



Food Additives and Child Health

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Increasing scientific evidence suggests potential adverse effects on children's health from synthetic chemicals used as food additives, both those deliberately added to food during processing (direct) and those used in materials that may contaminate food as part of packaging or manufacturing (indirect). Concern regarding food additives has increased in the past 2 decades in part because of studies that increasingly document endocrine disruption and other adverse health effects. In some cases, exposure to these chemicals is disproportionate among minority and low-income populations. This report focuses on those food additives with the strongest scientific evidence for concern. Further research is needed to study effects of exposure over various points in the life course, and toxicity testing must be advanced to be able to better identify health concerns prior to widespread population exposure. The accompanying policy statement describes approaches policy makers and pediatricians can take to prevent the disease and disability that are increasingly being identified in relation to chemicals used as food additives, among other uses.

More than 10 000 chemicals are allowed to be added to food in the United States, either directly or indirectly, under the 1958 Food Additives Amendment to the 1938 Federal Food Drug and Cosmetic Act (Public Law 85-929). An estimated 1000 chemicals are used under a "Generally Recognized as Safe" (GRAS) designation without US Food and Drug Administration (FDA) approval or notification.¹ Many chemical uses have been designated as GRAS by company employees or hired consultants.² Because of the overuse of the GRAS process and other key failings within the food safety system, there are substantial gaps in data about potential health effects of food additives. Of the 3941 food additives listed on the "Everything Added to Food in the United States" Web site, reproductive toxicology data were available for only 263 (6.7%), and developmental toxicology data were available for only 2.³

Accumulating evidence from nonhuman laboratory and human epidemiologic studies suggests that colorings, flavorings, chemicals deliberately added to food during processing (direct food additives), and substances in food contact materials (including adhesives, dyes,

abstract

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The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

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TABLE 1 Summary of Food-Related Uses and Health Concerns for the Compounds Discussed in This Report

Category	Chemical	Food-Related Use	Selected Health Concerns
Indirect food additives	Bisphenols	Polycarbonate plastic containers	Endocrine disruption ^{11–18}
		Polymeric, epoxy resins in food and beverage cans	Obesogenic activity, ^{19–22} neurodevelopmental disruption ^{23–26}
	Phthalates	Clear plastic food wrap	Endocrine disruption ^{6,27–29}
		Plastic tubing, storage containers used in industrial food production	Obesogenic activity ^{30–32}
Perchlorate	Perfluoroalkyl chemicals (PFCs)	Multiple uses in food manufacturing equipment	Oxidative stress, ^{33,34} cardiotoxicity ^{35,36}
		Grease-proof paper and paperboard	Immunosuppression, ^{37,38} endocrine disruption, ^{39–41} obesogenic activity, ⁴² decreased birth wt ⁴³
Direct food additives	Nitrates and nitrites	Food packaging	Thyroid hormone disruption ^{44–46}
		Direct additive as preservative and color enhancer, especially to meats	Carcinogenicity, ^{10,47,48} thyroid hormone disruption ^{49,50}

coatings, paper, paperboard, plastic, and other polymers) that may come into contact with food as part of packaging or processing equipment but are not intended to be added directly to food (indirect food additives) may contribute to disease and disability in the population (Table 1). Children may be particularly susceptible to the effects of these compounds because they have higher relative exposures compared with adults (because of greater dietary intake per pound), their metabolic (ie, detoxification) systems are still developing, and key organ systems are undergoing substantial changes and maturations that are vulnerable to disruptions.⁴ Chemicals of increasing concern include bisphenols, which are used in the lining of metal cans to prevent corrosion⁵; phthalates, which are esters of diphtalic acid that are used in adhesives and plasticizers during the manufacturing process⁶; nonpersistent pesticides, which have been addressed in a previous American Academy of Pediatrics (AAP) policy statement and thus are not discussed in this report⁷; perfluoroalkyl chemicals (PFCs), which are used in grease-proof paper and paperboard food packaging⁸; and perchlorate, an antistatic agent used for packaging in contact with dry foods with surfaces that do not contain free fat or oil.⁹ Nitrates and nitrites, which have been the subject of previous international reviews,¹⁰ and artificial food coloring also are addressed in this report.

This technical report will not address other contaminants that inadvertently enter the food and water supply (such as aflatoxins), polychlorinated biphenyls, dioxins, metals (including mercury), persistent pesticide residues (such as DDT), and vomitoxin. This report will not focus on genetically modified foods because they involve a separate set of regulatory and biomedical issues. Caffeine or other stimulants intentionally added to food products will not be covered.

The AAP is particularly concerned about food contact substances associated with the disruption of the endocrine system in early life, when the developmental programming of organ systems is susceptible to permanent and lifelong disruption. The international medical and scientific communities have called attention to these issues in several recent landmark reports, including a scientific statement from the Endocrine Society in 2009,⁵¹ which was updated in 2015 to account for rapidly accumulating evidence¹¹; a joint report from the World Health Organization and United Nations Environment Programme in 2013⁵²; and a statement from the International Federation of Gynaecology and Obstetrics in 2015.⁵³ Subsequent sections of this technical report focus on individual categories of chemicals and provide evidence on potential effects on children's health to support the accompanying AAP policy statement.⁵⁴

INDIRECT FOOD ADDITIVES

Bisphenols

The use of bisphenols as food additives accelerated in the 1960s, when bisphenol A (BPA) was identified as a useful ingredient in the manufacture of polycarbonate plastics and polymeric metal can coatings.⁵⁵ BPA has recently been banned from infant bottles,⁵⁶ and plastic beverage containers are increasingly designated as BPA free. However, BPA and related compounds are still used in polymeric resin coatings to prevent metal corrosion in food and beverage containers.⁵⁷

BPA has been the focus of significant research and attention. It can bind to the estrogen receptor and cause tissues to respond as if estradiol is present; thus, it is classified as an "endocrine disruptor."¹² Nonhuman laboratory studies and human epidemiologic studies suggest links between BPA exposure and numerous endocrine-related end points, including reduced fertility,^{13,14} altered timing of puberty,¹⁵ changes in mammary gland development,^{16,58} and development of neoplasias.⁵⁹ Environmentally relevant doses of BPA trigger the conversion of cells to adipocytes,^{19,60} disrupt pancreatic β -cell function in vivo,⁶¹ and affect glucose transportation in adipocytes.^{19–21} BPA exposure in utero has been associated with adverse neurodevelopmental outcomes,^{23–25} and cross-sectional studies have associated BPA with decrements in fetal growth,⁶² childhood obesity,^{63,64}

and low-grade albuminuria,⁶⁵ although longitudinal studies of prenatal exposure have yielded less consistent relationships with postnatal body mass.^{66–69}

