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Food Additives and Child Health

Leonardo Trasande, MD, MPP, FAAP[a], **Rachel M. Shaffer, MPH**[b], **Sheela Sathyanarayana, MD, MPH**[b,c], and **COUNCIL ON ENVIRONMENTAL HEALTH**

[a]Departments of Pediatrics, Environmental Medicine, and Health Policy, School of Medicine, New York University, New York, New York

Address correspondence to Leonardo Trasande, MD, MPP, FAAP. Leonardo.Trasande@nyumc.org.

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[b]Department of Environmental and Occupational Health Sciences, School of Public Health, University of Washington, Seattle, Washington

[c]Department of Pediatrics, University of Washington, Seattle, Washington

Abstract

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, 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 corrosion[5]; phthalates, which are esters of diphthalic acid that are used in adhesives and plasticizers during the manufacturing process[6]; nonpersistent pesticides, which have been addressed in a previous American Academy of

Pediatrics (AAP) policy statement and thus are not discussed in this report[7]; perfluoroalkyl chemicals (PFCs), which are used in grease-proof paper and paperboard food packaging[8]; 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 evidence[11]; a joint report from the World Health Organization and United Nations Environment Programme in 2013[52]; 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 manufaturing.[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 activity[95] 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 greaseproofing 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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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 Polymeric, epoxy resins in food and beverage cans	Endocrine disruption[11–18] Obesogenic activity,[19–22] neurodevelopmental disruption[23–26]
	Phthalates	Clear plastic food wrap Plastic tubing, storage containers used in industrial food production Multiple uses in food manufacturing equipment	Endocrine disruption[6,27–29] Obesogenic activity[30–32] Oxidative stress,[33,34] cardiotoxicity[35,36]
	Perfluoroalkyl chemicals (PFCs)	Grease-proof paper and paperboard	Immunosupression,[37,38] endocrine disruption,[39–41] obesogenic activity,[42] decreased birth wt[43]
	Perchlorate	Food packaging	Thyroid hormone disruption[44–46]
Direct food additives	Nitrates and nitrites	Direct additive as preservative and color enhancer, especially to meats	Carcinogenicity,[10,47,48] thyroid hormone disruption[49,50]