

ENVIRONMENTAL DEFENSE FUND, AMERICAN ACADEMY OF PEDIATRICS, AMERICAN PUBLIC HEALTH ASSOCIATION, BREAST CANCER PREVENTION PARTNERS, CENTER FOR FOOD SAFETY, CLEAN LABEL PROJECT, CONSUMER FEDERATION OF AMERICA, CONSUMER REPORTS, ENDOCRINE SOCIETY, ENVIRONMENTAL HEALTH STRATEGY CENTER, ENVIRONMENTAL WORKING GROUP, AND HEALTHY BABIES BRIGHT FUTURES

September 23, 2020

Division of Dockets Management  
Food and Drug Administration,  
Department of Health and Human Services  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

Re: Citizens petition requesting that FDA define key terms essential to consider the cumulative effect of a food additive, food contact substance, generally recognized as safe substance, or color additive, taking into account any chemically- or pharmacologically-related substances in the diet, when assessing safety as required by law.

Dear Commissioner:

More than 60 years ago, Congress sought “to protect public health by amending the Food, Drug, and Cosmetic Act [FFDCA] to prohibit the use in food of additives which have not been adequately tested to establish their safety.”<sup>1</sup> By enacting the Food Additives Amendment of 1958, Congress recognized the critical connection between disease and chemicals in the diet when it directed the Food and Drug Administration (FDA) to consider “the cumulative effect of such additive in the diet of man or animals, taking into account any chemically or pharmacologically related substance or substances in such diet.”<sup>2</sup>

In this petition, we demonstrate that FDA and food manufacturers have not taken into account the many chemicals we consume in our daily diet that are similar in structure or affect similar function(s) of organs in the body when making safety determinations for new additives, despite the Congressional mandate and the agency’s own regulations. Specifically, we found that:

- Only one of almost 900 safety determinations conducted by food manufacturers and submitted to FDA for review as Generally Recognized as Safe (GRAS) notifications for human food considered the requirement in a meaningful way. And we saw no evidence that FDA raised concerns about the notifier’s failure to include the legally mandated information.
- FDA’s guidance for industry fails to explain how food manufacturers should conduct the necessary evaluation of cumulative effects. When the requirement is mentioned, it is either incomplete or confused with “cumulative exposure” or “cumulative intake” of a single substance and does not address related substances in the diet.
- FDA, to a limited extent, recently recognized the need to look beyond individual chemicals when it prohibited long-chain perfluorinated alkyl substances and industrially-produced *trans* fatty acids as classes of substances in the diet. However, those actions focused on a narrow set of chemically-related substances. In these two cases and every other situation evaluated, FDA ignored pharmacologically-related substances that were not also chemically-related.

---

<sup>1</sup> Food Additives Amendment of 1958, Public Law 85-929, 72 Stat. 1784.

<sup>2</sup> *Id.* Section 4 adding Section 409(c)(5)(B) to the FFDCA, codified at [21 U.S.C. § 348\(c\)\(5\)\(B\)](#).

Given the growth of highly processed food that now dominates the diet of most Americans<sup>3</sup>, this failure may have contributed to the dramatic increases in a variety of chronic diseases such as obesity<sup>4</sup>, diabetes—especially in children<sup>5</sup>, and kidney disease.<sup>6</sup> This failure has significant consequences for public health, particularly for underserved communities, who already face significant health and socio-economic disparities, and for children, who are uniquely susceptible to dietary exposures because of: 1) their heightened vulnerability to the health effects of exposure to toxicants during key developmental periods; 2) their long time horizon for exposure to toxicants in their diet over their life span; and 3) their relatively higher intake of food and water as a proportion of their size compared to adults.

The American Academy of Pediatrics<sup>7</sup> recognized the health risks posed by chemicals in the diet in 2018 when it concluded that:

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. 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. Dietary interactions may also be important, given that iodine sufficiency is essential for thyroid function.<sup>8</sup>

For these reasons, Environmental Defense Fund, American Academy of Pediatrics, American Public Health Association, Breast Cancer Prevention Partners, Center for Food Safety, Consumer Reports, Clean Label Project, Consumer Federation of America, Endocrine Society, Environmental Health Strategy Center, Environmental Working Group, and Healthy Babies Bright Futures submit this petition pursuant to Section 4 of the Administrative Procedures Act<sup>9</sup> and [21 C.F.R. § 10.30](#) to request the Commissioner of Food and Drugs to revise the agency's food and color additive regulations and associated guidance to ensure compliance with the requirements in sections 409 and 706 of the FFDCA.<sup>10</sup> Below the actions requested are outlined in detail. Briefly the undersigned are requesting that FDA update its rules, issue clear guidance for industry, and revise its notification and petition forms so that the legal requirements can be achieved in practice.

---

<sup>3</sup> Baldrige, A et al. "The Healthfulness of the US Packaged Food and Beverage Supply: A Cross-Sectional Study, *Nutrients*. 2019 Aug; 11(8): 1704 at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6722673/>. See also Steele, E et al. "Ultra-Processed Foods and Added Sugars in the US Diet: Evidence from a Nationally Representative Cross-Sectional Study." *BMJ Open* 6, no. 3 (2016): e009892 and Poti, J et al. "Is the degree of food processing and convenience linked with the nutritional quality of foods purchased by US households?" *The American Journal of Clinical Nutrition*, Volume 101, Issue 6, June 2015, Pages 1251–1262, <https://doi.org/10.3945/ajcn.114.100925>.

<sup>4</sup> Federal Interagency Forum on Child and Family Statistics, America's children: Key National Indicators of Well-being, 2019. <https://www.childstats.gov/americaschildren/#:~:text=and%20local%20levels,-.America's%20Children%3A%20Key%20National%20Indicators%20of%20Well%2DBeing%2C%202019,important%20aspects%20of%20children's%20lives>.

<sup>5</sup> Center for Disease Control and Prevention. Rates of New Diagnosed Cases of Type 1 and Type 2 Diabetes Continue to Rise Among Children, Teens. <https://www.cdc.gov/diabetes/research/reports/children-diabetes-rates-rise.html#:~:text=The%20rate%20of%20new%20cases,of%20CDC's%20Morbidity%20and%20Mortality>

<sup>6</sup> Center for Disease Control and Prevention. Chronic Kidney Disease in the United States, 2019 <https://www.cdc.gov/kidneydisease/publications-resources/2019-national-facts.html>

<sup>7</sup> American Academy of Pediatrics, About the AAP, accessed on August 15, 2020 at <https://services.aap.org/en/about-the-aap/>.

<sup>8</sup> Trasande L, et al. American Academy of Pediatrics Council on Environmental Health. Food Additives and Child Health. *Pediatrics* 142 (2) e20181408; DOI: <https://doi.org/10.1542/peds.2018-1408>.

<sup>9</sup> Codified at [5 U.S.C. § 553e\(e\)](#).

<sup>10</sup> Codified at [21 U.S.C. § 348](#) and [21 U.S.C. § 379e](#) respectively.

## A. Action requested

We specifically request that the FDA revise its regulations for: color additives at 21 C.F.R. Parts [70](#) and [71](#); food additives, GRAS substances, and food contact substances (FCS) at 21 C.F.R. Part [170](#); and food additive petitions at 21 C.F.R. Part [171](#), as follows.

- 1) Add or revise definitions for the following terms to [§ 70.3](#) for color additives and [§ 170.3](#) for food additives, GRAS substances, and food contact substances as follows.
  - a) *Substance* means a food or food component consisting of one or more ingredients and includes: food additives; substances classified as generally recognized as safe (GRAS); pesticide chemical residues in or on a raw agricultural commodity or processed food; pesticide chemicals; color additives; substances covered by a prior sanction; new animal drugs; and ingredients in, or intended for use in a dietary supplement that may be contained in the diet.
  - b) *Cumulative effect* means a toxic or pharmacological effect of a class of chemically-related substances in the diet based on the timing and duration of exposure determined in accordance with [70.16 or 170.16 as appropriate] or pharmacologically-related substances in the diet based on the timing and duration of exposure determined in accordance with [[70.11](#) or [170.18](#) as appropriate].
  - c) *Chemically-related substances* mean a group of substances the members of which are similar in molecular structure, or in physical, chemical, or biological properties.
  - d) *Pharmacologically-related substances* mean substances that share scientifically documented properties of a similar or related pharmacological effect.
  - e) *Pharmacological effect* means an effect of a substance based on any one of three attributes:
    - (1) Mechanism of action based on the pharmacologic action at the receptor, membrane or tissue level; or
    - (2) Physiological effect at the cellular, organ, system or whole-body level; or
    - (3) Chemical structure.
  - f) *Diet* means:
    - (1) Food, beverages, and substances contained therein;
    - (2) Potable water as defined at [1240.3\(m\)](#); and
    - (3) Dietary supplements as defined at [Section 201 of the act](#).
- 2) Add new [§ 70.16](#) for color additives and [§ 170.16](#) for food additives, GRAS substances, and FCSs regarding the determination of classes of chemically-related substances.

[Sec. 70.16 or 170.16 as appropriate] Tolerances for chemically-related substances in the diet.

  - (a) Substances which are similar in molecular structure, or in physical, chemical, or biological properties are regarded as a class of chemically-related substances.
  - (b) In the absence of evidence to the contrary, the pharmacological or toxic effect of any member of a class of chemically-related substances is presumed to be applicable to the class as a whole.
  - (c) In the absence of evidence to the contrary, chemically-related substances will be considered as having additive effects.
- 3) Revise [§ 70.11](#) for color additives and [§ 170.18](#) for food additives, GRAS substances, and FCSs regarding the determination of classes of pharmacologically-related substances to refer to substances in the diet instead of food additives.
- 4) Revise requirements for the content of color additive petitions, threshold of regulation submissions, FCS notifications, GRAS notifications, and food additive petitions submitted pursuant to §§ [71.1](#), [170.39](#), [170.101](#), [170.250](#), and [171.1](#) respectively to specifically provide an evaluation of any

chemically- or pharmacologically-related substances in the diet that includes the following information:

- a) Pharmacological effects of substance;
- b) Classes of pharmacologically-related substances for each pharmacological effect pursuant to [\[70.11\]](#) and [\[70.18\]](#) as appropriate];
- c) Cumulative effect of each class of pharmacologically-related substances;
- d) Classes of chemically-related substances pursuant to [\[70.16\]](#) or [\[70.18\]](#) as appropriate];
- e) Cumulative effect of each class of chemically-related substances; and
- f) Tolerance or acceptable daily intake for each class.

In Appendix A we provide the exact wording of the requested changes to the regulations. In addition, we request that FDA revise associated guidance, forms, and instructions for petitions, notification and submissions. The changes requested for 21 C.F.R. Parts 170 and 171 apply only to human food.

## **B. Statement of grounds**

When Congress defined FDA's mission in Section 1003 of the FFDCA, it declared that FDA shall protect public health by ensuring that foods are safe, wholesome, sanitary, and properly labeled.<sup>11</sup> Consistent with that mission, Congress directed the agency to consider the cumulative effect of food and color additives, taking into account any chemically- or pharmacologically-related substances in the diet, when evaluating the safety of food and color additives.<sup>12</sup> While FDA has incorporated the directive into its regulatory definition of safety for food additives, GRAS substances, and food contact substances, it has fundamentally failed to make safety determinations consistent with that statutory requirement.

This failure has significant consequences for public health, particularly for underserved communities, who already face significant health and socio-economic disparities, and for children, who are uniquely susceptible to toxic substance exposure in their diet because of: 1) their heightened vulnerability to the health effects of exposure to toxicants during key developmental periods; 2) their long time horizon for exposure to toxicants in their diet over their life span; and 3) their relatively higher intake of food and water as a proportion of their size compared to adults.

In this petition, we request that FDA correct this failure and provide specific changes designed to accomplish that objective. We support our request with an analysis of the law and document the agency's shortcomings when evaluating or make safety determinations for additives. Our reasoning is summarized as follows:

1. To ensure food is safe and protect public health, FDA needs to consider the cumulative effect of a substance, taking into account any chemically- or pharmacologically-related substances in the diet.
2. The FFDCA and FDA regulations require that safety determinations regarding the use of food additives, GRAS substances, food contact substances, color additives and new animal drugs consider the cumulative effect of a substance, taking into account any chemically- or pharmacologically-related substances in the diet.

---

<sup>11</sup> Codified at [21 U.S.C. § 393\(b\)](#).

<sup>12</sup> Sections 409 and 706 of the FFDCA, codified at [21 U.S.C. § 348](#) and [21 U.S.C. § 379e](#), respectively.