A comprehensive, cross-sectional study of dust, indoor and outdoor air, and solid and liquid food in preschool-aged children suggested that dietary sources constitute 99% of BPA exposure.⁷⁰ Dental sealants and thermal copy paper are also sources.^{71,72} Higher urinary concentrations of BPA have been documented in African American individuals,⁶³ and BPA concentrations have been inversely associated with family income.⁷³ Given that obesity is well documented to be more prevalent among low-income and minority children,⁷⁴ disproportionate exposure to endocrine-disrupting chemicals, such as BPA, may partially explain sociodemographic disparities in health.⁷⁵

The FDA recently banned the use of BPA in infant bottles and sippy cups,⁵ and numerous companies are voluntarily removing BPA from their products because of consumer pressure. Yet, in many cases, it has been replaced with closely related alternatives, such as bisphenol S. These emerging alternatives have been identified in paper products and human urine.^{76,77} The few studies focused on evaluating bisphenol S have identified similar genotoxicity and estrogenicity to BPA^{78–82} and greater resistance to environmental degradation than BPA.^{83,84} Efforts to remove BPA from plastics and metal cans will only provide health and economic benefits if it is replaced with a safe alternative.⁵⁵

Phthalates

Phthalate esters have a diverse array of uses in consumer products, and they can be classified into 2 categories: low-molecular weight phthalates are frequently added to shampoos, cosmetics, lotions, and other personal care products to preserve scent,⁶

whereas high-molecular weight phthalates are used to produce vinyl plastics for diverse settings ranging from flooring, clear food wrap, and flexible plastic tubing commonly used in food manufacturing.⁸⁵ Within the high-molecular weight category, di-2-ethylhexylphthalate (DEHP) is of particular interest because industrial processes to produce food frequently use plastic products containing DEHP.⁸⁶ Racial and/or ethnic differences in phthalate exposures are well documented.^{87,88}

A robust literature, including numerous animal and human studies, shows that DEHP, benzyl butyl phthalate, and dibutyl phthalate are antiandrogenic and adversely affect male fetal genital development. These chemicals exert direct testicular toxicity, thereby reducing circulating testosterone concentrations within the body and increasing the risk of hypospadias and cryptorchidism at birth. These phthalates are also associated with changes in men's hormone concentrations and changes in sperm motility and quantity.^{6,27–29,89–91} Mono-(2-ethylhexyl)phthalate, a DEHP metabolite, also interacts with 3 peroxisome proliferator-activated receptors,³⁰ which play key roles in lipid and carbohydrate metabolism, providing biological plausibility for DEHP metabolites in contributing to childhood obesity and insulin resistance.⁹² Epidemiologic studies have also demonstrated an association between urinary phthalate metabolites and markers of oxidative stress.^{33,34} Laboratory studies have found that metabolites of phthalates are linked to oxidative stress.^{93,94} Oxidative stress appears to diminish the insulin-dependent stimulation of insulin-signaling elements and glucose transport activity⁹⁵ and modify the endothelial relaxant nitric oxide, promoting vasoconstriction, platelet adhesion, and the release of proinflammatory cytokines, such as interleukin-1.^{96,97} Therefore, if phthalates are proinflammatory and increase oxidative stress, these effects

could lead to changes to metabolic health outcomes. Emerging animal evidence also suggests that DEHP may produce arrhythmia,³⁵ change metabolic profiles, and produce dysfunction in cardiac myocytes.³⁶

Data from the National Health and Nutrition Examination Survey (NHANES) indicate that DEHP metabolites decreased by approximately 37% between 2001 and 2010.⁹⁸ These decreases are attributable to the replacement of DEHP with diisodecyl (DIDP) and diisononylphthalate (DINP), phthalates that have not been banned or restricted by regulatory agencies and are increasingly detected within the population. Urinary metabolites of DIDP and DINP were detected in 94% and 98% of the population, respectively, in the 2009–2010 NHANES.⁹⁸ DIDP and DINP have been widely identified as food contaminants,⁹⁹ and cross-sectional data from NHANES from 2009 to 2012 show positive associations of DIDP and DINP metabolite concentrations with insulin resistance and systolic blood pressure z scores in children and adolescents.^{31,32}

PFCs

PFCs are synthetic organic fluorinated compounds whose carbon-fluorine bonds impart high stability and thermal resistance. PFCs have wide utility in stain-resistant sprays for carpets and upholstery, fire-retarding foams, nonstick cooking surfaces, and grease-proofing of paper and paperboard used in food packaging.^{100,101} The 2003–2004 NHANES revealed that >98% of the US population has detectable concentrations of PFCs in their blood, including perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorohexane sulfonic acid (PFHxS), and perfluorononanoic acid (PFNA).¹⁰² Although exposure can occur through dermal contact and inhalation, consumption of contaminated food is a major route of exposure to PFOS and PFOA for most people.¹⁰⁰ Studies have

associated PFOA and PFOS exposure with adverse health outcomes, such as reduced immune response to vaccines,^{37,38} metabolic changes,⁴² and decreased birth weight.⁴³ There is also growing concern regarding the endocrine-disrupting potential of PFCs; studies have linked PFOA and PFOS to reduced fertility^{39,40} and thyroid alterations^{41,103–105} among other effects. These compounds are also extremely persistent and bioaccumulative, with half-lives between 2 and 9 years in the human body.¹⁰⁶

Because of health and environmental concerns, US production of PFOS was phased out in 2002, and PFOA was phased out in 2015.¹⁰⁷ However, these particular compounds are only 2 of more than a dozen members of the parent family. For example, closely related PFNA chiefly replaced PFOA; increasing PFNA concentrations were detected in the 2003–2004 NHANES and have remained stable thereafter.¹⁰²

In January 2016, the FDA banned the use of 3 classes of long-chain PFCs as indirect food additives.¹⁰⁸ Yet, structurally similar short-chain PFCs, such as PFHxS, may continue to be used. Median levels of PFHxS have been measured since NHANES 2003–2004 and have remained stable through NHANES 2009–2010.¹⁰⁹ A Swedish study of perfluoroalkyl acid trends between 1996 and 2010 confirmed increases in PFHxS concentrations (8.3% per year) but also noted increases of 11% per year in another short-chain PFC substitute for PFOS, perfluoroalkylbutane sulfonate (PFBS), which is increasingly found in food.¹¹⁰ Modest, infrequently (2%) detectable concentrations of PFBS were identified among the US population in NHANES 2011–2012. Although studies have not sufficiently evaluated the human health consequences of exposure to short-chain PFCs, the structural similarity to banned compounds suggests that they may also pose human health risks.^{111,112}

