making plastics. In murine adipocytes, cadmium mimicked the effects of insulin, thus promoting glucose metabolism and lipogenesis [43]. In their review, Edwards and Prozialeck elegantly illustrate a mechanism by which cadmium exposure can lead to elevated blood glucose, diabetes, and diabetic nephropathy [43]. Similar to arsenic, cadmium may not promote adiposity (it may even

reduce the size of adipocytes), but it may promote insulin resistance and type 2 diabetes [44].

Animal hormones and milk

Recombinant bovine growth hormone (rbGH; also known as recombinant bovine somatotropin, rbST) was introduced in the 1990's and has increased milk production in cows about 15% [48]. Despite the amount of press regarding rbGH in relation to obesity and early onset of puberty, the compositions of conventional milk, organic milk, and milk labeled "rbST-free" are very similar in regard to macronutrient composition and hormone content [49]. In fact, bovine growth hormone is not active in humans, even when injected directly into the bloodstream ([48] and references within). Thus, it is unlikely that rbGH is contributing to the obesity epidemic directly, but there may be an elusive intermediate factor that has yet to be discovered.

Methods for identifying obesogens

The mechanisms by which obesogens can cause weight gain are extremely diverse. Biochemical pathways involving estrogen, testosterone, catecholamines, thyroid hormones, steroids, growth hormone, and endocrine hormones (e.g., insulin, ghrelin, leptin) all influence anabolic and catabolic pathways [55]. In addition, the sympathetic and parasympathetic nervous systems regulate energy metabolism from the level of the brain (e.g., appetite) to the level of the cells (e.g., mobilization of fat stores). The reductionist approach of analyzing individual constituents of the biological system has been successful in identifying molecular targets for several obesogens. However, models developed with this approach are limited in that they cannot accommodate redundant pathways, they do not accurately represent multifarious interactions with a variety of receptors in different tissues, nor do they account for effects that require time to present. Holistic approaches are necessary to complement the reductionist approach in order to observe and understand effects on the entire system.

With the enormous number of potential obesogens that require study, high throughput screening (HTS) methods are necessary. Functional HTS methods are valuable for identifying compounds and also understanding the mechanisms by which the compounds interfere with normal metabolism. Examples of functional HTS screening methods include analysis of glucose output from hepatocytes, insulin secretion from β -cells, and lipid storage/lipolysis in adipocytes. Integrative models that utilize tools from genetics and epigenetics, transcriptomics, proteomics, metabolomics, systems biology, computational biology, and developmental biology are useful to best describe the effects of these compounds on humans without human studies themselves. The establishment of a database will allow pattern recognition and predictions of properties of novel chemicals.

The field of toxicology has been paramount in developing HTS methods and can currently analyze compounds at unprecedented rates. For example, the Tox21 initiative, funded by the United States' EPA, FDA, National Institute of Environmental Health Sciences, and National Institutes of Health Chemical Genomics Center uses a robotic HTS system to evaluate approximately 8,000 unique compounds daily for various biological effects.

ToxCast™ is an initiative from the EPA to collaborate with Tox21 [98]. Using HTS techniques, compounds can be tested for at least 650 biological effects, and then prioritized for further analysis by other laboratories, including the Endocrine Disruption Screening Program (EDSP) and the drinking water Candidate Contaminant List [99]. The EDSP has been evaluating compounds since 2009 for effects ranging from binding to the estrogen receptor (*in silico* and *in vitro*) to the effects on male and female puberty (*in vivo*, rats). In order to direct efforts towards obesogen identification, the National Toxicology Program enlists experts to identify relevant ToxCast targets for biological processes related to diabetes and obesity (e.g., insulin signaling, islet cell function, adipocyte differentiation, and feeding behavior in *Caenorhabditis elegans*). Positives and negatives were identified for each pathway from the Phase I ToxCast set using the ToxPi analytical prioritization tool [100]. Targeted testing of these putative obesogens is being carried out in relevant biological systems [34••].

As a new and rigorous *in vivo* model, zebrafish are an increasingly valuable screening model for the ability of compounds to cause obesity. Zebrafish hold an advantage over cell culture in that they are a complete biological system. Compared to mice, zebrafish experiments can be done more rapidly (11 days vs. about 3 months) and in a much smaller space. Protocols are available for use in screening compounds for their effects on adiposity specifically ([101•] and references within). For example, Lyche *et al.* introduced female zebrafish to POP mixtures extracted directly from fish in a Norwegian freshwater system [102]. They observed differences in weight gain, age of maturity, and a large spectrum of changes in the transcriptional profile.

In addition to assessing compounds on fat accumulation and metabolism in adults, it is also important to describe the effects of these compounds at sensitive stages in development. Metabolic effects of these compounds have the potential to invoke irreversible damage to prenatal organisms and infants [24••,103•].

For identifying avenues of future research, epidemiological correlations are extremely valuable [92]. Samples from the U.S. NHANES study have highlighted correlations between various obesogens and increased waist circumference, insulin resistance, low/high birth weights, and other potential association with exposure ([6,7,18,19,20••,24••,34••,36•,89•, 103•] and references within). However, we must keep in mind the limitations of correlational studies; increased microwave dinners, canned pasta meals, and soda from plastic bottles could increase intake of environmental plastics but the development of the person's obesity may be entirely unrelated to the plastic exposure. In addition, moving forward, a shift from food frequency questionnaires to metabolomics approaches for quantifying food intake will allow a more accurate assessment. Subsequently, additional testing is always essential to differentiate causation from correlation.