3. FDA regulations provide a general framework to consider the cumulative effect of a substance, taking into account any chemically- or pharmacologically-related substances in the diet, but leave key terms undefined.
4. FDA's regulations specifically mandate the submission of information on the cumulative effect of a substance, taking into account any chemically- or pharmacologically-related substances in the diet, for only color additive petitions and GRAS notifications.
5. Only one of almost 900 safety determinations conducted by food manufacturers and submitted to FDA for review as GRAS notifications for human food consider in a meaningful way the cumulative effect of a substance, taking into account any chemically- or pharmacologically-related substances in the diet, despite FDA regulations explicitly requiring the information.<sup>13</sup>
6. When reviewing FDA's responses to the GRAS notifications, there is no evidence that FDA raised concerns about the notifier's failure to consider the cumulative effect of a substance, taking into account any chemically- or pharmacologically-related substances in the diet.
7. FDA's failure to consider the cumulative effect of a substance, taking into account any chemically- or pharmacologically-related substances in the diet extends to all of the other notifications EDF reviewed in response to its FOIA requests.
8. FDA's guidance for industry fails to explain how food manufacturers should consider the cumulative effect of a substance, taking into account any chemically- or pharmacologically-related-substances in the diet.
9. In a different but relevant context, FDA has already considered and addressed the issue of "pharmacologically-related substances" when it defined "pharmacologic class" for drugs and biological products and could use that as a model for substances in diet.
10. FDA's definition of "substance" adopted in 1959 is limited to use in food additives but has not been updated since the rules now address GRAS and FCS.
11. FDA's failure to define "diet" in regulations, guidance and other materials has resulted in safety determinations that ignore the contribution of any chemically- or pharmacologically-related substances in potable water and dietary supplements to the cumulative effect that must be considered.

We explore each of these findings in more detail below.

***B.1 To ensure food is safe and protect public health, FDA needs to consider the cumulative effect of a substance, taking into account any chemically- or pharmacologically-related substances in the diet.***

To adequately protect public health, the safety of individual substances added to food cannot be considered in isolation and the impact of a chemical needs to be put in the context of the entire diet. Congress recognized this need when it adopted the Food Additives Amendment of 1958 and Color

---

<sup>13</sup> [GRN 107](#) for polydextrose identified 11 pharmacologically-related substances in the diet based on "laxation potential" effect.

Additives Amendment of 1960, directing FDA to consider the cumulative effect of food additives in the diet, taking into account any chemically- or pharmacologically-related substances in such diet.<sup>14</sup>

To a limited extent, FDA has recently recognized the need to look beyond individual chemicals when it:

- Revoked in 2016 the agency’s approvals of three perfluoroalkyl ethyls as additives for paper and paperboard finding that “data for subsets of long-chain [perfluorinated compounds] (demonstrating biopersistence and reproductive and developmental toxicity) are applicable to long-chain [perfluorinated compounds] on a general basis . . .”<sup>15</sup>
- Denied in 2018 a food additive petition from the Grocery Manufacturers Association, effectively prohibiting the use of industrially-produced *trans* fatty acids in food as a class because they presented a significantly increased risk of coronary heart disease.<sup>16</sup> The decision considered the cumulative effect of these substances and of natural occurring *trans* fatty acids in food.

While showing promise, these actions focused on a narrow set of chemically-related substances and ignored pharmacologically-related substances. For example, the decision regarding long-chain perfluorinated compounds (a subset of a class of substances known as per- and polyfluorinated alkyl substances (PFAS)) did not consider the cumulative effect of pharmacologically-related substances in the diet that also demonstrate reproductive and developmental toxicity risks such as bisphenol A, certain ortho-phthalates and perchlorate. In addition, the decision was grounded on a presumed distinction in biopersistence between PFAS with eight or more carbons with those having fewer than eight.

Similarly, FDA’s decision on industrially-produced *trans* fatty acids considered the risk of *cis*-saturated fatty acids but failed to consider other pharmacologically-related substances in the diet such as sodium that also contribute to a significantly increased risk of coronary heart disease. In fact, the agency never mentioned sodium in its decision even though it had already identified sodium reduction as a priority in 2016, finding “too much sodium can raise blood pressure, which is a major risk factor for heart disease and stroke” and “reducing sodium intake has the potential to prevent hundreds of thousands of premature deaths and illnesses in a decade.”<sup>17</sup>

Public health and medical organizations have recognized the need to consider related substances when determining the safety of an additive. For example, in its 2018 Policy Statement,<sup>18</sup> the American Academy of Pediatrics, “an organization of 67,000 pediatricians committed to the optimal physical, mental, and social health and well-being for all infants, children, adolescents, and young adults,”<sup>19</sup> stated that:

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

---

<sup>14</sup> Section 409 of the FFDCA, codified at [21 U.S.C. § 348](#), for food additives, and Section 706 of the FFDCA, codified at [21 U.S.C. § 379e](#), for color additives.

<sup>15</sup> FDA, Indirect Food Additives: Paper and Paperboard Components, Final Rule, 81 Federal Register 5, January 4, 2016, at page 7.

<sup>16</sup> FDA, Grocery Manufacturer’s Association; Denial of Food Additive Petition, 83 Federal Register 23382, May 21, 2018.

<sup>17</sup> FDA, Sodium Reduction, accessed on August 15, 2018 at <https://www.fda.gov/food/food-additives-petitions/sodium-reduction>.

<sup>18</sup> Trasande L, et al. American Academy of Pediatrics Council on Environmental Health. Food Additives and Child Health. Pediatrics. 2018;142(2):e20181408. <https://pediatrics.aappublications.org/content/142/2/e20181408>.

<sup>19</sup> American Academy of Pediatrics, About the AAP, accessed on August 15, 2020 at <https://services.aap.org/en/about-the-aap/>.

requirement to do so. 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. Dietary interactions may also be important, given that iodine sufficiency is essential for thyroid function.<sup>20</sup>

Thyroid toxicity is an issue of particular concern for pregnant women and the developing fetus and infants because thyroid hormones are crucial to brain development.<sup>21</sup> Children are particularly vulnerable to exposures substances in the diet known to disrupt thyroid function including some PFAS, bisphenol A, perchlorate, nitrates, and *ortho*-phthalates just to name a few.<sup>22</sup>

Similarly, the Endocrine Society, a global organization representing 18,000 endocrine professionals, issued a position statement that same year finding that:

Policy should be based on comprehensive data covering both low-level and high-level exposures, including cumulative effects, mixture effects, and other stressors. This includes synthesizing basic science (comprising animal and in vitro studies), clinical observations, and epidemiological data.<sup>23</sup>

To fulfill its statutory mission to protect public health by ensuring that foods are safe, FDA needs to consider the safety of individual substances added to food, taking into account any chemically- or pharmacologically-related substances in the entire diet.

***B.2 The FFDCa and FDA regulations require that safety determinations regarding the use of food additives, GRAS substances, food contact substances, color additives and new animal drugs consider the cumulative effect of a substance, taking into account any chemically- or pharmacologically-related substances in the diet.***

Congress enacted the Food Additives Amendment of 1958,<sup>24</sup> adding Section 409 to the FFDCa and codified it at [21 U.S.C. § 348](#). The section establishes the requirements that FDA must follow to issue regulations authorizing the use of substances in food in response to a food additive petition. Paragraph (c) provides specific procedures that the agency must follow. Subparagraph (c)(5) describes three factors that FDA must consider when it makes the safety determination. It states that:

- (5) In determining, for the purposes of this section, whether a proposed use of a food additive is safe, the Secretary shall consider among other relevant factors-
  - (A) the probable consumption of the additive and of any substance formed in or on food because of the use of the additive;

---

<sup>20</sup> Trasande L, et al. American Academy of Pediatrics Council on Environmental Health. Food Additives and Child Health. Pediatrics. 2018;142(2):e20181408. <https://pediatrics.aappublications.org/content/142/2/e20181408>.

<sup>21</sup> American Academy of Pediatrics Council on Environmental Health. Iodine deficiency, pollutant chemicals, and the thyroid: New information on an old problem. Pediatrics 2014;133:1163–1166

<sup>22</sup> Maffini MV and Neltner TN. Brain drain: The cost of neglected responsibilities in evaluating cumulative effects of environmental chemicals. J Epidemiol Community Health 2015;69:496–499

<sup>23</sup> Endocrine Society, Endocrine-Disrupting Chemicals, An Endocrine Society Position Statement. <https://www.endocrine.org/advocacy/position-statements/endocrine-disrupting-chemicals>

<sup>24</sup> [Public Law 85-929](#), 72 Stat. 1784.

- (B) **the cumulative effect of such additive in the diet of man or animals, taking into account any chemically- or pharmacologically-related substance or substances in such diet;** and
- (C) safety factors which in the opinion of experts qualified by scientific training and experience to evaluate the safety of food additives are generally recognized as appropriate for the use of animal experimentation data.” *[Emphasis added]*

In 1959, FDA promulgated regulations that defined “safe.”<sup>25</sup> In 1971, FDA revised its definition of “safe” to explicitly include the three factors that the agency must consider from 21 U.S.C. § 348(c)(5).

- (i) “Safe” means that after reviewing all available evidence, including:
  - (1) The probable consumption of the substance and of any substance formed in or on food because of its use;
  - (2) **The cumulative effect of the substance in the diet of man and animals, taking into account any chemically or pharmacologically related substance or substances in such diet;** and
  - (3) Safety factors which in the opinion of experts qualified by scientific training and experience to evaluate the safety of foods and food ingredients are generally recognized as appropriate in the use of animal experimentation data;
 the Food and Drug Administration can conclude that no significant risk of harm will result when the substance is used as intended.”<sup>26</sup> *[Emphasis added]*

This action, taken partly in response to an Executive Order by President Richard Nixon,<sup>27</sup> clarified that the three factors apply to GRAS substances.<sup>28</sup> Through these provisions, Congress and FDA recognized the need for a safety determination to put the use of the substance under consideration in the broader context of the diet and the overall impact of a safety decision on people’s health.

Today, the definition of safety, recodified at [21 C.F.R. § 170.3\(i\)](#) states:

- (i) *Safe or safety* means that there is a reasonable certainty in the minds of competent scientists that the substance is not harmful under the conditions of its intended use. It is impossible in the present state of scientific knowledge to establish with complete certainty the absolute harmlessness of the use of any substance. Safety may be determined by scientific procedures or by general recognition of safety. In determining safety, the following factors shall be considered:
  - (1) The probable consumption of the substance and of any substance formed in or on food because of its use.
  - (2) **The cumulative effect of the substance in the diet, taking into account any chemically or pharmacologically related substance or substances in such diet.**
  - (3) Safety factors which, in the opinion of experts qualified by scientific training and experience to evaluate the safety of food and food ingredients, are generally recognized as appropriate. *[Emphasis added]*

<sup>25</sup> 24 Fed. Reg. 2434 (1959) promulgating 21 C.F.R. § 121.1(i).

<sup>26</sup> 36 Fed. Reg. 12093 (1971) amending 21 C.F.R. § 121.1(i).

<sup>27</sup> President Richard M. Nixon, Special Message to Congress on Consumer Protection, October 30, 1969, Public Papers of the Presidents, pp. 888-889. “For example, I have already asked the Secretary of Health, Education, and Welfare to initiate a full review of food additives. This investigation should move as fast as our resources permit, re-examining the safety of substances which are now described by the phrase “generally recognized as safe” (GRAS).” FDA’s justification for the final rule referenced the President’s Special Message at 36 Federal Register 12093.

<sup>28</sup> 36 Fed. Reg. 12093 (1971), Friday, June 25, 1971, pages 12083 – 12156.

This definition of safety applies to food additives ([§ 170.20](#)), GRAS substances ([§ 170.30](#)), threshold of regulation for substances used in food-contact articles ([§ 170.39](#)), and food contact substances ([§ 170.100-105](#)) for human food. In addition, FDA's regulations apply this same definition of safety ([§ 570.3\(i\)](#)) to food additives and GRAS substances used in animal feed (including pet food).

The same three factors apply, with minor variations, to color additives and new animal drugs. In 1960, Congress enacted the Color Additives Amendment of 1960<sup>29</sup> that removed color additives from the definition of food additives and established the requirements that FDA must follow to issue regulations authorizing the use of color additives for foods, drugs, devices, and cosmetics in response to a color additive petition. The Act added Section 706 to the FFDCa and codified it at [21 U.S.C. § 379e](#). Paragraph (b) provides specific procedures that the agency must follow to approve use of a color additive. Subparagraph (b)(5)(A) describes four factors that FDA must consider in making the safety determination. It states that:

- (5) (A) In determining, for the purposes of this section, whether a proposed use of a color additive is safe, the Secretary shall consider, among other relevant factors-
  - (i) the probable consumption of, or other relevant exposure from, the additive and of any substance formed in or on food, drugs, or cosmetics because of the use of the additive;
  - (ii) **the cumulative effect, if any, of such additive in the diet of man or animals, taking into account the same or any chemically or pharmacologically related substance or substances in such diet;**
  - (iii) safety factors which, in the opinion of experts qualified by scientific training and experience to evaluate the safety of color additives for the use or uses for which the additive is proposed to be listed, are generally recognized as appropriate for the use of animal experimentation data; and
  - (iv) the availability of any needed practicable methods of analysis for determining the identity and quantity of (I) the pure dye and all intermediates and other impurities contained in such color additive, (II) such additive in or on any article of food, drug, or cosmetic, and (III) any substance formed in or on such article because of the use of such additive. *[Emphasis added]*

Eight years later, Congress took similar action for new animal drugs when it enacted the Animal Drug Amendment of 1968.<sup>30</sup> The Act removed new animal drugs from the definition of food additives and established the requirements that FDA must follow to issue regulations authorizing the use of the substances. In that Act, Congress added Section 360b to the FFDCa and codified it at [21 U.S.C. § 512](#). Paragraph (d) provides the specific procedures that the agency must follow to evaluate the use of a new animal drug. Subparagraph (d)(2) describes four factors that FDA must consider when determining the safety of a new animal drug. It states that:

- (2) In determining whether such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof, the Secretary shall consider, among other relevant factors,
  - (A) the probable consumption of such drug and of any substance formed in or on food because of the use of such drug,
  - (B) **the cumulative effect on man or animal of such drug, taking into account any chemically or pharmacologically related substance,**

---

<sup>29</sup> Public Law 86-618, 74 Stat. 397.

