

Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20093

Re: **Substances Generally Recognized as Safe (GRAS)**

Docket No.: FDA-1997-N-0020

The Center for Science in the Public Interest (CSPI), Consumers Union, Environmental Working Group (EWG), and Natural Resources Defense Council (NRDC) present this comment regarding the Food and Drug Administration’s (FDA) 1997 and 2010 proposals to use a voluntary notification process to designate a substance intended for use in food for humans or animals as “generally recognized as safe” (GRAS). The 1997 proposal is an invalid interpretation of the Food Additives Amendment of 1958 (FAA). To achieve its congressionally intended purpose of protecting the public from unsafe chemical additives and come into compliance with the FAA, FDA has an affirmative obligation to fix its proposal.

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I. Introduction: FDA's Oversight of the Safety of Substances in the Food Supply is Broken

The FDA's overarching obligation to oversee the safety of chemical additives derives from the agency's mission to "protect the public health by ensuring that – foods are safe, wholesome, sanitary, and properly labeled" under the Food, Drug, and Cosmetic Act (FDCA).¹ Its specific responsibilities with regard to food additives were expanded in the Food Additives Amendment of 1958 (FAA), which was subtitled "[a]n Act to protect the public health by amending the FDCA to prohibit the use in food of additives which have not been adequately tested to establish their safety."² Given Congress's description of the purpose of the Act, the American public would likely find it both disturbing and surprising that thousands of chemicals added to food today are *not* approved or even reviewed by FDA.

Instead, of the roughly 10,000 additives currently used in food, more than 3,000 have never been substantively reviewed by FDA.³ For an estimated 1,000 of these substances, safety decisions were made by the food industry without any notice at all to FDA.⁴ Rather than enabling FDA to fulfill its mission to ensure that the substances added to foods are safe, the current program leaves the agency in the dark. As Deputy FDA Commissioner for Foods Michael Taylor remarked in August 2014, "We simply do not have the information to vouch for the safety of many of these chemicals."⁵

The story is one of regulatory decline, decay, and disrepair. After decades of insufficient funding and internal will to accomplish its mission, punctuated by brief periods of greater transparency and accountability, FDA essentially granted itself permission to forgo one of its major jobs. In the 1997 GRAS notification proposal, the agency gave sanction to a twilight world in which the food industry has been permitted to impose its own set of metrics. The result of this irrational approach has been a regime in which the food industry has opted for the least onerous, least costly, and least protective route for introducing new substances into the food supply. Not only did the proposal create a toothless regulatory program, its voluntary nature allows industry to bypass FDA's oversight altogether. Troublingly, the substances designated as

¹ 21 U.S.C. § 393(2).

² Food Additives Amendment of 1958, Pub. L. No. 85-929, 52 Stat. 1041 (1958).

³ Thomas G. Neltner, et al., *Navigating the U.S. Food Additive Regulatory Program*, 10 *Comprehensive Reviews in Food Science & Food Safety* 291, 355 (2011).

⁴ The Pew Charitable Trusts, *Fixing the Oversight of Chemicals Added to Our Food* 5 (Nov. 2013), available at <http://www.pewtrusts.org/en/research-and-analysis/reports/2013/11/07/fixing-the-oversight-of-chemicals-added-to-our-food>. In addition, another 2,000 flavors have been approved as GRAS by the industry trade group that approves flavors, the Flavor and Extract Manufacturers Association (FEMA). FDA has received only the most basic information concerning the safety of these substances, but has not conducted any systematic review or approval of them. *Id.*

⁵ Kimberly Kindy, *Food additives on the rise as FDA scrutiny wanes*, *Washington Post*, Aug. 17, 2014, http://www.washingtonpost.com/national/food-additives-on-the-rise-as-fda-scrutiny-wanes/2014/08/17/828e9bf8-1cb2-11e4-ab7b-696c295ddfd1_story.html.

GRAS without FDA approval are likely to be the most dangerous in the food supply, further perverting the statute, and allowing the unknowns to swallow the law.⁶

The current secrecy around GRAS substances in foods also undermines FDA's ability to conduct meaningful scientific assessments of the safety of food additives or food contact substances.⁷ FDA cannot ascertain the cumulative effect of structurally-related or pharmacologically-related substances, as required by law,⁸ given that both the agency and food companies are in the dark concerning both the toxicology of and public exposure to such substances. Nor can the public, or public health groups, assist in rationally ordering risks given the dearth of information. As the evidence below makes clear, the current regime is a near-total abrogation of FDA's duty to protect public health and a violation of the statutory requirements laid out in the FAA.

For these reasons, among others, FDA should not finalize the 1997 proposal⁹ as written. To comply with the FAA, FDA should substantially revise and update its approach to GRAS in two main ways.