What we can do as scientists with identified obesogens

Once obesogens are identified, we have both responsibilities and opportunities. We have responsibility to inform public policy in order to minimize usage of offensive compounds. Scientists also must develop healthy alternatives to fit the needs of industry and/or antidotes

for the offensive compounds. Knowledge of obesogens and their mechanisms will undoubtedly allow a more thorough understanding of the etiology of obesity, which can inform prevention and treatment tactics, including anti-obesity pharmaceuticals. Focusing on these issues will lead to improved efficiency identifying obesogenic compounds and a more streamlined process for safely introducing novel compounds into our food supply. Finally, to prevent unnecessary redundant initiatives, a database should be developed for the tested compounds that do and do not contribute to obesity.

Identification of obesogens is akin to identification of carcinogens in that scientists and clinicians will drive change to provide solutions. In response to the identification of carcinogens, the 1958 Delaney Clause was established to prevent FDA approval of any chemical compound found to cause cancer in animals or humans. Thus, many compounds are already tested for long-term carcinogenic and toxic effects. An additional FDA requirement for reporting body weight increases could help prevent the introduction of future obesogens.

Conclusion

From farm to fork, our food carries thousands of compounds that we consume (Figure 1), some of which are harmful and some of which are helpful depending on quantity and context. Photolytic degradation products of compounds [68] as well as bioaccumulation of obesogens from water to crops (e.g., rice), fish, and farm animals [24••] demonstrate that toxicologists and environmental scientists in addition to nutrition and metabolic scientists are crucial in the endeavor to minimize the effects of environmental obesogens. Both holistic and reductionist approaches are needed while heeding physiologically relevant concentrations; zebrafish offer a new, promising model to help reach these goals. In the light of the current obesity epidemic, it is prudent to evaluate everything that is added to our food for potential contributions to obesity.

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References

1. Begley TH, White K, Honigfort P, Twaroski ML, Neches R, Walker RA. Perfluorochemicals: potential sources of and migration from food packaging. *Food Addit. Contam.* 2005; 22:1023–31. [PubMed: 16227186]
2. Micha R, Mozaffarian D. Saturated fat and cardiometabolic risk factors, coronary heart disease, stroke, and diabetes: a fresh look at the evidence. *Lipids.* 2010; 45:893–905. [PubMed: 20354806]
3. Mozaffarian D, Katan MB, Ascherio A, Stampfer MJ, Willett WC. Trans fatty acids and cardiovascular disease. *N. Engl. J. Med.* 2006; 354:1601–13. [PubMed: 16611951]
4. Kavanagh K, Jones KL, Sawyer J, Kelley K, Carr JJ, Wagner JD, et al. Trans fat diet induces abdominal obesity and changes in insulin sensitivity in monkeys. *Obesity.* 2007; 15:1675–84. [PubMed: 17636085]
5. Hu FB, van Dam RM, Liu S. Diet and risk of Type II diabetes: the role of types of fat and carbohydrate. *Diabetologia.* 2001; 44:805–17. [PubMed: 11508264]

6. Yu Z, Lowndes J, Rippe J. High-fructose corn syrup and sucrose have equivalent effects on energy-regulating hormones at normal human consumption levels. *Nutr. Res.* 2013; 33:1043–52. [PubMed: 24267044]
7. Grimes CA, Riddell LJ, Campbell KJ, Nowson CA. Dietary salt intake, sugar-sweetened beverage consumption, and obesity risk. *Pediatrics.* 2013; 131:14–21. [PubMed: 23230077]
8. Cederroth CR, Nef S. Soy, phytoestrogens and metabolism: A review. *Mol. Cell. Endocrinol.* 2009; 304:30–42. [PubMed: 19433245]
9. Cani PD, Everard A, Duparc T. Gut microbiota, enteroendocrine functions and metabolism. *Curr. Opin. Pharmacol.* 2013; 13:935–40. [PubMed: 24075718]
10. Saadeh M, Ferrante T, Kane A, Shirihai OS, Corkey BE, Deeney JT. Reactive oxygen species stimulate insulin secretion in rat pancreatic islets: Studies using mono-oleoyl-glycerol. *PLoS One.* 2012; 7:e30200. [PubMed: 22272304]
11. Ciardi C, Jenny M, Tschoner A, Ueberall F, Patsch J, Pedrini M, et al. Food additives such as sodium sulphite, sodium benzoate and curcumin inhibit leptin release in lipopolysaccharide-treated murine adipocytes in vitro. *Br. J. Nutr.* 2012; 107:826–33. [PubMed: 21801469]
12. Mitsuhashi H, Ikeuchi H, Nojima Y. Is sulfite an antiatherogenic compound in wine? *Clin. Chem.* 2001; 47:1872–3. [PubMed: 11568110]
13. Masic U, Yeomans MR. Does monosodium glutamate interact with macronutrient composition to influence subsequent appetite? *Physiol. Behav.* 2013; 116–117. 23–9. [PubMed: 24239994]
14. Goyal BA, Dureja AG, Kumar D, Dhiman K. A comprehensive insight into the development of animal models for obesity research. *Glob. J. Med. Res.* 2012; 12:39–44.
15. Schecter A, Malik N, Haffner D, Smith S, Harris TR, Paepke O, et al. Bisphenol A (BPA) in U.S. food. *Environ. Sci. Technol.* 2010; 44:9425–30. [PubMed: 21038926]
16. Biles JE, McNeal TP, Begley TH, Hollifield HC. Determination of bisphenol-A in reusable polycarbonate food-contact plastics and migration to food-simulating liquids. *J. Agric. Food Chem.* 1997; 45:3541–4.
17. Von Goetz N, Wormuth M, Scheringer M, Hungerbühler K. Bisphenol A: how the most relevant exposure sources contribute to total consumer exposure. *Risk Anal.* 2010; 30:473–87. [PubMed: 20136739]
18. Vandenberg LN, Hauser R, Marcus M, Olea N, Welshons WV. Human exposure to bisphenol A (BPA). *Reprod. Toxicol.* 2007; 24:139–77. [PubMed: 17825522]
19. Elobeid M, Allison D. Putative environmental-endocrine disruptors and obesity: A review. *Curr. Opin. Endocrinol., Diabetes, Obes.* 2008; 15:403–8. [PubMed: 18769210]
- 20•. Kuo C-C, Moon K, Thayer KA, Navas-Acien A. Environmental chemicals and type 2 diabetes: an updated systematic review of the epidemiologic evidence. *Curr. Diab. Rep.* 2013; 13:831–49. [PubMed: 24114039] This review summarizes 29 epidemiological publications (including 7 prospective studies) regarding how environmental chemicals relate to obesity, diabetes, and metabolic syndrome.
21. Wang T, Li M, Chen B, Xu M, Xu Y, Huang Y, et al. Urinary bisphenol A (BPA) concentration associates with obesity and insulin resistance. *J. Clin. Endocrinol. Metab.* 2012; 97:E223–E227. [PubMed: 22090277]
22. Schecter A, Lorber M, Guo Y, Wu Q, Yun SH, Kannan K, et al. Phthalate concentrations and dietary exposure from food purchased in New York State. *Environ. Health Perspect.* 2013; 121:473–94. [PubMed: 23461894]
23. Feige JN, Gerber A, Casals-Casas C, Yang Q, Winkler C, Bedu E, et al. The pollutant diethylhexyl phthalate regulates hepatic energy metabolism via species-specific PPAR α -dependent mechanisms. *Environ. Health Perspect.* 2010; 118:234–41. [PubMed: 20123618]
- 24•. Casals-Casas C, Desvergne B. Endocrine disruptors: from endocrine to metabolic disruption. *Annu. Rev. Physiol.* 2011; 73:135–62. [PubMed: 21054169] This is a great review on the mechanisms of endocrine disruptors.
25. Hatch EE, Nelson JW, Stahlhut RW, Webster TF. Association of endocrine disruptors and obesity: perspectives from epidemiological studies. *Int. J. Androl.* 2010; 33:324–32. [PubMed: 20113374]
26. Zuo Z, Chen S, Wu T, Zhang J, Su Y, Chen Y, et al. Tributyltin causes obesity and hepatic steatosis in male mice. *Environ. Toxicol.* 2011; 26:79–85. [PubMed: 19760618]