<sup>30</sup> Public Law 90-399, 82 Stat. 342.

- (C) safety factors which in the opinion of experts, qualified by scientific training and experience to evaluate the safety of such drugs, are appropriate for the use of animal experimentation data, and
  - (D) whether the conditions of use prescribed, recommended, or suggested in the proposed labeling are reasonably certain to be followed in practice.
- Any order issued under this subsection refusing to approve an application shall state the findings upon which it is based. *[Emphasis added]*

The agency incorporated the four factors into its regulations. Specifically, [§ 514.111](#) states that the FDA Commissioner shall refuse to approve a new animal drug application if the Commissioner determined that:

- (4) Upon the basis of the information submitted to the Food and Drug Administration as part of the application, or upon the basis of any other information before it with respect to such drug, it has insufficient information to determine whether such drug is safe for use under such conditions. In making this determination the Commissioner shall consider, among other relevant factors:

- ...
  - (ii) **The cumulative effect on man or animal of such drug, taking into account any chemically or pharmacologically related substances; ([§ 514.111](#))** *[Emphasis added]*

As a result, safety determinations for the following categories of uses of substances in human food or animal feed must consider the cumulative effect of the substance in the diet, taking into account any chemically- or pharmacologically-related substance or substances in such diet:

- 1) Food additives;
- 2) GRAS substances;
- 3) Food contact substances;
- 4) Color additives; and
- 5) New animal drugs.

In summary, after first establishing in 1958 the requirement that safety determinations consider the cumulative effect of the substance, taking into account any chemically- or pharmacologically-related substances in the diet, Congress reaffirmed the approach twice – for color additives in 1960 and for new animal drugs in 1968. And in 1971, FDA explicitly stated that the requirement applied to GRAS substances.<sup>31</sup>

---

<sup>31</sup> FDA last modified its definition of safe and safety at § 170.3(i) in its GRAS final rule at [81 Federal Register 54960](#) (August 17, 2016). In that rule, it did not alter the three factors. Note that the final rule has been challenged in court for multiple deficiencies and is awaiting a court decision. See *Ctr. for Food Safety v. Price*, No. 17-cv-3833 (VSB), 2018 WL 4356730 (S.D.N.Y. Sept. 12, 2018), ECF No. 44 (order denying motion to dismiss as to CFS and EDF). The rule allows the food industry to make GRAS safety determinations in secret without notifying FDA.

***B.3 FDA regulations provide a general framework to consider the cumulative effect of a substance, taking into account any chemically- or pharmacologically-related substances in the diet, but leave key terms undefined.***

Within six months of passage of the Food Additives Amendment of 1958, FDA finalized a rule establishing procedures to implement the law.<sup>32</sup> The rule defined safe as follows.

- (i) “Safe” means there is convincing evidence which establishes with reasonable certainty that no harm will result from the intended use of the food additive.<sup>33, 34</sup>

The rule also established a framework for how FDA will set tolerances – essentially acceptable daily intake (ADI) levels – for pharmacologically-related food additives.<sup>35</sup> The requirement was recodified at [§ 170.18](#) for human foods and at [§ 570.18](#) for animal feed and remains unchanged today. Those two sections say:

- (a) **Food additives that cause similar or related pharmacological effects will be regarded as a class, and in the absence of evidence to the contrary, as having additive toxic effects and will be considered as related food additives.**
- (b) **Tolerances established for such related food additives may limit the amount of a common component that may be present, or may limit the amount of biological activity (such as cholinesterase inhibition) that may be present or may limit the total amount of related food additives that may be present.**
- (c) **Where food additives from two or more chemicals in the same class are present in or on a food, the tolerance for the total of such additives shall be the same as that for the additive having the lowest numerical tolerance in this class,** unless there are available methods that permit quantitative determination of the amount of each food additive present or unless it is shown that a higher tolerance is reasonably required for the combined additives to accomplish the physical or technical effect for which such combined additives are intended and that the higher tolerance will be safe.
- (d) Where residues from two or more additives in the same class are present in or on a food and there are available methods that permit quantitative determination of each residue, the quantity of combined residues that are within the tolerance may be determined as follows:
  - (1) Determine the quantity of each residue present.
  - (2) Divide the quantity of each residue by the tolerance that would apply if it occurred alone, and multiply by 100 to determine the percentage of the permitted amount of residue present.

---

<sup>32</sup> 24 Federal Register 2434 (March 28, 1959). § 121.5 describes how safety factors are to be considered, setting a safety factor of 100 to 1 in applying animal testing data to humans. FDA recodified the section as [§ 170.22](#) verbatim. There is no section explicitly describing how the first factor regarding probable consumption is to be considered.

<sup>33</sup> 24 Federal Register 2434 (March 28, 1959) promulgating 21 C.F.R. § 121.1(i).

<sup>34</sup> When FDA promulgated rules implementing the Color Additives Amendment of 1960, it mirrored this definition of safety. The agency recodified the definition at [§ 70.3\(i\)](#) verbatim. It remains unchanged today and is consistent with Congress’ intent that color additives be subjected to greater scrutiny than food additives since the latter “have no value at all, except so-called eye appeal.” Color Additives Amendment of 1960: Hearings on H.R. 7624 and S. 2197 Before the H. Comm. on Interstate and Foreign Commerce, 86<sup>th</sup> Cong., 2d Sess. 108 (1960) (statement of Rep. James Delaney of New York). This intent is further shown by the fact that Congress did not include a GRAS exemption for color additives. See 21 U.S.C. § 321(t). The definitions of safe for color additives and food additives diverged in 1971 when FDA revised the definition for food additives in response to a directive by President Nixon to establish procedures to conduct safety determinations of GRAS substances. In that rulemaking, FDA amended the definition of safe to include the three factors as described above and extended it to GRAS substances.

<sup>35</sup> 24 Federal Register 2434 (March 28, 1959) promulgating 21 C.F.R. § 121.4.

- (3) Add the percentages so obtained for all residues present.
- (4) The sum of the percentages shall not exceed 100 percent. *[Emphasis added]*

The regulation essentially provides a six-step framework to determine an ADI or tolerance for a food additive in the context of the diet rather than in isolation:

- 1) Identify the pharmacological effects of a given food additive;
- 2) Identify other food additives that have similar or related pharmacologic effects;
- 3) Designate as a class those food additives having similar or related pharmacologic effects;
- 4) Unless there is evidence to the contrary, assume the effects are additive;
- 5) Set a tolerance that either limits the:
  - a. Amount of a common component that may be present; or
  - b. Amount of biological activity that may be present; or
  - c. Total amount of the class of related food additives that may be present.
- 6) If two or more food additives in a class may be present in a food, set the tolerance based on the most hazardous additive (the one with the lowest numerical tolerance) in the class unless another approach is safe and appropriate.

Despite being promulgated in 1959 and undergoing no changes in the intervening 60 years, the section has aged reasonably well. Still there are some provisions that warrant updating.

First, the text does not explicitly require consideration of cumulative effects of pharmacologically-related substances in the diet. In 1971, when the agency added the three factors into the definition of safe and explicitly applied the definition to GRAS substances, it did not appear to see the need to make the linkage. As noted below, EDF found that [§ 170.18](#) is never mentioned in FDA’s guidance on setting tolerances and found no evidence that it has been applied to safety determinations. Making the linkage explicit by adding a definition of cumulative effect that references [§ 170.18](#) should significantly reduce potential confusion.

Second, the section refers only to food additives as potential members of the class of pharmacologically-related substances, effectively excluding GRAS substances, color additives, and new animal drugs from the analysis.<sup>36</sup> This narrow scope is clearly inconsistent with the FFDCA requirements to consider “any chemically or pharmacologically related substance or substances in such diet.” [21 U.S.C. § 348\(c\)\(5\)\(B\)](#).

In the context of 1959, it is not surprising that FDA would think that food additives were all that was necessary. At the time, color additives and new animal drugs were included in the definition of food additives. Congress removed them in 1960 and 1968 respectively. In addition, the agency was less concerned with GRAS substances, especially because another section made clear that it expected to get a written request from food manufacturers in order to determine whether the designation was appropriate.<sup>37</sup> Given the growth of GRAS substances and FDA’s decision to allow food manufacturers to make safety determinations for GRAS substances without notice to or review by the agency, we believe it is essential to expand the section to reference substances in the diet to avoid misunderstanding.

Third, the regulation uses the term “pharmacological effects” without defining it, although it does use it as synonymous with “toxic effects” near the end of the same sentence.

Fourth, the classification framework at [§ 170.18](#) is focused on pharmacologically-related substances and does not explicitly apply to chemically-related substances. To avoid confusion, we think it would be

---

<sup>36</sup> Food contact substances was not created as a distinct category of food additives until 1997.

<sup>37</sup> See 21 C.F.R. § 121.3 in 24 Federal Register 2434 (March 28, 1959).

helpful for FDA to define both chemically-related substances and pharmacologically-related substances. In addition, we think FDA should promulgate a new section, §170.16, that addresses chemically-related substances using the framework from [§ 170.18](#) and links that section to the new definition of cumulative effect.

The foregoing recommendations also apply to FDA's color additive regulations that the agency promulgated in response to the Color Additives Amendment of 1960. In [§ 70.11](#), the agency retained the same framework as in [§ 170.18](#). That rule remains unchanged today after being recodified at [§ 70.11](#).<sup>38</sup> It says:

Sec. 70.11 Related substances.

- (a) Different color additives may cause **similar or related pharmacological or biological effects**, and, in the absence of evidence to the contrary, those that do so will be considered to have **additive toxic effects**.
- (b) Food additives may also cause **pharmacological or biological effects** similar or related to such effects caused by color additives, and, in the absence of evidence to the contrary, those that do so will be considered as having additive toxic effects.
- (c) Pesticide chemicals may also cause **pharmacological or biological effects** similar or related to such effects caused by color additives, and, in the absence of evidence to the contrary, those that do so will be considered to have additive toxic effects.
- (d) In establishing tolerances for color additives, the Commissioner will take into consideration, among other things, the amount of any common component permitted in other color additives, in food additives, and in pesticide chemical residues as well as the similar biological activity (such as cholinesterase inhibition) produced by such substance. *[Emphasis added]*

However, there is a difference in the color additive language. FDA added “or biological” to further describe the effects that may be pharmacologically-related. This language is not in the statute.

In summary, we request that:

- Amend § 170.18 to replace “food additives” with “substances in the diet” throughout to more closely match the statutory requirement;
- Amend § 70.11 to be clear that the statutory requirement applies to “substances in the diet” and not only “food additives;” and
- Adopt new sections for Parts 70 and 170 that apply the framework for pharmacologically-related substances to chemically-related substances.
- Add definitions of “cumulative effect,” “pharmacologic effect,” “pharmacologically-related substances,” and “chemically-related substances” to § 70.3 and § 170.3 that links the terms together and to the § 70.11 and § 170.18.

---

<sup>38</sup> Note that it did not limit the scope of the review to color additives, including food additives and pesticide chemicals, two categories of chemicals commonly found in the diet.

***B.4 FDA's regulations specifically mandate the submission of information on the cumulative effect of a substance, taking into account any chemically- or pharmacologically-related substances in the diet, for only color additive petitions and GRAS notifications.***

FDA regulations specify the mandatory content of a petition or notice. If they specifically require that information on the cumulative effect of chemically-related and pharmacologically-related substances must be provided, it would make it more straightforward for the agency to ensure the evaluation was properly done.

EDF found that the regulations for only two of the four types, color additive petitions and GRAS notifications, specifically require that the necessary information is submitted. The other two, food additive petitions and FCS Notifications, are silent. In addition, none of the forms or associated instructions provide a prompt of the requirement even when the corresponding regulation says it is needed (see Appendix B for details). To the contrary, they are focused on the additive and largely ignore the possibility of related substances in the diet.