First, the current breadth of the GRAS exemption far exceeds the intent of Congress in drafting the FAA. FDA should take a fresh look at both the language of the statute and its legislative history and thereby narrow the eligibility of substances for the GRAS exemption. In its final rule, FDA should delineate and define the category of GRAS substances exempt from the food additive petition process, by excluding novel substances (which include substances that do not have a history of safe use in food) and any substances flagged as potentially unsafe by the scientific community. Changes must also be made to the notification procedure to cure conflicts

⁶ The sometimes elaborate praise conferred on the agency's GRAS program by the food industry can be viewed as an attempt to confer reality on a program that lacks conformity with the law, like courtiers fawning over a naked Emperor about his beautiful clothes. *See, e.g.,* Robert S. McQuate & Richard C. Kraska, *The Future of GRAS Regulations*, Nutritional Outlook, March 4, 2015, <http://www.nutritionaloutlook.com/1503/GRAS> (last accessed 4/9/15). In this article prepared by GRAS consultants, the authors noted that the regulated industry has expressed support for the 1997 proposal, calling it "a very thorough and comprehensive process," and that the agency should not "disturb a system that's not broken" as the "[c]urrent GRAS system works well to adequately ensure the safety of our food supply." *Id.* Nevertheless, the central food trade association, the Grocery Manufacturers Association (GMA), concedes the program has credibility issues. Leon Bruner, GMA's chief science officer told *The Washington Post* last August, "It's the right time to take a step back...There are problems with transparency. How can we be sure that the FDA is aware of ingredients?" Kindy, *supra* note 5. In response, GMA has proposed a set of steps for industry to take to standardize GRAS assessments. *See* McQuate & Kraska, *supra*. While the proposal by GMA amounts to an industry admission of the program's profound deficiencies, a privatized, industry-dominated regulatory substitute could never fulfill the Congressional assignment to FDA to assure the safety of the food supply.

⁷ 21 U.S.C.A. § 348.

⁸ 21 C.F.R. § 170.3(i) (safety determination requires consideration of the "cumulative effect of the substance in the diet, taking into account any chemically or pharmacologically related substance or substances in such diet").

⁹ Substances Generally Recognized as Safe, 62 Fed. Reg. 18,938 (Apr. 17, 1997).

of interest between industry and experts making GRAS determinations and eliminate data gaps in the scientific support underlying such determinations.

Second, because FDA cannot assure public safety if GRAS notification remains voluntary, FDA must require notification and publication of all GRAS determinations, along with updated exposure data and reporting of adverse data and events on a periodic basis.

II. Legal Framework: The History of GRAS Reveals A Significant But Limited Exemption

The FDA's obligation to oversee the safety of chemical additives derives from the agency's mission to "protect the public health by ensuring that – foods are safe, wholesome, sanitary, and properly labeled" under the FDCA.¹⁰ The original FDCA allowed the FDA to ban poisonous or deleterious adulterants in food; however, it did not directly address food additives. In 1958, in response to the rapid development of food technology and public concern that unsafe and untested new additives were making their way into the food supply, Congress passed the FAA to improve FDA oversight of additives.¹¹

a. The Food Additives Amendment of 1958

The FAA established FDA's obligation to regulate food additives,¹² and required premarket testing to "prohibit the use in food of additives which have not been adequately tested to establish their safety."¹³ Under the FAA, a "food additive"¹⁴ must undergo an FDA pre-market approval process to determine whether the anticipated use and application of the new additive is safe.¹⁵

All additives not exempt under the statute are presumed unsafe unless proven otherwise.¹⁶ FDA approval requires a showing that the additive will be safe under the proposed

¹⁰ 21 U.S.C. § 393(2).

¹¹ 62 Fed. Reg. at 18939 (stating that the amendment was passed "in response to public concern about the increased use of chemicals in food and food processing"); Food Additives Amendment of 1958, Pub. L. No. 85-929, 72 Stat. 1784 (1958) (codified at 21 U.S.C. § 348) (purpose of amendment is "to prohibit the use in food of additives which have not been adequately tested to establish their safety").

¹² Food Additives Amendment of 1958, P.L. 85-929, 52 Stat. 1041 (1958).

¹³ *Id.* (codified at 21 U.S.C. § 348).

¹⁴ Food additives are defined broadly under the amendment to include "any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food," including substances used in packaging, transport, processing, and preparation. 21 U.S.C. § 321(s).

¹⁵ 21 U.S.C. § 348.