27. Grün F, Blumberg B. Environmental obesogens: organotins and endocrine disruption via nuclear receptor signaling. *Endocrinology*. 2006; 147:S50–S55. [PubMed: 16690801]
28. Yanik SC, Baker AH, Mann KK, Schlezinger JJ. Organotins are potent activators of PPAR γ and adipocyte differentiation in bone marrow multipotent mesenchymal stromal cells. *Toxicol. Sci*. 2011; 122:476–88. [PubMed: 21622945]
29. Schecter A, Colacino J, Haffner D, Patel K, Opel M, Pöpke O, et al. Perfluorinated compounds, polychlorinated biphenyls, and organochlorine pesticide contamination in composite food samples from Dallas, Texas, USA. *Environ. Health Perspect*. 2010; 118:796–802. [PubMed: 20146964]
30. Gray SL, Shaw AC, Gagne AX, Chan HM. Chronic exposure to PCBs (Aroclor 1254) exacerbates obesity-induced insulin resistance and hyperinsulinemia in mice. *J. Toxicol. Environ. Health. A*. 2013; 76:701–15. [PubMed: 23980837]
31. Pelletier C, Imbeault P, Tremblay A. Energy balance and pollution by organochlorines and polychlorinated biphenyls. *Obes. Rev*. 2003; 4:17–24. [PubMed: 12608524]
32. Wahlang B, Falkner KC, Gregory B, Ansert D, Young D, Conklin DJ, et al. Polychlorinated biphenyl 153 is a diet-dependent obesogen that worsens nonalcoholic fatty liver disease in male C57BL/6J mice. *J. Nutr. Biochem*. 2013; 24:1587–95. [PubMed: 23618531]
33. Baker NA, Karounos M, English V, Fang J, Wei Y, Stromberg 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; 121:105–10. [PubMed: 23099484]
- 34•. Thayer KA, Heindel JJ, Bucher JR, Gallo MA. Role of environmental chemicals in diabetes and obesity: A National Toxicology Program workshop review. *Environ. Health Perspect*. 2012; 120:779–89. [PubMed: 22296744] The National Toxicology Program organized a workshop in 2012 where experts reviewed published data relating environmental chemicals and diabetes and obesity. Their findings are presented here.
35. Slotkin TA. Does early-life exposure to organophosphate insecticides lead to prediabetes and obesity? *Reprod. Toxicol*. 2012; 31:297–301. [PubMed: 20850519]
- 36•. Lubrano C, Genovesi G, Specchia P, Costantini D, Mariani S, Petrangeli E, et al. Obesity and metabolic comorbidities: environmental diseases? *Oxid. Med. Cell. Longev*. 2013; 2013 Article ID 640673. This review uses incidents of high level dioxin contamination to assess effects of environmental contaminants on health. They also outline the initiatives underway in Europe to study endocrine disruptors and prevent contamination in our food supply.
37. Weber, JV.; Sharypov, VI. Ethyl Carbamate in Foods and Beverages - A Review. In: Lichtfouse, E., editor. *Clim. Chang. Intercropping, Pest Control Benef. Microorg. Sustain. Agric. Rev*. Springer; Netherlands: 2009. p. 429–52.
38. Schecter A, Pöpke O, Tung K-C, Staskal D, Birnbaum L. Polybrominated diphenyl ethers contamination of United States food. *Environ. Sci. Technol*. 2004; 38:5306–11. [PubMed: 15543730]
39. Parzefall W. Risk assessment of dioxin contamination in human food. *Food Chem. Toxicol*. 2002; 40:1185–9. [PubMed: 12067582]
40. Gilbert-Diamond D, Cottingham KL, Gruber JF, Punshon T, Sayarath V, Gandolfi AJ, et al. Rice consumption contributes to arsenic exposure in US women. *Proc. Natl. Acad. Sci. U. S. A*. 2011; 108:20656–60. [PubMed: 22143778]
41. Al Rmali SW, Haris PI, Harrington CF, Ayub M. A survey of arsenic in foodstuffs on sale in the United Kingdom and imported from Bangladesh. *Sci. Total Environ*. 337:23–30. [PubMed: 15626376]
42. Oymak T, Tokalio lu, Yilmaz V, Kartal, Aydin D. Determination of lead and cadmium in food samples by the coprecipitation method. *Food Chem*. 2009; 113:1314–7.
43. Edwards JR, Prozialeck WC. Cadmium, diabetes and chronic kidney disease. *Toxicol. Appl. Pharmacol*. 2009; 238:289–93. [PubMed: 19327375]
44. Kawakami T, Nishiyama K, Kadota Y, Sato M, Inoue M, Suzuki S. Cadmium modulates adipocyte functions in metallothionein-null mice. *Toxicol. Appl. Pharmacol*. 2013; 272:625–36. [PubMed: 23921151]

