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Food Additives and Child Health

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Abstract

Our purposes with this policy statement and its accompanying technical report are to review and highlight emerging child health concerns related to the use of colorings, flavorings, and chemicals deliberately added to food during processing (direct food additives) as well as substances in food contact materials, including adhesives, dyes, coatings, paper, paperboard, plastic, and other polymers, which may contaminate food as part of packaging or manufacturing equipment (indirect food additives); to make reasonable recommendations that the pediatrician might be able to adopt into the guidance provided during pediatric visits; and to propose urgently needed reforms to the current regulatory process at the US Food and Drug Administration (FDA) for food additives.

Concern regarding food additives has increased in the past 2 decades, in part because of studies in which authors document endocrine disruption and other adverse health effects. In some cases, exposure to these chemicals is disproportionate among minority and low-income populations.

Regulation and oversight of many food additives is inadequate because of several key problems in the Federal Food, Drug, and Cosmetic Act. Current requirements for a “generally recognized as safe” (GRAS) designation are insufficient to ensure the safety of food additives and do not contain sufficient protections against conflict of interest. Additionally, the FDA does not have adequate authority to acquire data on chemicals on the market or reassess their safety for human health.

These are critical weaknesses in the current regulatory system for food additives. Data about health effects of food additives on infants and children are limited or missing; however, in general, infants and children are more vulnerable to chemical exposures. Substantial improvements to the food additives regulatory system are urgently needed, including greatly strengthening or replacing the “generally recognized as safe” (GRAS) determination process, updating the scientific foundation of the FDA’s safety assessment program, retesting all previously approved chemicals, and labeling direct additives with limited or no toxicity data.

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INTRODUCTION

Today, more than 10 000 chemicals are allowed to be added to food and food contact materials in the United States, either directly or indirectly, under the 1958 Food Additives Amendment to the 1938 Federal Food, Drug, and Cosmetic Act (FFDCA) (public law number 85-929). Many of these were grandfathered in for use by the federal government before the 1958 amendment, and an estimated 1000 chemicals are used under a “generally recognized as safe” (GRAS) designation process without US Food and Drug Administration (FDA) approval.¹ Yet, suggested in accumulating evidence from nonhuman laboratory and human epidemiological studies is that chemicals used in food and food contact materials may contribute to disease and disability, as described in the accompanying technical report and summarized in Table 1. Children may be particularly susceptible to the effects of these compounds, given that 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 maturation that are vulnerable to disruptions.² In this policy statement and accompanying technical report, we will not address other contaminants that inadvertently enter the food and water supply, such as aflatoxins, polychlorinated biphenyls, dioxins, metals including mercury, pesticide residues such as DDT, and vomitoxin. In this statement, we 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 potential for endocrine system disruption is of great concern, especially in early life, when 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 2009,⁴² which was updated in 2015 to reflect rapidly accumulating knowledge³; a joint report from the World Health Organization and United Nations Environment Program in 2013⁴³; and a statement from the International Federation of Gynecology and Obstetrics in 2015.⁴⁴ Chemicals of increasing concern include the following:

- bisphenols, which are used in the lining of metal cans to prevent corrosion⁴⁵;
- phthalates, which are esters of diphthalic acid that are often used in adhesives, lubricants, and plasticizers during the manufacturing process¹⁷;
- nonpersistent pesticides, which have been addressed in a previous policy statement from the American Academy of Pediatrics and, thus, will not be discussed in this statement⁴⁶;
- perfluoroalkyl chemicals (PFCs), which are used in grease-proof paper and packaging⁴⁷; and
- perchlorate, an antistatic agent used for plastic packaging in contact with dry foods with surfaces that do not contain free fat or oil and also present as a degradation product of bleach used to clean food manufacturing equipment.⁴⁸

Additional compounds of concern discussed in the accompanying technical report include artificial food colors, nitrates, and nitrites.

Environmentally relevant doses (ie, low nanomolar concentrations that people are likely to encounter in daily life) of bisphenol A (BPA)⁴ trigger the conversion of cells to adipocytes,⁹ disrupt pancreatic β -cell function in vivo,⁴⁹ and affect glucose transport in adipocytes.^{9–11} Phthalates are metabolized to chemicals that influence the expression of master regulators of lipid and carbohydrate metabolism, the peroxisome proliferator-activated receptors,²¹ with specific effects that produce insulin resistance in nonhuman laboratory studies. Some studies have documented similar metabolic effects in human populations.²² Some phthalates are well known to be antiandrogenic and can affect fetal reproductive development.^{18,19,50} Authors of recent studies have linked perfluoroalkyl chemicals with reduced immune response to vaccine^{27,28} and thyroid hormone alterations,^{29,51,52} among other adverse health end points. Perchlorate is known to disrupt thyroid hormone³⁴ and, along with exposures to other food contaminants, such as polybrominated diphenyl ethers,^{53–55} may be contributing to the increase in neonatal hypothyroidism that has been documented in the United States.⁵⁶ Artificial food colors may be associated with exacerbation of attention-deficit/hyperactivity disorder symptoms.⁵⁷ Nitrates and nitrites can interfere with thyroid hormone production⁴⁰ and, under specific endogenous conditions, may result in the increased production of carcinogenic N-nitroso compounds.^{37,38}