¹⁶ In addition to the "generally recognized as safe" exemption, which is the subject of this comment, in 1995, FDA created the Threshold of Regulation rule, which exempts substances used in food contact materials from regulation as food additives if the dietary concentration is below 0.5 parts per billion (ppb) and if: (1) The chemical has not been shown to be a carcinogen; (2) There is no reason to suspect that it is a carcinogen; and (3) There is no evidence that it presents other health or safety concerns. Food Additives; Threshold of Regulation for Substances Used in Food-Contact Articles, 60 Fed. Reg. 36,595 (July 17, 1995) (codified at 21 U.S.C. § 170.39).

conditions of use.¹⁷ The premarket review process begins when someone files a petition seeking FDA’s approval for use of an additive.¹⁸ The petition must include the identity of the additive, the proposed use, the intended technical effect, the method of analysis in food, and full reports of all safety studies.¹⁹ A specific clause in the statute, known as the Delaney Clause, further provides that carcinogenic additives may never be approved under the food additive petition process.²⁰ Safety is determined by considering the potential cumulative effect on consumers of the substance in the diet, taking into account any chemically or pharmacologically related substance or substances, the probable consumption of the substance in the diet, and safety factors.²¹ If FDA finds the safety of an additive has been adequately established, the agency proposes a regulation sanctioning the proposed use of the additive, subject to notice and comment.

b. “Generally Recognized As Safe”

The bulk of the FAA outlines procedures for FDA’s safety evaluations of food additives and the appeals process for agency determinations. But in a scant few words, the term “food additive” specifically excludes substances that are “generally recognized as safe,” or GRAS.²²

Under the statute, an item is GRAS – and therefore not a “food additive” – if its use is generally recognized as safe by scientists knowledgeable about the safety of substances added to food.²³ General recognition of safety can be established through “scientific procedures,” or, for substances used in food prior to 1958, through experience based on the same common use in food prior to that date.²⁴ Safety is defined, by later FDA regulations, to mean “a reasonable

¹⁷ 21 U.S.C. § 348(b).

¹⁸ *Id.*

¹⁹ *Id.*

²⁰ 21 U.S.C.A. § 348 (c)(3)(A) (“[N]o additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal[.]”).

²¹ U.S. Food & Drug Administration, *Guidance for Industry and Other Stakeholders: Toxicological Principles for the Safety Assessment of Food Ingredients (Redbook 2000)*, updated July 2007, <http://www.fda.gov/downloads/Food/GuidanceRegulation/UCM222779.pdf>. The potential cumulative effects of additives are assessed based on toxicity studies as directed in FDA’s “Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food” (referred to as the Redbook). *Id.*

²² 21 U.S.C. § 321(s).

²³ *Id.*; Neltner et al., *supra* note 3, at 351.

²⁴ 21 U.S.C. § 321(s); 21 C.F.R. §§ 130.70(a), (c)(1). Importantly, the 1997 proposal states that it is the *use* of the substance, not its mere presence in the food supply, which confers eligibility for the GRAS exemption based on use. Thus, an “evaluation of whether an additional use of a substance that is GRAS through experience based on common use in food is also GRAS requires a scientific procedures GRAS determination when the *use* in question was not common prior to January 1, 1958.” 62 Fed. Reg. at 18950 (emphasis added). Until the 1980s, the agency refused to recognize use outside the United States; in the wake of a legal challenge, prior foreign use may now support GRAS status, but only if the information about such use is readily available and corroborated. Eligibility for Classification of Food Substances as Generally Recognized as Safe, 53 Fed. Reg. 16,544 (May 10, 1988) (codified at 21 C.F.R. § 170.3(f)).

certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use.”²⁵ However, FDA has not to date provided a definition of “harm” or what may be considered “harmful.”²⁶

i. Early Implementation of the GRAS Exemption

From the beginning, FDA’s authority to determine the GRAS status of a substance then in the food supply has correctly been presumed by both the agency and industry. However, FDA’s approach to assuring the safety of GRAS substances evolved significantly since the passage of the FAA. Immediately after the law was passed, FDA published a list of GRAS substances in the Code of Federal Regulations.²⁷ Once listed, these substances could be used, subject only to “good manufacturing practices” that address the quantity, quality, and grade of the substance used in food.²⁸

This list was updated over the following years.²⁹ The GRAS list was not intended to be “exhaustive,” and many substances considered GRAS by the food industry were not included on FDA’s 1958 GRAS list.³⁰ Although the FAA did not require premarket approval for GRAS substances, manufacturers would generally seek informal review by the agency before marketing substances by writing to FDA to request an informal “opinion letter” on the GRAS status of a particular substance for a particular use.³¹

This practice continued until 1970, when President Nixon directed FDA to make a critical evaluation of the safety of “food additives,” including listed GRAS substances, in response to rising public concern about potentially unsafe GRAS chemicals. In response to this directive, the Agency announced a comprehensive review of the safety of each substance on the GRAS list.³² The original inventories emerged “without any detailed scientific assessment of the original safety data, much less of the data subsequently generated with constantly improving detection and safety assessment methods.”³³ Thus, the purpose of the Agency’s review was to evaluate

²⁵ 21 C.F.R. § 170.3(i).