45. Gump BB, Stewart P, Reihman J, Lonky E, Darvill T, Parsons PJ, et al. Low-level prenatal and postnatal blood lead exposure and adrenocortical responses to acute stress in children. *Environ. Health Perspect.* 2008; 116:249–55. [PubMed: 18288326]
46. Waring RH, Harris RM. Endocrine disrupters: A human risk? *Mol. Cell. Endocrinol.* 2005; 244:2–9. [PubMed: 16271281]
47. Shao B, Han H, Tu X, Huang L. Analysis of alkylphenol and bisphenol A in eggs and milk by matrix solid phase dispersion extraction and liquid chromatography with tandem mass spectrometry. *J. Chromatogr. B. Analyt. Technol. Biomed. Life Sci.* 2007; 850:412–6.
48. Raymond R, Bales CW, Bauman DE, Clemmons D, Kleinman R, Lanna D, et al. Recombinant bovine somatotropin (rbST): A safety assessment. 2010
49. Vicini J, Etherton T, Kris-Etherton P, Ballam J, Denham S, Staub R, et al. Survey of retail milk composition as affected by label claims regarding farm-management practices. *J. Am. Diet. Assoc.* 2008; 108:1198–203. [PubMed: 18589029]
50. Ternak G. Antibiotics may act as growth/obesity promoters in humans as an inadvertent result of antibiotic pollution? *Med. Hypotheses.* 2005; 64:14–6. [PubMed: 15533603]
51. Phillips I, Casewell M, Cox T, De Groot B, Friis C, Jones R, et al. Does the use of antibiotics in food animals pose a risk to human health? A critical review of published data. *J. Antimicrob. Chemother.* 2004; 53:28–52. [PubMed: 14657094]
52. Food and Drug Administration. Everything Added to Food in the United States (EAFUS). cited 2013 Dec 8 <http://www.accessdata.fda.gov/scripts/fcn/fcnNavigation.cfm?rpt=eafusListing>
53. Apovian CM. The causes, prevalence, and treatment of obesity revisited in 2009: What have we learned so far? *Am. J. Clin. Nutr.* 2010; 91:277–9.
54. The International Health Racquet & Sportsclub Association. U.S. Health club membership exceeds 50 million, up 10.8%; Industry revenue up 4% as new members fuel growth. 2011
55. Baillie-Hamilton PF. Chemical toxins: a hypothesis to explain the global obesity epidemic. *J. Altern. Complement. Med.* 2002; 8:185–92. [PubMed: 12006126]
56. Gidley MJ. Hydrocolloids in the digestive tract and related health implications. *Curr. Opin. Colloid Interface Sci.* 2013; 18:371–8.
57. He J, Giusti M. Anthocyanins: Natural colorants with health-promoting properties. *Annu. Rev. Food Sci. Nutr.* 2010; 1:163–87.
58. Bhattacharyya S, O-Sullivan I, Katyal S, Unterman T, Tobacman JK. Exposure to the common food additive carrageenan leads to glucose intolerance, insulin resistance and inhibition of insulin signalling in HepG2 cells and C57BL/6J mice. *Diabetologia.* 2012; 55:194–203. [PubMed: 22011715]
59. Hu FB. Are refined carbohydrates worse than saturated fat? *Am. J. Clin. Nutr.* 2010; 91:1541–2. [PubMed: 20410095]
60. Van Dam RM, Willett WC, Rimm EB, Stampfer MJ, Hu FB. Dietary fat and meat intake in relation to risk of type 2 diabetes in men. *Diabetes Care.* 2002; 25:417–24. [PubMed: 11874924]
61. Popkin BM. The nutrition transition and obesity in the developing world. *J. Nutr.* 2001; 131:871S–873S. [PubMed: 11238777]
62. Ludwig DS, Majzoub JA, Al-Zahrani A, Dallal GE, Blanco I, Roberts SB. High glycemic index foods, overeating, and obesity. *Pediatrics.* 1999; 103:E26. [PubMed: 10049982]
63. Cordain L, Eaton SB, Sebastian A, Mann N, Lindeberg S, Watkins BA, et al. Origins and evolution of the Western diet: health implications for the 21st century. *Am. J. Clin. Nutr.* 2005; 81:341–54. [PubMed: 15699220]
64. Nagao K, Yanagita T. Medium-chain fatty acids: functional lipids for the prevention and treatment of the metabolic syndrome. *Pharmacol. Res.* 2010; 61:208–12. [PubMed: 19931617]
65. Kyriazis GA, Soundarapandian MM, Tyrberg B. Sweet taste receptor signaling in beta cells mediates fructose-induced potentiation of glucose-stimulated insulin secretion. *Proc. Natl. Acad. Sci. U. S. A.* 2012; 109:E524–E532. [PubMed: 22315413]
66. Collison KS, Makhoul NJ, Zaidi MZ, Inglis A, Andres BL, Ubungen R, et al. Prediabetic changes in gene expression induced by aspartame and monosodium glutamate in Trans fat-fed C57BL/6 J mice. *Nutr. Metab.* 2013; 10:44.

