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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

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

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.

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

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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

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. 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 [PubMed: 21543423]
3. 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 [PubMed: 26414233]
4. Howdeshell KL, Hotchkiss AK, Thayer KA, Vandenberg JG, vom Saal FS. Exposure to bisphenol A advances puberty. *Nature*. 1999;401 (6755):763–764 [PubMed: 10548101]
5. Rubin BS. Bisphenol A: an endocrine disruptor with widespread exposure and multiple effects. *J Steroid Biochem Mol Biol*. 2011;127 (1–2):27–34 [PubMed: 21605673]
6. 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(suppl 6):S56–S69 [PubMed: 16690810]
7. 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 Persp* 2016;124 (3) :321–328
8. 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 [PubMed: 23014629]

9. 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 [PubMed: 11971937]
10. 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 [PubMed: 14707028]
11. 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 [PubMed: 19079714]
12. 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 [PubMed: 22249005]
13. 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 [PubMed: 22025598]
14. 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 [PubMed: 21524981]
15. 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 [PubMed: 26956939]
16. Mustieles V, Pérez-Lobato R, Olea N, Fernández MF. Bisphenol A: human exposure and neurobehavior. *Neurotoxicology*. 2015;49:174–184 [PubMed: 26121921]
17. Sathyanarayana S Phthalates and children's health. *Curr Probl Pediatr Adolesc Health Care* 2008;38(2) :34–49 [PubMed: 18237855]
18. Swan SH, Sathyanarayana S, Barrett ES, et al.; TIDES Study Team. First trimester phthalate exposure and anogenital distance in newborns. *Hum Reprod* 2015;30(4):963–972 [PubMed: 25697839]
19. 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 [PubMed: 11099647]
20. 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 [PubMed: 25121464]
21. 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 [PubMed: 19433246]
22. 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(71):2640–2650 [PubMed: 25993640]
23. 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 [PubMed: 25402001]
24. Ferguson KK, Loch-Carusio 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 [PubMed: 21349512]
25. 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 [PubMed: 20863871]
26. 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 [PubMed: 22672789]
27. 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 [PubMed: 22274686]

28. 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 [PubMed: 23350954]
29. 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 [PubMed: 24577800]
30. Ve  lez MP, Arbuckle TE, Fraser WD. Maternal exposure to perfluorinated chemicals and reduced fecundity: the MIREC study. *Hum Reprod* 2015;30(3):701–709 [PubMed: 25567616]
31. Fei C, McLaughlin JK, Fipworth F, Olsen J. Maternal levels of perfluorinated chemicals and subfecundity. *Hum Reprod.* 2009;24(5): 1200–1205 [PubMed: 19176540]
32. TI Halldorsson, Rytter D Haug FS, 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 [PubMed: 22306490]
33. 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)4040–1051
34. 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
35. Steinmaus CM. Perchlorate in water supplies: sources, exposures, and health effects. *Curr Environ Health Rep* 2016;3(2):136–143 [PubMed: 27026358]
36. 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 [PubMed: 29760680]
37. 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 [PubMed: 21141240]
38. 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 [PubMed: 26514947]
39. 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 [PubMed: 19216997]
40. De Groef B, Decallonne BR, Vander 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 [PubMed: 16793945]
41. 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 [PubMed: 15650353]
42. Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, et al. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. *Endocr Rev.* 2009;30(4) :293–342 [PubMed: 19502515]
43. Bergman  , 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
44. 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 [PubMed: 26433469]
45. US Food and Drug Administration. Update on bisphenol A for use in food contact applications: 1 2010 Available at: <https://www.fda.gov/downloads/NewsEvents/PublicHealthFocus/UCM197778.pdf>. Accessed May 18, 2017

46. 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
47. 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 [PubMed: 21793199]
48. US Food and Drug Administration Filing of food additive petition. Available at: www.gpo.gov/fdsys/pkg/FR-2015-03-16/html/2015-05937.htm. Accessed May 18, 2017
49. 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 [PubMed: 16079065]
50. 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 [PubMed: 25742517]
51. C8 Science Panel. Probable link evaluation of thyroid disease. C8 Probable Link Reports. 2012 Available at: www.c8sciencepanel.org/pdfs/Probable_Fink_C8_Thyroid_30Jul2012.pdf. Accessed May 18, 2017
52. 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
53. Jacobson MH, Barr DB, Marcus M, et al. Serum polybrominated diphenyl ether concentrations and thyroid function in young children. *Environ Res* 2016;149:222–230 [PubMed: 27228485]
54. Schecter A, Päpke 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 [PubMed: 17035135]
55. 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
56. 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 [PubMed: 20435716]
57. 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 [PubMed: 22176942]
58. 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 [PubMed: 17366830]
59. 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
60. 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 [PubMed: 22990270]
61. 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 [PubMed: 22394520]
62. 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 [PubMed: 22253363]
63. Maffini MV, Alger HM, Olson ED, Neltner TG. Looking back to look forward: a review of FDA's food additives safety assessment and recommendations for modernizing its program. *Compr Rev Food Sci Food Sat* 2013;12(4) :439–453

