CENTER FOR Science IN THE Public Interest
Your Food and Health Watchdog

OBESOGENS

ASSESSING THE EVIDENCE LINKING CHEMICALS IN FOOD TO OBESITY

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About CSPI

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CSPI envisions a healthy population with reduced impact and burden of preventable diseases and an equitable food system that makes healthy, sustainable food accessible to all. CSPI values independence, scientific rigor, and transparency.

Founded in 1971, CSPI is an independent, science-based consumer advocacy organization with an impressive record of accomplishments and a clear and ambitious agenda for improving the food system to support healthy eating.

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Executive Summary

The prevalence of obesity and overweight in the United States has risen sharply since the 1970s, now affecting an astonishing 70% of adults and over a third of children, according to the Centers for Disease Control and Prevention (CDC). Globally, the prevalence of obesity nearly tripled between 1975 and 2016, and the prevalence of overweight and obesity among children and adolescents aged 5-19 increased more than four-fold during that time period, according to the World Health Organization (WHO). Increases in weight gain translate into increased risks for cancer, cardiovascular disease, diabetes, and premature mortality.

Notwithstanding these alarming trends and impacts from obesity, "we have a very limited understanding of its pathogenesis, despite decades of research and billions of dollars spent each year on its treatment," according to the Endocrine Society (ES), the primary professional organization for endocrine scientists and clinicians.

The obesogen hypothesis proposes that certain chemicals, called obesogens, influence individual susceptibility to obesity by interfering with metabolic systems that regulate appetite, weight gain, and fat development and distribution, and thereby have contributed to the rise in obesity. Obesogens, which are also sometimes referred to as metabolic disruptors (more precisely, a type of metabolic disruptor,) are generally considered[i] to be a type of endocrine disrupting chemical (EDC), meaning they interfere with the body's hormones and the overall hormone (endocrine) system. Obesogens may act through a number of mechanisms. For example, some obesogens direct stem cells to differentiate preferentially into fat cells rather than bone cells. Some may mimic estrogen and influence fat cell development. Exposures to obesogens are thought to have the greatest impact during key developmental windows, especially those occurring before birth. Transgenerational effects, or effects in subsequent, unexposed generations, have been observed in animal studies for some obesogens.

The question taken up in this report is, what is the evidence that chemicals identified as capable of disrupting metabolism and energy homeostasis, particularly those added to food, actually increase susceptibility to obesity in humans and meaningfully contribute to the dramatic increase in obesity prevalence in humans? In other words, how much evidence supports the obesogen hypothesis? How should researchers, health advocates, and government respond to this evidence?

In 2017, the ES published a scientific statement that provides a framework for conceptualizing the obesity pathogenesis process and understanding the role of different factors that can contribute to obesity susceptibility, including EDC exposures, as well as diet composition, lifestyle, genetics, developmental factors, and social and economic factors, among others. The ES statement concluded that there are two distinct yet related components of obesity pathogenesis—(1) sustained positive energy balance and (2) resetting of the body weight set point. These contribute to obesity pathogenesis by influencing (a) the accumulation of body fat; (b) the biological defense of elevated body fat (i.e., the body's propensity to protect against losing excess body fat); and (c) the tendency for lost body fat to be regained.

It seems clear that diet, and in particular, the increased and widespread availability of cheap, tasty, and calorie-dense foods over the last several decades, has played a key role in a sustained positive energy balance ((1) from above), and the acquisition of excess body fat ((a) from above) and thus the increase in obesity prevalence. But what about the biological defense of elevated body fat (b), the tendency for lost body fat to be regained (c), and the resetting of the body weight set point (2)? Diet and the widespread availability of calorie-dense foods may not be adequate to fully explain those facets of obesity. The ES statement concludes that to be viable, theories (collectively) of obesity pathogenesis must account not only for how excess body fat is acquired, but also for how excess body fat comes to be biologically defended. The overarching unified framework for understanding obesity pathology provided in the ES statement is comprehensive enough to accommodate both the obesogen hypothesis and other hypotheses.

The obesogen hypothesis also appears compatible with the energy balance model of obesity, which describes body weight regulation as operating below our conscious awareness via complex endocrine, metabolic, and nervous system signals to control food intake in response to environmental influences as well as the body's energy needs. Obesogens or metabolic disruptors can interfere with these signals, which can increase or decrease overall energy intake.

[i] Some also consider obesogens to include any chemicals that may increase susceptibility to obesity, including through mechanisms other than endocrine disruption (e.g., damaging the gut or altering the gut microbiome). In this report, we are focused on obesogens that are a subset of endocrine disruptors.

A concept known as the Developmental Origins of Health and Disease (DOHaD) adds plausibility to the obesogen hypothesis. The DOHaD concept states that early life exposures to adverse conditions during key windows of tissue and organ development increase disease risk later in life. Diseases thought to result at least in part from such developmental conditions include obesity, type 2 diabetes, insulin resistance, cardiovascular disease, asthma, and some cancers, according to the National Institute of Environmental Health Sciences (NIEHS). Obesity risk in adults appears to be increased by exposures that result in a period of growth restriction in early development, such as famine or smoking, which is followed by subsequent catch-up growth. For example, the 2017 ES statement noted that a meta-analysis of 21 studies in rodents and 9 studies in humans supported the hypothesis that developmental exposure to perfluorinated chemicals (or per- and polyfluoroalkyl substances (PFAS)) reduces fetal growth, and that this may account at least in part for the purported obesogenic effects of PFAS.

The established causal relationship between certain pharmaceutical drugs and weight gain provides proof of principle that chemicals can cause weight gain and thus provides support for the obesogen hypothesis. Weight gain is a known side-effect of several pharmaceutical classes, especially atypical antipsychotics (AATP), and strong mechanistic evidence demonstrates that AATPs affect weight gain through metabolic (endocrine) disruption. The level of evidence that certain pharmaceutical drugs induce weight gain far exceeds the level of evidence available for many environmental chemicals or chemicals added to food, as multiple randomized control trials (RCTs) in humans are required and available for pharmaceuticals, but such trials are not required and are rarely available for food additives or contaminants.

Several authoritative and regulatory bodies recognize the potential contribution of obesogens towards the obesity problem. NIEHS dedicates a webpage on their official website to obesogens, listing potential obesogens and provides recommendations to limit exposure. NIEHS also dedicates a webpage to DOHaD. Additionally, NIEHS supports research in this field through numerous grants, and the National Institutes of Health (NIH) Strategic Plan for NIH Obesity Research highlights the importance of research in this area.

In 2011, the National Toxicology Program, an interagency program[ii] headquartered at the NIEHS, hosted a workshop in tandem with the US Environmental Protection Agency (EPA) and other agencies, investigating the evidence linking endocrine disrupting chemical exposure with obesity outcomes. The workshop concluded that the existing literature "supports the plausibility of an 'obesogen' hypothesis," and it identified data gaps to stimulate focused research to move the field forward. Similarly, the National Academies of Sciences, Engineering, and Medicine (NASEM) hosted a workshop in 2015 exploring the associations between exposures to environmental chemicals and weight gain. The workshop was not intended to achieve a consensus, but instead provided insight into the progress the obesogen field had made since its inception and perspective from leading scientists in the field. Several researchers expressed their views that metabolic disruptors likely play a role in the obesity epidemic, although the available studies did not prove causation.

In 2017, the ES scientific statement noted that the links between EDC exposure and obesity risk are a focus of ongoing research, that key questions remain unanswered, and it described the challenges in transitioning from in vitro studies to animal models that are surrogates for humans, using bisphenol A (BPA) and PFAS as examples. The statement concluded that, "Although available evidence suggests that EDCs can impact the function of genes important for the control of energy balance and adipocyte function, human data and results from in vivo animal studies have yet to clearly demonstrate an increased risk of obesity conferred by developmental EDC exposure." The ES recommended that meta-analyses of prospective epidemiological data may help to identify the combinations and doses of EDC exposures that are most often associated with increased adiposity and that are observed consistently across species.

Three such meta-analyses have now been published for chemicals found in food, one examining the evidence on obesogenicity for perfluorooctanoic acid (PFOA, a PFAS), one for a variety of persistent organic pollutants (POPs), and one for two related POPs, the pesticide dichlorodiphenyltrichloroethane (DDT) and its metabolite, dichlorodiphenyldichloroethylene (DDE).[iii]

[ii] The National Toxicology Program is an interagency program composed of and supported by the National Center for Toxicological Research (NCTR) of the Food and Drug Administration (FDA), NIEHS, and the National Institute of Occupational Safety and Health (NIOSH) of the Centers for Disease Control and Prevention. Other agencies serve on NTP's Executive Committee.

[iii] Concerning possible obesogens, there have also been meta-analyses of epidemiological data on chemicals found in food that are not limited to prospective studies (e.g., phthalates, chlordanes). In addition, a pooled analysis (rather than a meta-analysis) has been conducted on prenatal phthalate exposures and body mass index among 4- to 7-year old children from three prospective cohorts; and a meta-analysis of rodent studies on phthalates has also been conducted. There are meta-analyses of obesogens not found in food, for example of antibiotics, drugs, and air pollutants. Also, meta-analyses have been conducted on the effect of chemicals on low birth weight, which in turn appears to be related to obesity. For example, a meta-analysis on acrylamide was for birth weight, and it included a pooled analysis from one study that suggested that children had a higher risk of developing overweight/obesity in the future.

The 2018 meta-analysis by Liu and colleagues evaluated ten prospective studies of 6076 participants and concluded that exposure to PFOA in early life (in utero or first year postnatal) is associated with an increased risk for childhood adiposity (odds ratio [OR] for childhood overweight is 1.25 (95% confidence interval [CI]: 1.04, 1.50; $I^2 = 40.5\%$)).

The 2022 meta-analysis by Stratakis and colleagues separately evaluated the relationship between a variety of POPs and obesity, including 33 studies assessing prenatal exposure to organochlorines, including DDE, DDT, polychlorinated biphenyls (PCBs), and hexachlorobenzene (HCB); 21 studies assessing prenatal exposure to PFAS; and five studies assessing polybrominated diphenyl ethers (PBDEs). Meta-analysis results showed that prenatal exposure to DDE and HCB was associated with increased body mass index (BMI) in childhood (2-9 years), drawing on studies from 17 and 7 countries, respectively. For PCBs, PFAS, and PBDEs, there was no conclusive evidence that prenatal exposure was associated with the development of obesity in childhood.

The 2017 meta-analysis on DDE/DDT by Cano-Sancho and colleagues is of particular interest since it used "evidence integration" (EI), an approach increasingly being used by authorities and academic researchers to evaluate chemical hazards. EI is a structured process that allows investigators to reach conclusions about hazards to humans—even when human evidence is minimal, low quality, or nonexistent, as it so often is for food and environmental chemicals—through a transparent and repeatable approach. EI involves the evaluation of a body of evidence for each evidence stream (human, animal, and mechanistic), rating the confidence of each, and then integrating the ratings of each stream into one overall conclusion about the hazard to humans. The authors of the DDE/DDT meta-analysis relied on the Handbook for Evidence Integration and Systematic Review developed by the National Toxicology Program (NTP) Office of Health Assessment and Translation (OHAT), widely considered to be authoritative. It found that both the human and animal evidence supporting the association between DDT/DDE exposure and obesity outcomes were "moderate," as was the mechanistic evidence. It concluded that DDT and DDE are "presumed" obesogens. This review serves as a model that researchers may look to for guidance in undertaking more comprehensive assessments of potential obesogens in the future.

We used an EI approach, following the NTP OHAT Handbook, to do an initial screen of various chemicals found in food for evidence of obesogenicity, as described below. The initial confidence rating is determined by the ability of the study design to ensure that exposure preceded, and was associated with, the outcome.

Specifically, we examined the human and animal evidence for 12 substances that had been identified in the literature as potentially having obesogenic effects, and which are added to food: benzoates, BPA, 3-butylated hydroxyanisole (3-BHA), caffeine, di-2-ethylhexyl phthalate (DEHP), dioctyl sodium sulfosuccinate (DSS), monosodium glutamate (MSG), parabens, perfluorooctanoic acid (PFOA), propionate, sorbitan monooleate, and sulfites.

According to the OHAT handbook, for a substance to be classified as, at a minimum, a "suspected" hazard (ratings include: not classifiable, suspected, presumed, and known), either the animal or human evidence must achieve at least a "moderate" rating. For this reason, "moderate" evidence is required to pass this initial screen.

This initial confidence screen found that ten of the 12 chemicals added to food were found to have an initial confidence rating of at least "moderate" for either human or animal evidence. In other words, there is enough confidence in the quality of the evidence that they are candidates for further assessment to determine the final confidence rating in the body of evidence and if they are "known," "presumed," "suspected," or "not classifiable" as obesogens, under the OHAT scheme. Sorbitan monooleate and sulfites were found to have insufficient evidence to qualify for an initial confidence rating of "moderate" for either the animal or human evidence stream, and thus, more research, specifically animal and/or human studies (case-control, cohort, or RCTs), is needed in order for them to possibly classify as even suspected obesogens under the OHAT scheme.

CONCLUSIONS AND RECOMMENDATIONS

The obesogen hypothesis—while still a hypothesis, and not yet proven—could provide a partial explanation for the global rise in obesity prevalence and the tenacity of obesity despite efforts to shed weight. A recent meta-analysis concluded that there is "moderate" evidence DDT/DDE is obesogenic, (and a second meta-analysis on DDE also confirmed the association with obesity), and meta-analyses suggest that PFOA and HCB may be as well. However, the extent to which chemicals actually contribute to the increase in obesity prevalence remains unknown. Studying the obesogen hypothesis is challenging since effects can vary depending on dose, timing of exposure, timing and type of outcome measurement, species,

and chemical. Issues relating to mixtures of obesogens, cumulative effects, and the presence of other dietary, environmental, and obesogenic factors add to the complexity.

The Food and Drug Administration (FDA) currently lacks a framework for identifying and evaluating metabolic disruptors, as well as endocrine disruptors more generally, when reviewing food and color additive petitions, Generally Recognized as Safe (GRAS) notifications, food contact substance notifications, or otherwise assessing the safety of substances in or intended for the food supply. The Center for Science in the Public Interest (CSPI) and our partner organizations will continue to press FDA to use robust science and develop updated guidance on assessing new chemicals entering the food supply and to include endocrine and metabolic disruption.

FDA could greatly benefit from expert input as it seeks to improve its assessments of chemicals added to food. For many years, NASEM has provided advice to EPA on improving its assessments of hazard, exposure, and risk; the FDA could benefit from such advice. NASEM last hosted a workshop exploring the association between environmental chemical exposure and weight gain in 2015. Given this history and more recent evidence, FDA, in collaboration with the NIEHS and/or the ES, should fund NASEM to develop recommendations for incorporating information on metabolic disruption into its assessments of food chemicals and into guidance for companies that seek to introduce substances into the food supply.

CSPI will continue to update its consumer-facing online materials to reflect the findings of this report and as new information is developed, in particular, its chemical-specific entries in Chemical Cuisine and its information on contaminants.