Racial and ethnic differences in food additive exposures are well documented.^{58,59} Higher urinary concentrations of BPA have been documented in African American individuals,⁶⁰ and BPA concentrations have been inversely associated with family income.⁶¹ Given that obesity is well recognized to be more prevalent among low-income and minority children in the United States,⁶² disproportionate exposures to obesogenic chemicals such as BPA partially explain sociodemographic disparities in health.

REGULATORY FRAMEWORK FOR DIRECT AND INDIRECT FOOD ADDITIVES

The Food Additives Amendment of 1958 was passed as an amendment to the FFDCA and was used to provide specific guidance for food additives. The legislation required a formal agency review, public comment, and open rulemaking process for new chemical additives. It also contained an exemption for common food additives, such as oil or vinegar, when used in ways that were GRAS.⁶³ Under these specific scenarios, a formal rulemaking process was not required.

Despite this framework, there remain substantial gaps in data about potential health effects of food additives. A recent evaluation of 3941 direct food additives revealed that 63.9% of these had no feeding data whatsoever (either a study of the lethal dose in 50% of animals or an oral toxicology study). Only 263 (6.7%) had reproductive toxicology data, and 2 had developmental toxicology data.⁶⁴

This lack of data on food additives stems from 2 critical problems within the food regulatory system. First, the GRAS process, although intended to be used in limited situations, has

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become the process by which virtually all new food additives enter the market. Consequently, neither the FDA nor the public have adequate notice or review. The Government Accountability Office conducted an extensive review of the FDA GRAS program in 2010 and determined that the FDA is not able to ensure the safety of existing or new additives through this approval mechanism.⁶⁵ Concerns also have been raised about conflicts of interest in the scientific review of food additives leading to GRAS designation. A recent evaluation of 451 GRAS evaluations voluntarily submitted to the FDA revealed that 22.4% of evaluations were made by an employee of the manufacturer, 13.3% were made by an employee of a consulting firm selected by the manufacturer, and 64.3% were made by an expert panel selected by the consulting firm or manufacturer. None were made by a third party.⁶⁶

Second, the FDA does not have authority to obtain data on or reassess the safety of chemicals already on the market.¹ This issue is of great importance and concern for chemicals approved decades ago on the basis of limited and sometimes antiquated testing methods. For instance, some compounds, such as styrene and eugenol methyl ether, remain approved for use as flavoring agents, although they have been subsequently classified as reasonably anticipated to be human carcinogens by the US National Toxicology Program.⁶⁷

Further compounding the problems noted above are other shortcomings within agency procedures. For example, the FDA does not regularly consider cumulative effects of food additives in the context of other chemical exposures that may affect the same biological receptor or mechanism, despite their legal requirement to do so.^{68–70} Synergistic effects of chemicals found in foods are also not considered. Synergistic and cumulative effects are especially important, given that multiple food contaminants, such as polybrominated diphenyl ethers, perchlorate, and organophosphate pesticides, can disrupt various aspects of the thyroid hormone system.⁷¹ Dietary interactions may also be important, given that iodine sufficiency is essential for thyroid function.⁷²

In addition, the FDA's toxicological testing recommendations have not been updated on the basis of new scientific information. Testing guidelines for food contact materials are based on estimated dietary exposure, and only genotoxicity tests are recommended for exposures estimated to be less than 150 µg per person per day, regardless of body weight.⁷³ Thus, toxicological testing may not account for behavioral or other end points that may be more likely to be impaired by early life exposures, especially to additives that act at low doses to disrupt endocrine pathways. Furthermore, these guidelines may not be adequately protective for children, given that they may receive higher relative doses than adults because of their lower body weights.

RECOMMENDATIONS FOR PEDIATRICIANS AND THE HEALTH SECTOR

It is difficult to know how to reduce exposures to many of these chemicals, but some recommendations are cited here.^{74–76} Insofar as these modifications can pose additional costs, barriers may exist for low-income families to reduce their exposure to food additives of concern. Pediatricians may wish to tailor guidance in the context of practicality, especially because food insecurity remains a substantial child health concern. Pediatricians

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also can advocate for modernization of the FFDCA, as described in the subsequent section, which is of unique importance for low-income populations who may not be as readily able to reduce exposure to food additives.