Perchlorate

Perchlorate most commonly enters the food supply through its presence as a contaminant in water or as a component of nitrate fertilizers.^{44,45,113} Exposed crops may retain elevated levels of the compound, as described in exploratory studies conducted by the FDA.¹¹⁴ In addition, perchlorate is an indirect food additive. Contamination in food occurs through its use as an antistatic agent for plastic packaging in contact with dry foods with surfaces that do not contain free fat or oil (such as sugar, flour, and starches) or through degradation from hypochlorite bleach, which is used as a cleaning solution in food manufacturing.¹¹⁵

Perchlorate is known to disrupt thyroid hormone production through interference with the sodium iodide symporter (NIS), which allows essential iodide uptake in the thyroid gland.^{44,116} The thyroid hormone is critical for early life brain development, among other processes, and alterations to normal hormone concentrations can have lifelong cognitive consequences.^{117–121} Exposure to perchlorate among pregnant women, especially those who are iodine deficient, raises particular concern given that the developing fetus is entirely reliant on the maternal thyroid hormone during the first trimester of pregnancy.^{117,122,123} Maternal hypothyroidism during pregnancy has been associated with cognitive deficits in children.^{120,121} Infants represent another important susceptible population, and the intake of powdered formula may result in high perchlorate exposure from associated packaging materials. Perchlorate and other food contaminants that alter thyroid hormone homeostasis, such as polybrominated diphenyl ethers,^{124–126} may be contributing to the increase in neonatal hypothyroidism and other thyroid system perturbations that have been documented in the United States.^{127,128} In addition, the thyroid hormone is critical for normal

growth processes, and recent evidence suggests that high exposure to multiple compounds that interfere with iodide uptake is associated with poor growth outcomes.⁴⁹

DIRECT FOOD ADDITIVES

Artificial Food Colors

Synthetic artificial food colors (AFCs) are added to foods and beverages for aesthetic reasons, and the resulting brightly colored products are appealing to young children in particular. In some cases, AFCs serve as substitutes for nutritious ingredients, such as in fruit juice drinks that contain little or no actual fruit. Nine AFCs currently are approved for use in the United States: Blue 1, Blue 2, Green 3, Yellow 5, Yellow 6, Red 3, Red 40, Citrus Red 2, and Orange B.¹²⁹ FDA data indicate that the use of AFCs increased more than fivefold between 1950 and 2012, from 12 to 68 mg per capita per day.¹³⁰

Over the last several decades, studies have raised concerns regarding the effect of AFCs on child behavior and their role in exacerbating attention-deficit/hyperactivity disorder symptoms.^{131–136} Elimination of AFCs from the diet may provide benefits to children with attention-deficit/hyperactivity disorder.^{131,137–139} Although the mechanisms of action have not yet been fully elucidated, at least one AFC, Blue 1, may cross the blood-brain barrier.^{135,140} Overall, however, further work is needed to better understand the implications of AFC exposure and resolve the uncertainties across the scientific evidence. The available literature should be interpreted with caution because of the absence of information about the ingredients for a number of reasons, including patent protection.

The FDA has set acceptable daily intakes for each of the AFCs.¹⁴¹ However, these standards, as well as original safety approval for the color additives, are based on animal studies that do not include neurologic or neurobehavioral end points.^{140,142}

Given that such effects have been observed in children, a thorough reassessment of AFCs is warranted to determine whether they meet the agency's benchmark of safety: "convincing evidence that establishes with reasonable certainty that no harm will result from the intended use of the color additive."¹⁴²

Nitrates and Nitrites

There has been longstanding concern regarding the use of nitrates and nitrites as preservatives in cured and processed meats, fish, and cheese.¹⁴³ In a 2004 statement, the American Medical Association emphasized that infants are particularly vulnerable to methemoglobinemia from nitrates and nitrites because of the chemical composition of their gastric tracts.¹⁴⁴ The American Medical Association statement also highlighted the risk of gastrointestinal or neural cancer from the ingestion of nitrates and nitrites, which (although not carcinogenic themselves) may react with secondary amines or amides to form carcinogenic N-nitroso compounds (NOCs) in the body. In 2006, the International Agency for Research on Cancer classified ingested nitrates and nitrites, in situations that would lead to endogenous nitrosation (production of NOCs), as "probable human carcinogens" (Group 2A).^{10,145} In 2015, the International Agency for Research on Cancer specifically classified processed meat (which includes meat that has been salted, cured, or otherwise altered to improve flavor and preservation) as "carcinogenic to humans" (Group 1).⁴⁷ Such processing can result in the increased formation of NOCs, and there is convincing evidence linking consumption of processed meats with colorectal cancer.⁴⁷ High maternal intake of nitrite-cured meats has also been linked to an increased risk of childhood brain tumors in the offspring, especially tumors of the astroglia.^{48,145} Current FDA regulations currently allow up to 500 ppm of sodium nitrate and 200 ppm of

sodium nitrite in final meat products. However, no nitrates or nitrites can be used in food produced specifically for infants or young children.¹⁴⁶ Nitrates, like perchlorate, can also disrupt thyroid function by blocking the NIS and thereby interfering with essential iodide uptake. Although its relative potency is much lower than that of other common NIS inhibitors, nitrate is still a significant concern, given that (1) combined exposures from food and water may account for a larger proportion of NIS inhibition than from perchlorate exposure and (2) NIS inhibitors may act together additively.^{50,147} Thyroid hormones are essential for many physiologic processes in the body, including normal growth, and recent evidence suggests that high exposure to NIS inhibitors, including nitrate, is associated with reductions in growth measures.⁴⁹ In addition, as noted above with regard to perchlorate, maternal thyroid disruption during pregnancy is of particular concern because the fetus is entirely reliant on the maternal thyroid hormone during the first trimester. Thyroid hormone is critical for neurologic developmental processes, and early life deficiencies can result in lifelong adverse effects on cognitive health.^{117–121}

In recent years, there has been increasing use of alternative sources of nitrate and nitrite preservatives, such as celery powder, in products labeled as "natural" and "organic."^{148,149} These products may contain nitrates and nitrites in concentrations that can be equivalent to or higher than those found in traditional products using sodium-based sources.^{149,150} Thus, consumers should be aware that with respect to nitrates and nitrites alone, natural and organic products may not provide advantages over conventional products.