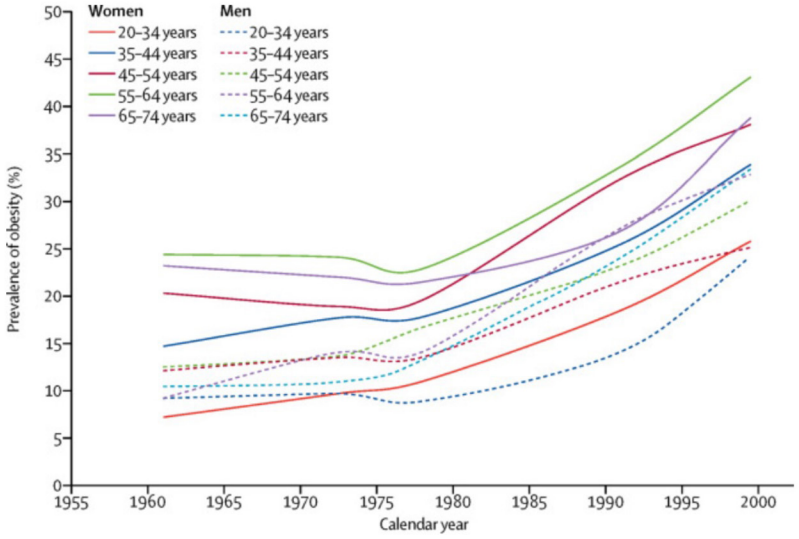
Additional recommendations for the federal government and researchers are contained in A Coordinated Research and Action Agenda to Build the Evidence Base Related to Metabolic Disrupting Chemicals, which CSPI developed with the help of experts in the field. We hope this agenda will stimulate new and focused research to better characterize metabolic disrupters.

As new information emerges, researchers should also consider conducting more thorough investigations of chemicals that we identified as having passed the initial confidence screen, ideally employing the OHAT handbook, similar to the Cano-Sancho review on DDE/DDT. The results of such rigorous assessments would inform policy and research decisions. Additionally, work to identify populations vulnerable to obesogen exposure and solutions to prevent exposure to these populations, should also be considered.

Understanding Obesity and Introducing the Obesogen Hypothesis

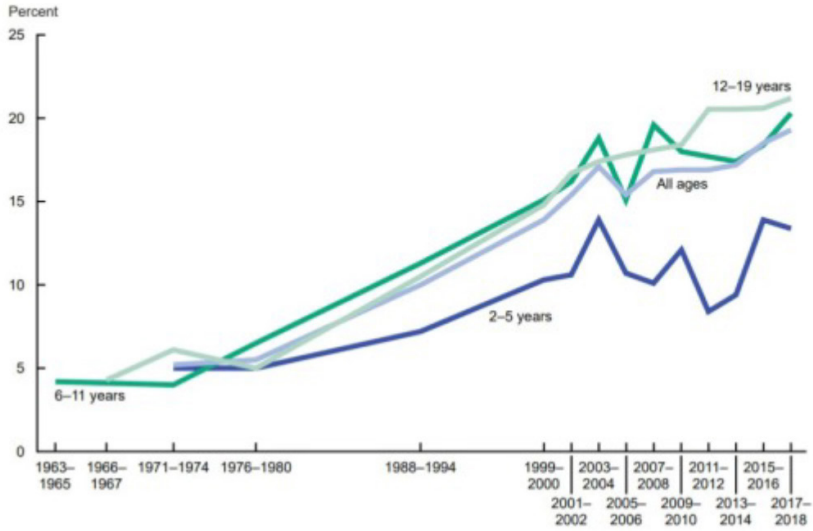
The prevalence of adult and childhood obesity poses a significant public health threat and has increased sharply[iv] over the last several decades.

Figure 1A: Prevalence of Obesity in Adults in the United States by Age and Sex



Source: Rogers et al. 2018[1]

Figure 1B: Trends in Obesity in Children and Adolescents Aged 2-19 years in the United States by Age



Source: National Center for Health Statistics (NCHS) , using NCHS, National Health Examination Surveys and National Health and Nutrition Examination Surveys. Obesity is defined as body mass index at or above the 95th percentile from the age-specific BMI-for-age 2000 CDC Growth Charts.

[iv] There were some deviations from these upward trends, according to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); but these appear to have been temporary. For example, NIDDKD notes that among children ages 2 to 5, obesity prevalence increased between 1988-1994 and 2003-2004, deceased between 2003-2004 and 2011-2012, and then increased again. Furthermore, the observed change in obesity prevalence between 2013-2014 and 2015-2016 was not significant among both adults and youth, according to CDC. However, CDC found that from 1999-2000 through 2017-2018, the prevalence of both obesity and severe obesity increased among adults. CDC has not yet published 2017-2018 data for children and adolescents.

According to the Centers for Disease Control and Prevention, 73% of adults and 35% of children and adolescents had overweight or obesity in the United States in 2017-2018,[3,4] compared to 56% of adults (age 20 and over) and 23% of children in 1988-1994, and 15% of children in 1971-1974.[5,6] Adult obesity prevalence was 42.5% in 2017-2018,[7] up from 39.8% in 2015-2016.[8]

Globally, the worldwide prevalence of obesity nearly tripled between 1975 and 2016, and the prevalence of overweight and obesity among children and adolescents aged 5-19 increased more than four-fold during that time period, from 4% to 18%, according to the World Health Organization (WHO),[9] though these rates are lower than US rates. There are now more people who have obesity than underweight, and this occurs in every region except parts of sub-Saharan Africa and Asia; and overweight and obesity are linked to more deaths worldwide than underweight, according to the WHO.[10]

Excess weight is a risk factor for several chronic diseases and conditions such as diabetes, cardiovascular diseases, and some cancers,[11] and every five-unit increase in body mass index (BMI) is associated with a 30% increase in all-cause mortality.[12] Among adults, the excess annual medical costs of obesity were estimated to be $1,861 per person, accounting for $172.74 billion of annual expenditures in the U.S., based on data from 2011-2016 and reported in 2019 dollars.[13] The direct healthcare costs of chronic disease associated with obesity and overweight was estimated to be $480.7 billion in 2016 in the United States, with an additional $1.24 trillion in indirect costs due to lost economic productivity.[14]

It is widely accepted that obesity results primarily from prolonged calorie imbalance (where calorie input exceeds calorie output). But this imbalance is not as simple as it might seem. A number of factors influence calorie intake and expenditure and appear to contribute to obesity development, although how they do so is not always entirely clear.[v] Calorie imbalance is influenced in part by the food environment, which includes factors such as the ubiquity of cheap, calorie-dense foods, large portions, marketing, and advertising.[15] Some argue that increases in the food supply, particularly in the availability of cheap, tasty, and highly promoted energy-dense foods, pushed enough calories into the food environment to completely explain the rise in obesity in the United States.[16] While not traditionally considered part of the food environment, obesogenic food additives and contaminants could be so considered.

The rise in obesity can also be viewed from the reverse perspective. Obesity can be seen as the inability of the body's systems for controlling food intake, satiety, and metabolic rate to cope with the external forces acting upon it in order to sustain a normal body weight through development, growth, and aging.[17] Viewed in this way, calorie-rich processed foods with intense added flavors and/or high amounts of fats, sugars, or salt are likely one type of powerful external force that can overwhelm our physiological systems. Environmental chemicals with the ability to disrupt metabolic systems may be another, and could account for differences in susceptibility to the increased availability of these calorie-rich, highly flavored foods.

In a 2017 scientific statement, the Endocrine Society[vi] (ES) presented a framework to describe obesity pathogenesis that is comprehensive enough to effectively accommodate different perspectives of obesity.[18] The statement assessed current knowledge regarding mechanisms underlying [a] excess body-fat accumulation, [b] the biological defense of excess fat mass, and [c] the tendency for lost weight to be regained, and describes obesity pathogenesis as involving two related but distinct processes: 1) sustained positive energy balance and 2) a resetting of the body weight "set point."

The ES statement recognizes the influence of sustained positive energy balance on excess fat accumulation. However, the statement (p. 269) describes evidence that demonstrates that non-obese individuals tend to restore body weight to normal following weight gain induced by forced overfeeding. Once the forced overfeeding stops, the individuals increase energy expenditure and experience a decreased drive to eat, which tends to restore body weight to normal. In fact, it is surprisingly difficult for normal-weight individuals to achieve and sustain experimentally induced weight gain, according to the statement. In obese individuals, the same homeostatic mechanisms are used, but there is a dysfunction of the energy homeostasis system, such that elevated body fat and weight levels seem to be biologically defended and weight loss to normal levels is difficult to maintain.

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[v] These factors may include, for example, genetic factors, a lack of sleep, smoking cessation, disturbances of the gut microbiome, viruses, and certain pharmaceuticals.

[vi] The Endocrine Society is the primary and world's largest professional organization for endocrine research scientists and clinical practitioners.

The statement asserts (p. 267):

> "Growing evidence suggests that obesity is a disorder of the energy homeostasis system, rather than simply arising from the passive accumulation of excess weight. We need to elucidate the mechanisms underlying this 'upward setting' or 'resetting' of the defended level of body fat mass, whether inherited or acquired."

Or put another way, obesity is a maladaptive response to the food environment.

The remainder of the scientific statement explores the multiple underlying mechanisms that may contribute to this disorder of the energy homeostasis system, including genetic factors, developmental factors (parental body weight and diet), social and economic factors, diet composition and lifestyle, and other factors, as well as the role of EDCs, specifically BPA and perfluorinated compounds (PFCs, some of which are PFAS).

The scientific statement notes (p. 268) that for obesity, unlike for most other endocrine disorders, "we have a very limited understanding of its pathogenesis, despite decades of research and billions of dollars spent each year on its treatment." It concludes (p. 287):

> "To be viable, theories of obesity pathogenesis must account not only for how excess body fat is acquired, but also for how excess body fat comes to be biologically defended."

The obesogen hypothesis posits that exogenous chemicals play a role in promoting obesity by disrupting the systems of the body that regulate body weight, specifically: the endocrine system and associated hormones and nuclear receptors[vii] involved in regulating fat cell development and physiology, hunger, satiety, and various other metabolic processes. These disruptive chemical exposures—which could occur in utero, at other times during development, or even in adulthood—may influence food consumption and/or energy expenditure, as well as how nutrients and calories are metabolized and partitioned in the body.

For example, some obesogens might activate peroxisome proliferator-activated receptor gamma (PPARγ), a nuclear receptor considered to be a "master regulator" of adipogenesis, thereby influencing body composition and excess retention of fat by directing stem cells to differentiate preferentially into fat cells rather than bone cells. BPA, DSS, parabens, PFAS, and phthalates activate PPARγ, at least in vitro. Some obesogens (e.g., BPA, DDE) activate estrogen receptors, which can influence fat cell development depending on the dose and timing.[19,20,21]

What is the Obesogen Hypothesis?

According to a 2020 review published by the Endocrine Society, "The obesogen hypothesis proposes that there are chemicals in our environment termed obesogens that can affect individual susceptibility to obesity and thus help explain the recent large increases in obesity."

Source: Egusquiza RJ, Blumberg B. Environmental obesogens and their impact on susceptibility to obesity: New mechanisms and chemicals.

Endocrinology 2020;161(3):bqaa024.

Transgenerational effects, or effects that occur in subsequent generations that have received no direct exposure, have been observed in animal studies for at least some obesogens.[22] In other words, exposure of a pregnant female in one generation (F0) not only can impact the next generation (F1) via in utero exposure, as well as the next generation after that (F2) via germ cells present in the developing fetus, but in subsequent generations (F3 and beyond) as well, indicating transgenerational inheritance of obesity. For females who are not pregnant and for males, exposure in one generation can affect not only the next generation (F1) from exposed germ cells (sperm and egg cells), but in the unexposed F2 generation, and possibly beyond. Transgenerational effects may be brought about at least in part by epigenetic mechanisms, meaning, they do not result from changes to the DNA code, but by changes that affect the expression of genes.

The obesogen hypothesis is consistent with the overarching framework articulated by the ES, as well as the energy balance model as described by Kevin Hall, a scientist at the National Institutes of Health (NIH), which describes body weight regulation as operating below our conscious awareness via complex endocrine, metabolic, and nervous system signals to control food intake in response to environmental influences as well as the body's energy needs.[23]

[vii] Nuclear receptors (a type of transcription factor) are proteins that bind to specific DNA sequences and regulate (turn on/off) genes to make sure they are expressed in the right place at the right time. They are activated by hormones and are involved in directing the division, growth, and death of cells, and play a key role during development.

The obesogen hypothesis is also compatible with the concept that changes in diet and the marketing of foods explain obesity trends. As the availability of cheap, tasty, highly promoted, and energy-dense foods in the United States increased, so too did production, processing, and packaging technologies and associated additives and contaminants. Some of these new additives and contaminants are suspected obesogens (e.g., certain pesticides, direct food additives, generally recognized as safe (GRAS) substances, food contact substances, lipophilic environmental contaminants (see Table 1)).[24]

What is an Obesogen? What is a Metabolic Disruptor?

Obesogenic chemicals, or "obesogens," are usually considered to be endocrine disrupting chemicals (EDCs) that disrupt metabolic processes and increase susceptibility to weight gain. EDCs are exogenous substances that interfere with the production or activity of hormones in the body, for example by blocking or mimicking a natural hormone. EDCs are notable because very low doses may disrupt the endocrine system, and because they don't necessarily follow a linear "dose-response" pattern typical of most chemical effects.

Obesogens can disrupt metabolism and promote obesity, for example, by increasing the number and size of fat cells, shifting energy balance to favor calorie storage, altering metabolic rate, altering hormonal control of appetite and satiety, and/or altering brain circuitries controlling food intake and energy expenditures.

The term "obesogen" was first coined by Bruce Blumberg and Felix Grün in 2006, to mean "molecules that inappropriately regulate lipid metabolism and adipogenesis to promote obesity." In 2015, a panel of experts convened at a workshop in Parma, Italy (see Authorities Recognize the Potential Threat of Obesogens) and determined that the term "obesogen" had become too restrictive. While there may be chemicals that exclusively increase susceptibility to obesity (and thus are appropriately called "obesogens"), some may also cause other aspects of metabolic syndrome, fatty liver disease, and/or diabetes. Thus, a more inclusive term, "metabolic disruptors," was preferred.

Some researchers consider chemicals that are not endocrine disrupters but influence obesity in other ways (e.g., disruption of the gut microbiome) as obesogens. For the purposes of this report, we exclude from our definition ingredients that may influence obesity but are not considered to be EDCs such as added salt, flavorings, and additives that may disrupt the gut microbiome (e.g., emulsifiers, low calorie sweeteners). Sugars and fats are also outside the scope of this report.

Sources: Grün F, Blumberg B. Environmental Obesogens: Organotins and Endocrine Disruption via Nuclear Receptor Signaling. *Endocrinology* 2006;147(6):s50-s55.

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Examining the Obesogen Hypothesis

It seems very likely there is not one simple explanation for obesity trends. A number of different mechanisms are likely involved in weight gain, weight maintenance, and weight loss, according to the ES scientific statement on obesity pathogenesis, as well as the energy balance model as articulated by Hall et al. Below we summarize some of the strengths and weaknesses of the evidence underlying the obesogen and other hypotheses aimed at helping to understand obesity trends.