The agency's failure does not excuse industry from providing the required information, but it certainly is a shortcoming that needs to be addressed. This reinforces the need for FDA to be clear in its regulations, guidance documents, forms, and instructions that the information is essential and must be provided.

- 1) **Color additive petitions:** [Section 71.1](#) explicitly requires information on any chemically- or pharmacologically-related substances in the diet. It says:
  - (c) Petitions shall include the following data and be submitted in the following form:
    - E. Complete data which will allow the Commissioner to consider, among other things, the probable consumption of, and/or other relevant exposure from the additive and of any substance formed in or on food, drugs, or cosmetics because of such additive; and **the cumulative effect, if any, of such additive in the diet of man or animals, taking into account the same or any chemically or pharmacologically related substance or substances in the diet including, but not limited to food additives and pesticide chemicals for which tolerances or exemptions from tolerances have been established.**
- 2) **GRAS Notice for Human Food (GRN):** [Section 170.250](#), promulgated in 2016, explicitly requires information that takes into account any chemically- or pharmacologically-related substances in the diet. It says:

In Part 6 of your GRAS notice, you must include a narrative that provides the basis for your conclusion of GRAS status, in which:

  - (a)(1) You must explain why the data and information in your notice provide a basis for your view that the notified substance is safe under the conditions of its intended use. In your explanation, you must address the safety of the notified substance, **considering all dietary sources and taking into account any chemically or pharmacologically related substances in such diet; [Emphasis added]**

We ask that FDA amend the § 170.101 for FCS notifications and § 171.1 for food additive petition to specifically mandate the submission of the necessary information.

***B.5 Only one of almost 900 safety determinations conducted by food manufacturers and submitted to FDA for review as GRAS notifications for human food consider in a meaningful way the cumulative effect of a substance, taking into account any chemically- or pharmacologically-related substances in the diet, despite FDA regulations explicitly requiring the information.***

To determine whether safety determinations conducted by food manufacturers for GRAS substances for human food consider in a meaningful way the cumulative effect of the substance, taking into account any chemically- or pharmacologically-related substances in the diet, EDF reviewed the [GRAS notifications](#) voluntarily submitted to FDA for review. Under this program, notifiers seek a “no questions” letter from the agency that agrees with, but does not approve, the manufacturer’s conclusion that the use is safe and compliant with the FFDCA and agency regulations. The agency posts the notice and its “no questions” letters on its website in a [searchable database](#).

EDF downloaded the 877 notices from the website as of March 24, 2020,<sup>39</sup> searched for either “cumulative effect” or “pharmacologic” presuming that any analysis of the cumulative effect of pharmacologically-related substances would include those terms. When EDF’s search found either word, it looked for context and reviewed the document more closely when warranted.

Only 112 GRAS notices (13%) used the term “cumulative effect.” However, 95 of those simply acknowledged the requirement to consider the cumulative effect and conducted no evaluation. Of the remaining 17 GRAS notices, 16 only considered chemically-related substances without defining a class and establishing a tolerance for a class or addressing pharmacologically-related substances. The one remaining GRAS notice, [GRN 107](#) for polydextrose, identified 11 pharmacologically-related substances in the diet based on “laxation potential” effects.

However, after considering the average daily amount at which half of the tested subjects experience laxation of the substances, the notice stopped short of establishing a tolerance for the class and only considered the effect from polydextrose alone on the risk of laxation symptoms. In addition, the eleven omitted a sugar alcohol, hydrogenated starch hydrolysate, as well as allulose, a sugar substance that is not a sugar alcohol but has similar laxative effects.

From our perspective, the notifier conducted a modest, but incomplete evaluation since it missed other substances in the diet with similar effect and did not establish a tolerance for the class. Appendix C summarizes EDF’s methodology and findings from its review of the GRAS notifications.

Based on these results for voluntary GRAS notifications, clearly, food manufacturers are not following the law when making safety determinations for GRAS substances. Surprisingly, they are not even following the mandatory requirement at [§ 170.250\(a\)\(1\)](#) that says “In your explanation, you **must** address the safety of the notified substance, considering all dietary sources and taking into account any chemically or pharmacologically related substances in such diet.”<sup>40</sup> *[Emphasis added]*

To help remedy the failure of food manufacturers to follow the law and FDA’s request for the information, we recommend that the agency revise requirements for the content of color additive petitions, threshold of regulation submissions, food contact substance notifications, GRAS notifications,

---

<sup>39</sup> The total does not include six notices that had broken or incorrect links. In response to EDF’s request, FDA corrected the problem.

<sup>40</sup> The requirement was promulgated in the August 17, 2016 (81 Federal Register 54960). However, the requirement mirrored the 1997 proposed rule (62 Federal Register 18938, April 17, 1997) that FDA and food manufacturers were using to define the GRAS notifications. Food manufacturers submitted more than 200 GRAS notifications pursuant to the 2016 final rule.

and food additive petitions submitted pursuant to §§ [71.1](#), [170.39](#), [170.101](#), [170.250](#), and [171.1](#) respectively to explicitly include the following information:

- Pharmacological effects of substance;
- Classes of pharmacologically-related substances for each pharmacological effect pursuant to [\[70.11\]](#) and [170.18](#) as appropriate];
- Cumulative effect of each class of pharmacologically-related substances;
- Classes of chemically-related substances pursuant to [\[70.16 or 170.16\]](#) as appropriate];
- Cumulative effect of each class of chemically-related substances; and
- Tolerance or acceptable daily intake for each class.

***B.6 When reviewing FDA’s responses to the GRAS notifications, there is no evidence that FDA raised concerns about the notifier’s failure to consider the cumulative effect of a substance, taking into account any chemically- or pharmacologically-related substances in the diet.***

About 82% of almost 700 “no questions” letters issued by the agency indicate FDA considers the food manufacturer’s GRAS safety determination to be sufficient to meet the requirements of the law. Most of the remainder withdrew the notice, typically to avoid agency objections. Only [17](#) have received a letter finding that the notice does not provide a basis for a GRAS safety determination.<sup>41</sup>

EDF reviewed the 709 “no questions” letters that the agency provided to the petitioners. It found no mention by FDA of the notifiers’ failure to consider the cumulative effect of chemically- or pharmacologically-related substances in the diet in their letters, despite the explicit requirement in [§ 170.250\(a\)\(1\)](#) that food manufacturers include it in the notice.

***B.7 FDA’s failure to consider the cumulative effect of a substance, taking into account any chemically- or pharmacologically-related substances in the diet extends to all of the other notifications EDF reviewed in response to its FOIA requests.***

The GRAS notices are the only public repository of food manufacturers safety determinations. Over the years, EDF has submitted Freedom of Information Act (FOIA) requests for [32 food contact substance notifications](#) (FCN) related to per- and poly fluorinated alkyl substances. It reviewed those responses and found no consideration of the cumulative effect of the substance, taking into account any chemically- or pharmacologically-related substances in the diet.

The FOIA responses also included the correspondence between FCN notifiers and FDA for more than 30 notices. EDF found no request for or consideration of the cumulative effect of pharmacologically-related substances in the diet in those correspondences.

---

<sup>41</sup> The one GRAS notification, [GRN 107](#) for polydextrose, was withdrawn at notifiers request. EDF has not submitted a FOIA request to determine the reason.

**B.8 FDA’s guidance for industry fails to explain how food manufacturers should consider the cumulative effect of a substance, taking into account any chemically- or pharmacologically-related substances in the diet.**

Beyond regulations, FDA often uses guidance documents to help explain to industry how they should ensure compliance with the law. Therefore, EDF reviewed those documents to determine if the agency had provided guidance on how the cumulative effect of pharmacologically-related substances in the diet should be considered. It found next to nothing and what was there was either incomplete, confusing, or simply a restatement of the requirement without any evaluation or further analysis.

EDF started with a review of the FDA’s guidance documents on the topic of food using the agency’s [on-line search tool](#)<sup>42</sup> and identified 21 documents that related in some way to food additives, color additives, food contact substances, or GRAS substances. It reviewed the text of the documents, focusing on key terms used in the FFDCA and FDA regulations describing the factor to be considered in safety assessment as well as citations to those sections of the law and regulations. Specifically, it searched for the following:

- Use of the terms – cumulative effect, chemically-related, pharmacological effect, pharmacologically-related substances – that are used in consideration as described by Congress in the FFDCA or by FDA in the implementing regulations.
- Reference to the key regulations or statutory provisions – § 70.3(i), § 70.11, § 170.3(i), § 170.18, § 570.3(i), § 570.18, § 409(c)(5), or § 379e(b)(5)(A) – that are directly related to the consideration.

As described in Appendix B, EDF categorized the results of its review of the documents as follows:

- *No assistance*: Ten guidance documents made no reference to the consideration and provided no assistance.
- *Incomplete*: Five guidance documents were incomplete, and could be misleading, either because they: 1) only provided the opening part of the definition of safety and omitted the part that listed the three factors that must be considered– probable consumption, cumulative effect, and safety factors; or 2) paraphrased the requirement in a manner that limited the assessment to the additive and not pharmacologically-related substances in the diet.
- *Confuses terms*: Four guidance documents create confusion because they used the words “cumulative exposure” or “cumulative intake” without distinguishing them from the statutory term of “cumulative effect.”
- *Only restates requirement*: Two guidance documents simply restate the requirement, which is helpful, but provides no real guidance to industry.

While it is not an excuse for food manufacturers to fail to follow the law, FDA’s shortcomings in the guidance create confusion that needs to be corrected.

---

<sup>42</sup> <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>

**B.9 In a different but relevant context, FDA has already considered and addressed the issue of “pharmacologically-related substances” when it defined “pharmacologic class” for drugs and biological products and should use that as a model for substances in diet.**

In 2006, FDA promulgated a rule that required labels for human prescription drugs and biological products to “make it easier for health care practitioners to access, read, and use information in prescription drug labeling.”<sup>43</sup> It was designed to “enhance the safe and effective use of prescription drug products and reduce the number of adverse reactions resulting from medication errors due to misunderstood or incorrectly applied drug information.” [Section 201.57\(a\)\(6\)](#) describes the indications and usage that must appear on the prescription drug label. FDA revised the provision to require identification of the “pharmacologic class” of the drug if it is a member of an “established pharmacologic class.”

To be clear, by referring to FDA’s drug labeling regulations, we do NOT suggest that food additives, GRAS substances, food contact substances, and color additives are drugs or that they should be labeled as such; they have distinctly different purposes and safety standards. Rather, we maintain that the scientific basis for evaluating and classifying pharmacological effects of these substances are the same since the body does not distinguish between a drug and a food additive when both have the same effect (*e.g.*, bind to hormone receptor) or utilize the same transporter (*e.g.*, sodium/iodide symporter).

In 2009, FDA issued implementing guidance titled “[Labeling for Human Prescription Drug and Biological Products — Determining Established Pharmacologic Class for Use in the Highlights of Prescribing Information](#).” This provides a science-based approach to defining pharmacologically-related substances that is both relevant and appropriate for additives. It defines a “pharmacologic class” as follows:

For purposes of this guidance, a *pharmacologic class* is a group of drugs that share scientifically documented properties. Specifically, for purposes of this guidance, *pharmacologic class* is defined on the basis of any one of the following three attributes of the drug:

1. **Mechanism of action (MOA)** — Pharmacologic action at the receptor, membrane, or tissue level
2. **Physiologic effect (PE)** — Pharmacologic effect at the organ, system, or whole body level
3. **Chemical structure (CS).**<sup>44</sup>

For drug labeling purposes, only “Established Pharmacologic Class” needs to be identified. To be “established” the effect or action must be both scientifically valid and clinically meaningful. Those terms are described as follows:

- A *scientifically valid* pharmacologic class is supported by documented and submitted empiric evidence showing that the drug’s pharmacologic class is known, not theoretical, and relevant and specific to the indication.
- A *clinically meaningful* pharmacologic class term or phrase enhances the ability of professionals to understand physiologic effects related to the indication or to anticipate undesirable effects that may be associated with the drug or pharmacologic class.

Since the “clinically meaningful” requirement is designed to guide healthcare practitioners reading a drug label to help them consider whether to prescribe a particular drug or to recognize a potential adverse

---

<sup>43</sup> FDA, Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Federal Register 3921 (January 24, 2006).

<sup>44</sup> <https://www.fda.gov/media/77834/download> on page 3.

reaction, we do not think it is appropriate to a safety determination for an additive to food. Therefore, for additives to food, we think FDA should adopt the definition of “pharmacologically-related substances” that is similar to “pharmacologic class” rather than “established pharmacologic class” and be specific that the class should be based on scientifically valid information.