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ABBREVIATIONS

AAP: American Academy of Pediatrics
AFC: artificial food color
BPA: bisphenol A
DEHP: di-2-ethylhexylphthalate
DIDP: diisodecyl
DINP: diisononylphthalate
FDA: Food and Drug Administration
GRAS: generally recognized as safe
NHANES: National Health and Nutrition Examination Survey
NIS: sodium iodide symporter
NOC: N-nitroso compound
PFC: perfluoroalkyl chemical
PFHxS: perfluorohexane sulfonic acid
PFNA: perfluorononanoic acid
PFOA: perfluorooctanoic acid
PFOS: perfluorooctane sulfonic acid

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REFERENCES

1. Neltner TG, Kulkarni NR, Alger HM, et al. Navigating the U.S. Food Additive Regulatory Program. *Compr Rev Food Sci Food Saf*. 2011;10(6):342–368
2. Neltner TG, Alger HM, O'Reilly JT, Krimsky S, Bero LA, Maffini MV. Conflicts of interest in approvals of additives to food determined to be generally recognized as safe: out of balance. *JAMA Intern Med*. 2013;173(22):2032–2036
3. Neltner TG, Alger HM, Leonard JE, Maffini MV. Data gaps in toxicity testing of chemicals allowed in food in the United States. *Reprod Toxicol*. 2013;42:85–94
4. Landrigan PJ, Goldman LR. Children's vulnerability to toxic chemicals: a challenge and opportunity to strengthen health and environmental policy. *Health Aff (Millwood)*. 2011;30(5):842–850
5. US Food and Drug Administration. Update on bisphenol A for use in food contact applications: January 2010. Available at: <https://www.fda.gov/downloads/NewsEvents/PublicHealthFocus/UCM197778.pdf>. Accessed May 18, 2017
6. Sathyanarayana S. Phthalates and children's health. *Curr Probl Pediatr Adolesc Health Care*. 2008;38(2):34–49
7. Forman J, Silverstein J; Committee on Nutrition; Council on Environmental Health; American Academy of Pediatrics. Organic foods: health and environmental advantages and disadvantages. *Pediatrics*. 2012;130(5): Available at: www.pediatrics.org/cgi/content/full/130/5/e1406
8. Buck RC, Franklin J, Berger U, et al. Perfluoroalkyl and polyfluoroalkyl substances in the environment: terminology, classification, and origins. *Integr Environ Assess Manag*. 2011;7(4):513–541
9. US Food and Drug Administration. Filing of food additive petition. *Fed Regist*. 2015;80(50):13508–13510
10. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. IARC monographs on the evaluation of carcinogenic risks to humans. Ingested nitrate and nitrite, and cyanobacterial peptide toxins. *IARC Monogr Eval Carcinog Risks Hum*. 2010;94:v–vii, 1–412
11. Gore AC, Chappell VA, Fenton SE, et al. Executive summary to EDC-2: the Endocrine Society's second scientific statement on endocrine-disrupting chemicals. *Endocr Rev*. 2015;36(6):593–602
12. Rubin BS. Bisphenol A: an endocrine disruptor with widespread exposure and multiple effects. *J Steroid Biochem Mol Biol*. 2011;127(1–2):27–34
13. Ehrlich S, Williams PL, Missmer SA, et al. Urinary bisphenol A concentrations and early reproductive health outcomes among women undergoing IVF. *Hum Reprod*. 2012;27(12):3583–3592
14. Cantonwine DE, Hauser R, Meeker JD. Bisphenol A and human reproductive health. *Expert Rev Obstet Gynecol*. 2013;8(4)
15. Howdeshell KL, Hotchkiss AK, Thayer KA, Vandenberg JG, vom Saal FS. Exposure to bisphenol A advances puberty. *Nature*. 1999;401(6755):763–764
16. Vandenberg LN, Maffini MV, Wadia PR, Sonnenschein C, Rubin BS, Soto AM. Exposure to environmentally relevant doses of the xenoestrogen bisphenol-A alters development of the fetal mouse mammary gland. *Endocrinology*. 2007;148(1):116–127
17. Welshons WV, Nagel SC, vom Saal FS. Large effects from small exposures. III. Endocrine mechanisms mediating effects of bisphenol A at levels of human exposure. *Endocrinology*. 2006;147(6 Suppl):S56–S69
18. Jukic AM, Calafat AM, McConaughy DR, et al. Urinary concentrations of phthalate metabolites and bisphenol A and associations with follicular-phase length, luteal-phase length, fecundability, and early pregnancy loss. *Environ Health Perspect*. 2016;124(3):321–328
19. Masuno H, Kidani T, Sekiya K, et al. Bisphenol A in combination with insulin can accelerate the conversion of 3T3-L1 fibroblasts to adipocytes. *J Lipid Res*. 2002;43(5):676–684
20. Hugo ER, Brandebourg TD, Woo JG, Loftus J, Alexander JW, Ben-Jonathan N. Bisphenol A at environmentally relevant doses inhibits adiponectin release from human adipose tissue explants and adipocytes. *Environ Health Perspect*. 2008;116(12):1642–1647
21. Sakurai K, Kawazuma M, Adachi T, et al. Bisphenol A affects glucose transport in mouse 3T3-F442A adipocytes. *Br J Pharmacol*. 2004;141(2):209–214
22. Vom Saal FS, Nagel SC, Coe BL, Angle BM, Taylor JA. The estrogenic endocrine disrupting chemical bisphenol A (BPA) and obesity. *Mol Cell Endocrinol*. 2012;354(1–2):74–84
23. Braun JM, Kalkbrenner AE, Calafat AM, et al. Impact of early-life bisphenol A exposure on behavior and executive function in children. *Pediatrics*. 2011;128(5):873–882
24. Sathyanarayana S, Braun JM, Yolton K, Liddy S, Lanphear BP. Case report: high prenatal bisphenol A exposure and infant neonatal neurobehavior. *Environ Health Perspect*. 2011;119(8):1170–1175
25. Ejaredar M, Lee Y, Roberts DJ, Sauve R, Dewey D. Bisphenol A exposure and children's behavior: A systematic review. *J Expo Sci Environ Epidemiol*. 2017;27(2):175–183
26. Mustieles V, Pérez-Lobato R, Olea N, Fernández MF. Bisphenol A: Human exposure and neurobehavior. *Neurotoxicology*. 2015;49:174–184
27. Gray LE Jr, Ostby J, Furr J, Price M, Veeramachaneni DN, Parks L. Perinatal