Researchers have calculated that increases in the amount of calories available in the environment can more than explain the gains in obesity prevalence in the US over the last several decades.[25,26] Additionally, increases in food availability are positively correlated with increases in obesity prevalence in other countries,[27-29] with Vandevijvere and colleagues concluding that, "increases in food energy supply are sufficient to explain increases in average population body weight, especially in high-income countries."

We note that other researchers have reached conclusions that are not consistent with these conclusions. Yancy and colleagues found that energy intakes have been similar across BMI classes between the 1970s and early 2000s,[30] and Scarborough and colleagues found that increased energy intake could account for bodyweight increases between 1986 and 2000 in UK women, but not men.[31]

One frequently cited study supporting the role of additional factors (i.e., beyond caloric balance) was conducted by Brown and colleagues in 2016.[32] The authors examined trends in National Health and Nutrition Examination Survey (NHANES) data to determine whether the association between BMI and calorie intake, percent macronutrient intake, and exercise habits was different over time. For a given level of calorie intake, macronutrient intake, and physical activity, BMI was significantly higher (+ 2.3 kg/m^2, $P<0.05$) in 2006 than in 1988. Results were adjusted for age, education, ethnicity, and smoking status. Thus, despite an overall increase in caloric intake over the past four decades and concurrent increases in obesity, there was not a direct relationship between caloric intake and BMI over time. The authors concluded, "factors other than diet and physical activity may be contributing to the increase in BMI over time," and point to several such possible factors, including environmental chemicals/pollutants, prescription drugs, higher maternal age, weight cycling, and decreased prevalence of smoking, among others.[33] The results might be explained by biases in reporting of diet and physical activity over time; however, while surveys tend to overreport exercise and underreport calorie intake, self-report bias would need to change over time in order for self-report bias to explain the results. The authors state that self-report bias has remained relatively consistent or has slightly improved over time.

Additionally, in 2019 Hall published a randomized clinical trial (RCT) that investigated the effects of processed foods on calorie intake and weight gain.[34] Participants (10 men, 10 women) were admitted to the NIH Clinical Center and randomized to receive either ultra-processed or unprocessed diets for 2 weeks, immediately followed by the alternate diet for 2 weeks. The participants were presented with twice as much food as they needed and could eat as much or as little as they wanted. The diets were matched for total calories, energy density, macronutrients, fiber, sugars, and sodium. Hall and colleagues found that participants consumed roughly 500 more calories per day when provided an ultra-processed diet, which led participants to gain on average about 2 pounds of weight after 2 weeks of consuming this diet ad libitum.[viii] Conversely, participants lost on average about 2 pounds after 2 weeks of consuming an unprocessed diet ad libitum. The participants did not report significant differences in the pleasantness or familiarity of the meals between the ultra-processed and unprocessed diets. These findings suggest that there may be other factors beyond calorie availability or tastiness that caused calorie consumption to increase. Interestingly, circulating levels of the appetite-suppressing hormone PYY (peptide tyrosine tyrosine) were significantly higher after participants consumed the unprocessed diet as compared with both the ultra-processed diet and baseline. Also, circulating levels of ghrelin (called the "hunger hormone") and adiponectin, hormones that help regulate glucose and lipid metabolism, were significantly lower after the unprocessed diet compared to baseline. The study was not designed to identify the cause of the observed differences in energy intake. Potentially obesogenic additives and other substances from packaging and processing in ultra-processed foods could be one possible explanation for why participants gained more weight on the ultra-processed diet compared with the unprocessed diet. However, factors unrelated to obesogenic additives/contaminants may well explain the results. For example, participants ate significantly more food and more calories per minute when presented with the ultra-processed diet than with the unprocessed diet, perhaps because ultra-processed foods are easier to chew and swallow than unprocessed foods.[35]

Bruce Blumberg of UC Irvine, author of "The Obesogen Effect" (2018),[36] cites several studies (listed below) to bolster the argument that the calories in/calories out model may be insufficient to describe increases in obesity prevalence. However, we find that the following studies do not provide much if any support for this view:

- Kim and colleagues observed trends in weight gain among preschool-aged children between 1980 and 2001 and found that overweight rates were increasing in very young children and even infants, with a 73% increase in overweight prevalence in infants under 6 months.[37] However, this study did not control for maternal BMI, or birthweight. Exposure to maternal obesity during pregnancy is associated with an increased risk of obesity in offspring and is thus a likely explanation for the changes observed.[38]
- Klimentidis and colleagues conducted a cross-species analysis investigating weight trends over several decades among 12 different animal populations representing eight species in close physical proximity to humans, including domestic cats and dogs, feral rodents, and lab or research facility animals (primates and rodents).[39] They found increasing trends in overweight/obesity, sometimes dramatic, in every population assessed. Even animals kept in labs under constant conditions over several decades, such as control (unexposed) animals fed controlled ad libitum diets by the National

[viii] As much as desired.

Toxicology Program (NTP), were also found to be increasing in weight compared to historical controls. The authors concluded that the consistency observed across varying populations suggests, "the intriguing possibility that the etiology of increasing body weight may involve several as-of-yet unidentified and/or poorly understood factors," such as endocrine disrupting chemicals in the environment, or infection with a virus such as adenovirus-36 which leads to obesity in multiple experimental models. However, the authors note that there are many plausible explanations. For example, changes in husbandry practices, such as those generated by the 1966 Animal Welfare Act, could explain greater weight of animals in controlled research settings, and populations in close physical proximity to humans, including pets and feral rodents, may simply be consuming more calorie-dense foods left over from humans.

Additionally, Richard Sharpe of the University of Edinburgh and Anthony Rogers of the University of New South Wales have offered several criticisms of the obesogen hypothesis. Sharpe points out in his 2013 review that diet is a significant confounder in the relationship between obesogens and obesity, as an increasingly "Western" diet is likely to increase exposure to obesogenic chemicals and influence obesity outcomes because these foods tend to be processed, packaged, and energy-dense.[40] However, Sharpe's assessment mostly considered cross-sectional studies, noting that these were particularly confounded by diet, although diet remains a confounder in prospective studies as well. In the years following his review, many prospective cohort studies in humans have been conducted. Sharpe concludes by noting that the relationship between obesogen exposure and diet must be further understood in order to substantiate the obesogen hypothesis.

In their 2018 review, Rogers and colleagues note that the rise of obesity prevalence occurred across multiple age groups largely starting at the same time. They argue that, if prenatal exposures to obesogens contributed significantly to the obesity epidemic, then each age group would need to be discretely exposed to obesogens with different lag times in order for obesity to occur in all age groups simultaneously.[41] However, this is not necessarily the case. Obesogens may have provided a "first hit" to damage the metabolic system, leaving the body metabolically vulnerable to a calorie-rich environment, the "second hit."

The 2017 ES statement (p. 288) concluded that, "Although available evidence suggests that EDCs can impact the function of genes important for the control of energy balance and adipocyte function, human data and results from animal studies have yet to clearly demonstrate an increased risk of obesity conferred by developmental EDC exposure."

Later in this report, additional evidence concerning the obesogen hypothesis will be considered. Next, we will explore other concepts that add plausibility to the obesogen hypothesis, including the Developmental Origins of Health and Disease concept and a proof of principle through the causal relationship between some pharmaceutical drugs and weight gain.

The Developmental Origins of Health and Disease Concept is Consistent with the Obesogen Hypothesis

The Developmental Origins of Health and Disease (DOHaD) concept states that early life exposures to adverse conditions during key windows of tissue and organ development increase disease risk later in life. Diseases thought to result at least in part from such developmental exposures or conditions include obesity, type 2 diabetes, insulin resistance, cardiovascular diseases, asthma, behavioral disorders, neurodegenerative diseases, reproductive disorders, and some cancers, according to the National Institute of Environmental Health Sciences (NIEHS) and other researchers.[42-45]

Early life exposures hypothesized to impact adulthood disease outcome such as obesity include parental diet, BMI, stress, smoking (also see next chapter), and gestational diabetes mellitus (GDM), as well as alcohol, drug, environmental chemical exposures, and others.[46-51] Windows of susceptibility occur not only in utero but also perinatally, in early childhood, and during adolescence. Researchers are also considering the period prior to conception as a window of susceptibility.[52] Many aspects of development are regulated by hormones and the placenta is an endocrine organ as well, making EDCs particularly important to the DOHaD concept.[53]

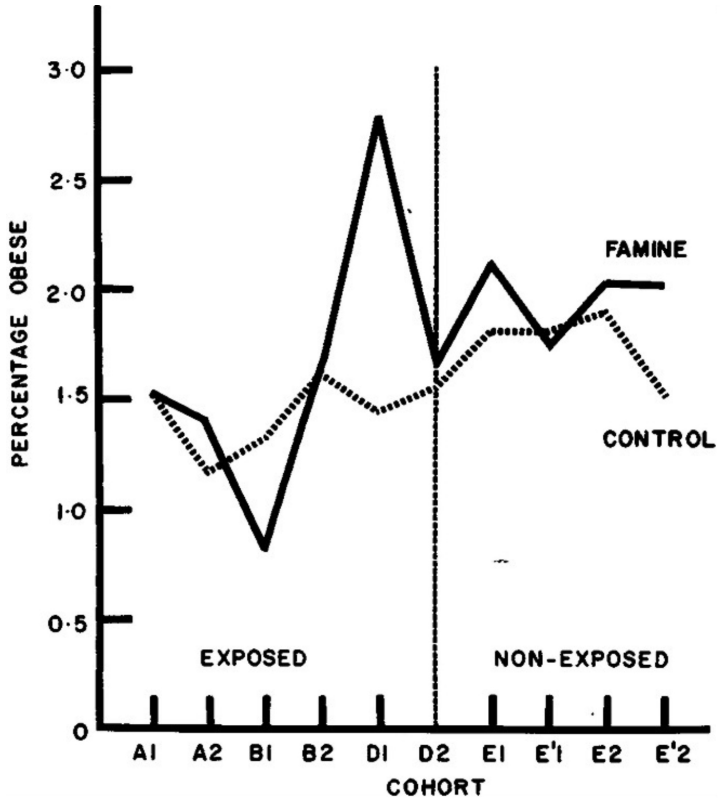
Sir David Barker and Nick Hales were pioneers in the DOHaD field who conducted some of the most influential early research characterizing the associations between poor fetal and infant growth and

increased risk of diseases and health conditions in adulthood, including impaired glucose tolerance, metabolic syndrome, and cardiovascular disease.[54,55] Early versions of the DOHaD concept were called the Barker hypothesis, the "thrifty phenotype" hypothesis, the thrifty gene hypothesis, and Fetal Origins of Adult Disease.[56-58]

The DOHaD concept is well exemplified by the Dutch Famine Study, a 1976 cohort study that observed the association between in utero undernutrition and obesity outcomes in 19-year-old men.[59] The Dutch Famine took place in the western region of the Netherlands over a 6-month period near the end of World War II (late October 1944 to early May of 1945) when imported resources, including food, were severely limited by Nazi occupation. This study used food rationing records as an index for exposed populations and data from the Dutch military draft system to obtain birth date, birthplace, height, and weight of participants. Using this data, the authors were able to use time and place population controls, comparing groups that experienced famine in utero (exposed) with those born before or after the famine (time controls) and in unaffected cities in the Netherlands (place controls).

The authors found that exposure to famine in key windows of in utero development resulted in obesity rates that varied from control populations. Subjects born between November 1, 1944 and January 31, 1945 (the "B1" cohort) were exposed to famine only in the third trimester and 3-5 months of postnatal exposure, whereas subjects born between June 1 and September 31, 1945 (the "D1" cohort) experienced it exclusively prenatally, especially the first two trimesters. For men in the B1 cohort, the obesity rate was statistically significantly lower in areas affected by famine than in the unaffected control areas, whereas for men in the D1 cohort, the obesity rate was statistically significantly higher in areas affected by famine than in the unaffected control areas. For the D1 cohort, sons of both manual and non-manual workers experienced high obesity rates. And, within the area affected by famine, obesity rates for the B1 and D1 cohorts differed significantly from those in the cohorts born immediately before and immediately after (Figure 2).

Figure 2: Obesity Prevalence Rates among Birth Cohorts in Famine and Control Areas



Source: Ravelli et al. 1976. Solid line: participants born in famine-affected areas. Dotted line: place-controls, participants born in areas not affected by famine. For men in famine affected areas, those from cohorts A1 and A2 had no prenatal exposure, only postnatal (1-10 months); those from cohorts B1 and B2 had no first-trimester exposure, only later (B1 exposed in third trimester and 3-5 months postnatal, B2 exposed in second and third trimester and 1-2 months postnatal); and those from D1 and D2 had exposure that included the first trimester (D1 first two trimesters, D2 was limited to whole or part of the first trimester). Cohorts E1 through E'2 were conceived and born after the famine and never exposed to it.

These findings suggest that exposure to undernutrition in key developmental windows can influence the development of obesity later in life. The authors inferred that exposure to famine late in pregnancy and early postnatal life affected a critical period of development for adipose tissue, and exposure earlier in pregnancy affected the differentiation of hypothalamic centers regulating food intake and growth, with subsequent food availability producing excess fat. In other words, the timing of an adverse exposure, and not just the adverse exposure itself, is key to determining its consequences.

At age 50, women, but not men, exposed in early gestation to the Dutch famine had significantly higher BMI (by 7.4%) than that of non-exposed women.[60] Interestingly, subsequent studies have shown multigenerational obesity effects from prenatal exposure to famine, with adult (37 years mean age) offspring of men prenatally exposed to the Dutch famine having higher weights (+4.9 kg, P=0.03) and BMIs (+1.6 kg/m2, P=0.006) compared to adult offspring of men not prenatally exposed to famine, although no such effect was found for the offspring of prenatally exposed mothers.[61]

Similarly, other exposures that restrict growth during key periods of development, like maternal smoking (which results in low birth weight[62]) or other chemical exposures, may result in increased weight gain, overweight, and obesity later in life. For example, the 2017 ES statement noted that a meta-analysis of 21 studies in rodents[63] and 9 studies in humans[64] supported the hypothesis that developmental exposure to PFAS reduces fetal growth, and that this may account at least in part for the purported obesogenic effects of PFAS.[65] In the next chapter we discuss the evidence linking maternal smoking and overweight/obesity later in life.

Proof of Principle that Chemicals Can Cause Weight Gain

The causal relationship between some pharmaceuticals and weight gain can serve as a proof of principle for weight gain in adults following obesogen exposure. Weight gain is a known side-effect of several pharmaceutical classes, especially atypical antipsychotics (AATPs).[ix] In the 2015 ES systematic review and meta-analysis, 257 RCTs involving 54 different drugs and 84,696 total patients were analyzed for weight-gain endpoints.[66] This review found that AATPs were the drug class associated with the most weight gain compared to placebo, with the AATP olanzapine associated with a 2.4 kg (5.3 lb.) weight gain over 3 months compared to placebo.