To accomplish this objective, we request that FDA amend § 70.3 and § 170.3 to add definitions of “cumulative effect,” “chemically-related substances,” “pharmacologically-related substances,” and “pharmacological effect,” as follows:

- *Cumulative effect* means a toxic or pharmacological effect of a class of chemically-related substances in the diet determined in accordance with 170.16 or pharmacologically-related substances in the diet determined in accordance with [170.18](#).
- *Chemically-related substances* mean a group of substances the members of which are similar in molecular structure, or in physical, chemical, or biological properties.
- *Pharmacologically-related substances* mean substances that share scientifically documented properties of a similar or related pharmacological effect.
- *Pharmacological effect* means an effect of a substance based on any one of three attributes:
  - (1) Mechanism of action based on the pharmacologic action at the receptor, membrane or tissue level; or
  - (2) Physiological effect at the cellular, organ, system or whole-body level; or
  - (3) Chemical structure.

***B.10 FDA’s definition of “substance” adopted in 1959 is limited to use in food additives but has not been updated since the rules now address GRAS and FCS.***

In the Food Additives Amendment of 1958, Color Additives Amendment of 1960 and New Animal Drug Act of 1968, Congress directed FDA to consider the cumulative effect of the substance, taking into account any chemically- or pharmacologically-related substances in the diet. However, the FFDCA did not define “substance.”

In 1959, FDA promulgated regulations<sup>45</sup> implementing the Food Additives Amendment of 1958 that defined “substance” as follows:

(g) The word *substance* in the definition of the term "food additive" includes a food or food component consisting of one or more ingredients. [Section 121.4]

Today, the definition remains the same. It has only been recodified to [§ 170.3\(g\)](#) for human food and [§ 570.3\(g\)](#) for animal feed.

While the definition references food additives, FDA’s 2010 guidance titled “[Considerations Regarding Substances Added to Foods, Including Beverages and Dietary Supplements](#)” extends it to other substances covered by Title 170. It states that:

We are issuing this guidance for two purposes. The first purpose of the guidance is to remind manufacturers and distributors of conventional foods about the requirements of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) regarding substances added to conventional foods, including beverages. **“Substance” is defined in FDA’s food additive regulations to include foods and food components consisting of one or more ingredients (21 CFR 170.3(g)).** Thus, a

---

<sup>45</sup> 24 Federal Register 2434 (March 28, 1959) promulgating 21 C.F.R. § 121.1(i).

**“substance” for purposes of the regulations and this guidance may be a food (e.g., an apple) that can be eaten on its own as well as used as an ingredient in other foods, or it may be a food that is used only as a component of other foods (e.g., flour).** A second purpose of the guidance is to remind dietary supplement manufacturers and distributors that the same requirements apply to certain substances that are added to dietary supplements -- namely, those that are not dietary ingredients as defined in section 201(ff)(1) of the FD&C Act (21 U.S.C. § 321(ff)(1)). [*Emphasis added*].

In addition, substance includes “pesticide chemicals” applies to food. For example, the FFDCA also specifically refers to a “pesticide chemical” as a substance when it defines the term.

[T]he term "pesticide chemical" means any substance that is a pesticide within the meaning of the Federal Insecticide, Fungicide, and Rodenticide Act [7 U.S.C. 136 et seq.], including all active and inert ingredients of such pesticide. Notwithstanding any other provision of law, the term "pesticide" within such meaning includes ethylene oxide and propylene oxide when such substances are applied on food. [[21 U.S.C. § 321\(q\)\(1\)\(A\)](#)]

Therefore, we think it reasonable to revise the definition of “substances” to include all those substances exempted from the statutory definition of “food additives” at 21 U.S.C. § 321(s) because they were regulated by other programs but may still be in the diet. Specifically, we recommend updating the definition of substance in [21 C.F.R. § 70.3](#) and [21 C.F.R. § 170.3](#) to say:

*Substance* means a food or food component consisting of one or more ingredients and includes: food additives; substances classified as generally recognized as safe (GRAS); pesticide chemical residues in or on a raw agricultural commodity or processed food; pesticide chemicals; color additives; substances covered by a prior sanction; new animal drugs; and ingredients in, or intended for use in a dietary supplement that may be contained in the diet.

***B.11 FDA’s failure to define “diet” in regulations, guidance and other materials has resulted in safety determinations that ignore the contribution of any chemically- or pharmacologically-related substances in potable water and dietary supplements to the cumulative effect that must be considered.***

In the Food Additives Amendment of 1958 and Color Additives Amendment of 1960, Congress directed FDA to consider the cumulative effect of the substance, taking into account any chemically- or pharmacologically-related substances in the diet. However, the FFDCA did not define “diet.” Unfortunately, EDF could not find a definition of diet in FDA’s regulations or guidance. Clearly it includes food which Congress broadly defines as:

(f) The term "food" means (1) articles used for food or drink for man or other animals, (2) chewing gum, and (3) articles used for components of any such article. [[21 U.S.C. § 321\(f\)](#)]

However, if Congress intended to limit the meaning of “diet” to “food,” it would have used the word food instead of diet. Therefore, although we think potable water should be included in the definition of food, since FDA has not generally interpreted food or beverage to include potable water, we think diet should explicitly include potable water. Functionally, there is no difference between bottled water, which FDA regulates, and tap water, which the Environmental Protection Agency (EPA) regulates. No matter how it is delivered, water is an essential nutrient and the cumulative effect of the substance, taking into account any chemically- or pharmacologically-related substances in the potable water should be considered.

Whether or not FDA regulates the medium is irrelevant, considering the effect of these substances does not mean the agency has authority over them.

We also think food includes dietary supplements and ingredients in those products. Until Congress enacted the Dietary Supplement Health and Education Act of 1994,<sup>46</sup> dietary supplement ingredients were regulated as food additives. As support for our position, look no further than the labeling requirements for health claims on food at [§ 101.14](#). Paragraph (a) defines a health claim as:

- (1) *Health claim* means any claim made on the label or in labeling of a food, including a dietary supplement.

It is also worth noting that the same paragraph has the following definition of a substance:

- (2) *Substance* means a specific food or component of food, regardless of whether the food is in conventional food form or a dietary supplement that includes vitamins, minerals, herbs, or other similar nutritional substances.

In summary, we think FDA should adopt a definition of diet in the relevant section for Parts 70, 170, and 570 as follows:

*Diet* means:

- (1) Food including beverages;
- (2) Potable water as defined at [1240.3\(m\)](#);
- (3) Dietary supplements as defined at [Section 201 of the act](#), and
- (4) Substances contained in food, potable water, and dietary supplements.

## Summary

From our review of the evidence, FDA has failed to follow a requirement that Congress included in the law with the intent to protect the public from cumulative effects leading to chronic diseases potentially caused by consumption of classes of chemically- or pharmacologically-related substances collectively present in the diet. This failure has exposed vulnerable populations to unnecessary substances and left the health of Americans at risk. We now ask the agency to redress this deficiency by taking the necessary steps to:

- Update its rules by defining key terms so they remove any ambiguity and removing outdated references;
- Issue guidance to industry to explain the steps those conducting safety determinations should take to follow the law; and
- Revise its forms for notices and petitions to more clearly require the necessary information.

## C. Environmental impact

This citizens petition is categorically excluded from the need to prepare an Environmental Assessment under 21 CFR § 25.30(h) as an “Issuance, amendment, or revocation of procedural or administrative regulations and guidance documents, including procedures for submission of applications for product development, testing and investigational use, and approval.” The requested regulations and guidance documents clarify an existing statutory requirement to ensure compliance.

---

<sup>46</sup> Public Law 103-417-OCT. 25, 1994, 108 STAT. 4325

We have identified no extraordinary circumstances as defined at 21 CFR § 25.21 for the action requested in this petition which would require the submission of an Environmental Assessment.

**D. Economic impact**

Not requested by FDA.

**E. Certification**

The undersigned certifies, that, to their best knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.



Tom Neltner, Chemicals Policy Director  
Environmental Defense Fund  
1875 Connecticut Ave. NW  
Washington, DC 20009  
202-572-3263  
[tneltner@edf.org](mailto:tneltner@edf.org)  
Maricel Maffini  
Independent Consultant  
Frederick, MD 21701  
617-470-3842  
[drmvma@gmail.com](mailto:drmvma@gmail.com)

Sara H. Goza, MD, FAAP, President  
American Academy of Pediatrics  
60113<sup>th</sup> St. NW, Suite. 400N  
Washington, DC 20005

Georges C. Benjamin, MD, Executive Director  
American Public Health Association  
800 I Street NW  
Washington, DC 20001

Lisette van Vliet, Senior Policy Coordinator  
Breast Cancer Prevention Partners  
1388 Sutter Street, Suite 400  
San Francisco, CA 94109-5400  
415-321-2912

Jaydee Hanson, Policy Director  
Center for Food Safety  
660 Pennsylvania Avenue, SE  
Washington DC 20003  
Cell: 703-231-5956

Jaclyn Bowen MPH, MS, Executive Director  
Clean Label Project  
280 E. 1st Ave.  
Broomfield, CO 80038  
734-678-9871

Thomas Gremillion, Director of Food Policy  
Consumer Federation of America  
1620 I Street, NW  
Washington, DC 20006  
803-447-6639

Brian Ronholm, Director of Food Policy  
Consumer Reports  
1101 17th St. NW - #500  
Washington, DC 20036  
202-744-5291

Robert Lash, MD, Interim CEO  
Endocrine Society  
2055 L St. NW  
Washington, DC 20036  
202-971-3636

Michael Belliveau, Executive Director  
Environmental Health Strategy Center  
565 Congress Street  
Portland, ME 04101  
207-631-5565

Melanie Benesh, Legislative Attorney  
Environmental Working Group  
1436 U St. NW  
Washington, DC 20009  
202-669-4461

Charlotte Brody, National Director  
Jane Houlihan, Research Director  
Healthy Babies Bright Futures  
703 Concord Avenue  
Charlottesville VA 22903

- Appendix A: Specific Changes Requested to FDA's Regulations
- Appendix B: Review of FDA's Regulations, Forms, and Associated Instructions for Industry Regarding Petitions and Notifications
- Appendix C: Review of GRAS Notifications
- Appendix D: Review of FDA Guidance to Industry

## Appendix A: Specific Changes Requested to FDA's Regulations

We specifically request that FDA revise its regulations: a) for color additives at 21 C.F.R. Parts [70](#) and [71](#); b) for food additives, GRAS substances, and food contact substances at 21 C.F.R. Part [170](#); and c) for food additive petitions at 21 C.F.R. Part [171](#). The changes requested for 21 C.F.R. Part 170 apply only to human food. We are not requesting at this time that corresponding changes be made to 21 C.F.R. Part 570 for animal food.

**1. Revise [§ 70.3](#) regarding definitions for color additives by adding new paragraphs (w) to (bb) as follows:**

- (w) Substance means a food or food component consisting of one or more ingredients and includes: food additives; substances classified as generally recognized as safe (GRAS); pesticide chemical residues in or on a raw agricultural commodity or processed food; pesticide chemicals; color additives; substances covered by a prior sanction; new animal drugs; and ingredients in, or intended for use in a dietary supplement that may be contained in the diet.
- (x) Cumulative effect means a toxic or pharmacological effect of a class of chemically-related substances in the diet determined in accordance with 70.16 or pharmacologically-related substances in the diet determined in accordance with [70.11](#).
- (y) Chemically-related substances mean a group of substances the members of which are similar in molecular structure, or in physical, chemical, or biological properties.
- (z) Pharmacologically-related substances mean substances that share scientifically documented properties of a similar or related pharmacological effect.
- (aa) Pharmacological effect means an effect of a substance based on any one of three attributes:
  - (1) Mechanism of action based on the pharmacologic action at the receptor, membrane or tissue level; or
  - (2) Physiological effect at the cellular, organ, system or whole-body level; or
  - (3) Chemical structure.
- (bb) Diet means:
  - (1) Food including beverages;
  - (2) Potable water as defined at [1240.3\(m\)](#);
  - (3) Dietary supplements as defined at [Section 201 of the act](#); and
  - (4) Substances contained in food, potable water, and dietary supplements.

**2. Revise [§ 70.11](#) regarding related substances for evaluation color additive petitions as follows:**

Sec. 70.11 Related substances.

- (a) Different color additives may cause similar or related pharmacological or biological effects, and, in the absence of evidence to the contrary, those that do so will be considered to have additive toxic effects.
- (b) Substances in the diet, including food ~~Food~~ additives, may also cause pharmacological or biological effects similar or related to such effects caused by color additives, and, in the absence of evidence to the contrary, those that do so will be considered as having additive toxic effects.
- (c) Pesticide chemicals may also cause pharmacological or biological effects similar or related to such effects caused by color additives, and, in the absence of evidence to the contrary, those that do so will be considered to have additive toxic effects.
- (d) In establishing tolerances for color additives, the Commissioner will take into consideration, among other things, the amount of any common component permitted in other color

additives, in food additives, ~~and~~ in pesticide chemical residues, and other substances in the diet as well as the similar biological activity (such as cholinesterase inhibition) produced by such substance.

**3. Add new § 70.16 regarding tolerances for chemically-related substances in the diet for evaluating color additive petitions as follows:**

Sec. 70.16 Tolerances for chemically-related substances in the diet.