- Prioritize consumption of fresh or frozen fruits and vegetables when possible, and support that effort by developing a list of low-cost sources for fresh fruits and vegetables.
- Avoid processed meats, especially maternal consumption during pregnancy.
- Avoid microwaving food or beverages (including infant formula and pumped human milk) in plastic, if possible.
- Avoid placing plastics in the dishwasher.
- Use alternatives to plastic, such as glass or stainless steel, when possible.
- Look at the recycling code on the bottom of products to find the plastic type, and avoid plastics with recycling codes 3 (phthalates), 6 (styrene), and 7 (bisphenols) unless plastics are labeled as “biobased” or “greenware,” indicating that they are made from corn and do not contain bisphenols.
- Encourage hand-washing before handling foods and/or drinks, and wash all fruits and vegetables that cannot be peeled.

RECOMMENDATIONS FOR POLICY MAKERS

Just as the American Academy of Pediatrics had recommended principles for the modernization of the Toxic Substances Control Act (TSCA) to strengthen regulation of chemicals in nonfood products to protect children’s health,⁷⁷ the Academy endorses previously described priority areas for improvements to the food additive regulatory program⁷⁸ and provides additional recommendations below, some of which could be accomplished by the FDA, whereas others may require congressional action to change the current law.

RECOMMENDATIONS FOR GOVERNMENT

1. The GRAS process is in need of substantial revision. A more robust and transparent process of evaluation is needed, including additional requirements for toxicity testing before approval of chemicals for the marketplace. The GRAS system should be revised as soon as possible and should fully document and disclose conflicts of interest in the evaluation process.
2. The FDA should leverage expertise and technical evaluations from other agencies to gather missing data and identify knowledge gaps, while the current GRAS process remains in place.
3. The FDA should establish requirements for prioritization and retesting of previously approved chemicals.

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4. Congress should provide the FDA authority to collect information about the use of food additives and to require additional data from the industry when gaps in knowledge and potential safety concerns are raised.
5. There should be dedicated resources for research and testing that will allow for a more effective evidence-based database to support a revised FDA safety review process.
6. The FDA should update the scientific foundation for the FDA safety assessment process, including but not limited to the following: expand the scope of recommended testing battery to cover endocrine-related and neurobehavioral effects, ensure adequate safety factors for pregnant and breastfeeding women and additional vulnerable populations, and develop strategies to integrate emerging testing techniques.
7. The FDA should consider cumulative and mixture effects from dietary sources, including other additives and contaminants that interact with relevant biological pathways.
8. The FDA should establish requirements for labeling of additives with limited or no toxicity data and those not reviewed for safety by the FDA.
9. The federal government should encourage provisions that ensure transparency and public access to information, including potential conflicts of interest.

The changes described above can be used to help restore public confidence in the safety of food additives. The FDA can and should make improvements within the scope of current agency authority. Ultimately, congressional action may be required to reform the food additives regulatory process. To aid in this process, the pediatrician community should come together on these issues to advocate for the protection of children's health.

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Appendix

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Dr. Trasande developed the initial idea for the document. Ms. Shaffer and Dr. Trasande researched, wrote, and revised the statement.

Dr. Sathyaranayana critically reviewed the document; and all authors approved the final manuscript as submitted.

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The guidance in this statement 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.

All policy statements from the American Academy of Pediatrics automatically expire 5 years after publication unless reaffirmed, revised, or retired at or before that time.

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ABBREVIATIONS

BPA	bisphenol A
FDA	US Food and Drug Administration
FFDCA	Federal Food, Drug, and Cosmetic Act
GRAS	generally recognized as safe

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

Category	Chemical	Food-Related Use	Selected Health Concerns
Indirect food additives	Bisphenols	Polycarbonate plastic containers Polymeric, epoxy resins in food and beverage cans Clear plastic food wrap	Endocrine disruption ³⁻⁸ Obesogenic activity ⁹⁻¹² neurodevelopmental disruption ¹³⁻¹⁶
	Phthalates	Plastic tubing, storage containers used in industrial food production Multiple uses in food manufacturing equipment	Endocrine disruption ¹⁷⁻²⁰ Obesogenic activity ²¹⁻²² Oxidative stress, ²³⁻²⁴ cardiotoxicity ^{25,26}
Perfluoroalkyl chemicals (PFCS)		Grease-proof paper and paperboard	Immunosuppression, ^{27,28} endocrine disruption, ²⁹⁻³¹ obesogenic activity, ³² decreased birth wt ³³
	Perchlorate	Food packaging	Thyroid hormone disruption ³⁴⁻³⁶
Direct food additives	Nitrates and nitrites	Direct additive as preservative and color enhancer, especially to meats	Carcinogenicity, ³⁷⁻³⁹ thyroid hormone disruption ^{40,41}