A recent systematic review and meta-analysis by Barton and colleagues assessed 27 RCTS specifically concerned with AATPs and AATP-induced weight-gain.[67] They found that all AATPs led to significantly more weight gain compared to controls and that most led to a relative weight gain of ≥7%, which characterizes a clinically relevant weight gain, compared to placebo (relative risk [RR]=2.04 (CI: 1.54-2.71)). Weight gain occurred over periods of time between 3 to 12 weeks and the most weight gain was caused by olanzapine.

AATPs are thought to affect weight gain through metabolic (endocrine) disruption. Mechanistically, these drugs interact with receptors in the brain, most notably HTR2C, a receptor that plays a role in food intake, body weight regulating, and glucose metabolism.[68] Consequently, the administration of AATPs in humans can lead to binge eating and food cravings as side effects. A 2017 experimental study in mice from Lord and colleagues assessed the effects of administering an olanzapine-supplemented diet to C57BL/6 mice (levels chosen to be relevant to human blood levels of the drug).[69] They found that exposure to olanzapine acutely increased food intake, impaired glucose tolerance, and decreased physical activity, although unexpectedly, increased energy expenditure in mice. Additionally, the authors found that these effects were not observed when they administered the same treatment to mice lacking the HTR2C receptor, indicating that olanzapine impacted metabolism via antagonism of HTR2C.

This evidence serves as proof of principle that chemicals can contribute to weight gain.

Other drugs[x] associated with statistically significant weight gain compared to placebo include certain hypoglycemic agents, anticonvulsants and mood stabilizers, and antidepressants.[70] Some hypoglycemic agents (e.g., pioglitazone) activate PPARγ.[71] Conversely, significant weight loss is also associated with some drugs (e.g., sodium-glucose c-transporter 2 (SGLT-2) inhibitors[72] used to lower blood sugar, the anticonvulsants zonisamide and topiramate[73]). There are six prescription medications approved to treat overweight and obesity,[74] including one just recently approved,[75] and another that was only recently allowed to be used in children 12 years and older.[76]

[ix] A family of antipsychotics associated with fewer negative side effects than typical antipsychotics.
[x] For example, hypoglycemic agents include tolbutamide (2.8 kg), pioglitazone (2.6 kg), glimepiride (2.1 kg), glyburide (2.6 kg), glipizide (2.2 kg), anticonvulsants and mood stabilizers include gabapentin (2.2 kg after 1.5 months), and antidepressants include amitriptyline (1.8 kg) (Domecq, 2015).

Of course, this level of evidence (multiple RCTs in humans) is rarely if ever available for chemicals added to food, or other non-drug exposures. The law requires "substantial evidence" of drug safety and effectiveness,[77] whereas the standard is "reasonable certainty" of no harm for food additives.[78]

In addition to pharmaceuticals, the evidence that chemicals can contribute to weight gain is also compelling for maternal smoking during pregnancy. A 2013 National Toxicology Program (NTP) sponsored review of 83 studies in humans and 18 in animals concluded that, "the linkages between maternal smoking during pregnancy and childhood overweight/obesity provide proof-of-concept of how early-life exposures to an environmental toxicant can be a risk factor for childhood obesity." Although it considered that "the data strongly suggest a causal relation," it also acknowledged that the possibility that the association was attributable to unmeasured residual confounding could not be completely ruled out.[79] More recent meta-analyses also show an increased risk of overweight/obesity in offspring from maternal smoking.[80,81,82] The population attributable risk of smoking during pregnancy on obesity in offspring was estimated as 5.5% in the United States, 5.1% in England, and 6.3% in Canada.[83] In the U.S., the authors estimated that the associated health care costs exceed $9 billion a year.

Authorities Recognize the Potential Threat of Obesogens

The evidence on obesogens has been recognized at least to some extent, by a variety of authorities (see Appendix I), including:

- U.S. government agencies and task forces, including the Environmental Protection Agency (EPA), NIH, NIEHS, NTP, and the White House Task Force on Childhood Obesity;
- Professional organizations, including the American Academy of Pediatrics, the ES, and the Pediatric Endocrine Society;
- International agencies, including the European Food Safety Authority, the United Nations Environment Program and WHO;
- International convenings of scientists and health professionals, including in Parma, Italy and Uppsala, Sweden, where consensus statements were developed.

This widespread recognition provides some perspective on the national and global conversation surrounding obesogens.

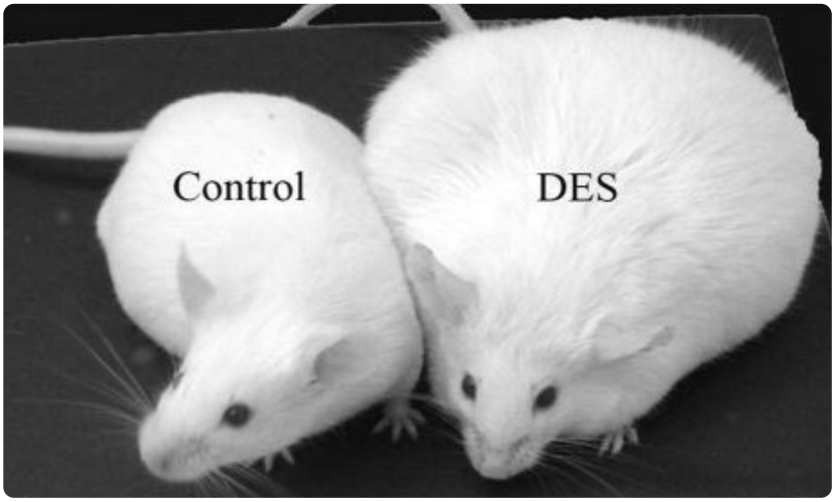
LOOKING BACK TO LOOK FORWARD: IMPORTANT FINDINGS—WITH UPDATES—FROM THE NASEM 2015 WORKSHOP

One particularly noteworthy proceeding for understanding the role that chemical exposures may play in the development of obesity was a workshop hosted by the National Academies of Sciences, Engineering, and Medicine in 2015 and sponsored by NIEHS titled "The Interplay Between Environmental Exposures and Obesity." The proceedings were documented in a report (hereafter, the NASEM report),[84] and contain perspectives from leading scientists in the field on the evidence, research needs, and policy solutions that provide grounding and insight into the obesogen field. Some of the most notable findings and solutions highlighted at the workshop are summarized below, and in some cases expanded upon and updated, as relevant:

- Obesity is multifactorial, with many factors influencing energy intake and expenditure. These can be grouped into seven categories: food production, food consumption, societal influences, individual psychology, individual activity, the activity environment, and biology. Shifting from mostly unprocessed food consumption prepared at home to the increased availability and lower cost of highly processed foods, as well as increased portion sizes, have no doubt played a role in obesity trends. Non-biological factors are considered to affect the susceptibility of an individual to an energy imbalance, rather than cause obesity. (NASEM report, p. 8).
- The study of obesogens has focused on the link between exposures that occur during critical windows of sensitivity, especially in utero and early childhood exposures, and an increased likelihood of obesity later in life. The prenatal window of exposure is likely the most influential in determining obesity outcomes, although early childhood and the pubescent window are also areas of increased susceptibility. However, researchers have begun to realize that there are other sensitive windows, such as paternal and maternal exposure before pregnancy. (NASEM report, pp. 18, 27-28). In addition, some EDC exposures are correlated with early onset of puberty (NASEM report pp. 26, 30, 33-35), although effects can vary between males and females, the specific EDC, and timing of exposure, with some exposures leading to delayed puberty.[85] Early onset of puberty is in turn is linked with obesity later in life.[86]

- Groundbreaking research by Newbold and colleagues revealed that newborn mice treated with low doses (0.001 mg/kg/day or 1 ug/kg/day) of the estrogenic drug diethylstilbestrol (DES)[xi] for five days began gaining weight significantly faster than unexposed controls upon reaching puberty, and were later morbidly obese (NASEM report p. 14).[87,88] The photograph below shows the control and treated mice from this experiment at 6 months old, which is equivalent to about 20 human years.[89] Only female mice showed this increase in body weight and notably, no increase in weight occurred during the treatment itself.

Figure 3: The effects of in utero exposure to DES in mice



Source: Newbold et al. 2009

The researchers also tested exposure to other estrogenic substances (estrogen metabolites 2OH estradiol and 4OH estradiol, and the plant estrogen genistein) on days 1-5 at doses with the equivalent estrogenic activity as 1 ug/kg/day of DES and these also caused significant increases in body weight at 3 and/or 4 months of age.[90]

It is important to note that different doses produce different effects; unlike the low dose of DES, Newbold and colleagues[91] found that a higher dose of DES (1000 ug/kg/day) to newborn mice caused a significant decrease in body weight during treatment, followed by a "catch up" period around puberty and then finally resulted in an increase in body weight compared to controls after about 2 months of age. Prior to becoming overweight and obese, the treated mice showed other signs of metabolic disruption, including elevated serum levels of leptin, adiponectin, interleukin-6 (IL-6, a protein involved in cell signaling) and triglycerides (a type of fat found in blood). The treated mice did not eat significantly more or exercise significantly less than unexposed controls. Another study in mice found that perinatal exposures of 10 ug/kg/day caused significant increases in body weight gain in female mice.[92]

Although DES is no longer prescribed, the animal model of exposure to DES is useful for studying obesogens that are environmental estrogens (e.g., BPA, DDT/DDE, PCBs), specifically, in elucidating the mechanisms involved in the abnormal programming of various target cells and tissues, including those responsible for adipocyte differentiation and mechanisms involved in weight homeostasis.[93]

There is scant human evidence on the obesogenicity of DES, and little information about dose and timing of exposures (NASEM report, p. 17), although a large[xii] prospective study found that women exposed prenatally to a "low" estimated total DES dose had a slightly increased risk of obesity (adjusted RR of 1.23 (CI: 1.07-1.42).[94] The increase for women exposed to a higher total dose of DES was not statistically significant (adjusted RR 1.05 (CI: 0.91-1.20)). As previously noted, low doses appear to be more effective at inducing obesity than high doses of DES in animal studies. Even the women in the "low" dose group were exposed to far higher doses of DES than the doses used in animals that triggered such dramatic obesogenic effects.[xiii]

[xi] Diethylstilbestrol (DES) is no longer in use, but was prescribed in the past to millions of women during pregnancy to prevent miscarriage and other pregnancy complications.

[xii] The study evaluated 2871 prenatally exposed and 1352 unexposed women between ages 23 and 52 using data from the National Cancer Institute DES Follow-Up Study.

[xiii] The study authors noted that the median cumulative dose in the low-dose group in the human study was 2510 mg, or an average of 0.2 mg/kg/day, assuming 210 days of exposure in pregnancy for a 60 kg woman. The prenatally administered low doses that triggered obesity in animal studies ranged from 0.001 mg/kg/d (Newbold 2009) to 0.01 mg/kg/day (Hao 2012). The higher of those (Hao 2012) is equivalent to a dose of 0.001 mg/kg in humans, according to the study authors, far lower than the low dose in the human study (Hatch 2015).

- At the time of the workshop in 2015, over 30 human epidemiology studies linked developmental exposure to environmental chemicals with weight gain in children later in life, including PCBs, BPA, HCB, polycyclic aromatic hydrocarbons (PAHs), and maternal smoking, and NIEHS was providing 57 grants related to obesity (32 in humans) (NASEM report, pp. 15-16). A 2022 review identified over 100 epidemiological studies that found a positive or increased effect/association between chemical exposures and metabolic disruption, including over 80 specifically linked with an increased risk of adiposity.[95]
- The effects of obesogens can vary not only by chemical but by species, sex, dose (e.g., low doses may produce completely different and sometimes more concerning effects than high doses), timing of exposure (e.g., during critical windows of exposure or not), outcome measured, and timing of outcome measurement (e.g., effects may manifest only at certain times over the lifespan). This has already been illustrated in research previously discussed on DES, and was discussed in regard to many other EDCs. Different EDCs may affect the same metabolic pathway or mechanism in opposite ways. For example, in in vitro studies, tributyltin (TBT) and a brominated flame retardant, BDE 47, increased differentiation of pre-adipocytes into mature fat cells in a dose-response fashion, whereas others, such as tetrachlorodibenzo-p-dioxin (TCDD) actually inhibited fat cell differentiation. (NASEM report p. 38).

Obelix.

- According to the Director of the OBELIX project, a 4.5 year European effort which examined the hypothesis that prenatal exposure to EDCs in food plays a role in obesity later in life, "the OBELIX project provided evidence that endocrine-disrupting chemicals do indeed play a role in obesity, affecting growth and metabolic pathways." The project, which involved seven institutes in five European countries, was named for a famous French cartoon character who got his huge size and strength from falling into a cauldron of magic potion as a young boy. (NASEM report pp. 35-36, 38)
- Groundbreaking research by Blumberg and colleagues revealed important mechanisms by which some chemicals, including TBT,[xiv] can exert obesogenic effects. TBT activates the nuclear receptors retinoid X receptor (RXR) and PPARγ which are both considered master regulators of adipogenesis. This discovery led him to conduct several animal studies with TBT, finding that in utero exposure to TBT resulted in a 15% increase in body fat in exposed mice compared to controls (NASEM report p. 55). (The dosing occurred by injection into the body cavity and used moderately low doses: 0.05 or 0.5 mg/kg-bw.[96]) Notably, despite this increase in body fat, the mice exposed to TBT did not weigh more than controls. Instead, the gains in fat seemed to be compensated for by decreases in the relative mass of other body tissues. These fatter mice consume less food than the controls, which Blumberg potentially attributed to increased lipid storage capacity or increased numbers of pre-fat and fat cells. (NASEM report pp. 55-56),
- After pregnant mice were exposed to very low doses of TBT,[xv] Blumberg measured increased adiposity (e.g., increased weight of fat, fat cell size and number) and other obesogenic effects (e.g., increased activity of genes related to production of fat cells) relative to controls through the F3 generation of mice (NASEM report pp. 56-57).[97] Transgenerational effects have also been reported for other suspected obesogens including BPA, DEHP, dibutyl phthalate, DDT, methoxychlor, and jet fuel JP-8.[98]
- Exposure to obesogens can exacerbate the obesogenic effects of a high fat diet. Blumberg and colleagues observed that the introduction of a slightly higher-fat diet to fourth generation (F4) mice (from the previously mentioned experiment) for 6 weeks induced "striking" effects on fat mass accumulation in males. Through the 6-week diet period, exposed males continued to accumulate fat faster than the controls and retained an increased body fat percentage after the normal diet was reintroduced. Interestingly, strong differences in body weight were not observed between groups.

Illustration: https://www.asterix.com/en/portfolio/obelix/.

[xiv] Tributyltin was previously used in antifouling paint applied to ship hulls to prevent the accumulation of mollusks and other organisms, until an international treaty prohibited that use in 2008. Certain uses are still permitted, including on farm and animal premises, and in building and textile-related materials (e.g., carpet backing, fiberfill, rubber mats). Minimal human exposure data for TBT is available, although trace amounts of butyltins have been detected in human blood, milk, and liver samples. (Sources: U.S. EPA, Reregistration Eligibility Decision for the Tributyltin Compounds: Bis(tributyltin) oxide, Tributyltin benzoate, and Tributyltin maleate, June 2008; Holtcamp W. Obesogens: an environmental link to obesity. Environ Health Perspect. 2012;120(2):a62–a68.)

