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,"[1] 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."[2]

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.

[1] Food Additives Amendment of 1958, Public Law 85-929, 72 Stat. 1784.
[2] *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[3], this failure may have contributed to the dramatic increases in a variety of chronic diseases such as obesity[4], diabetes —especially in children[5], and kidney disease.[6] 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[7] 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.[8]

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[9] 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.[10] 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.

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[3] Baldridge, 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.

[4] 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.

[5] 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

[6] 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

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

[8] 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.

[9] Codified at 5 U.S.C. § 553e(e).

[10] 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 170.18 as appropriate];
c) Cumulative effect of each class of pharmacologically-related substances;
d) Classes of chemically-related substances pursuant to [70.16 or 170.16 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.[11] 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.[12] 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.

[11] Codified at 21 U.S.C. § 393(b).
[12] 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.[13]

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

[13] 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.[14]

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 . . ." [15]
- 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.[16] 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."[17]

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,[18] 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,"[19] 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

[14] 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.
[15] FDA, Indirect Food Additives: Paper and Paperboard Components, Final Rule, 81 Federal Register 5, January 4, 2016, at page 7.
[16] FDA, Grocery Manufacturer's Association; Denial of Food Additive Petition, 83 Federal Register 23382, May 21, 2018.
[17] FDA, Sodium Reduction, accessed on August 15, 2018 at https://www.fda.gov/food/food-additives-petitions/sodium-reduction.
[18] 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.
[19] 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.[20]

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.[21] 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.[22]

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.[23]

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,[24] 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;

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[20] 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.
[21] 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
[22] 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
[23] Endocrine Society, Endocrine-Disrupting Chemicals, An Endocrine Society Position Statement. https://www.endocrine.org/advocacy/position-statements/endocrine-disrupting-chemicals
[24] 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."[25] 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."[26] *[Emphasis added]*

This action, taken partly in response to an Executive Order by President Richard Nixon,[27] clarified that the three factors apply to GRAS substances.[28] 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]*

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[25] 24 Fed. Reg. 2434 (1959) promulgating 21 C.F.R. § 121.1(i).
[26] 36 Fed. Reg. 12093 (1971) amending 21 C.F.R. § 121.1(i).
[27] 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.
[28] 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[29] 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.[30] 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,**

[29] Public Law 86-618, 74 Stat. 397.
[30] 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.[31]

[31] 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.[32] 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.[33, 34]

The rule also established a framework for how FDA will set tolerances – essentially acceptable daily intake (ADI) levels – for pharmacologically-related food additives.[35] 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.

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[32] 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.
[33] 24 Federal Register 2434 (March 28, 1959) promulgating 21 C.F.R. § 121.1(i).
[34] 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, 86th 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 established 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.
[35] 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.[36] 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.[37] 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

[36] Food contact substances was not created as a distinct category of food additives until 1997.
[37] 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.[38] 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.

[38] 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,[39] 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."[40] *[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,

[39] The total does not include six notices that had broken or incorrect links. In response to EDF's request, FDA corrected the problem.
[40] 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.[41]

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.

[41] 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[42] 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.

[42] 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."[43] 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)**.[44]

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

[43] FDA, Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Federal Register 3921 (January 24, 2006).
[44] 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[45] 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**

[45] 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,[46] 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.

[46] 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.

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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