- (a) Substances which are similar in molecular structure, or in physical, chemical, or biological properties are regarded as a class of chemically-related substances.
- (b) In the absence of evidence to the contrary, the pharmacological or toxic effect of any member of a class of chemically-related substances is presumed to be applicable to the class as a whole.
- (c) In the absence of evidence to the contrary, chemically-related substances will be considered as having additive effects.

**4. Amend § 71.1 regarding color additive petitions by amending paragraph (c) subparagraph (F) as follows:**

F. The petition must include the following:

- (1) Evaluation of any chemically- or pharmacologically-related substances in the diet:
  - (a) Pharmacological effects of substance;
  - (b) Classes of pharmacologically-related substances for each pharmacological effect pursuant to 70.11;
  - (c) Cumulative effect of each class of pharmacologically-related substances;
  - (d) Classes of chemically-related substances pursuant to 70.16;
  - (e) Cumulative effect of each class of chemically-related substances; and
  - (f) Tolerance or acceptable daily intake for each class.
- (2) Proposed tolerances and other limitations on the use of the color additive, if tolerances and limitations are required in order to ensure ~~insure~~ its safety. The petitioner may include a proposed regulation

**5. Revise § 170.3 regarding definitions for food additives and related substances by amending paragraph (g) and adding new paragraphs (p) to (t) as follows:**

- (g) ~~The word~~ Substance means in the definition of the term "food additive" includes a food or food component consisting of one or more ingredients and includes: food additives; substances classified as generally recognized as safe (GRAS); pesticide chemical residues in or on a raw agricultural commodity or processed food; pesticide chemicals; color additives; substances covered by a prior sanction; new animal drugs; and ingredients in, or intended for use in a dietary supplement that may be contained in the diet.
- (p) Cumulative effect means a toxic or pharmacological effect of a class of chemically-related substances in the diet determined in accordance with 170.16 or pharmacologically-related substances in the diet determined in accordance with 170.18.
- (q) Chemically-related substances mean a group of substances the members of which are similar in molecular structure, or in physical, chemical, or biological properties.
- (r) Pharmacologically-related substances mean substances that share scientifically documented properties of a similar or related pharmacological effect.
- (s) Pharmacological effect means an effect of a substance based on any one of three attributes:

- (1) Mechanism of action based on the pharmacologic action at the receptor, membrane or tissue level; or
- (2) Physiological effect at the cellular, organ, system or whole-body level; or
- (3) Chemical structure.
- (t) Diet means:
  - i) Food including beverages;
  - (2) Potable water as defined at 1240.3(m);
  - (3) Dietary supplements as defined at Section 201 of the act; and
  - (4) Substances contained in food, potable water, and dietary supplements.

**6. Add new § 170.16 regarding tolerances for chemically-related substances in the diet as follows:**

Sec. 170.16 Tolerances for chemically-related substances in the diet.

- (a) Substances which are similar in molecular structure, or in physical, chemical, or biological properties are regarded as a class of chemically-related substances.
- (b) In the absence of evidence to the contrary, the pharmacological or toxic effect of any member of a class of chemically-related substances is presumed to be applicable to the class as a whole.
- (c) In the absence of evidence to the contrary, chemically-related substances will be considered as having additive effects.

**7. Revise § 170.18 regarding tolerances for pharmacologically-related substances in the diet as follows:**

Sec. 170.18 Tolerances for ~~pharmacologically-related substances in the diet~~ food additives.

- (a) Substances in the diet~~Food additives~~ that cause similar or related pharmacological effects will be regarded as a class, and in the absence of evidence to the contrary, as having additive toxic effects~~and will be considered as related food additives.~~
- (b) Tolerances established for the class such related food additives may limit the amount of a common component that may be present, or may limit the amount of biological activity (such as cholinesterase inhibition) that may be present or may limit the total amount of substances in the class related food additives that may be present.
- (c) Where ~~food additives from~~ two or more chemicals in the same class are present in or on a food, the tolerance for the total of such substances additives shall be the same as that for the substance additive having the lowest numerical tolerance in this class, unless there are available methods that permit quantitative determination of the amount of each substance food additive present or unless it is shown that a higher tolerance is reasonably required for the combined substances additives to accomplish the physical or technical effect for which such combined substances additives are intended and that the higher tolerance will be safe.
- (d) Where residues from two or more substances additives in the same class are present in or on a food and there are available methods that permit quantitative determination of each residue, the quantity of combined residues that are within the tolerance may be determined as follows:
  - (1) Determine the quantity of each residue present.
  - (2) Divide the quantity of each residue by the tolerance that would apply if it occurred alone, and multiply by 100 to determine the percentage of the permitted amount of residue present.
  - (3) Add the percentages so obtained for all residues present.
  - (4) The sum of the percentage shall not exceed 100 percent.

**8. Revise [§ 170.39](#) regarding threshold of regulation submissions by adding new subparagraph (c)(7) as follows:**

- (c) (7) Evaluation of any chemically- or pharmacologically-related substances in the diet:
- (i) Pharmacological effects of substance;
  - (ii) Classes of pharmacologically-related substances for each pharmacological effect pursuant to [170.18](#);
  - (iii) Cumulative effect of each class of pharmacologically-related substances;
  - (iv) Classes of chemically-related substances pursuant to [170.16](#);
  - (v) Cumulative effect of each class of chemically-related substances; and
  - (vi) Tolerance or acceptable daily intake for each class.

**9. Revise [§ 170.101](#) regarding food contact substance notifications by adding new paragraph (f) as follows:**

- (f) Evaluation of any chemically- or pharmacologically-related substances in the diet:
- (1) Pharmacological effects of substance;
  - (2) Classes of pharmacologically-related substances for each pharmacological effect pursuant to [170.18](#);
  - (3) Cumulative effect of each class of pharmacologically-related substances;
  - (4) Classes of chemically-related substances pursuant to [170.16](#);
  - (5) Cumulative effect of each class of chemically-related substances; and
  - (6) Tolerance or acceptable daily intake for each class.

**10. Revise [§ 170.250](#) regarding GRAS notifications by adding new paragraph (f) as follows:**

- (f) (1) You must explain why the data and information in your notice provide a basis for your view that the notified substance is safe under the conditions of its intended use. In your explanation, you must address the safety of the notified substance, considering all dietary sources and taking into account any chemically or pharmacologically related substances in such diet;
- (2) In your explanation, you must identify what specific data and information that you discuss in accordance with paragraph (a)(1) of this section are generally available, and what specific data and information that you discuss in accordance with paragraph (a)(1) of this section are not generally available, by providing citations to the list of data and information that you include in Part 7 of your GRAS notice in accordance with [170.255](#);
- (3) You must explain the evaluation of any chemically- or pharmacologically-related substances in the diet including providing:
- (i) Pharmacological effects of substance;
  - (ii) Classes of pharmacologically-related substances for each pharmacological effect pursuant to [170.18](#);
  - (iii) Cumulative effect of each class of pharmacologically-related substances;
  - (iv) Classes of chemically-related substances pursuant to [170.16](#);
  - (v) Cumulative effect of each class of chemically-related substances; and
  - (vi) Tolerance or acceptable daily intake for each class.

**11. Revise [§ 171.1](#) regarding food additive petitions by amending paragraph (c) subparagraph (F) as follows:**

- F. The petition must include the following:

- (1) Evaluation of any chemically- or pharmacologically-related substances in the diet:
  - (a) Pharmacological effects of substance;
  - (b) Classes of pharmacologically-related substances for each pharmacological effect pursuant to [170.18](#);
  - (c) Cumulative effect of each class of pharmacologically-related substances;
  - (d) Classes of chemically-related substances pursuant to 170.16;
  - (e) Cumulative effect of each class of chemically-related substances; and
  - (f) Tolerance or acceptable daily intake for each class.
- (2) Proposed tolerances and other limitations on the use of ~~for~~ the food additive, if tolerances and limitations are required in order to ~~ensure~~ insure its safety.

## Appendix B: Review of FDA’s Regulations, Forms, and Associated Instructions for Industry Regarding Petitions and Notifications

FDA regulations specify the mandatory content of a petition or notice. If they specifically require that information on the cumulative effect of chemically-related and pharmacologically-related substances must be provided, it would make it more straightforward for the agency to ensure the evaluation was properly done.

EDF found that the regulations for only two of the four types, color additive petitions and GRAS notifications, specifically require that the necessary information. The other two, food additive petitions and FCS Notifications, are silent. In addition, none of the forms or associated instructions provide a prompt of the requirement even when the corresponding regulation says it is needed (see Appendix B for details). To the contrary, they are focused on the additive and largely ignore the possibility of related substances in the diet.

The agency’s failure does not excuse industry from providing the required information, but it certainly is a shortcoming that needs to be addressed. This reinforces the need for FDA to be clear in its regulations, guidance documents, forms, and instructions that the information is essential and must be provided.

### Methodology:

EDF evaluated the regulations that describe what must be submitted to the agency. After considering those regulations, it used [FDA’s search tool for forms](#), to identify relevant forms and associated instructions.

### Results for each of the forms and instructions:

- 1) **Color additive petitions:** [Section 71.1](#) explicitly requires information on any chemically- or pharmacologically-related substances in the diet. It says:
  - (c) Petitions shall include the following data and be submitted in the following form:
    - E. Complete data which will allow the Commissioner to consider, among other things, the probable consumption of, and/or other relevant exposure from the additive and of any substance formed in or on food, drugs, or cosmetics because of such additive; and **the cumulative effect, if any, of such additive in the diet of man or animals, taking into account the same or any chemically or pharmacologically related substance or substances in the diet including, but not limited to food additives and pesticide chemicals for which tolerances or exemptions from tolerances have been established.**

The agency provides [Form 3503](#) and associated [instructions](#) for industry to use when submitting a Color Additive Petition and Color Master File. The documents do not specifically request the identification of any chemically- or pharmacologically-related substances in the diet. The information might best fit under either the “Chemistry” or “Safety” sections of the form. However, none of the 15 categories under “Chemistry” or the 22 categories of “Safety” mention related substances in the diet. The instructions provide no helping information, describing the “Chemistry” section as “Chemistry information (such as specifications and analytical methods)” and the “Safety” as “Safety information (such as a safety narrative and studies conducted in animals).”

- 2) **Food additive petitions:** Unlike the requirement for color additive petitions, [§ 171.1](#) does not mention cumulative effect of any chemically- or pharmacologically-related substances in the diet.

The regulation is focused exclusively on the substances and makes no mention of related substances other than mandating that petitioners shall supply a list of all substances used in the synthesis, extraction, or other method of preparation, regardless of whether they undergo chemical change in the process if the food additive is a mixture of chemicals.

The agency uses the same form and instructions for both color additives and food additives. As noted above, [Form 3503](#) and associated [instructions](#) do not specifically request the identification of any chemically- or pharmacologically-related substances in the diet. The information might best fit under either the “Chemistry” or “Safety” sections of the form. However, none of the 15 categories under “Chemistry” or the 22 categories of “Safety” mention related substances in the diet. The instructions provide no helping information, describing the “Chemistry” section as “Chemistry information (such as specifications and analytical methods)” and the “Safety” as “Safety information (such as a safety narrative and studies conducted in animals).”

- 3) **Food contact substance notifications (FCN):** [Section 170.101](#) does not mention cumulative effect of any chemically- or pharmacologically-related substances in the diet. Such information would fall under “(b) All data and other information that form the basis of the determination that the food contact substance is safe under the intended conditions of use. Data must include primary biological data and chemical data.”

The agency provides two forms, [Form 3479](#) for Notification for a Food Contact Substance Formulation and [Form 3480](#) for Notification for a New Use of a Food Contact Substance, to help the notifier ensure all of the necessary information is provided. Unfortunately, the form is focused on the food contact substance, impurities, and degradation products, providing no location to identify any chemically- or pharmacologically-related substances in the diet. The [instructions](#) do not address the issue either.

- 4) **GRAS Notice for Human Food (GRN):** [Section 170.250](#), promulgated in 2016, explicitly requires information that takes into account any chemically- or pharmacologically-related substances in the diet. It says:

In Part 6 of your GRAS notice, you must include a narrative that provides the basis for your conclusion of GRAS status, in which:

- (a)(1) You must explain why the data and information in your notice provide a basis for your view that the notified substance is safe under the conditions of its intended use. In your explanation, you must address the safety of the notified substance, **considering all dietary sources and taking into account any chemically or pharmacologically related substances in such diet; [Emphasis added]**

The agency provides [Form 3667](#) for Generally Recognized as Safe (GRAS) Notice to help industry prepare and format their notices. There is a checkbox for Part 6 of the notice but no other elements that would prompt the notifier to provide the information described above. The [instructions](#) associated with the form only say “PART 6 of a GRAS notice: Narrative (170.250).”