[xv] According to the NASEM report (p. 56), Blumberg said the doses were 5-50 times less than the reported no observed adverse effects level (NOAEL).

However, compared to controls, the fourth-generation mice had significantly more fat tissue and less lean tissue. These effects were observed to a much lesser extent in female mice (NASEM report p. 58).[99] Similar synergistic effects with high-fat diets have been observed with low levels of BPA[xvi] (NASEM report pp. 64-65).[100]

At the NASEM workshop, it was noted that the available studies did not prove causation at this time due to the limited available evidence (NASEM report p. 18). Panelists stressed the importance of consistency in future research study designs (NASEM report pp. 116, 130). A panel of scientists discussed research needs (NASEM report pp. 111-122), including:

- Then NIEHS and NTP Director Linda Birnbaum recommended not only prospective cohort studies but also RCTs, and said that body fat composition, and not simply BMI, should be studied as endpoints. Furthermore, she suggested that metabolic syndrome and diabetes should receive more focus. She also noted that animal studies should be mindful of follow-up time, given that obesogenic effects may not be seen until puberty or beyond, and recommended that developmental toxicity tests be extended to follow animals at least until they are 1 year of age in order to see the sorts of effects on weight and metabolism of interest. (See recommendations section). In addition, she suggested that it was important to look past effects on fat cells and consider effects on the gastrointestinal tract, the pancreas, the liver, muscle tissue, and the brain. She also said, given that it is practically impossible to test all the 80,000 chemicals currently in commerce, it is important to get a better sense of how to prioritize which chemicals to screen.
- The Acting Director of the U.S. Geological Survey Suzette Kimball, who explained that the USGS spends approximately $5 million per year on research related to EDCs, said a major research challenge is identifying and characterizing environmental drivers of exposure, and that new and better methods to measure the presence of these chemicals in the environment are needed, as is research on mechanisms and cumulative effects.
- Johns Rogers, Director of the Toxicity Assessment Division of the National Health and Environmental Effects Research Laboratory in the Office of Research and Development at EPA, underscored that standard regulatory studies, including developmental toxicity, teratology, and multigenerational studies, would miss most metabolic and obesity-related effects. Not only are offspring not followed long enough, things like insulin resistance, blood pressure, blood lipids, or changes in body composition (fat content and location) that may not affect body weight would not be detected at all; more complete evaluations to measure these and other aspects of the metabolic syndrome are needed. The most appropriate animal models need to be identified; some of the inconsistencies among studies may be due to differences in animal models used. He stressed the importance of using low doses in animal studies to account for the non-monotonic dose response (NMDR)[xvii] typical to endocrine disruptors. (See recommendations section). Traditionally, toxicological testing anticipates a linear dose response, however, an exposure-outcome relationship with a NMDR pattern could elicit an effect at a low dose, while not at a high dose. (NMDR patterns are also found with some vitamins, nutrients, hormones, and drugs.[101,102])
- Overall, the panelists encouraged collaboration among scientists to develop a cohesive picture on key obesogens, using in vitro, in vivo, and epidemiological studies. This approach has been increasingly taken on-board, especially in Europe (see section on identifying new obesogens).

With regard to policy solutions, a key question identified was "whether sufficient and clear evidence should be required before the next step is taken, whether that would be too late and the next steps should be taken in the absence of such evidence" (NASEM report p. 123).

Jeanne Conry, representing the American College of Obstetricians and Gynecologists (ACOG), said that a main message of a 2013 ACOG committee opinion on reproductive health and the environment was that "not all exposures are created equal." For example, "underserved and minority populations are disproportionally affected by environmental chemicals" (NASEM report, p. 124).

Since then, ACOG has updated its earlier opinion, which continues to highlight environmental justice issues, and encourages policies that reduce prenatal exposures to toxic environmental agents.[103]

In addition, a 2021 review by a panel of experts examining the role of obesogenic EDCs in the etiology of childhood obesity among Latino youth in the United States and Latin America concluded that the evidence, "implicates early life EDC exposure in the etiology of childhood obesity."[104] The review also concluded that, "pregnant women, infants, and young children are populations of special concern.

[xvi] According to the NASEM report (pp. 62-65), the doses administered were all below the lowest observed adverse effect level (LOAEL), established by the EPA.

[xvii] Non-monotonic dose response (NMDR) curves are dose-response curves whose slope changes direction within the range of tested doses, resulting in for example a U-shaped dose-response curve.

Therefore, promoting education, awareness, and vigilance of EDC exposure in these populations is especially important when considering EDCs as an actionable target for childhood obesity prevention programs. Such efforts are especially salient … in regions of the United States comprising large Latino/Hispanic populations and/or where agricultural work or other jobs with a high burden of chemical exposures (e.g., firefighting, textile, and paper manufacturing) represent a large proportion of the economic output."

Other policy solutions discussed at the NASEM workshop included legislation by Congress to shift the burden of proof of chemical safety from scientists and healthcare providers to the chemical industry. The important role that FDA has in regulating chemicals that may play a role in obesity was highlighted (NASEM report p. 125, 132-137).

USING SYSTEMATIC REVIEW AND EVIDENCE INTEGRATION TO EVALUATE POSSIBLY OBESOGENIC SUBSTANCES IN FOOD

Since 2002, when Paula Baillie-Hamilton first hypothesized the link between increased chemical production and the rise of obesity,[105] numerous chemicals and chemical classes have been identified as possible obesogens (Table 1).[106-122,123,124,125,126] Some of these are present in our foods, either intentionally (e.g., food additives, food contact substances) or unintentionally (e.g., environmental contaminants, cooking byproducts). The strength and quality of evidence varies by chemical.

Table 1: Some Chemicals and Chemical Classes Identified in the Literature as Possible Metabolic Disruptors

Chemical Class / Chemical	
Consumer Product-Related[xviii]	
Avobenzone (sunscreen)	Ethoxylated alkylphenols and Alkylphenols (e.g., Nonylphenol ethoxylates, Nonylphenol, 4-Hexylphenol) (surfactants) *[P 127]
Benzophenone 3 and 8 (sunscreen)	Sorbitan monooleate* (emulsifier, surfactant)
Cannabis	Triclosan (antibacterial)*[128]
Cigarette Smoke/Nicotine	
Chemicals Listed on Food Labels	
Acesulfame Potassium*	Parabens (e.g., Butylparaben, Methylparaben)*
Aspartame*	Polysorbate 80*
Benzoates (e.g., Sodium Benzoate)*	Propionate*
3-Butylated Hydroxyanisole (3-BHA) (a component of BHA*)	Saccharin*
Caffeine*	Stevia leaf extracts*
Carboxymethylcellulose*	Sucralose*
Dioctyl sodium sulfosuccinate (DSS)*	Sulfites (e.g., Sodium sulfite)*
Monosodium glutamate (MSG)*	
Heavy Metals	
Arsenic*	Lead*
Cadmium*	Mercury*
Miscellaneous	
Acrylamide*[xix]	Microplastics*
Air Pollution (including Particulate Matter (e.g., PM 2.5), Polycyclic Aromatic Hydrocarbons (PAHs))	Triphenyl Phosphate (flame retardant, plasticizer)

[xviii] Also see substances listed under "Plastics, Resins, and Rubber-Related."
[xix] Forms when certain foods are cooked at high temperatures. Also found in cigarette smoke. Used to manufacture paper, dye, and other industrial products. (Source: NIEHS, https://www.niehs.nih.gov/health/topics/agents/acrylamide/index.cfm).

Organotins	
Dibutyltin	Triphenyltin (TPT)*
Tributyltin (TBT)*	
Persistent Organic Pollutants	
Dichlorodiphenyltrichloroethane (DDT)*◊	Hexachlorobenzene (HCB)*◊
Dichlorodiphenyldichloroethylene (DDE)*	Polybrominated diphenyl ethers (PBDEs)*
Dioxins*	Polychlorinated biphenyls (PCBs)*
Endrin*◊P	Tetrabromobisphenol A (TBBPA)*
Pesticides (excluding POPs already listed)	
Atrazine*P	Imidacloprid*
Carbendazim*	Permethrin*
Chlorpyrifos*◊xx	Strobilurin pesticides*P
Diazinon*P	Tolylfluanid*
Glyphosate*P	Triflumizole*P
Pharmaceuticals	
Anticonvulsants (e.g., Divalproex, Gabapentin, Oxcarbazepine,Δ Valproate Δ)	Selective Serotonin Reuptake Inhibitor Antidepressants (e.g., Escitalopram,Δ Sertraline Δ)
Atypical Antipsychotics (e.g., Olanzapine, Quetiapine, Risperidone)	Thiazolidinediones (e.g., Pioglitazone)
Estrogens, natural and synthetic (Diethylstilbestrol (DES), 2-hydroxyestradiol, 4-hydroxyestradiol)	Tricyclic (e.g., Amitriptyline) and Mirtazapine (tetracyclic) Antidepressants
Glucocorticoids (e.g., Prednisone)	Typical antipsychotics (e.g., Haloperidol)
Hypoglycemics (e.g., Nateglinide and Sulfonylureas (e.g., Gliclazide, Glimepiride, Glipizide, Glyburide, Tolbutamide))	
Phytoestrogens	
Daidzein*	Genistein*
Plastics, Resins, and Rubber-Related (includes Food Contact Substances)	
Bisphenols (BPA, BPS)*	Per- and polyfluoroalkyl substances (PFAS)*
Bisphenol A Diglycidyl ether (BADGE)*P	Phthalates*

* May be present in food.

◊ Banned from use on foods sold in the U.S., but residues may persist.

P Classified as a potential obesogen by Heindel et al, since only in vitro data or a single unsubstantiated in vivo study. Source: Heindel 2022.

Δ Caused significant weight gain specifically in children/adolescents treated for psychiatric disorders. Source: Solmi 2020.

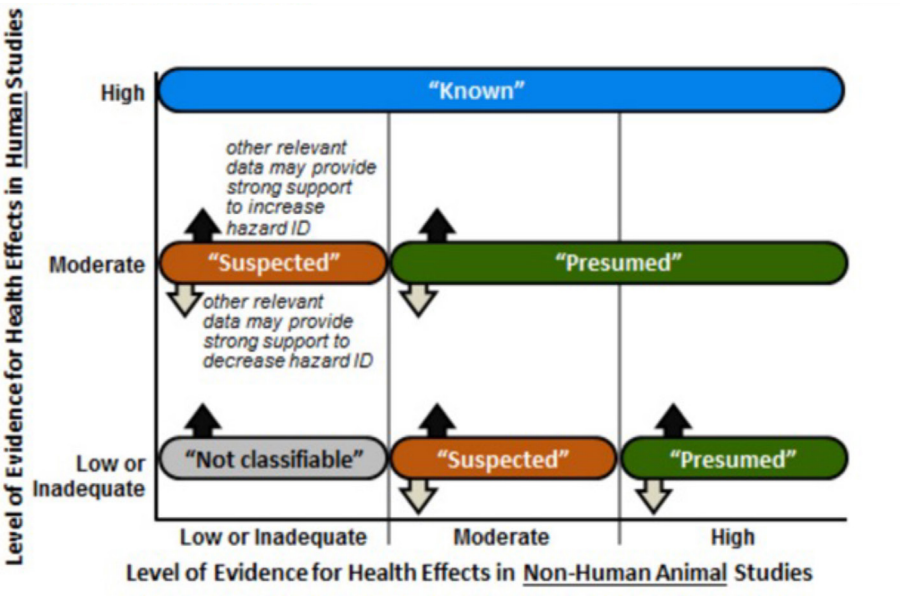
To better understand the evidence on intentionally added food chemicals and obesity, we conducted an initial screen of the evidence using an approach based on a systematic review and evidence integration (SR/EI) approach developed by the NTP Office of Hazard Assessment and Translation (OHAT).

SR/EI is a structured process that allows investigators to reach conclusions about hazards to humans—even when human evidence is minimal, low quality, or nonexistent—through a transparent and repeatable approach. SR/EI is increasingly being used for chemical assessments by regulatory and other authoritative bodies, including the NTP (see below), the International Agency for Research on Cancer (IARC),[129] the U.S. Environmental Protection Agency (EPA),[130] and the European Food Safety Authority (EFSA),[131] as well as many universities.[132,133] Generally, SR/EI involves the systematic evaluation of a body of evidence for each evidence stream (human, animal, and mechanistic), rating the confidence of each, and then integrating the ratings of each stream into one overall conclusion about the hazard to humans.

[xx] 86 FR 48315

Unlike for drugs, high quality human evidence is rare when conducting evaluations of chemicals added to food. Human evidence at best is generally limited to observational data, which usually cannot be considered strong enough to demonstrate causality on its own. In order to identify hazardous chemicals with confidence, other evidence streams beyond human data must be relied upon, sometimes in tandem with any available (often limited) human evidence. For example, a review might classify a substance as "presumed" to cause a health effect in humans when the level of human evidence is "low," and the level of animal evidence is "high" as illustrated by this schematic used by the NTP Office of Health Assessment and Translation (OHAT).[134]

Figure 4: Hazard Identification Scheme Used by the National Toxicology Program Office of Health Assessment and Translation



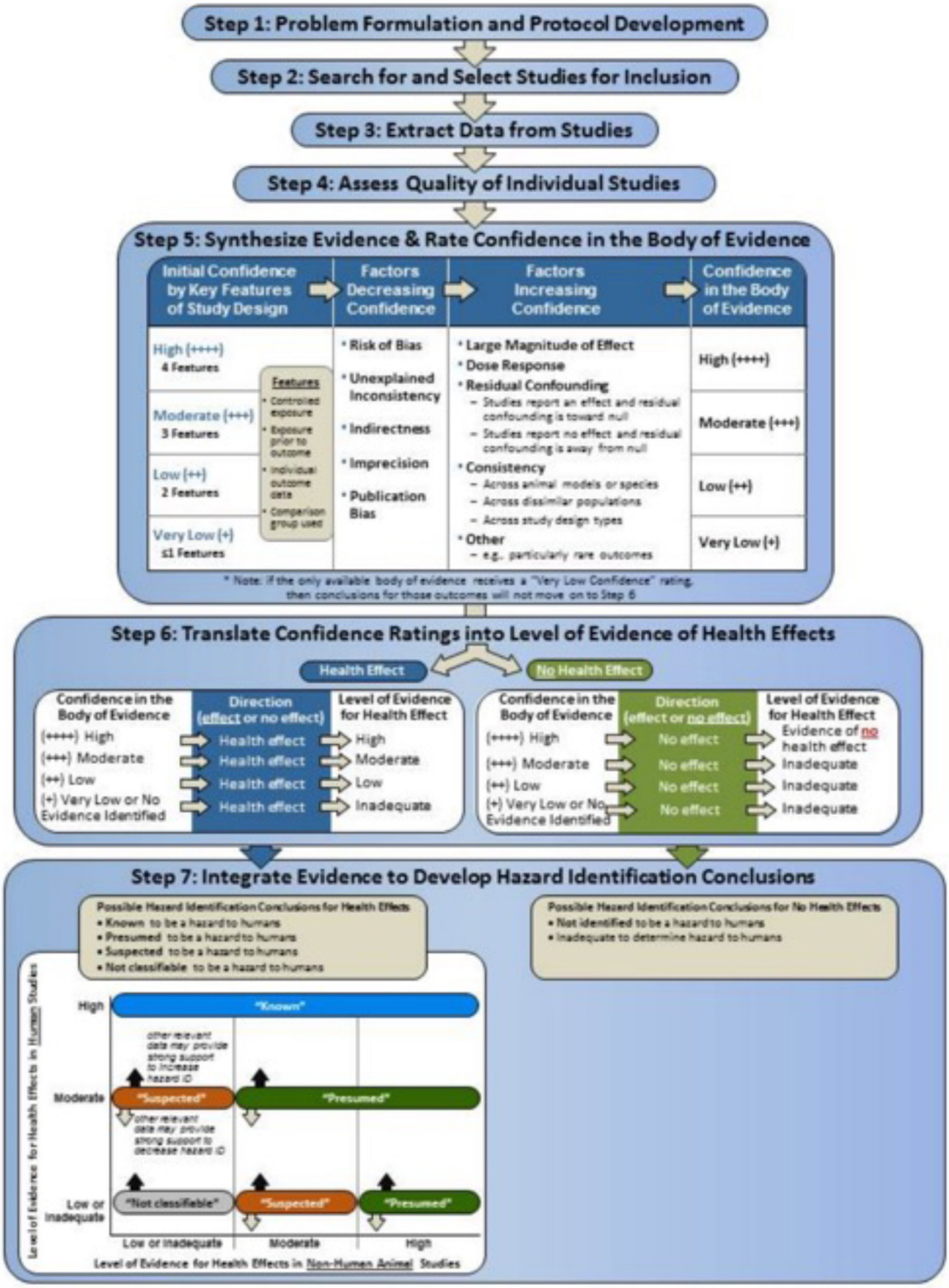
Source: NTP, 2019, p. 69.