67. Mohd-Radzman NH, Ismail WIW, Adam Z, Jaapar SS, Adam A. Potential roles of *Stevia rebaudiana* Bertoni in abrogating insulin resistance and diabetes: A review. *Evidence-Based Complement. Altern. Med.* 2013; 2013:1–10.
68. Sang Z, Jiang Y, Tsoi Y-K, Leung KS-Y. Evaluating the environmental impact of artificial sweeteners: A study of their distributions, photodegradation and toxicities. *Water Res.* 2013;1–15.
69. Stevens LJ, Kuczek T, Burgess JR, Stochelski Ma, Arnold LE, Galland L. Mechanisms of behavioral, atopic, and other reactions to artificial food colors in children. *Nutr. Rev.* 2013; 71:268–81. [PubMed: 23590704]
70. Amin K, Abdel Hameid H, Abd Elsttar AH. Effect of food azo dyes tartrazine and carmoisine on biochemical parameters related to renal, hepatic function and oxidative stress biomarkers in young male rats. *Food Chem. Toxicol.* 2010; 48:2994–9. [PubMed: 20678534]
71. Corkey BE, Shirihai O. Metabolic master regulators: sharing information among multiple systems. *Trends Endocrinol. Metab. Elsevier Ltd.* 2012; 23:594–601.
72. Axon A, May FEB, Gaughan LE, Williams FM, Blain PG, Wright MC. Tartrazine and sunset yellow are xenoestrogens in a new screening assay to identify modulators of human oestrogen receptor transcriptional activity. *Toxicology.* 2012; 298:40–51. [PubMed: 22562034]
73. Takahashi S, Mukai H, Tanabe S, Sakayama K, Miyazaki T, Masuno H. Butyltin residues in livers of humans and wild terrestrial mammals and in plastic products. *Environ. Pollut.* 1999; 106:213–8. [PubMed: 15093048]
74. Mino Y, Amano F, Yoshioka T, Konishi Y. Determination of organotins in human breast milk by gas chromatography with flame photometric detection. *J. Heal. Sci.* 2008; 54:224–8.
75. Carfi' M, Croera C, Ferrario D, Campi V, Bowe G, Pieters R, et al. TBTC induces adipocyte differentiation in human bone marrow long term culture. *Toxicology.* 2008; 249:11–8. [PubMed: 18501494]
76. Le Maire A, Grimaldi M, Roecklin D, Dagnino S, Vivat-Hannah V, Balaguer P, et al. Activation of RXR-PPAR heterodimers by organotin environmental endocrine disruptors. *EMBO Rep.* 2009; 10:367–73. [PubMed: 19270714]
77. Hiromori Y, Nishikawa J, Yoshida I, Nagase H, Nakanishi T. Structure-dependent activation of peroxisome proliferator-activated receptor (PPAR) γ by organotin compounds. *Chem. Biol. Interact.* 2009; 180:238–44. [PubMed: 19497422]
78. Grün F, Watanabe H, Zamanian Z, Maeda L, Arima K, Cubacha R, et al. Endocrine-disrupting organotin compounds are potent inducers of adipogenesis in vertebrates. *Mol. Endocrinol.* 2006; 20:2141–55. [PubMed: 16613991]
79. Kirchner S, Kieu T, Chow C, Casey S, Blumberg B. Prenatal exposure to the environmental obesogen tributyltin predisposes multipotent stem cells to become adipocytes. *Mol. Endocrinol.* 2010; 24:526–39. [PubMed: 20160124]
80. Chamorro-García R, Sahu M, Abbey RJ, Laude J, Pham N, Blumberg B. 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; 121:359–66. [PubMed: 23322813]
81. Wei J, Lin Y, Li Y, Ying C, Chen J, Song L, et al. Perinatal exposure to bisphenol A at reference dose predisposes offspring to metabolic syndrome in adult rats on a high-fat diet. *Endocrinology.* 2011; 152:3049–61. [PubMed: 21586551]
82. Somm E, Schwitzgebel VM, Toulotte A, Cederroth CR, Combescure C, Nef S, et al. Perinatal exposure to bisphenol A alters early adipogenesis in the rat. *Environ. Health Perspect.* 117:1549–55. [PubMed: 20019905]
83. Sargis RM, Johnson DN, Choudhury RA, Brady MJ. Environmental endocrine disruptors promote adipogenesis in the 3T3-L1 cell line through glucocorticoid receptor activation. *Obesity Nature Publishing Group.* 2010; 18:1283–8.
84. Angle BM, Do RP, Ponzi D, Stahlhut RW, Drury BE, Nagel SC, 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. *Reprod. Toxicol.* 2013; 42:256–68. [PubMed: 23892310]