- exposure to the phthalates DEHP, BBP, and DINP, but not DEP, DMP, or DOTP, alters sexual differentiation of the male rat. *Toxicol Sci.* 2000;58(2):350–365
28. Meeker JD, Ferguson KK. Urinary phthalate metabolites are associated with decreased serum testosterone in men, women, and children from NHANES 2011-2012. *J Clin Endocrinol Metab.* 2014;99(11):4346–4352
 29. Swan SH, Main KM, Liu F, et al; Study for Future Families Research Team. Decrease in anogenital distance among male infants with prenatal phthalate exposure. *Environ Health Perspect.* 2005;113(8):1056–1061
 30. Desvergne B, Feige JN, Casals-Casas C. PPAR-mediated activity of phthalates: a link to the obesity epidemic? *Mol Cell Endocrinol.* 2009;304(1–2):43–48
 31. Trasande L, Attina TM. Association of exposure to di-2-ethylhexylphthalate replacements with increased blood pressure in children and adolescents. *Hypertension.* 2015;66(2):301–308
 32. Attina TM, Trasande L. Association of exposure to di-2-ethylhexylphthalate replacements with increased insulin resistance in adolescents from NHANES 2009-2012. *J Clin Endocrinol Metab.* 2015;100(7):2640–2650
 33. Ferguson KK, Loch-Caruso R, Meeker JD. Urinary phthalate metabolites in relation to biomarkers of inflammation and oxidative stress: NHANES 1999-2006. *Environ Res.* 2011;111(5):718–726
 34. Ferguson KK, McElrath TF, Chen YH, Mukherjee B, Meeker JD. Urinary phthalate metabolites and biomarkers of oxidative stress in pregnant women: a repeated measures analysis. *Environ Health Perspect.* 2015;123(3):210–216
 35. Posnack NG, Lee NH, Brown R, Sarvazyan N. Gene expression profiling of DEHP-treated cardiomyocytes reveals potential causes of phthalate arrhythmogenicity. *Toxicology.* 2011;279(1–3):54–64
 36. Posnack NG, Swift LM, Kay MW, Lee NH, Sarvazyan N. Phthalate exposure changes the metabolic profile of cardiac muscle cells. *Environ Health Perspect.* 2012;120(9):1243–1251
 37. Grandjean P, Andersen EW, Budtz-Jørgensen E, et al. Serum vaccine antibody concentrations in children exposed to perfluorinated compounds. *JAMA.* 2012;307(4):391–397
 38. Granum B, Haug LS, Namork E, et al. Pre-natal exposure to perfluoroalkyl substances may be associated with altered vaccine antibody levels and immune-related health outcomes in early childhood. *J Immunotoxicol.* 2013;10(4):373–379
 39. Vélez MP, Arbuckle TE, Fraser WD. Maternal exposure to perfluorinated chemicals and reduced fecundity: the MIREC study. *Hum Reprod.* 2015;30(3):701–709
 40. Fei C, McLaughlin JK, Lipworth L, Olsen J. Maternal levels of perfluorinated chemicals and subfecundity. *Hum Reprod.* 2009;24(5):1200–1205
 41. Wang Y, Rogan WJ, Chen PC, et al. Association between maternal serum perfluoroalkyl substances during pregnancy and maternal and cord thyroid hormones: Taiwan maternal and infant cohort study. *Environ Health Perspect.* 2014;122(5):529–534
 42. Halldorsson TI, Rytter D, Haug LS, et al. Prenatal exposure to perfluorooctanoate and risk of overweight at 20 years of age: a prospective cohort study. *Environ Health Perspect.* 2012;120(5):668–673
 43. Lam J, Koustas E, Sutton P, et al. The navigation guide - evidence-based medicine meets environmental health: integration of animal and human evidence for PFOA effects on fetal growth. *Environ Health Perspect.* 2014;122(10):1040–1051
 44. Centers for Disease Control and Prevention; Agency for Toxic Substances and Disease Registry. Public health statement for perchlorates. 2008. Available at: www.atsdr.cdc.gov/phs/phs.asp?id=892&tid=181. Accessed May 18, 2017
 45. Steinmaus CM. Perchlorate in water supplies: sources, exposures, and health effects. *Curr Environ Health Rep.* 2016;3(2):136–143
 46. Ghassabian A, Trasande L. Disruption in thyroid signaling pathway: a mechanism for the effect of endocrine-disrupting chemicals on child neurodevelopment. *Front Endocrinol (Lausanne).* 2018;9:204
 47. Bouvard V, Loomis D, Guyton KZ, et al; International Agency for Research on Cancer Monograph Working Group. Carcinogenicity of consumption of red and processed meat. *Lancet Oncol.* 2015;16(16):1599–1600
 48. Pogoda JM, Preston-Martin S, Howe G, et al. An international case-control study of maternal diet during pregnancy and childhood brain tumor risk: a histology-specific analysis by food group. *Ann Epidemiol.* 2009;19(3):148–160
 49. Mervish NA, Pajak A, Teitelbaum SL, et al; Breast Cancer and Environment Research Project (BCERP). Thyroid antagonists (perchlorate, thiocyanate, and nitrate) and childhood growth in a longitudinal study of U.S. girls. *Environ Health Perspect.* 2016;124(4):542–549
 50. Tonacchera M, Pinchera A, Dimida A, et al. Relative potencies and additivity of perchlorate, thiocyanate, nitrate, and iodide on the inhibition of radioactive iodide uptake by the human sodium iodide symporter. *Thyroid.* 2004;14(12):1012–1019
 51. Diamanti-Kandarakis E, Bourguignon J-P, Giudice LC, et al. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. *Endocr Rev.* 2009;30(4):293–342
 52. Bergman Å, Heindel JJ, Jobling S, Kidd KA, Zoeller RT, eds. United Nations Environment Programme, World Health Organization. *State of the Science of Endocrine Disrupting Chemicals – 2012*. Geneva, Switzerland: WHO and UNEP; 2013. Available at www.who.int/ceh/publications/endocrine/. Accessed May 18, 2017
 53. Di Renzo GC, Conry JA, Blake J, et al. International Federation of Gynecology and Obstetrics opinion on reproductive health impacts of exposure to toxic environmental chemicals. *Int J Gynaecol Obstet.* 2015;131(3):219–225
 54. Trasande L, Shaffer RM, Sathyanarayana S; American Academy of Pediatrics Council on Environmental Health. Technical report: Food additives and child health. *Pediatrics.* 2018;142(2):e20181408
 55. Trasande L. Further limiting bisphenol A in food uses could provide health