Similarly, IARC would rate a substance as "probably carcinogenic to humans" in situations where there is "limited" human evidence and "sufficient" evidence of cancer in experimental animals.[135]

Under OHAT's approach, mechanistic information can influence the final characterization only if it is particularly strong.[xxi] NTP's OHAT developed a 7-step framework for systematic review and evidence integration (Figure 5).

[xxi] IARC gives more weight to mechanistic evidence than does OHAT, perhaps because scientific understanding of cancer mechanisms is greater than that for other endpoints. So, for example, an agent would be classified as "carcinogenic to humans" (the strongest classification), even where human evidence is limited or inadequate, if there was sufficient evidence of cancer in experimental animals and strong mechanistic evidence in human cells or tissues. (Source: IARC 2019, p. 37)

Figure 5: OHAT Framework



Source: NTP, 2019, p. 6.

The OHAT framework has previously been used to assess obesogen evidence. The banned pesticide DDT and its metabolite, DDE, were comprehensively assessed using the NTP OHAT framework by Cano-Sancho and colleagues in a 2017 systematic review.[136] That assessment was the first such integrated analysis of an obesogen.[137] The review concluded that DDT and DDE are "presumed" obesogens, finding a "moderate" level of human evidence (based on 7 human studies), a "moderate" level of primary animal evidence (based on 2 primary animal studies), and "moderate" supporting in vivo and in vitro evidence (based on 25 mechanistic and other studies supporting biological plausibility).

Similarly, an international panel of epidemiological and toxicological experts panel, although using a different approach and criteria,[xxii] also rated the quality of both the human and animal evidence on DDE and childhood obesity as "moderate," based on 13 epidemiological studies and 3 rodent studies. The panel considered DDE,[xxiii] BPA, and phthalates to have the strongest evidence for obesity.[138]

We note that these conclusions on DDE are also supported by a 2022 meta-analysis of prospective studies (see below).

INITIAL CONFIDENCE RATINGS FOR POSSIBLE OBESOGENS ADDED TO FOOD

Using the OHAT Handbook for guidance, we determined initial confidence ratings (i.e., the first part of "Step 5" above) in the human and animal evidence streams for a subset of possible obesogens we identified through literature searches. Our goal was to identify those that at least have a moderate level of human and/or animal evidence after initial screening, since that level of evidence is a prerequisite for being considered at least a "suspected" hazard (a classification that would require further analysis (Steps 5- 7). The initial confidence rating is determined by the ability of the study design to ensure that exposure preceded, and was associated with, the outcome. It considers whether four key features of the study design are present or absent: controlled exposure, exposure prior to outcome, individual outcome data, and comparison group used. The table below shows how OHAT initially rates different study designs based on those four criteria.

Figure 6: Study Design Features for OHAT Initial Confidence Rating

Study Design	Controlled Exposure	Exposure Prior to Outcome	Individual Outcome Data	Comparison Group Used	Initial Confidence Rating
Human controlled trial[a]	likely	likely	likely	likely	high
Experimental animal	likely	likely	likely	likely	high
Cohort	unlikely	may or may not	likely	likely	low to moderate
Case-control	unlikely	may or may not	likely	likely	low to moderate
Cross-sectional[b]	unlikely	unlikely	likely	likely	low
Ecologic[b]	unlikely	may or may not	may or may not	likely	very low to moderate
Case series/report	unlikely	may or may not	likely	unlikely	very low to low

[a]Human controlled trial study design as used here refers to studies in humans with a controlled exposure, including randomized controlled trials and non-randomized experimental studies.
[b]Cross-sectional study design as used here refers to population surveys with individual data (e.g., NHANES), as distinct from population surveys with aggregate data on participants (i.e., ecologic studies).

Source: NTP, 2019, p. 50.

Conclusions for the body of evidence are primarily based on the study with the highest confidence (NTP OHAT 2019, p. 63). A "high" confidence in the evidence is required to demonstrate a "no effect" conclusion due to "the inherent difficulty in proving a negative," according to the OHAT (see Step 6 in Figure 5).

The rating describes the initial confidence in the quality of the evidence supporting an obesogenic association—it is not the confidence that a substance is or is not an obesogen. As Step 5 in Figure 5 shows, the initial rating must be downgraded for factors that decrease confidence in the results (e.g., risk of bias, unexplained inconsistency) and upgraded for factors that increase confidence in the results (e.g., large

[xxii] A steering committee of scientists identified epidemiological and toxicological experts, based upon their scholarly contribution in the diseases under consideration and endocrine disruptor toxicology, and invited them to attend a 2-day meeting. Teleconferences with participants were held biweekly over a 3-month period. A modified Delphi approach to evaluating the strength of the epidemiological and toxicological evidence and the nature of the association between exposures and outcomes was used. The World Health Organization Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group criteria were adapted to evaluate the epidemiologic evidence, and definitions promulgated by the Danish Environmental Protection Agency for evaluating laboratory and animal evidence of endocrine disruption. Source: Trasande et al. Estimating Burden and Disease Costs of Exposure to Endocrine-Disrupting Chemicals in the European Union. J Clin Endocrinol Metab 2015;100(4):1245-1255.

[xxiii] The panel also examined adult DDE exposure associated with type 2 diabetes and classified the epidemiological evidence (based on 5 studies) as "low" and the toxicological evidence (based on 4 studies) as "moderate." Furthermore, based on an adapted model from the Intergovernmental Panel on Climate Change (IPCC) used to model probability of causation and uncertainty, the experts estimated the probability of causation between prenatal DDE exposure and childhood obesity to be 40 to 69% and between adult DDE exposure and diabetes to be 20-39%.

magnitude of effect, dose-response, consistency across study designs/populations/animal models or species).

We performed the initial screen on substances intentionally added to food that were identified in the literature as possibly obesogenic in Table 1, excluding:

- Carboxymethylcellulose and polysorbate 80, because evidence suggests they act by impacting the gut and altering gut microbiota and not as endocrine disruptors,[139-143] although other mechanisms may be involved.[144]
- Similarly, low-calorie sweeteners acesulfame potassium, aspartame, saccharin, sucralose, and stevia leaf extracts since they may not be acting via an endocrine mechanism and thus may not fit our definition of obesogens.[145-151] The evidence on low calorie sweeteners as possible obesogens should be re-examined as additional data are generated.

Other possible obesogens in food, including food contaminants, cooking by-products, and naturally occurring food substances (e.g., acrylamide, heavy metals, PAHs, persistent organic pollutants (e.g., dioxins, TBBPA, PCBs, PBDEs, DDT/DDE), pesticides, phytoestrogens) were not included since the focus was substances intentionally added to food.

In total, we assessed the evidence for 12 chemicals or chemical classes (Table 2). PFOA, DEHP, and butylparaben were chosen as representatives of the chemical classes PFAS, phthalates, and parabens, respectively, because they had more evidence than other substances within their respective classes.

With regards to human evidence, we only considered cohort and case-control studies (typically there were no human RCTs or ecologic studies), since cross-sectional studies and case reports would receive an initial confidence rating of no higher than "low," as indicated in the table, above.

Table 2: Potentially Obesogenic Chemicals Added to Food and Evaluated in this Report

Chemical	Description
Benzoates (e.g., Sodium Benzoate)	Sodium benzoate and its close relative benzoic acid are preservatives used in acidic foods like fruit juice, carbonated drinks, and pickles. Some people experience allergic reactions such as hives or asthma in response to benzoates. When added to beverages that also contain ascorbic acid (Vitamin C) or erythorbic acid (d-ascorbic acid), small amounts of benzene, a carcinogen, can form, although many previously affected beverages have been reformulated to avoid this problem.[152]
Bisphenols (e.g., Bisphenol A (BPA))	BPA is used to make polycarbonate plastic and epoxy resins that are used in food and beverage containers and packaging, including water bottles, the lining of bottle tops, and metal food cans, as well as in water supply pipes, cash register and ATM receipts, hospital equipment, and many other products.[153-155] BPA can migrate into food from food packaging and other food contact materials (e.g., water dispensers), and this appears to be the primary way humans are exposed to BPA.[156] Exposure to BPA is widespread: 93% of NHANES participants age 6 years and older were reported to have BPA in their urine.[157]* BPA is no longer permitted in baby bottles and packaging for infant formula.[158,159] Other bisphenols used to replace BPA are not as well studied, but may not be any safer, and some, such as bisphenol F (BPF) and bisphenol S (BPS), are also suspected of being obesogenic.[160,161]
3-BHA	The antioxidant BHA, used to retard rancidity in oils and fatty foods such as potato chips and snacks, is composed of over 85% 3-BHA and less than 15% 2-BHA. The U.S. government's Report on Carcinogens classifies BHA as "Reasonably Anticipated to be a Human Carcinogen."[162]
Caffeine	The most used psychoactive drug worldwide, caffeine naturally occurs in coffee, tea, and chocolate and is added to soda, energy drinks, chewing gum, and other foods and beverages as well as supplements and personal care products.[163]
Dioctyl Sodium Sulfosuccinate (DSS)	An emulsifier and wetting agent added to food (including beverages),[164,165] DSS is also used in stool softeners,[166] and to clean up oil spills.[167]
Monosodium Glutamate (MSG)	A flavor enhancer to produce a "umami" or savory flavor in food. The use of MSG allows companies to reduce the amount of real ingredients in their foods, such as chicken in chicken soup.[168,169]

Parabens (e.g., Butylparaben, Methylparaben)	Parabens are used as preservatives and flavoring agents and found in foods, beverages, makeup, moisturizers, shaving creams and other products.[170,171]* Exposure is widespread: 98% of NHANES participants aged 3 years old or older for which paraben measurements were completed in 2015-2016 were reported to have detectable levels of methylparaben or propylparaben in their urine.[172]
Per- and polyfluoroalkyl substances (PFAS) (e.g., PFOA)	A group of more than 9,000 different chemicals used in hundreds of products worldwide, including non-stick cookware, grease-resistant paper, and paperboard food packaging, as well as many non-food products. PFAS are persistent in the environment and bioaccumulate in the body. Exposure to PFAS is widespread; 97-100% of NHANES (2011-2012) participants 12-80 years old were reported to have detectable levels of PFAS in their blood.[173,174]*
Phthalates (e.g., DEHP)	A group of chemicals used primarily as plasticizers to increase the flexibility of plastic, including some plastics used for food contact purposes; food is the major route of exposure to phthalates.[175-177] Exposure to phthalates is widespread; multiple phthalates were reported to be detected in at least 98% of NHANES (2001-2010) participants age six years and older.[178]*
Propionate, Propionic Acid	Calcium and sodium propionate and propionic acid are preservatives added to foods like baked goods and cheese to prevent mold.[179]
Sorbitan monooleate	Used as an emulsifier, in adhesives used in food contact articles and as a secondary additive in sugar production.[180] Also a component of Corexit oil dispersant used to clean up the Deepwater Horizon oil spill and as a surfactant in personal care products.[181]
Sulfites	Sulfiting agents, including sodium sulfite, sodium or potassium bisulfite, sodium, or potassium metabisulfite, and sulfur dioxide are used to prevent discoloration in some dried fruit, "fresh" shrimp, and dried, fried, or frozen potatoes. They are also used to prevent bacterial growth in wine. Sulfites destroy vitamin B-1, and can cause severe reactions, especially in asthmatics. FDA banned the most dangerous uses of sulfites in the wake of several deaths linked to sulfites.[182]

* Being able to detect a chemical or a chemical metabolite in urine or blood does not mean that the chemical has caused or will cause an adverse health effect. However, these chemicals are endocrine disrupting chemicals, which can affect normal hormone functioning, and even small changes may cause significant effects. NIEHS says "Even low doses of endocrine-disrupting chemicals may be unsafe."

To identify relevant articles in the literature, we adapted the search terms developed by Cano-Sancho and colleagues for their assessment of DDT/DDE (discussed above) and applied them to the PubMed database.[xxiv] In addition to studies returned by our search, additional relevant studies cited by recent reviews were also added.

The results of our assessment are presented in Table 3. Only sorbitan monooleate and sulfites failed to pass the initial screen as there were only mechanistic data or human cross-sectional studies available linking these additives with obesity pathogenesis at the time of our review. These chemicals are not classifiable with respect to obesogenicity; additional studies, specifically animal studies and/or human (case-control, cohort, or RCTs) are needed in order for them to even be considered as "suspected" obesogens, under the OHAT scheme. For the remaining ten substances, the animal evidence was given an initial confidence rating of "high." No human studies on the obesogenic effects of benzoates, DSS, or propionic acid were available. For the other chemicals screened, the human evidence received an initial confidence rating of "moderate." These ten chemicals passed the initial screen and are candidates for further assessment to determine whether they are, for example, "presumed," "suspected," or "not classifiable" as obesogens.