85. Mackay H, Patterson ZR, Khazall R, Patel S, Tsirlin D, Abizaid A. 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; 154:1465–75. [PubMed: 23493373]
86. Anderson OS, Peterson KE, Sanchez BN, Zhang Z, Mancuso P, Dolinoy DC. Perinatal bisphenol A exposure promotes hyperactivity, lean body composition, and hormonal responses across the murine life course. *FASEB J*. 2013; 27:1784–92. [PubMed: 23345456]
87. Ryan KK, Haller AM, Sorrell JE, Woods SC, Jandacek RJ, Seeley RJ. Perinatal exposure to bisphenol-A and the development of metabolic syndrome in CD-1 mice. *Endocrinology*. 2010; 151:2603–12. [PubMed: 20351315]
88. Chou K, Wright RO. Phthalates in food and medical devices. *J. Med. Toxicol.* 2006; 2:126–35. [PubMed: 18077888]
89. Centers for Disease Control and Prevention. Fourth National Report on Human Exposure to Environmental Chemicals. 2013 http://www.cdc.gov/exposurereport/pdf/FourthReport_UpdatedTables_Sep2013.pdf The CDC compiled whole blood or serum concentrations and urine concentrations of 250 chemicals in NHANES participants (hundreds of children and thousands of adults).
90. Feige JN, Gelman L, Rossi D, Zoete V, Métivier R, Tudor C, et al. The endocrine disruptor monoethyl-hexyl-phthalate is a selective peroxisome proliferator-activated receptor gamma modulator that promotes adipogenesis. *J. Biol. Chem.* 2007; 282:19152–66. [PubMed: 17468099]
91. Hurst CH, Waxman DJ. Activation of PPAR α and PPAR γ by environmental phthalate monoesters. *Toxicol. Sci.* 2003; 74:297–308. [PubMed: 12805656]
92. Trasande L, Attina TM, Sathyanarayana S, Spanier AJ, Blustein J. Race/ethnicity-specific associations of urinary phthalates with childhood body mass in a nationally representative sample. *Environ. Health Perspect.* 2013; 121:501–6. [PubMed: 23428635]
93. Navas-Acien A, Silbergeld EK, Pastor-Barriuso R, Guallar E. Arsenic exposure and prevalence of type 2 diabetes in US adults. *J. Am. Med. Assoc.* 2008; 300:814–22.
94. Kozul CD, Ely KH, Enelow RI, Hamilton JW. Low-dose arsenic compromises the immune response to influenza A infection in vivo. *Environ. Health Perspect.* 2009; 117:1441–7. [PubMed: 19750111]
95. Douillet C, Currier J, Saunders J, Bodnar WM, Matousek T, Stýblo M. Methylated trivalent arsenicals are potent inhibitors of glucose stimulated insulin secretion by murine pancreatic islets. *Toxicol. Appl. Pharmacol.* 2013; 267:11–5. [PubMed: 23261974]
96. Paul DS, Walton FS, Saunders RJ, Stýblo M. Characterization of the impaired glucose homeostasis produced in C57BL/6 mice by chronic exposure to arsenic and high-fat diet. *Environ. Health Perspect.* 2011; 119:1104–9. [PubMed: 21592922]
97. Garciafigueroa DY, Klei LR, Ambrosio F, Barchowsky A. Arsenic-stimulated lipolysis and adipose remodeling is mediated by G-protein-coupled receptors. *Toxicol. Sci.* 2013; 134:335–44. [PubMed: 23650128]
98. United States Environmental Protection Agency. ToxCast™. 2013. cited 2013 Nov 20 <http://www.epa.gov/ncct/toxcast/>
99. United States Environmental Protection Agency. Endocrine Disruptor Screening Program (EDSP). 2013. cited 2013 Nov 20 Available from: <http://www.epa.gov/endo/>
100. Reif DM, Martin MT, Tan SW, Houck KA, Judson RS, Richard AM, et al. Endocrine profiling and prioritization of environmental chemicals using ToxCast data. *Environ. Health Perspect.* 2011; 118:1714–20. [PubMed: 20826373]
101. Seth A, Stemple DL, Barroso I. The emerging use of zebrafish to model metabolic disease. *Dis. Model. Mech.* 2013; 6:1080–8. [PubMed: 24046387] This review discusses the advantages and disadvantages of zebrafish models for the study of obesity and diabetes.
102. Lyche J, Nourizadeh-Lillabadi R, Almaas C, Stavik B, Berg V, Skare J, et al. Natural mixtures of persistent organic pollutants (POP) increase weight gain, advance puberty, and induce changes in gene expression associated with steroid hormones and obesity in female zebrafish. *J. Toxicol. Environ. Heal. Part A*. 2010; 73:1032–57.

- 103•. Heindel JJ, vom Saal FS. Role of nutrition and environmental endocrine disrupting chemicals during the perinatal period on the aetiology of obesity. *Mol. Cell. Endocrinol.* 2009; 304:90–6. [PubMed: 19433253] This is a critical discussion of the “fetal basis of disease” hypothesis and how prenatal exposure to obesogens can influence weight management as an adult.

Figure 1.

Compounds are introduced into our food at many stages of the food production process. Waste from factories including persistent organic pollutants (POPs) and heavy metals (e.g., arsenic (As), cadmium (Cd), and lead (Pb)) contaminate the water supply. These compounds can be consumed by fish and then be ingested by humans directly or after further processing. At the farm, these chemicals leach into the crops in the soil, and farmers introduce pesticides to increase crop yield. Animals are fed with antibiotics and hormones (e.g., recombinant bovine growth hormone, rbGH), which have the potential to be transferred to animal products for human consumption. Crops are then refined in order to produce the raw ingredient: insects are removed, organic waste is removed, some products are washed and/or cooked, and solvents are added to wash away chemicals or isolate desired components. At the processing plant, ingredients are combined to produce the final product. Many of the ingredients used in our food supply have not been tested for their effects on key metabolic pathways (see Table 2). During processing and packaging, food is exposed to plastic-coated pipes and is packaged into plastic containers or plastic-coated cans. Bisphenol A (BPA) is an example of a compound in plastic that can diffuse into food, especially at high temperatures (e.g., during retorting). Next, preparation of the food, especially during heating, can mobilize chemicals in the packaging (e.g., BPA from baby bottle into milk during microwaving) or the cookware (e.g., perfluorocarbons (PFCs) from non-stick pans [1]), which can subsequently contaminate the food. Thus, the final food product often contains

much more than simply the ingredients added in the large mixer. (Figure courtesy of Ian Robert Kleckner).