- and economic benefits. *Health Aff (Millwood)*. 2014;33(2):316–323
56. Tavernise S. F.D.A. makes it official: BPA can't be used in baby bottles and cups. *New York Times*. July 17, 2012. Available at: www.nytimes.com/2012/07/18/science/fda-bans-bpa-from-baby-bottles-and-sippy-cups.html. Accessed July 18, 2012
 57. Schechter A, Malik N, Haffner D, et al. Bisphenol A (BPA) in U.S. food. *Environ Sci Technol*. 2010;44(24):9425–9430
 58. Muñoz-de-Toro M, Markey CM, Wadia PR, et al. Perinatal exposure to bisphenol-A alters peripubertal mammary gland development in mice. *Endocrinology*. 2005;146(9):4138–4147
 59. Seachrist DD, Bonk KW, Ho SM, Prins GS, Soto AM, Keri RA. A review of the carcinogenic potential of bisphenol A. *Reprod Toxicol*. 2016;59:167–182
 60. Masuno H, Iwanami J, Kidani T, Sakayama K, Honda K. Bisphenol a accelerates terminal differentiation of 3T3-L1 cells into adipocytes through the phosphatidylinositol 3-kinase pathway. *Toxicol Sci*. 2005;84(2):319–327
 61. Alonso-Magdalena P, Laribi O, Ropero AB, et al. Low doses of bisphenol A and diethylstilbestrol impair Ca²⁺ signals in pancreatic alpha-cells through a nonclassical membrane estrogen receptor within intact islets of Langerhans. *Environ Health Perspect*. 2005;113(8):969–977
 62. Snijder CA, Heederik D, Pierik FH, et al. Fetal growth and prenatal exposure to bisphenol A: the generation R study. *Environ Health Perspect*. 2013;121(3):393–398
 63. Trasande L, Attina TM, Blustein J. Association between urinary bisphenol A concentration and obesity prevalence in children and adolescents. *JAMA*. 2012;308(11):1113–1121
 64. Wang T, Li M, Chen B, et al. Urinary bisphenol A (BPA) concentration associates with obesity and insulin resistance. *J Clin Endocrinol Metab*. 2012;97(2):E223–E227
 65. Trasande L, Attina TM, Trachtman H. Bisphenol A exposure is associated with low-grade urinary albumin excretion in children of the United States. *Kidney Int*. 2013;83(4):741–748
 66. Braun JM, Lanphear BP, Calafat AM, et al. Early-life bisphenol A exposure and child body mass index: a prospective cohort study. *Environ Health Perspect*. 2014;122(11):1239–1245
 67. Valvi D, Casas M, Mendez MA, et al. Prenatal bisphenol A urine concentrations and early rapid growth and overweight risk in the offspring. *Epidemiology*. 2013;24(6):791–799
 68. Harley KG, Aguilar Schall R, Chevrier J, et al. Prenatal and postnatal bisphenol A exposure and body mass index in childhood in the CHAMACOS cohort. *Environ Health Perspect*. 2013;121(4):514–520
 69. Legler J, Fletcher T, Govarts E, et al. Obesity, diabetes, and associated costs of exposure to endocrine-disrupting chemicals in the European Union. *J Clin Endocrinol Metab*. 2015;100(4):1278–1288
 70. Wilson NK, Chuang JC, Morgan MK, Lordo RA, Sheldon LS. An observational study of the potential exposures of preschool children to pentachlorophenol, bisphenol-A, and nonylphenol at home and daycare. *Environ Res*. 2007;103(1):9–20
 71. Fleisch AF, Sheffield PE, Chinn C, Edelstein BL, Landrigan PJ. Bisphenol A and related compounds in dental materials. *Pediatrics*. 2010;126(4):760–768
 72. Schwartz AW, Landrigan PJ. Bisphenol A in thermal paper receipts: an opportunity for evidence-based prevention. *Environ Health Perspect*. 2012;120(1):A14–A15, author reply A15
 73. Nelson JW, Scammell MK, Hatch EE, Webster TF. Social disparities in exposures to bisphenol A and polyfluoroalkyl chemicals: a cross-sectional study within NHANES 2003–2006. *Environ Health*. 2012;11:10
 74. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010. *JAMA*. 2012;307(5):491–497
 75. Patel CJ, Ioannidis JP, Cullen MR, Rehkopf DH. Systematic assessment of the correlations of household income with infectious, biochemical, physiological, and environmental factors in the United States, 1999–2006. *Am J Epidemiol*. 2015;181(3):171–179
 76. Liao C, Liu F, Alomirah H, et al. Bisphenol S in urine from the United States and seven Asian countries: occurrence and human exposures. *Environ Sci Technol*. 2012;46(12):6860–6866
 77. Liao C, Liu F, Kannan K. Bisphenol s, a new bisphenol analogue, in paper products and currency bills and its association with bisphenol A residues. *Environ Sci Technol*. 2012;46(12):6515–6522
 78. Kuruto-Niwa R, Nozawa R, Miyakoshi T, Shiozawa T, Terao Y. Estrogenic activity of alkylphenols, bisphenol S, and their chlorinated derivatives using a GFP expression system. *Environ Toxicol Pharmacol*. 2005;19(1):121–130
 79. Chen MY, Ike M, Fujita M. Acute toxicity, mutagenicity, and estrogenicity of bisphenol-A and other bisphenols. *Environ Toxicol*. 2002;17(1):80–86
 80. Yoshihara S, Mizutare T, Makishima M, et al. Potent estrogenic metabolites of bisphenol A and bisphenol B formed by rat liver S9 fraction: their structures and estrogenic potency. *Toxicol Sci*. 2004;78(1):50–59
 81. Okuda K, Fukuuchi T, Takiguchi M, Yoshihara S. Novel pathway of metabolic activation of bisphenol A-related compounds for estrogenic activity. *Drug Metab Dispos*. 2011;39(9):1696–1703
 82. Audebert M, Dolo L, Perdu E, Cravedi JP, Zalko D. Use of the γ H2AX assay for assessing the genotoxicity of bisphenol A and bisphenol F in human cell lines. *Arch Toxicol*. 2011;85(11):1463–1473
 83. Danzl E, Sei K, Soda S, Ike M, Fujita M. Biodegradation of bisphenol A, bisphenol F and bisphenol S in seawater. *Int J Environ Res Public Health*. 2009;6(4):1472–1484
 84. Ike M, Chen MY, Danzl E, Sei K, Fujita M. Biodegradation of a variety of bisphenols under aerobic and anaerobic conditions. *Water Sci Technol*. 2006;53(6):153–159
 85. Schettler T. Human exposure to phthalates via consumer products. *Int J Androl*. 2006;29(1):134–139, discussion 181–185