[xxiv] ("DDT"[MeSH] OR Dichlorodiphenyltrichloroethane [tiab] OR "Dichlorodiphenyl trichloroethane" [tiab] "50-29-3"[tiab] OR DDE [tiab] OR "Dichlorodiphenyl Dichloroethylene" [MeSH] OR DichlorodiphenylDichloroethylene [tiab] OR "72-55-9" OR "Dichlorodiphenyldichloroethane"[MeSH] OR "53-19-0") AND ("Diabetes Mellitus"[Mesh] OR diabetes [tiab] OR hyperglycemia [MeSH] OR "hypoglycemia"[MeSH] OR insulin [MeSH] OR insulin* [tiab] OR "blood glucose" [MeSH] OR "hemoglobin A, Glycosylated" [MeSH] OR gluconeogenesis [MeSH] OR "Glycolysis"[Mesh] OR glycolysis [tiab] OR "Glucose Transport Proteins, Facilitative"[Mesh] OR "metabolic syndrome x" [MeSH] OR "islets of Langerhans" [MeSH] OR "insulin-secreting cells"[MeSH] OR obesity [MeSH] OR obes* [tiab] OR overweight [MeSH] OR "body weight" [MeSH] "body mass index" [MeSH] OR "Waist-Hip Ratio"[MeSH] OR "Waist Circumference"[MeSH] OR "Skinfold Thickness"[MeSH] OR "Weight Gain"[MeSH] OR "Body Fat Distribution"[MeSH] OR "Adipose Tissue"[Mesh] OR Adipokines [MeSH] OR Adipogenesis [MeSH] adipokine*[tiab] OR adipocytokine*[tiab] OR adiponectin[mh] OR adiponectin*[tiab] OR ghrelin[mh] OR ghrelin[tiab] OR leptin[mh] OR leptin*[tiab] OR resistin[mh] OR resistin[tiab] OR Lipid metabolism[mh] OR lipogen*[tiab] OR lipid*[tiab] OR lipoprotein OR triacylglycerol OR triglyceride OR thermogenesis [MeSH] OR thermogen*[tiab])

The next step would be to downgrade for factors that decrease confidence in the results (e.g., risk of bias, unexplained inconsistency) and upgrade for factors that increase confidence in the results (e.g., large magnitude of effect, dose response, consistency across study designs/populations/species). The resulting final confidence ratings on the body of evidence could then be used to develop conclusions related to a level of evidence of health effects (and research needs), and then integrated to develop hazard identification conclusions (e.g., "presumed," "suspected," or "not classifiable" as obesogens).

Table 3: Initial Confidence Ratings of Evidence of Obesogenicity for Chemicals Added to Food*

Chemical	Human Evidence	Animal Evidence	Passed Initial Screen?
Benzoates	N/A[xxv]	High (+/-)[183,184]	Yes
BPA	Moderate (+/-)[185-196]	High (+/-)[197-208]	Yes
3-BHA	N/A	High (+/-)[209]	Yes
Caffeine	Moderate (+/-)[210-215]	High (+)[216,217]	Yes
DSS	N/A	High (+/-)[218,219]	Yes
Butylparaben	Moderate (+)[220]	High (+/-)[221,222]	Yes
Monosodium Glutamate (MSG)	Moderate (+/-)[223-226]	High (+/-)[227-230]	Yes
PFOA	Moderate (+/-)[231-255]	High (+/-)[256-260]	Yes
DEHP	Moderate (+/-)[261-271]	High (+/-)[272-282]	Yes
Propionic acid/propionate	N/A	High (+)[283]	Yes
Sorbitan monooleate[xxvi]	N/A	N/A	No
Sulfites[xxvii]	N/A	N/A	No

This assessment was primarily conducted by a single scientist at CSPI.

* Initial Confidence Ratings follow guidance in the National Toxicology Program. Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. 2015, based on key study design features. Substances rated as "moderate" possess 3 of 4 key study design features, and those rated "high" possessed all 4. Observational studies do not have controlled exposure and can therefore never receive a "high" rating. The ratings are primarily based on the study with the highest confidence. Initial confidence ratings may be downgraded or upgraded before arriving at a final confidence rating, for example after assessing risk of bias across studies, unexplained inconsistency, residual confounding, and magnitude of the association. See text for more details. Final confidence ratings not determined.

+ indicates an effect was found on body weight, BMI, adiposity, or similar measure

- indicates no effect was found on body weight, BMI, adiposity, or similar measure

+/- indicates that for some studies and/or outcomes, an effect was found, and for other studies and/or outcomes, no effect was found, on body weight, BMI, adiposity, or similar measure. These differences may be explained for example by differences in the amount and/or timing of exposure, sex of subjects, which outcomes were measured and/or when.

N/A: not available

META-ANALYSES OF PROSPECTIVE EPIDEMIOLOGICAL STUDIES ON OBESOGENS

For human data, RCTs are considered the gold standard for measuring the effectiveness of an intervention or treatment. RCTs are rarely available for chemicals added to food, and may not be appropriate for studying some chemicals, such as those with hazardous profiles, or long-term outcomes. Generally, the strongest available human evidence is from prospective epidemiological studies.

[xxv] There is a study on effects of sodium benzoate on glucose homeostasis and metabolic profiles in humans (Lennerz B et al, Mol Genet Metab 2015;114(1):73-79), but it did not measure effects on weight or adiposity.

[xxvi] Sorbitan monooleate (also called Span 80) has some in vitro evidence of obesogenicity (it binds to and activates RXRα). Source: Bowers, 2016.

[xxvii] Sodium sulfite has some in vitro evidence of obesogenicity (it decreases leptin release of fat cells stimulated with lipopolysaccharide, which is produced within the gut and is thought to play a role in inflammation associated with obesity). Source: Ciardi C 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(6):826-33.

In considering future directions for research on obesogens, the 2017 ES scientific statement on obesity pathogenesis recommended, "Meta-analyses of prospective epidemiological data may ultimately help to identify those combinations and doses of EDC exposures that are most often associated with increased adiposity and that are observed consistently across species."[284]

Three such meta-analyses have now been published for chemicals found in food. The first was the 2017 meta-analysis on DDE/DDT by Cano-Sancho discussed above, which evaluated prospective epidemiological studies, in addition to using EI.[285]

The second was a 2018 meta-analysis by Liu and colleagues that evaluated ten prospective studies of 6076 participants. It concluded that exposure to PFOA in early life (in utero or first year postnatal) is associated with an increased risk for childhood adiposity (OR for childhood overweight is 1.25 ((95% CI: 1.04, 1.50; I^2 = 40.5%).[286]

The third was a 2022 meta-analysis that separately evaluated 33 studies assessing prenatal exposure to organochlorines DDE, DDT, polychlorinated biphenyls (PCBs), and hexachlorobenzene (HCB), 21 studies assessing prenatal exposure to PFAS, and five studies assessing polybrominated diphenyl ethers (PBDEs). Meta-analysis results showed that prenatal exposure to DDE and HCB was associated with increased BMI in childhood (2-9 years), drawing on studies from 17 and 7 countries, respectively. For PCBs, PFAS, and PBDEs, there was no conclusive evidence that prenatal exposure was associated with the development of obesity in childhood. (For example, for PCBs, there was a positive association with BMI, but the confidence interval included the null; for some PFAS and PBDEs, a small inverse association was noted with BMI).[287]

These are not the only meta-analyses examining the relationship between chemicals and obesity or other metabolic disruption, but to the best of our knowledge, they are the only ones for chemicals added to food limited to prospective epidemiological studies, as recommended by the ES statement, and examining obesity, overweight, or weight gain. For example, there are meta-analyses of epidemiological data on chemicals in food that are not limited to prospective studies, for example on phthalates,[288] chlordanes,[289] and many other chemicals,[290] and a pooled analysis (from three prospective cohorts) on prenatal phthalate exposures and body mass index among 4- to 7-year old children.[291] And, there are meta-analyses of obesogens that are not found in food, for example, of antibiotics,[292] other drugs,[293,294] air pollutants,[295,296] and secondhand smoke.[297] (Earlier we discussed recent meta-analyses on maternal smoking and childhood overweight/obesity.) Also, meta-analyses have been conducted on the effect of chemicals on low birth weight, which in turn appears to be related to obesity, as discussed previously using PFAS as an example. To cite another example, a meta-analysis on exposure to acrylamide during pregnancy examined effects on birth weight, finding that birth weight was significantly lower in the high gestational acrylamide exposure group compared to the low exposure group, and it included a pooled analysis from one study that suggested that children in the high gestational exposure group had a higher risk of developing overweight/obesity in the future.[298] Finally, there are also other meta-analyses of animal studies evaluating chemicals added to food and obesity, such as for phthalates[299] and BPA.

In the future (see Recommendations section), RCTs should be considered for direct additives and substances considered generally recognized as safe (GRAS) that may be obesogenic. A full SR/EI approach should be utilized where there is sufficient evidence, such as for PFOA, BPA, and DEHP.

Identifying New Obesogens

The obesogen field has primarily focused on a relatively short list of potential metabolic disruptors, especially, bisphenols, PFAS, phthalates, various POPs (e.g., PCBs, DDT/DDE), and TBT. Work is underway to develop sophisticated screening methods to rapidly identify other chemicals that might have the mechanistic properties of metabolic disruptors, including PPARγ activation. However, much progress is needed to improve the accuracy of these methods.

In 2016, Janesick and colleagues explored the potential of ToxCast™ to identify obesogenic chemicals.[301] ToxCast™, short for Toxicity Forecaster, is a program the EPA developed in 2007 to prioritize the thousands of chemicals of interest to EPA. ToxCast is part of Tox21, a collaboration among EPA, NIH, and FDA to develop better toxicity assessment methods to quickly and efficiently test chemicals for their potential to disrupt biological processes that may cause harm.[302] ToxCast utilizes a robotic high-throughput screening (HTP), where chemicals are quickly screened for potential toxic effects using assays that indicate whether a chemical may act on a certain biological pathway. Janesick and colleagues identified 21 chemicals as predicted PPARγ activators using ToxCast™ and then tested them to confirm these results using traditional lab methods for PPARγ activation. They found that 5 out of the 21 (24%) substances were confirmed as

PPARγ activators in lab tests. They also developed a tool called a toxicological priority index (ToxPi) that was expected to predict the ability of chemicals to promote adipogenesis in cell culture models. The ToxPi used 16 ToxCast assays and targeted PPARγ and RXRα (chosen for their role in regulating fat cell development). They found that 7 of the 17 chemicals predicted by the tool actually promoted adipogenesis. Two chemicals of 7 predicted not to promote adipogenesis actually did promote adipogenesis. The authors concluded that ToxCast™ PPARγ and RXRα assays do not correlate well with lab measurements of PPARγ and RXRα activity.

Foley and colleagues performed a similar experiment in 2017 to assess 49 chemicals identified as possible PPARγ activators.[303] Comprehensive in vitro lab testing aimed at evaluating the ability of the chemicals to interfere with seven different key events in PPARγ-dependent adipogenesis revealed that only 14 of the 49 (29%) had "moderate-to-strong" activity for human adipogenesis, based on the frequency of "hits," efficacy, and potency for the different adipogenesis endpoints assessed.

Auerbach and colleagues analyzed varying concentrations of 1,860 chemicals in the ToxCast library that interact with gene-based ToxCast assay targets determined by experts that participated in a 2011 NTP workshop on metabolic disruptors as relevant to several biological processes related to the development of diabetes and obesity (e.g., fat cell differentiation, feeding behavior, insulin sensitivity, pancreatic islet and β cell function).[304] Based on their ability to interact with these targets, the authors ranked the top 30 substances. They also analyzed a subset of 1,061 chemicals that had the most complete testing coverage to see which chemicals had a similar profile to metabolic-disrupting chemicals identified in the 2011 NTP workshop or documented in clinical observations of drug effects. Some of the substances ranked in the top 30 included substances previously linked to metabolic disruption (e.g., acrylamide, several phthalates, PFOS), but also included were many more substances not previously identified as metabolic disruptors, including the synthetic color additives FD&C Red 40 and FD&C Yellow 6, and the flavorings ethyl butyrate, methyl salicylate, and methyl eugenol.[xxviii] Similarly, substances not previously identified as possibly disrupting metabolism, including the synthetic color additive FD&C Yellow 5, as well as FD&C Yellow 6, were identified in the analysis identifying the top 10 chemicals similar to metabolic disrupting chemicals identified in the 2011 NTP workshop or documented in clinical observations of drug effects. The similarity analysis also identified benzoic acid, which has not been well studied for metabolic disruption, sodium saccharin hydrate (a form of the artificial sweetener), and sucrose. The authors concluded that the research community has focused too narrowly on a relatively short list of potential metabolic disrupters when many others may exist.

Substances Added to Food That Preliminary Screening Indicates May Disrupt Metabolism and Require Further Testing

Ethyl Butyrate (Flavoring)

Methyl Salicylate (Flavoring)

Red 40 (color additive)

Yellow 5 (color additive)

Yellow 6 (color additive)

Source: Source: Auerbach 2016

In 2021, Kassotis and colleagues evaluated the reproducibility of an established in vitro assay called the 3T3-L1 murine preadipocyte model system across 10 laboratories. Although there was poor reproducibility across laboratories for the metabolic-disrupting chemicals tested, the ability of the different laboratories to accurately differentiate chemicals that exhibited obesogenic activity from those that did not was more consistent.[305]

In addition, several EU projects, including the EDCMET, OBERON, and GOLIATH projects, are underway to develop batteries of tests to identify environmental EDCs that can disrupt metabolism. The EDCMET ("Metabolic effects of Endocrine Disrupting Chemicals: novel testing METhods and adverse outcome pathway") project brings toxicologists, experimental biologists, and environmental epidemiologists together to develop predictive models that can identify mechanisms and pathways behind the observed associations between endocrine disruptors and metabolic effects and generate validated test methods for detecting metabolic effects of EDCs.[306] The OBERON project will employ an integrated approach to develop, improve, and validate a battery of tests to better detect metabolic disorders related to EDCs.[307] The project will combine in vivo, in vitro, in silico, high throughput technologies, and epidemiological data to develop a conceptual framework for testing and assessing both single endocrine disruptors as

[xxviii] FDA banned the synthetic flavoring methyl eugenol in 2018 in response to a petition from CSPI and other groups that it is a carcinogen.

well as mixtures. The GOLIATH project aims to generate the first integrated approach to testing and assessing metabolic disrupting chemicals and is linked with initiatives of the Organization for Economic Development (OECD) for test method validation.[308]

A recent review discussed the limitations, strengths, and new directions for obesogen assays, including in vitro, in vivo (not only rodents but fruit flies, roundworms, and fish), and in silico assays, and emphasized that no single approach or assay will be sufficient, and instead recommended integrated approaches to both testing and assessment.[309]

Recommendations

In July 2021, CSPI convened with experts in the field to discuss and build consensus on the current understanding of metabolic disrupting chemicals, and to discuss recommendations for regulators, researchers, and others. Out of that meeting, and drawing from our own evaluation, we developed A Coordinated Research and Action Agenda to Build the Evidence Base Related to Metabolic Disrupting Chemicals. We hope this agenda will stimulate new and focused research to better characterize metabolic disrupters. Below we further elaborate and expand on that agenda.

RECOMMENDATIONS FOR AUTHORITATIVE BODIES

1. FDA Should Consider Metabolic Disruption When Assessing the Safety of Food Additives

Despite the alarming trends in obesity prevalence and the mounting scientific evidence on metabolic disruptors, FDA currently lacks a framework for identifying and evaluating possible metabolic disruptors when reviewing food and color additive petitions, GRAS notifications, Food Contact Substance notifications, Threshold of Regulation exemption requests, or otherwise considering the safety of substances in or intended for the food supply.