Table 1
What in our food is making us fat? Putative contributors to obesity

Compound	Where it is found and concentration in food (if available)	Comments	Key refs.
<i>Macronutrients</i>			
Saturated fat	animal fat including lard and cream, palm kernel oil	Not all saturated fats have equivalent biological activity; compared with carbohydrates and unsaturated fat, the saturated fats palmitic acid and myristic acid may have the most negative effects on circulating lipid levels.	[2]
Trans-fat	partially hydrogenated vegetable oil (e.g., packaged cookies, microwave popcorn, icing, fried foods); up to 3 g per serving	2% of energy can lead to a 23% increase in coronary heart disease [3]. The U.S. Food and Drug Administration (FDA) proposed a ban in Nov. 2013.	[4,5]
High fructose corn syrup and sucrose	soda, candy, breakfast cereal, granola/nutrition bars; about 37 g/12 oz. soda	Despite popular reproach, the metabolic fate of high fructose corn syrup is similar to that of sucrose, yet the taste, convenience, and low cost of products with high fructose corn syrup may encourage excessive intake.	[6]
<i>Micronutrients</i>			
Salt	processed foods	May be indirectly related to obesity because of increased fluid consumption, including consumption of sugar-sweetened beverages.	[7]
<i>Ingredients that incidentally contain bioactive compounds</i>			
Soy	vegetarian meat substitutes, tofu; up to 50 mg soy isoflavones/serving	Although isoflavones bind the estrogen receptor, they may protect against obesity. Effects may be gender and age dependent.	[8]
<i>Food additives and ingredients "generally recognized as safe" (GRAS; added purposefully)</i>			
Mono-oleoylglycerol (MOG)	as an emulsifier in ice cream, whipped toppings, margarine, shortening, 0.1-1.0%	Can also be formed in the gut from triglycerides by hydrolysis of fatty acids at sn-1 and sn-3 positions. Can stimulate GLP-1 secretion from L intestinal cells [9] and insulin secretion from rat islets [10].	[9, 10]
Sodium benzoate (preservative)	soda, salad dressing, fruit juices and jams, margarine; <0.1%	Can decrease leptin release in vitro.	[11]
Sodium sulfite (preservative)	wine; up to 6 mM (750 mg/L)	Can reduce leptin release and potentiate lipopolysaccharide-induced interleukin-6 secretion in vitro.	[11, 12]
Monosodium glutamate (MSG) and autolyzed yeast/yeast extract (a natural source of MSG)	as a flavor enhancer in savory foods including soups, meat products, Asian sauces, and savory snacks (e.g., Doritos®); up to about 1.0-1.2%	May increase food consumption due to flavor enhancement, but elevated caloric intake has not been shown to be sustained [13]. "Monosodium glutamate-induced obesity" was an experimental technique used mainly in the 1970's and 1980's. The researcher injected rodents with 2-4 g/kg MSG 5 times every other day for the first 10 days of life. The MSG destroyed arcuate nucleus neurons and disrupted the hypothalamic-pituitary-adrenal axis, thus causing obesity [14].	[13, 14]
<i>Food additives (accidentally)</i>			
<i>Plastic Components</i>			

Compound	Where it is found and concentration in food (if available)	Comments	Key refs.
Bisphenol A (BPA)	polycarbonate bottles, canned food Content: 0.23-65.0 ng/g in foods sold in plastic or cans [15], 0-5 ppb in water [16] Bottle-fed infants are exposed to about 0.4-1.7 µg/kg body weight/day, adults, about .01-0.2 µg/kg/day [17]	Environmental Protection Agency limit = 50 µg/kg body weight/day, although this is controversial. Perinatal exposure leads to increased weight gain in mouse models, although there are studies that say the opposite. BPA modifies adipocyte differentiation and function in vitro and in animal models, though detrimental concentrations are not consistent. Epidemiological studies show positive correlations between urinary BPA concentrations and waist circumference.	[18, 19, 20 ^{••} , 21]
Phthalates	foods and beverages of all types; quantity varies depending on congener and packaging (plastic packaging increases phthalate content) [22]	Phthalate monoesters are PPAR γ ligands that induce adipocyte differentiation and fat accumulation. Epidemiological studies have shown a positive correlation between some phthalate metabolites and waist circumference.	[20 ^{••} , 23, 24 ^{••} , 25]
Organotins	seafood, shellfish; quantity in food is unknown but monobutyltin, dibutyltin, and tributyltin detected in tens ng/mL in blood [26]	Tributyltin chloride and triphenyltin activate PPAR γ and RXR α ligands with a binding constant in the nanomolar range. As these receptors participate in regulation of gene expression, activation can afflict a wide range of consequences in homeostatic regulation including dysregulation of fatty acid storage, adipocyte differentiation, and energy metabolism.	[27, 28]
<i>Persistent organic pollutants and pesticides</i>			
Perfluorinated compounds, polychlorinated biphenyls and organochlorine pesticides (including dichlorodiphenyl-trichloroethane (DDT))	canola and olive oil, butter, salmon, canned sardines, hard and soft cheeses, whole milk yogurt, ice cream, peanut butter [29], foods cooked in non-stick pans, microwave popcorn [1]; most common: DDT metabolite <i>p,p'</i> -DDE at up to 9.0 ng/g in catfish filets	PCB exposure has been shown to impair glucose homeostasis, exacerbate high-fat-diet-induced insulin resistance, and disrupt lipid metabolism in mice. These compounds accumulate in adipose tissue and exposure can increase to dangerous levels during diet- and/or exercise-induced fat loss. Although mechanistic evidence is currently weak, these compounds have been associated with dysregulation of energy metabolism.	[20 ^{••} , 30, 33]
Organophosphates	blueberries, strawberries, celery	These inhibit acetylcholinesterase (AChE), which is their appreciated mechanism of action against insects. Prenatal exposure of chlorpyrifos, diazinon, or parathion have been associated with development of metabolic dysfunction resembling prediabetes.	[34 ^{••} , 35]
Carbamates	fermented foods, especially alcoholic beverages; up to 12 ppm ethyl carbamate	Albeit via a different mechanism than organophosphates, carbamates also inhibit acetylcholinesterase (AChE). Carbamates can also react with ethanol to form ethyl carbamate (also known as urethane).	[36 [•] , 37]
Flame retardants including polybrominated diphenyl ethers (PBDEs) and polybrominated biphenyls (PBCs)	highest quantity in meat, lower quantities in animal products; up to 3 ng/g in salmon	The U.S. EPA set a maximum daily dose of 7 µg/kg body weight. Some compounds in this class are endocrine disrupting compounds, carcinogens, and disruptors of development and nerve function.	[38]
Dioxins	meat, eggs, milk and milk products, fish; about 0.5-1.5 pg toxicity equivalents (TE)/kg	Dioxins are formed during incineration of waste, production of organochlorine chemicals, and forest fires. Some congeners may regulate energy metabolism via the aryl hydrocarbon receptor (AhR) and/or the estrogen receptor.	[36 [•] , 39]
<i>Heavy metals</i>			