## Appendix C: Review of GRAS Notifications

To determine whether safety determination conducted by food manufacturers for GRAS substances for human food consider in a meaningful way the cumulative effect of the substance, taking into account any chemically- or pharmacologically-related substances in the diet, EDF reviewed the [GRAS notifications](#) that they voluntarily submitted to FDA for review. Under this program, notifiers seek a “no questions” letter from the agency that essentially affirms the manufacturer’s conclusion that the use is safe and compliant with the FFDCA and agency regulations. The agency posts the notice and its “no questions” letters on its website in a [searchable database](#).

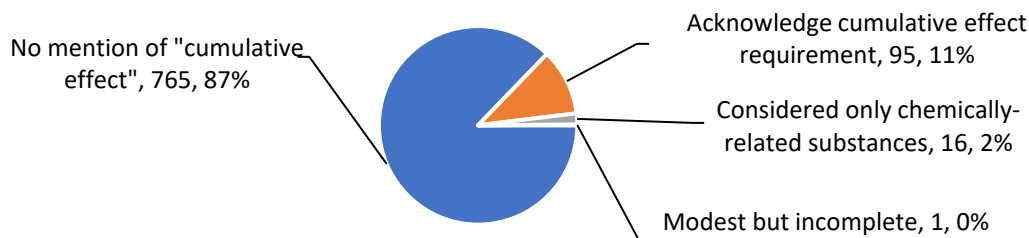
### Methodology:

EDF downloaded the 877 notices from the website as of March 24, 2020<sup>47</sup> and ran them through optical character recognition so that key words could be searched. As it did with FDA guidance documents, EDF searched for either “cumulative effect” or “pharmacologic” presuming that any analysis of the cumulative effect of pharmacologically-related substances would include those terms. When its search found the word, EDF looked for context and reviewed the document more closely when warranted.

### Finding:

Only 112 GRAS notices (13%) used the term “cumulative effect”; the most recent was filed in 2012. However, 95 simply acknowledged the requirement to consider the cumulative effect but conducted no evaluation. Of the remaining 17 GRAS notices, 16 only considered chemically-related substances without addressing pharmacologically-related substances. The one GRAS notice that considered both chemically-related and pharmacologically-related substances conducted a modest, but incomplete evaluation. Figure 1 summarizes EDF’s findings

Figure 1: Only one of 877 GRAS Notices gave modest or serious consideration to cumulative effect of pharmacologically substances in the diet



### Sixteen GRAS notices considered only chemically-related substances

EDF identified sixteen GRAS notices that conducted some consideration, typically by defining a class of chemically-related substances, comparing them to natural sources of the substances in the diet and concluding the increased exposure was not significant. While identifying chemically-related substances fulfills one element of the requirement, it is insufficient to address all pharmacologically-related substances.

Based on the CBER/CDER guidance,<sup>48</sup> we would expect that the notifier also considers substances that have either a similar:

<sup>47</sup> The total does not include six notices that had broken or incorrect links. In response to EDF’s request, FDA corrected the problem.

<sup>48</sup> <https://www.fda.gov/media/77834/download> on page 3.

- Mechanism of action – meaning the pharmacologic action at the receptor, membrane, or tissue levels; or
- Physiological effect – meaning the pharmacologic effect at the organ, system, or whole body level.
- Chemical structure (CS).

The notices omitted essential information necessary to fulfill the requirements in [§ 170.18](#) for human foods. Without it, the safety determination is fundamentally flawed because it makes it impossible to designate a class of substances in the diet having similar or related pharmacologic effects and, therefore, to set an appropriate tolerance as required by the FFDCA and FDA’s regulations.

The sixteen GRAS notices are as follows:

- **Four notices addressed the use of acidified proteins:** 1) [GRN 147](#) for extracted “seafood species” protein; 2) [GRN 168](#) for poultry protein; 3) [GRN 313](#) for beef protein; and 4) [GRN 314](#) for pork protein). The acidification process is similar to pickling a protein in acid. The text of each was similar. They defined a class of acid soluble proteins based on their chemical similarities but did not consider their cumulative effect, primarily because they claimed that they were “unable to find references to the ill effects of consuming acidified, pickled fish products could have? on chemical.”<sup>49</sup>
- **Four notices for fish oils:** 1) [GRN 105](#) for eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from a trademarked product; 2) [GRN 109](#) for tuna oil; [GRN 138](#) for fish oil; and [GRN 200](#) for tailored triglycerides enriched in omega-3 fatty acids from fish oil.<sup>50</sup> There were other GRNs for EPA and DHA omega-3 fatty acids filed between [GRN 16](#)<sup>51</sup> in 1999 and [GRN 200](#) in 2006. These notices only considered the impact of these two omega-3 fatty acids on the risk of bleeding.

The focus on bleeding was driven by a 1997 rule promulgated by FDA limiting the total consumption of EPA and DHA to three grams per person per day (g/person/day) at [21 CFR § 184.1472](#).<sup>52</sup> In that rulemaking, FDA had identified three pharmacologic effects of these substances in the diet based on clinical studies: 1) bleeding time; 2) glycemic control; and 3) LDL cholesterol. It concluded a tolerance of 3 g/person/day for the first two effects and 5 g/person/day was appropriate for LDL cholesterol.

Unfortunately, the agency never took the next step in the analysis required by [§ 170.18](#) to identify other substances in the diet that contributed to those three pharmacologic effects. It was focused on only EPA and DHA, failing even to mention alpha-linolenic acid (ALA) as another omega-3 fatty acid. As a result, the tolerance it set failed to consider the cumulative effect of all pharmacologically-related substances in the diet as required by the FFDCA and the agency’s own regulations.

Note that EPA and DHA were also the subject of three notifications to FDA seeking the agency’s acceptance of marketing claims regarding these substances as nutrients. In 2016, FDA issued a rule prohibiting nutrient content claims for EPA and DHA and took no action on similar claims

<sup>49</sup> [GRN 147](#) for extracted “seafood species” protein.

<sup>50</sup> Other GRAS notices also dealt with EPA/DHA from fish oil, but none mentioned cumulative effect beyond repeating the regulations.

<sup>51</sup> GRN 16 was withdrawn by the notifier (which typically happens to avoid a rejection).

<sup>52</sup> [62 Federal Register 30751](#) (June 5, 1997) promulgating 21 C.F.R. § 184.1472.

for ALA, effectively allowing them.<sup>53</sup> Companies cannot use phrases such as “high in,” “rich in,” or excellent source of” DHA and EPA.<sup>54</sup>

- **GRN 1 for soy isoflavone extracts:** The notice identifies isoflavones as having a common effect, namely estrogenic activity. While isoflavones may be chemically-related, there is no evaluation of pharmacologically-related substances in the diet.

Isoflavones have known estrogenic activity and these effects are pharmacological and not toxicological, unless there is specific species sensitivity. As noted above, significant species sensitivity exists. [Page 18]

The term ‘pharmacological’, however, is used in a different context. Section 170.18 uses the terms pharmacological and toxicological as synonyms. The notice differentiates between the two inferring that pharmacological effect are good, potentially therapeutic effects while the toxicological effects are negative.

- **GRN 028 for seaweed-derived calcium:** The notice sought to add calcium as a mineral supplement to oil-based dairy, snack and flour confectionery uses. The notice had a section titled “Cumulative Effects” that defined the class of chemically-related substances as calcium carbonate. However, it did not consider the potentially negative health effect of the increased calcium carbonate.
- **GRN 095 for transglutaminase (TG) from streptovercillium mobaraense:** The notice identified five types (blood, tissue-type, epidermal, keratinocyte, and prostrate) of the enzyme TG as a chemically-related class, considered natural sources of the TG and, after considering the amount of TG from natural sources, concluded that “it is apparent that natural consumption of TG is likely to exceed consumption of TG employed as a food additive.”<sup>55</sup>
- **GRN 116 for carrot fiber:** The notice had a section titled “Consumer Exposure and Cumulative Effect in the Diet” but only estimated the daily intake of the substance and concluded it would be a small increase over the amount of carrot fiber in the diet.
- **GRN 144 for adenosine 5-monophosphoric acid and its monosodium and disodium salts:** The notice identified the GRAS substance as members of the chemically-related purines. There are natural sources of purines that act on three families of purinergic receptors. The notice describes ‘pharmacological effects’ in the context of therapeutic uses.
- **GRN 164 for lauramide arginine ethyl ester (LAE):** It had a section titled “Cumulative Effect of LAE in the Diet” but only estimated the daily intake of the two metabolites of the substances, arginine and lauric acid. It concluded that “These amounts represent incremental increases of approximately 3% for arginine and 20% for lauric acid. Both of these figures are well within the ranges of normal variability of individual intakes of these substances and are not believed to be biologically significant.”<sup>56</sup>

---

<sup>53</sup> [72 Federal Register 23262](#) (April 28, 2014) amending 21 C.F.R. § 101.

<sup>54</sup> <https://www.fda.gov/food/cfsan-constituent-updates/fda-releases-small-entity-compliance-guide-omega-3-fatty-acids-final-rule>

<sup>55</sup> [GRN 095](#) for transglutaminase (TG) from streptovercillium mobaraense on page 56 of PDF.

<sup>56</sup> [GRN 164](#) for lauramide arginine ethyl ester (LAE) on page 33 of PDF.

- [GRN 181](#) for **phytosterols**. The notice considered only the cumulative dietary exposure to the substances and reviewed other GRAS notices. For example, the notice stated that:

Because phytosterols in egg products including egg whites, and egg substitutes have not previously been the subject of a GRAS notification, we considered **the cumulative effect of consuming phytosterols in egg products including egg whites, and egg substitutes in addition to the phytosterol intake that may occur from other foods that have been the subject of GRAS notifications.** (Page 20 of notice)

While phytosterols may be chemically-related, there is no evaluation of pharmacologically-related substances other than phytosterols.

- [GRN 224](#) for **trans-resveratrol**: The notice uses the term ‘pharmacological’ in two ways: 1) in the context of dose, concentration of the GRAS substance used in experiments, and 2) “pharmacological and toxicological similarity” because of structural similarity between resveratrol and “some estrogenic substances such as diethylstilbestrol”.

**One GRAS Notice gave modest, but incomplete, consideration of any chemically- or pharmacologically-related substances in the diet:**

[GRN 107](#) for polydextrose identified 11 pharmacologically-related substances in the diet based on “laxation potential” effect as described in the table below from the notice.

**LAXATION THRESHOLDS OF VARIOUS CARBOHYDRATES**

| <u>SUBSTANCE</u>    | <u>SINGLE DOSE (g)*</u> | <u>DAILY DOSE (g)*</u> |
|---------------------|-------------------------|------------------------|
| Mannitol            | 10                      | 20                     |
| Inulin/FOS          | 20                      | 30                     |
| Lactitol            | 25                      | 70                     |
| Sorbitol            | 30                      | 70                     |
| Xylitol             | 35                      | 70                     |
| Isomalt             | 40                      | 50                     |
| Maltitol            | 40                      | 50                     |
| Lycasin 80/55       | 40                      | 80                     |
| Erythritol          | 48                      | >90                    |
| <b>Polydextrose</b> | <b>50</b>               | <b>90</b>              |
| Fructose            | 70                      | >90                    |

\* Single Dose = the single dose at which the first subject would experience laxation

Daily Dose = the average daily intake at which half of the subjects would experience laxation

However, after considering the average daily amount at which half of the tested subjects experience laxation for of the substances, the notice only considered the effect from polydextrose alone on the risk of laxation symptoms. In addition, the eleven omitted a sugar alcohol, hydrogenated starch hydrolysate, as well as allulose, a sugar substance that is not a sugar alcohol but has similar laxative effects.

## Appendix D: Review of FDA Guidance to Industry

EDF reviewed FDA’s relevant guidance documents to determine if they helped industry understand how to consider the cumulative effect of the substance, taking into account any chemically- or pharmacologically-related substances in the diet as required by the FFDCA and FDA regulations. It found next to nothing and what was there was either incomplete or confusing.

### Methodology:

EDF started with a review of the FDA’s guidance documents on the topic of food using the agency’s [on-line search tool](#)<sup>57</sup> and identified 21 documents that related in some way to food additives, color additives, food contact substances, or GRAS substances. It reviewed the text of the documents, focusing on key terms used in the FFDCA and FDA regulations describing the factor to be considered in safety assessment as well as citations to those sections of the law and regulations. Specifically, EDF searched for the following:

- Use of the terms – cumulative effect, chemically-related, pharmacological effects, pharmacologically-related substances.
- Reference to the key regulations or statutory provisions – 70.3(i), 70.11, 170.3, 170.18, 409(c)(5), or 379e(b)(5)(A) – that are directly related to the consideration.

### Findings:

Table 1 summarizes the results of EDF’s review of the 21 guidance documents. EDF categorized its assessment of the documents as follows:

- *No assistance*: Ten guidance documents made no reference to the consideration and provided no assistance.
- *Incomplete*: Five guidance documents were incomplete and could be misleading either because they: 1) only provided the opening part of the definition of safety and omitted the part that listed the three factors that must be considered– probable consumption, cumulative effect, and safety factors; or 2) paraphrased the requirement in a manner that limited the assessment to the additive and not pharmacologically-related substances.
- *Confuses terms*: Four guidance documents create confusion because they used the words “cumulative exposure” or “cumulative intake” without distinguishing them from the statutory term of “cumulative effect.”
- *Only restates requirement*: Two guidance documents simply restate the requirement, which is helpful, but provides no real guidance to industry.