86. Fromme H, Gruber L, Schlummer M, et al. Intake of phthalates and di(2-ethylhexyl)adipate: results of the Integrated Exposure Assessment Survey based on duplicate diet samples and biomonitoring data. *Environ Int.* 2007;33(8):1012–1020
87. Wolff MS, Teitelbaum SL, Windham G, et al. Pilot study of urinary biomarkers of phytoestrogens, phthalates, and phenols in girls. *Environ Health Perspect.* 2007;115(1):116–121
88. Silva MJ, Barr DB, Reidy JA, et al. Urinary levels of seven phthalate metabolites in the U.S. population from the National Health and Nutrition Examination Survey (NHANES) 1999–2000. *Environ Health Perspect.* 2004;112(3):331–338
89. Gray LE Jr, Wilson VS, Stoker T, et al. Adverse effects of environmental antiandrogens and androgens on reproductive development in mammals. *Int J Androl.* 2006;29(1):96–104, discussion 105–108
90. Hauser R, Meeker JD, Singh NP, et al. DNA damage in human sperm is related to urinary levels of phthalate monoester and oxidative metabolites. *Hum Reprod.* 2007;22(3):688–695
91. Hauser R, Skakkebaek NE, Hass U, et al. Male reproductive disorders, diseases, and costs of exposure to endocrine-disrupting chemicals in the European Union. *J Clin Endocrinol Metab.* 2015;100(4):1267–1277
92. Trasande L, Attina TM, Sathyanarayana S, Spanier AJ, Blustein J. Race/ethnicity-specific associations of urinary phthalates with childhood body mass in a nationally representative sample. *Environ Health Perspect.* 2018;121(4):501
93. Jepsen KF, Abildtrup A, Larsen ST. Monophthalates promote IL-6 and IL-8 production in the human epithelial cell line A549. *Toxicol In Vitro.* 2004;18(3):265–269
94. Seo KW, Kim KB, Kim YJ, Choi JY, Lee KT, Choi KS. Comparison of oxidative stress and changes of xenobiotic metabolizing enzymes induced by phthalates in rats. *Food Chem Toxicol.* 2004;42(1):107–114
95. Henriksen EJ, Diamond-Stanic MK, Marchionne EM. Oxidative stress and the etiology of insulin resistance and type 2 diabetes. *Free Radic Biol Med.* 2011;51(5):993–999
96. Singh U, Jialal I. Oxidative stress and atherosclerosis. *Pathophysiology.* 2006;13(3):129–142
97. Harrison D, Griendling KK, Landmesser U, Hornig B, Drexler H. Role of oxidative stress in atherosclerosis. *Am J Cardiol.* 2003;91(3A):7A–11A
98. Zota AR, Calafat AM, Woodruff TJ. Temporal trends in phthalate exposures: findings from the National Health and Nutrition Examination Survey, 2001–2010. *Environ Health Perspect.* 2014;122(3):235–241
99. Serrano SE, Braun J, Trasande L, Dills R, Sathyanarayana S. Phthalates and diet: a review of the food monitoring and epidemiology data. *Environ Health.* 2014;13(1):43
100. Trudel D, Horowitz L, Wormuth M, Scheringer M, Cousins IT, Hungerbühler K. Estimating consumer exposure to PFOS and PFOA. *Risk Anal.* 2008;28(2):251–269
101. Centers for Disease Control and Prevention; Agency for Toxic Substances and Disease Registry. Public health statement: perfluoroalkyls. 2009. Available at: www.atsdr.cdc.gov/toxprofiles/tp200-c1-b.pdf. Accessed May 18, 2017
102. Calafat AM, Wong LY, Kuklennyik Z, Reidy JA, Needham LL. Polyfluoroalkyl chemicals in the U.S. population: data from the National Health and Nutrition Examination Survey (NHANES) 2003–2004 and comparisons with NHANES 1999–2000. *Environ Health Perspect.* 2007;115(11):1596–1602
103. Wen L-L, Lin L-Y, Su T-C, Chen P-C, Lin C-Y. Association between serum perfluorinated chemicals and thyroid function in U.S. adults: the National Health and Nutrition Examination Survey 2007–2010. *J Clin Endocrinol Metab.* 2013;98(9):E1456–E1464
104. C8 Science Panel. Probable link evaluation of thyroid disease. July 20, 2012. Available at: www.c8sciencepanel.org/pdfs/Probable_Link_C8_Thyroid_30Jul2012.pdf. Accessed May 18, 2017
105. Melzer D, Rice N, Depledge MH, Henley WE, Galloway TS. Association between serum perfluorooctanoic acid (PFOA) and thyroid disease in the U.S. National Health and Nutrition Examination Survey. *Environ Health Perspect.* 2010;118(5):686–692
106. US Environmental Protection Agency. Emerging contaminants - perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA). 2014
107. US Environmental Protection Agency. Long-chain perfluorinated chemicals (PFCs) action plan. 2009. Available at: https://www.epa.gov/sites/production/files/2016-01/documents/pfcs_action_plan1230_09.pdf. Accessed May 18, 2017
108. US Food and Drug Administration. Indirect food additives: paper and paperboard components. 2016. Available at: <https://www.federalregister.gov/documents/2016/01/04/2015-33026/indirect-food-additives-paper-and-paperboard-components>. Accessed May 18, 2017
109. Calafat AM, Wong LY, Kuklennyik Z, Reidy JA, Needham LL. Polyfluoroalkyl chemicals in the U.S. population: data from the National Health and Nutrition Examination Survey (NHANES) 2003–2004 and comparisons with NHANES 1999–2000. *Environ Health Perspect.* 2007;115(11):1596–1602
110. Glynn A, Berger U, Bignert A, et al. Perfluorinated alkyl acids in blood serum from primiparous women in Sweden: serial sampling during pregnancy and nursing, and temporal trends 1996–2010. *Environ Sci Technol.* 2012;46(16):9071–9079
111. Scheringer M, Trier X, Cousins IT, et al. Helsingør statement on poly- and perfluorinated alkyl substances (PFASs). *Chemosphere.* 2014;114:337–339
112. Blum A, Balan SA, Scheringer M, et al. The Madrid statement on poly- and perfluoroalkyl substances (PFASs). *Environ Health Perspect.* 2015;123(5):A107–A111
113. European Commission. Food contaminants. 2015. Available at: http://ec.europa.eu/food/food/chemicalsafety/contaminants/index_en.htm. Accessed May 18, 2017
114. US Food and Drug Administration. Preliminary estimation of perchlorate