FDA should, in collaboration with NIEHS and other agencies as appropriate, develop revised recommended screening and testing protocols for substances that are the subject of food or color additive petitions, GRAS notifications, or food contact substance notifications. Furthermore, for substances already on the market, FDA should prioritize substances for re-evaluation, taking information on metabolic disruption into account.

The agency's guidance for toxicological testing, the Redbook,[310] was most recently only partially updated in 2007 and do not reflect current scientific understanding of metabolic disruption and more generally, endocrine disruption. As we stated in our comments to the FDA in May 2015 regarding its proposed update to the Redbook, a substantive update is sorely needed and long overdue. Unfortunately, progress on an update seems to have stalled.

Several protocols typical to traditional toxicological testing, such as those outlined in the Redbook, overlook many important metabolic disrupting (and other endocrine disrupting) effects, as was discussed at the NASEM workshop in 2015. For example, chronic toxicological testing typically uses high doses, however, effects at low doses are frequently observed for endocrine disruptors, which may be different than effects at high doses. A wider range of doses should be employed if those studies are conducted. Also, according to FDA's Redbook guidelines for developmental toxicity studies, the test should be terminated one day prior to the expected day of parturition (e.g., day 20 or 21 for rats). Because obesogenic effects sometimes do not manifest until later (e.g., after puberty), as discussed previously and highlighted by Dr. Linda Birnbaum, this should be changed to be 1 year or later. Additionally, as discussed previously, traditional toxicity testing fails to use appropriate endpoints (e.g., to capture effects on body composition and fat distribution, insulin resistance), and these should be incorporated into FDA's Redbook guidelines. FDA's assessment procedures also do not adequately consider cumulative exposures and effects, nor sensitive subpopulations, and FDA should develop clear protocols to do so.

2. FDA or Congress Should Request NASEM To Develop Recommendations for FDA on Developing and Incorporating Metabolic Disruption Information Into its Assessments

Since as long ago as 1983 when it published Risk Assessment in the Federal Government: Managing the Process, the National Academies has provided advice to federal agencies on improving its assessments of hazard, exposure, and risk.[311] EPA has frequently taken advantage of this advice, but FDA, much less so. For example, EPA requested that NASEM develop a strategy to evaluate the evidence for low-dose

effects, which ultimately led to the NASEM publication in 2017, *Application of Systematic Review Methods in an Overall Strategy for Evaluating Low-Dose Toxicity from Endocrine Active Chemicals*.[312] NASEM last hosted a workshop exploring the association between environmental chemical exposure and weight gain in 2015. Other important convenings, such as the Uppsala and Parma workshops (detailed in the "Authorities Recognize the Potential Threat of Obesogens" section of this report) also occurred in 2015. Given the new evidence since then, FDA or Congress should request that NASEM, in collaboration with NIEHS and/or the ES, develop recommendations to FDA about how to incorporate information on metabolic disruption into its assessments and guidance to companies that seek to introduce substances into the food supply.

3. The National Institutes of Health (NIH) Should Fund Additional Research on Metabolic Disrupting Chemicals

NIH, primarily through the NIH Obesity Research Task Force, NIEHS (through its Obesity and Diabetes program), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute of Child Health and Human Development (NICHD), and the NIH ECHO (Environmental Influences on Child Health Outcomes) program should encourage collaborations among experts from different fields and fund additional research on metabolic disrupting chemicals that will reduce uncertainties and data gaps on the role that dietary and environmental chemicals play in obesity, and permit initial estimates of the attributable fraction of metabolic disrupting chemicals to overweight, obesity, and other metabolic outcomes.

In particular, short-term randomized controlled trials (RCTs), in which participants are randomized to consume specific diets with varying acceptable doses of substances permitted in food in a multiple-arm crossover trial with a washout period, should be funded. Candidate chemicals could include the nine substances that have passed the initial confidence ratings, and are currently considered safe, such as propionate or butylparaben, rather than PFOA or DEHP, for which there is growing evidence for adverse effects.

Funding prospective studies using existing ECHO pediatric cohorts and others to examine metabolic outcomes associated with exposure to possible metabolic disrupting chemicals during critical windows of susceptibility is also needed.

As additional data are generated, integrated assessments of human, animal, and mechanistic evidence that follow the NTP OHAT Handbook should be funded to provide clarification on several suspected obesogens, such as PFOA, BPA, and DEHP and other phthalates. The results of these assessments would indicate where more research is needed and allow decision makers to manage risk effectively.

4. NIEHS Should Host a Workshop on Metabolic Disrupting Chemicals

NIEHS should host a workshop on metabolic disrupting chemicals to examine the progress made since its 2011 workshop and the 2015 IOM workshop, identify recommended screening and testing protocols for metabolic disruptors, determine reliable biomarkers of exposure for possible obesogens, and identify future research needs. The workshop should be informed by ongoing efforts to develop testing systems, such as the GOLIATH, EDCMET, and OBERON projects. Following the workshop, NIEHS could issue a request for application (RFA) to invite grant applications.

RECOMMENDATIONS FOR FUTURE RESEARCH

1. Improve Human and Toxicological Evidence

As noted above, RCTs will strengthen the evidence base for metabolic disruptors, and estimates of the attributable fraction of metabolic disrupting chemicals to overweight, obesity, and other metabolic outcomes are needed. Additional RCTs and other studies will be useful to build on and better understand the reasons for the findings from Kevin Hall's 2019 RCT, which found that the consumption of ultra-processed food resulted in increased caloric intake and a 2-pound bodyweight increase in participants within two weeks, compared to unprocessed food, despite being matched for nutrient density and macronutrient ratios, consumed ad libitum, and no differences in pleasantness or familiarity of the appearance reported.

Investigators interested in exploring associations between obesogen exposure and obesity outcomes should keep several considerations in mind. In order to accurately assess prenatal exposure and depending on the body's handling of the substance under investigation, data collection for prospective cohort studies should consider including parental blood, serum, or urine collection at multiple intervals

during pregnancy to capture exposure throughout pregnancy. Of course, variables such as parental consumption of caffeine, smoking status, diet, BMI, and diabetes status should always be recorded and assessed for confounding in data analysis. Diet, in particular, is frequently an important confounder as high-fat, heavily processed diets can both increase exposure to possible obesogens and be high in calories. Investigators should utilize multiple endpoints in addition to body weight and BMI--ideally body fat percentage, but additionally waist circumference and waist-to-hip ratio, which are relatively easy and low-cost methods to evaluate fat accumulation—since some obesogens can divert stem cells away from bone cell development and toward becoming fat cells with no or minimal increases in total body mass but increases in body fat mass.

Transgenerational effects have been reported for TBT, BPA, DEHP, dibutyl phthalate, methoxychlor, jet fuel JP-8, and DDT in animal studies, according to a 2019 review.[313] These studies should be carefully assessed, and results confirmed by additional studies, taking into account findings from the NTP OHAT scoping review, *State of the Science Evaluation for Transgenerational Inheritance of Health Effects*.[314]

Preliminary screening suggests that the widely used synthetic color additives Red 40, Yellow 5, and Yellow 6, the preservative benzoic acid, and the flavorings ethyl butyrate and methyl salicylate, may have metabolic disrupting potential and these should undergo further testing to determine if they are metabolic disruptors.

2. Improve Screening Tools

Additional work is needed to develop and validate screening tools and integrated screening batteries that can help identify new metabolic disrupters. Tox 21 tools which focus on receptor binding can be used.

Another approach to screening is afforded by the DOHaD concept, which predicts that chemicals that adversely affect growth in utero may result in obesity later in life, as discussed previously. Such chemicals should be identified and prioritized for additional testing.

3. Incorporating Evidence Integration into Obesogen Assessment

Where there is sufficient evidence, researchers should undertake integrated systematic reviews and meta-analyses of the human, animal, and mechanistic evidence, following NTP's OHAT guidelines, to better clarify the level of confidence in the evidence on specific chemicals and metabolic disruption, and highlight data gaps and risk management opportunities. PFOA, BPA, and DEHP and other phthalates would appear to be good candidates for such integrated assessments.

Appendix I: Authoritative Conclusions Related to Obesogens

U.S. Agencies and Task Forces	
Environmental Protection Agency (EPA)	Co-hosted 2011 workshop (see below under NTP). EPA has numerous activities related to endocrine disruption,[315] including an Endocrine Disruptor Screening Program that screens chemicals for their potential effect on estrogen, androgen, and thyroid hormone systems.[316] It also funds research, for example at the University of Michigan to explore "Perinatal exposures, epigenetics, child obesity, and sexual maturation." The research focuses on lead, BPA, and phthalates, and is measuring birth outcomes, child weight gain/status, body composition, activity patterns, hormonal levels, and sexual maturation.[317]
National Institutes of Health (NIH)	In 2018-2019, the Obesity Research Task Force confirmed that a Strategic Plan released in 2011 would continue to guide obesity research. This "Strategic Plan for NIH Obesity Research"[318] highlighted important research opportunities, including: • "Increase the understanding of the role of common drugs/medications ... on obesity development. • "Identify how environmental toxicants and other chemical exposures affect the development of obesity in children and adults • Explore interactions between genetic and en-vironmental factors related to weight stability, loss, or gain across the lifespan. These interac-tions, in which environment is broadly defined to include the individual, built, social, economic, policy, and natural environments, may help identify new and more personalized targets for prevention and treatment."
National Institutes of Environmental Health Sciences (NIEHS)	Features a webpage on obesity that includes an "Obesogens" section describing how obesogens are believed to work and sensitive exposure periods. Lists chemicals that may be obesogens and offers recommendations to minimize exposure.[319] Lists information on grants funded by NIEHS dedicated to exploring obesity, the endocrine system, and the links between environmental exposure and metabolic disruption.[320-323] Many grants have been completed and are discussed in this report, while others remain in progress. NIEHS also sponsored a workshop in 2015, described in more detail below.
National Toxicology Program (NTP)	Hosted a workshop in 2011 in tandem with NIEHS, EPA, and the FDA National Center for Toxicological Research on the existing literature linking EDC exposure to obesity, which concluded that the existing literature "supports the plausibility of the obesogen hypothesis, as well as linkages between type 2 diabetes and exposures to certain chemical classes." The workshop also made research recommendations.[324]
White House Task Force on Childhood Obesity	A 2010 Report to the President recommended that federal and state agencies conducting health research prioritize research into the effects of potentially obesogenic chemicals.[325]

Professional Organizations	
American Academy of Pediatrics (AAP)	In its Policy Statement and accompanying Technical Report, both titled, "Food Additives and Child Health," the obesogenic activity of bisphenols, phthalates, and PFCs is summarized. AAP states that, "the potential for endocrine system disruption is of great concern, especially early in life," and identifies bisphenols and phthalates as chemicals, "of increasing concern," stating for example that doses of BPA that people are likely to encounter in daily life trigger the conversion of cells to adipocytes, and affect glucose transport in adipocytes; and that phthalates are metabolized to chemicals that influence the expression of master regulators of lipid and carbohydrate metabolism and produce other metabolic effects. It further states that, "Given that obesity is well recognized to be more prevalent among low-income and minority children in the United States, disproportionate exposures to obesogenic chemicals such as BPA partially explain sociodemographic disparities in health."[326]

Endocrine Society (ES)	Issued a scientific statement in 2017 on obesity pathogenesis, recognizing the growing body of evidence demonstrating obesity to be a disorder of the energy homeostasis system and noting chemical exposures may present an obesity risk.[327] Additionally, issued two scientific statements on endocrine disrupting chemicals in 2009 and 2015.[328,329] Conclusions from the latter report state that, "there is sufficient evidence to conclude that some EDCs at as obesogens and others act as diabetogens." It also states, "both cellular and animal models demonstrate a role for EDCs in the etiology of [obesity and type 2 diabetes (T2D)]," and that, "Epidemiological studies in humans also point to an association between EDC exposure and obesity and/or T2D; however, because many epidemiological studies are cross-sectional, with diet as an important confounding factor in humans, it is not yet possible to infer causality." In 2019, the ES EDC Advisory Group gathered a Task Force to develop resources for clinicians and patients, and the Task Force led the creation of a series of short videos "which follow from the science presented in the Endocrine Society's scientific statements on EDCs," including one on "Environmental Endocrine Disruptors & Metabolic Disorders" by Robert Sargis, MD, PhD, where he states, "There is indeed robust causal evidence that environmental toxicants are linked to obesity, fatty liver [disease], and diabetes."[330]
Pediatric Endocrine Society (PES)	PES, joined with the European Society for Paediatric Endocrinology, released a "call to action" statement in 2011 regarding the exposure of fetuses and children to EDCs, mentioning unexplained trends in endocrine diseases including some cases of childhood obesity as well as type 1 diabetes as spurring debate about EDCs.[331]

International Agencies and Meetings	
European Food Safety Authority (EFSA)	EFSA has not issued a statement on obesogens per se. Mentioned obesogenic potential of phthalates in a 2019 risk assessment update on four phthalates used in food contact materials,[332] but did not draw firm conclusions, although noted that effects on the metabolic system could be more sensitive endpoints compared to reproductive toxicity, which could lead to the risks being underestimated. A 2018 Scientific Opinion on PFOA and PFOS concluded that there was insufficient support for causal associations between PFOS or PFOA and obesity, diabetes, and metabolic syndrome.[333] EFSA has published guidance on identifying endocrine disruptors.[334]
Parma Consensus	A group of experts gathered in 2015 to "address concerns about the potential relationship between environmental metabolic disrupting chemicals, obesity, and related metabolic disorders." The resulting consensus statement made many important conclusions, including that participants were "confident" that "susceptibility to metabolic disorders is, at least in part, 'programmed' in utero and early postnatal life by exposures to environmental factors including stress, drugs, nutrition, and environmental chemicals," and predicted that the importance of metabolic disruptors in obesity, diabetes, and metabolic syndrome was underestimated because studies focused on one or a small subset of chemicals at a time, during limited windows of sensitivity, in single tissues, and often only for endpoints related to a single disease outcome per study.[335]
Uppsala Consensus	The 2nd International Workshop on Obesity and Environmental Contaminants was convened in 2015 to discuss updates in the field. A report following the workshop indicates a strong consensus among attendees supporting the obesogen hypothesis. Attendees concluded that, "the findings from numerous animal and epidemiological studies are consistent with the hypothesis that environmental contaminants could contribute to the global obesity epidemic." Potential actions to reduce global exposure were considered.[336]
United Nations Environment Program (UNEP) and World Health Organization (WHO)	Released a report in 2012 describing the state of the science on endocrine disruptors. This report concluded that EDCs pose a global threat due to their capacity to interfere with tissue and organ development and function, which may therefore alter susceptibility to different diseases through life. Acknowledged that EDCs interfere with metabolism and fat storage, and that animal data show that embryonic exposure to known or potential EDCs leads to possible weight gain in adulthood. Stated that limited epidemiological data exist to support the notion that EDC exposure during pregnancy can affect weight gain in infants and children.[337] Builds on a report published in 2002 on the effects of endocrine disruptors that recognized the essential role endocrine systems play in metabolism but that did not acknowledge obesity as an endpoint. It did acknowledge the interaction between endocrine disrupting chemicals and timing of puberty, which may be associated with obesity.[338,339]

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