Compound	Where it is found and concentration in food (if available)	Comments	Key refs.
Arsenic	rice, contaminated water, crops grown in contaminated fields; up to 10 µg/0.56 cups rice in the U.S. [40], up to 60.8 µg/kg in European cabbage, up to 257 µg/kg in Arum tuber grown in Bangladesh [41]	There is sufficient support for a positive correlation between arsenic and diabetes when levels in drinking water are >150 ppb, such as in regions of Taiwan or Bangladesh.	[20••, 34••]
Cadmium	spinach, lettuce, herbs (e.g., dill, parsley) that were irrigated in contaminated water or soil; up to 0.51 µg/g [42]	Cadmium may bind the estrogen receptor and/or mimic the effect of insulin. Cadmium exposure may elevate blood glucose and increase risk for diabetes.	[20••, 36• 43,44]
Lead	spinach, lettuce, herbs that were irrigated in contaminated water or soil, up to 3.3 µg/g [42]	Prenatal lead exposure and exposure in childhood may interfere with signaling in the hypothalamic-pituitary-adrenal axis.	[45]
<i>Other</i>			
Alkylphenols (e.g., nonylphenol (NP), butylphenol BP))	bottled water, eggs, milk, up to 465 ng/L. Intakes estimated at about 7.5 µg NP/day in Germans [46]	Alkylphenols are used as precursors to detergents, among other uses. They are endocrine disruptors that perpetuate estrogenic effects. There are regulated by the European Union but not yet by the U.S.	[46, 47]
Hormones given to animals	milk; there are no more hormones in milk from cows treated with hormones than cows without treated with hormones	Recombinant bovine growth hormone (GH), or recombinant bovine somatotropin, increases the efficiency of milk production. Substantial evidence shows that bovine GH does not affect the composition of the milk. In fact, bovine GH is not active in humans, even when directly injected into the system.	[48, 49]
Antibiotics given to animals	unknown	Antibiotics are administered to farm animals to prevent disease and also to promote growth. Antibiotics can contaminate the environment and could potentially promote growth in humans. Additionally, meat and animal products can possess antibiotic-resistance strains of bacteria.	[50, 51]

Table 2
Common food additives and GRAS substances that have not been assessed for their effects on obesity

<i>Thickening agents</i>
hydrocolloids
<i>Preservatives</i>
sorbic acid benzoic acid EDTA calcium propionate sodium nitrate/nitrite sodium benzoate sodium sulfite
<i>Antioxidants</i>
butylated hydroxyanisole (BHA) butylated hydroxytoluene (BHT) tert-butylhydroquinone (tBHQ) propyl gallate
<i>Antimicrobials</i>
nisin natamycin dimethyl- and diethyl dicarbonate medium chain fatty acids and esters lysozyme
<i>Sequestrants</i>
calcium acetate potassium citrate sodium/calcium EDTA glucono delta-lactone sodium/potassium/ferrous gluconate sodium tripolyphosphate
<i>High intensity sweeteners</i>
saccharin aspartame sucralose stevia
<i>Polyols (including sugar alcohols)</i>
maltitol sorbitol xylitol erythritol isomalt glycerol
<i>Emulsifiers</i>
lecithin diacetylated tartaric acid with mono- and diglycerides (DATEM)
<i>Acidulants</i>
hydroxyl citric acid carbon dioxide
<i>Phosphates</i>
<i>Flavors</i>
benzaldehyde vanillin isoamyl acetate cinnamaldehyde
<i>Flavor potentiators</i>
monosodium glutamate (MSG)
<i>Colors</i>
FD&C Blue No. 1 (brilliant blue FCF)

FD&C Blue No. 2 (indigotine)
FD&C Green No. 3 (fast green FCF)
FD&C Red No. 40 (allura red AC)
FD&C Red No. 3 (erythrosine)
FD&C Yellow No. 5 (tartrazine)
FD&C Yellow No. 6 (sunset yellow)