- dietary exposure based on FDA 2004/2005 exploratory data. Available at: www.fda.gov/Food/FoodbornenessContaminants/ChemicalContaminants/ucm077653.htm. Accessed May 18, 2017
115. Maffini MV, Trasande L, Neltner TG. Perchlorate and diet: human exposures, risks, and mitigation strategies. *Curr Environ Health Rep.* 2016;3(2):107–117
 116. Rogan WJ, Paulson JA, Baum C, et al; Council on Environmental Health. Iodine deficiency, pollutant chemicals, and the thyroid: new information on an old problem. *Pediatrics.* 2014;133(6):1163–1166
 117. Zoeller RT, Rovet J. Timing of thyroid hormone action in the developing brain: clinical observations and experimental findings. *J Neuroendocrinol.* 2004;16(10):809–818
 118. Miller MD, Crofton KM, Rice DC, Zoeller RT. Thyroid-disrupting chemicals: interpreting upstream biomarkers of adverse outcomes. *Environ Health Perspect.* 2009;117(7):1033–1041
 119. Moog NK, Entringer S, Heim C, Wadhwa PD, Kathmann N, Buss C. Influence of maternal thyroid hormones during gestation on fetal brain development. *Neuroscience.* 2017;342:68–100
 120. Pääkkilä F, Männistö T, Hartikainen AL, et al. Maternal and child's thyroid function and child's intellect and scholastic performance. *Thyroid.* 2015;25(12):1363–1374
 121. Haddow JE, Palomaki GE, Allan WC, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med.* 1999;341(8):549–555
 122. US Environmental Protection Agency; Science Advisory Board. Perchlorate - Approaches for Deriving Maximum Contaminant Level Goals for Drinking Water. 2013. Available at: <https://yosemite.epa.gov/sab/sabproduct.nsf/02ad90b136fc21ef85256eba00436459/d3bb75d4297ca4698525794300522ace!OpenDocument&TableRow=2.2>. Accessed May 18, 2017
 123. Steinmaus C, Pearl M, Kharrazi M, et al. Thyroid hormones and moderate exposure to perchlorate during pregnancy in women in southern California. *Environ Health Perspect.* 2016;124(6):861–867
 124. Abdelouahab N, Langlois MF, Lavoie L, Corbin F, Pasquier JC, Takser L. Maternal and cord-blood thyroid hormone levels and exposure to polybrominated diphenyl ethers and polychlorinated biphenyls during early pregnancy. *Am J Epidemiol.* 2013;178(5):701–713
 125. Schechter A, Pöpke O, Harris TR, et al. Polybrominated diphenyl ether (PBDE) levels in an expanded market basket survey of U.S. food and estimated PBDE dietary intake by age and sex. *Environ Health Perspect.* 2006;114(10):1515–1520
 126. Wu N, Herrmann T, Paepke O, et al. Human exposure to PBDEs: associations of PBDE body burdens with food consumption and house dust concentrations. *Environ Sci Technol.* 2007;41(5):1584–1589
 127. Hinton CF, Harris KB, Borgfeld L, et al. Trends in incidence rates of congenital hypothyroidism related to select demographic factors: data from the United States, California, Massachusetts, New York, and Texas. *Pediatrics.* 2010;125(suppl 2):S37–S47
 128. Cao Y, Blount BC, Valentin-Blasini L, Bernbaum JC, Phillips TM, Rogan WJ. Goitrogenic anions, thyroid-stimulating hormone, and thyroid hormone in infants. *Environ Health Perspect.* 2010;118(9):1332–1337
 129. US Food and Drug Administration. Summary of color additives for use in the United States in foods, drugs, cosmetics, and medical devices. Available at: www.fda.gov/ForIndustry/ColorAdditives/ColorAdditiveInventories/ucm115641.htm. Accessed May 18, 2017
 130. Stevens LJ, Burgess JR, Stochelski MA, Kuczek T. Amounts of artificial food colors in commonly consumed beverages and potential behavioral implications for consumption in children. *Clin Pediatr (Phila).* 2014;53(2):133–140
 131. Nigg JT, Lewis K, Edinger T, Falk M. Meta-analysis of attention-deficit/hyperactivity disorder or attention-deficit/hyperactivity disorder symptoms, restriction diet, and synthetic food color additives. *J Am Acad Child Adolesc Psychiatry.* 2012;51(1):86–97.e8
 132. Stevens LJ, Kuczek T, Burgess JR, Stochelski MA, Arnold LE, Galland L. Mechanisms of behavioral, atopic, and other reactions to artificial food colors in children. *Nutr Rev.* 2013;71(5):268–281
 133. Millichap JG, Yee MM. The diet factor in attention-deficit/hyperactivity disorder. *Pediatrics.* 2012;129(2):330–337
 134. Weiss B. Synthetic food colors and neurobehavioral hazards: the view from environmental health research. *Environ Health Perspect.* 2012;120(1):1–5
 135. Arnold LE, Lofthouse N, Hurt E. Artificial food colors and attention-deficit/hyperactivity symptoms: conclusions to dye for. *Neurotherapeutics.* 2012;9(3):599–609
 136. Kleinman RE, Brown RT, Cutter GR, Dupaul GJ, Clydesdale FM. A research model for investigating the effects of artificial food colorings on children with ADHD. *Pediatrics.* 2011;127(6):e1575–e1584
 137. Nigg JT, Holton K. Restriction and elimination diets in ADHD treatment. *Child Adolesc Psychiatr Clin N Am.* 2014;23(4):937–953
 138. Arnold LE, Hurt E, Lofthouse N. Attention-deficit/hyperactivity disorder: dietary and nutritional treatments. *Child Adolesc Psychiatr Clin N Am.* 2013;22(3):381–402, v
 139. Stevenson J, Buitelaar J, Cortese S, et al. Research review: the role of diet in the treatment of attention-deficit/hyperactivity disorder—an appraisal of the evidence on efficacy and recommendations on the design of future studies. *J Child Psychol Psychiatry.* 2014;55(5):416–427
 140. US Food and Drug Administration. Food advisory committee meeting. March 30–31, 2011. Available at: <https://wayback.archive-it.org/org-1137/20170406211705/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/FoodAdvisoryCommittee/UCM255119.pdf>. Accessed May 18, 2017
 141. US Food and Drug Administration; Background Document for the

- Food Advisory Committee. Certified color additives in food and possible association with attention deficit hyperactivity disorder in children. March 30–31, 2011. Available at: <https://wayback.archive-it.org/org-1137/20170406211659/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/FoodAdvisoryCommittee/UCM248549.pdf>. Accessed May 18, 2017
142. Food and drugs color additives. *Fed Regist.* 1977; Codified as 21 CFR 70
143. Tricker AR, Preussmann R. Carcinogenic N-nitrosamines in the diet: occurrence, formation, mechanisms and carcinogenic potential. *Mutat Res.* 1991;259(3–4):277–289
144. American Medical Association; Council on Scientific Affairs. *Labeling of Nitrite Content of Processed Foods*. Chicago, IL: American Medical Association; 2004
145. Grosse Y, Baan R, Straif K, Secretan B, El Ghissassi F, Coglianò V; WHO International Agency for Research on Cancer Monograph Working Group. Carcinogenicity of nitrate, nitrite, and cyanobacterial peptide toxins. *Lancet Oncol.* 2006;7(8):628–629
146. Food additives permitted for direct addition to food for human consumption - food preservatives - sodium nitrite. *Fed Regist.* 2005; Codified as 21 CFR 172.175
147. De Groef B, Decallonne BR, Van der Geyten S, Darras VM, Bouillon R. Perchlorate versus other environmental sodium/iodide symporter inhibitors: potential thyroid-related health effects. *Eur J Endocrinol.* 2006;155(1):17–25
148. Sebranek JG, Jackson-Davis AL, Myers KL, Lavieri NA. Beyond celery and starter culture: advances in natural/organic curing processes in the United States. *Meat Sci.* 2012;92(3):267–273
149. Neuman W. What’s inside the bun? *New York Times*. July 1, 2011. Available at www.nytimes.com/2011/07/02/business/02hotdog.html. Accessed May 18, 2017
150. Nuñez De González MT, Osburn WN, Hardin MD, et al. Survey of residual nitrite and nitrate in conventional and organic/natural/uncured/indirectly cured meats available at retail in the United States. *J Agric Food Chem.* 2012;60(15):3981–3990

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