Table 1: Evaluation of FDA’s guidance documents for explanation to industry of how they should ensure compliance with the law by considering the cumulative effect of the substance in the diet, taking into account any chemically- or pharmacologically-related substance or substances in such diet.

| Guidance, forms, instructions and other materials                                       | Uses “cumulative effect.” “chemically-related” or “pharmacologic” terms | Cites key regulatory sections*                | Assessment  |
|-----------------------------------------------------------------------------------------|-------------------------------------------------------------------------|-----------------------------------------------|-------------|
| 1) Food Additives: <a href="#">Frequently Asked Questions about GRAS</a> (October 2016) | No.                                                                     | Yes, but omits factors in stating definition. | Incomplete. |

<sup>57</sup> <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>

|                                                                                                                                                                                                                                                                                                          |                                                                                         |                                               |                            |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|-----------------------------------------------|----------------------------|
| 2) Ingredients and Packaging: <a href="#">Considerations Regarding Substances Added to Foods, Including Beverages and Dietary Supplements</a> (January 2014)                                                                                                                                             | No.                                                                                     | Yes, but omits factors in stating definition. | Incomplete .               |
| 3) Food Additives: <a href="#">Microbiological Considerations-Antimicrobial Food Additive Submissions</a> (September 2007; Revised June 2008)                                                                                                                                                            | No.                                                                                     | Yes, but omits factors in stating definition. | Incomplete .               |
| 4) Ingredients and Packaging: <a href="#">Providing Regulatory Submissions in Electronic or Paper Format to the Office of Food Additive Safety</a> (March 2010)                                                                                                                                          | Yes, paraphrases requirement but limits to single additive.                             | No.                                           | Incomplete .               |
| 5) Food Additives: <a href="#">Toxicological Principles for the Safety Assessment of Food Ingredients: Redbook 2000</a> (July 2007)                                                                                                                                                                      | Yes, but in different context and limits to single chemical or type of study.           | Yes.                                          | Incomplete .               |
| 6) Food Additives: <a href="#">Preparation of Food Contact Notifications and Food Additive Petitions for Food Contact Substances: Chemistry Recommendations</a>                                                                                                                                          | No, but uses “cumulative exposure.”                                                     | No.                                           | Confuses terms.            |
| 7) Food Additives: <a href="#">Summary Table of Recommended Toxicological Testing for Additives Used in Food</a> (June 2006)                                                                                                                                                                             | No, but uses “cumulative human exposure.”                                               | No.                                           | Confuses terms.            |
| 8) Food Additives: <a href="#">Preparing a Claim of Categorical Exclusion or an Environmental Assessment for Submission to the Center for Food Safety and Applied Nutrition</a> (May 2006)                                                                                                               | No, but uses “cumulative effect” in context of environmental assessment.                | No.                                           | Confuses terms.            |
| 9) Food Additives: <a href="#">Estimating Dietary Intake of Substances in Food</a> (August 2006)                                                                                                                                                                                                         | No, but uses “cumulative intake.”                                                       | No.                                           | Confuses terms.            |
| 10) Ingredients and Packaging: <a href="#">Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that are Color Additives</a> (June 2014) | Yes, restates requirement.                                                              | Yes, simply restates requirement.             | Only restates requirement. |
| 11) Color Additives: <a href="#">Color Additive Petitions - FDA Recommendations for Submission of Chemical and Technological Data on Color Additives for Food, Drugs, Cosmetics, or Devices</a> (July 2009)                                                                                              | Yes, restates requirement and implies more than food additives and pesticide chemicals. | No.                                           | Only restates requirement. |
| 12) Food Additives: <a href="#">Enzyme Preparations: Recommendations for Submission of Chemical and Technological Data for Food Additive Petitions and GRAS Notices</a> (January 1993; Revised July 2010)                                                                                                | No.                                                                                     | No.                                           | No assistance.             |
| 13) Color Additives: <a href="#">Colored Sea Salt</a> (September 2015)                                                                                                                                                                                                                                   | No.                                                                                     | No.                                           | No assistance.             |

|                                                                                                                                                                                                                       |     |     |                |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|-----|----------------|
| 14) Food Additives: <a href="#">Questions And Answers About the Food Additive Petition Process</a> (September 2003; Revised April 2006 and April 2011)                                                                | No. | No. | No assistance. |
| 15) Food Additives: <a href="#">Food Additive Petition Expedited Review</a> (January 4, 1999; Revised October 2010)                                                                                                   | No. | No. | No assistance. |
| 16) Color Additives: <a href="#">Cochineal Extract and Carmine: Declaration by Name on the Label of All Foods and Cosmetic Products That Contain These Color Additives Small Entity Compliance Guide</a> (April 2009) | No. | No. | No assistance. |
| 17) Food Additives: <a href="#">Recommendations for Submission of Chemical and Technological Data for Direct Food Additive Petitions</a> (March 2006; Revised March 2009)                                             | No. | No. | No assistance. |
| 18) Food Additives: <a href="#">Pre-Petition Consultations for Food Additives and Color Additives</a> (April 2005)                                                                                                    | No. | No. | No assistance. |
| 19) Food Additives: <a href="#">Templates for Reporting Toxicology Data</a> (March 2004; Revised April 2005)                                                                                                          | No. | No. | No assistance. |
| 20) Food Additives: <a href="#">Submitting Requests under 21 CFR 170.39 Threshold of Regulation for Substances Used in Food-Contact Articles</a> (March 1996; Revised April 2005)                                     | No. | No. | No assistance. |
| 21) Food Additives: <a href="#">Antimicrobial Food Additives</a> (July 1999)                                                                                                                                          | No. | No. | No assistance. |
| * The key regulatory citations are § 70.3(i), § 70.11, § 170.3(i), § 170.18, § 570.3(i), § 570.18, § 409(c)(5), or § 379e(b)(5)(A).                                                                                   |     |     |                |

**Five guidance documents are incomplete by incorrectly paraphrasing the definition of safety:**

1. The [Frequently Asked Questions about GRAS](#) (Item 1 in Table 1) guidance was issued in October 2016. It says:

FDA has defined "safe" (21 CFR 170.3(i) and 21 CFR 570.3(i)) as a reasonable certainty in the minds of competent scientists that the substance is not harmful under the conditions of its intended use. The specific data and information that demonstrate safety depend on the characteristics of the substance, the estimated dietary exposure, the population that will consume the substance, and other relevant considerations. [Page 7]

The first sentence captures the opening sentence of the definition but fails to indicate there is more. It indirectly refers to the first of the three mandatory considerations – the probable consumption of the substance in the diet – but makes no mention of the duty to consider pharmacologically-related substances in the diet and their cumulative effect. By incompletely describing the definition, it is more than simply a missed opportunity to provide guidance, it sows confusion.

2. The [Considerations Regarding Substances Added to Foods, Including Beverages and Dietary Supplements](#) (Item 2 in Table 1) guidance was issued in January 2014 with a similar flaw as the previous one. It says:

In other words, the GRAS standard first requires that the scientific evidence about the substance establish that the intended use of the substance is safe; i.e., that there is a reasonable certainty in the minds of competent scientists that the substance is not harmful under its intended conditions of use (21 CFR 170.3(i)). [Page 4]

3. The [Microbiological Considerations-Antimicrobial Food Additive Submissions](#) (Item 3 in Table 1) guidance was issued in September 2007 and revised in June 2008. The relevant sentence says:

The standard that FDA applies to determine whether the intended use of a food additive is safe is reasonable certainty of no harm (see 21 CFR 170.3(i)). [Page 5]

As with the others, the sentence omits any mention of the three mandatory considerations and, therefore, is incomplete and confusing.

4. The [Providing Regulatory Submissions in Electronic or Paper Format to the Office of Food Additive Safety](#) (Item 4 in Table 1) guidance was issued in March 2010. The relevant sentence says:

[Color Additive Petition]: Complete data to allow us to consider the probable consumption of, and/or other relevant exposure from the additive and of any substance formed in or on food, drugs, or cosmetics because of such additive; and the cumulative effect, if any, of such additive in the diet of man or animals. [Page 32]

While subtle, this sentence is also confusing because it narrows the consideration to only the additive and fails to mention the requirement to consider that additive with other pharmacologically-related substances in the diet.

5. The [Toxicological Principles for the Safety Assessment of Food Ingredients: Redbook 2000](#) (Item 5 in Table 1), guidance was first published in 1982 and last updated in July 2007. This document is central to the agency's guidance to industry on designing and evaluating toxicology studies of substances in the diet.

For example, the Redbook uses the term "cumulative effect" four times.

Safety is generally determined by considering the potential **cumulative effect of the substance** in consumers and the probable consumption of the substance in the diet. The **potential cumulative effects** are determined by the outcome of toxicity studies and knowledge of compounds and their structures. [Page 6 in printable version] *[Emphasis added]*

The guideline for reproduction studies detailed below pertains to substances given orally to rodents. It is designed to evaluate the effects of **a test substance** on the reproductive systems of both males and females, the postnatal maturation and reproductive capacity of offspring, and potential **cumulative effect of the substance** through several generations. [Page 194 in printable version] *[Emphasis added]*

If overt reproductive, morphologic, and/or toxic effects of a test substance are observed in offspring during the two-generation reproduction study, the study may be extended to a

third generation to determine **cumulative effects of the substance**. [Page 196 in printable version] *[Emphasis added]*

Unfortunately, the consideration of cumulative effect is only for a single substance and not related substances in the diet; in other words, what effects are caused by the consumption of the same substance over time. As with the previous guidance, because it implicitly narrows the consideration to only a single substance and fails to mention the requirement to consider that additive with other pharmacologically-related substances in the diet. This creates confusion and could be misleading.

In addition, the Redbook is confusing because it uses the term “pharmacologic” 27 times but never defines it. Usually, it is used in conjunction with the word “toxic” or “toxicologic,” seemingly treating the terms as equivalent to “pharmacologic.” For example:

- In sections titled “Observation of Test Animals” that is repeated several times for various types of studies, it says
  - “Routine cage-side observations should be made on all animals at least once or twice a day throughout the study for general signs of **pharmacologic and toxicologic effects**, morbidity and mortality.” (Page 29, 105, 115, 126, 137, 158 in printable version)
  - “An expanded set of clinical evaluations, performed inside and outside of the cage, should be carried out in short-term and subchronic toxicity studies in rodents and non-rodents, in one-year non-rodent toxicity studies, and reproductive toxicity studies in rodents to enable detection not only of **general pharmacologic and toxicologic effects** but also of neurologic disorders, behavioral changes, autonomic dysfunctions, and other signs of nervous system toxicity.” (Page 29, 105, 115, 126, 137, 159 in printable version)
  - “During the course of a study, **toxic and pharmacologic signs** may suggest the need for additional clinical tests or expanded post-mortem examinations.” (Page 29, 105, 116, 126, 137, 159, 187 in printable version)
- In Section III.C.14 on “Clinical Observations,” and Section III.C.9 on “Clinical Observation and Examination of Dams and Fetuses,” it says:
  - “Observation times should be selected to permit detection of the onset and progression of all **toxic and pharmacologic effects of the test substance** and to minimize the loss of animals and organs/tissues.” (Page 197, 208 in printable version)
  - “**Toxicological and pharmacological symptoms and signs**, including behavioral abnormalities, should be recorded daily; records should include the date of onset, duration, and intensity of symptoms and signs.” (Page 197 in printable version) *[only in first section]*
- In Section V.B. on “Metabolism and Pharmacokinetic Studies,” it says:
  - “Early determination of metabolic pathways and the rates of metabolism in different test species may provide explanations for species differences in any effects which are observed, and suggest **biochemical or pharmacologic experiments** which might be used to test explanations of such phenomena.” (Page 225 in printable version)

- o “Studies of enzyme induction and **potential pharmacological adaptation** should be conducted whenever chronic studies are recommended.” (Page 231 in printable version)
- o “Routine differential WBC counts are used to differentiate among some types of infections and inflammatory responses; they also are used as a screen for **toxicologic or pharmacologic effects**: for example, immunosuppressive drugs may cause lymphopenia.” (Page 240 in printable version)
- o “Use of the dog for various **immunopharmacologic studies** has been described in the scientific literature.” (Page 245 in printable version)

Without a definition, the reader is left to speculate or refer to other sources as to what the agency means when it uses this term that must be understood in order to follow the law and adequately consider the cumulative effect of pharmacologically-related substances in the diet.

To address these shortcomings, FDA needs to revise relevant guidance and other documents to explain how the cumulative effect of pharmacologically-related substances in the diet should be identified and properly evaluate to ensure the proposed use of a substance is safe.