64. 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 [PubMed: 23954440]
65. Government Accountability Office. Food safety: FDA should strengthen its oversight of food ingredients determined to be generally recognized as safe (GRAS). 2010 Available at: www.gao.gov/products/GAO-10-246. Accessed May 18, 2017
66. Neltner TG, Alger HM, O'Reilly JT, Krinsky 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 [PubMed: 23925593]
67. Huff J, Center for Science in the Public Interest; Natural Resources Defense Council; Center for Food Safety; Consumers Union; Improving Kids' Environment; Center for Environmental Health; Environmental Working Group. Food additive petition pursuant to 21 USC § 348 seeking amended food additive regulation to: 1) remove FDA's approval at 21 CFR § 172.515 of seven synthetic flavors; and 2) add to that section a prohibition on use of these seven flavors and one additional flavor approved as GRAS by the flavor industry because all eight have been found by the National Toxicology Program to induce cancer in man or animal. 2015 Available at: https://www.nrdc.org/sites/default/files/hea_15060901a.pdf. Accessed May 18, 2017
68. Maffini MV, Trasande L, Neltner TG. Perchlorate and diet: human exposures, risks, and mitigation strategies. *Curr Environ Health Rep* 2016;3(2) :107–117 [PubMed: 27029550]
69. Maffini MV, Neltner TG. Brain drain: the cost of neglected responsibilities in evaluating cumulative effects of environmental chemicals. *J Epidemiol Community Health* 2015;69(5) :496–499 [PubMed: 25336676]
70. Food additives, 21 USC 348(c)(5) (1997)
71. Shimizu R, Yamaguchi M, Uramaru N, et al. Structure-activity relationships of 44 halogenated compounds for iodotyrosine deiodinase-inhibitory activity. *Toxicology.* 2013;314(1):22–29 [PubMed: 24012475]
72. 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 [PubMed: 24864180]
73. Sotomayor RE, Arvidson KB, Mayer JN, McDougal AJ, Sheu C. Regulatory report: assessing the safety of food contact substances. 2007 Available at: <http://wayback.archive-it.org/7993/20171114191242/https://www.fda.gov/Food/IngredientsPackagingLabeling/PackagingFCS/ucm064166.htm>. Accessed May 18, 2017
74. Otter D, Sathyanarayana S, Galvez M, Sheffield PE; National Pediatric Environmental Health Specialty Unit Education Committee. Consumer guide: phthalates and bisphenol A. 2014 Available at: www.pehsu.net/_Phthalates_and_Bisphenol_A_Advisory.html. Accessed May 18, 2017
75. Rudel RA, Gray JM, Engel CL, et al. Food packaging and bisphenol A and bis(2-ethylhexyl) phthalate exposure: findings from a dietary Intervention. *Environ Health Perspect* 2011 ;119(7): 914–920 [PubMed: 21450549]
76. Zota AR, Phillips CA, Mitro SD. Recent fast food consumption and bisphenol A and phthalates exposures among the U.S. population in NHANES, 2003–2010. *Environ Health Perspect.* 2016;124(10):1521–1528 [PubMed: 27072648]
77. Council on Environmental Health. Chemical-management policy: prioritizing children's health. *Pediatrics.* 2011 ;127(5): 983–990 [PubMed: 21518722]
78. The Pew Charitable Trusts. Fixing the Oversight of Chemicals Added to Our Food. Findings and Recommendations of Pew's Assessment of the US Food Additives Program. Philadelphia, PA: The Pew Charitable Trusts; 2013 Available at: www.pewtrusts.org/en/research-and-analysis/reports/2013/11/07/fixing-the-oversight-of-chemicals-added-to-our-food Accessed May 18, 2017

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

TABLE 1

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