²⁶ Laurie J. Beyranevand, *Generally Recognized As Safe?: Analyzing Flaws in the FDA's Approach to GRAS Additives*, 37 Vt. L. Rev. 887, 889 (2013).

²⁷ The list was incorporated into the agency’s regulations as 21 CFR parts 182 and 582. 24 Fed. Reg. at 9,368 (Nov. 20, 1959).

²⁸ 62 Fed. Reg. at 18,939. GRAS status does not free a substance of FDA controls; use is still subject to food grade specifications in the Food Chemicals Codex, and its use cannot differ significantly from those providing the basis for eligibility. Institute of Medicine, *Enhancing the Regulatory Decision-Making Approval Process for Direct Food Ingredient Technologies* 24 (1999), available at <http://www.nap.edu/catalog/9453/enhancing-the-regulatory-decision-making-approval-process-for-direct-food-ingredient-technologies> [hereinafter “IOM Workshop Summary”].

²⁹ IOM Workshop Summary, *supra* note 28, at 23.

³⁰ *Id.* at 24.

³¹ U.S. Food & Drug Administration, *FDA’s Approach to the GRAS Provision: A History of Processes* (April 2006), available at <http://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/ucm094040.htm> (last accessed Feb. 24, 2015) [hereinafter “FDA’s Approach to the GRAS Provision”]; Food Additive Status Opinion Letters: Statement of Policy, 35 Fed. Reg. 5810, 5810 (Apr. 9, 1970).

³² *FDA’s Approach to the GRAS Provision: A History of Processes*, *supra* note 31.

³³ IOM Workshop Summary, *supra* note 28 at 23.

each substance using “contemporary standards” and “issue each item in a new (*i.e.*, affirmed) GRAS list, a food additive regulation, or in an interim food additive regulation pending completion of additional studies.”³⁴

FDA contracted with Federation of American Societies for Experimental Biology (FASEB) to establish the Select Committee on GRAS Substances (SCOGS) to review and evaluate the available scientific information on all GRAS substances.³⁵ By 1982, SCOGS had submitted opinions to FDA on the health aspects of more than 400 substances.³⁶ Of these, the Committee recommended revocation of GRAS status for 30 substances, and found that an additional five substances raised safety concerns.³⁷ As of 2009, the FDA had affirmed the GRAS status of 17 of these substances and taken no action on the remaining ones.³⁸ According to the U.S. Government Accountability Office (GAO), FDA “could not readily explain why, even though almost 30 years had passed since the committee completed its work[,] FDA has not revoked the GRAS status of any of the 18 substances whose safety the committee questioned.”³⁹

Also in 1970, FDA proposed revising the existing regulations regarding safety to state that “[s]afe must be understood to connote that the Food and Drug Administration, after reviewing all available evidence, can conclude there is no significant risk of harm from using the substance as intended.”⁴⁰ For substances not already on the GRAS list, manufacturers could seek affirmation of GRAS status by submitting relevant information to the Agency. FDA also made clear that new tests establishing harm could prompt removal from the GRAS list.⁴¹

In 1972, FDA promulgated a rule formalizing the opinion letter practice and providing for regulatory approval of GRAS substances. Individuals could petition FDA to review the GRAS status of a substance and issue a regulation confirming GRAS status.⁴² This process, known as the GRAS affirmation petition (GAP) process, was subject to notice and comment.⁴³ While such petitions were never mandatory, the GAP process was considered the “primary mechanism for manufacturers to protect themselves from FDA enforcement actions.”⁴⁴ Thus, in the comparably few instances that industry made private GRAS determinations under the GAP process, manufacturers would commission safety reviews by reputable scientific organizations in order to address the “obvious regulatory risks” then posed by industry self-determinations.⁴⁵

³⁴ 62 Fed. Reg. at 18,939.

³⁵ *FDA’s Approach to the GRAS Provision: A History of Processes*, *supra* note 31.

³⁶ *Id.*

³⁷ U.S. Government Accountability Office (GAO), *FDA Should Strengthen Its Oversight of Food Ingredients Determined to Be Generally Recognized as Safe (GRAS)*, GAO-10-246 21 (Feb. 2010).

³⁸ *Id.*

³⁹ *Id.*

⁴⁰ Eligibility of Substances for Classification as Generally Recognized As Safe in Food, 35 Fed. Reg. 18,623, 18,624 (Dec. 8, 1970) (codified at 21 C.F.R. § 121.3).

⁴¹ *Id.*

⁴² 21 C.F.R. § 170.35(a).

⁴³ *Id.*

⁴⁴ IOM Workshop Summary, *supra* note 28, at 3-4.

⁴⁵ *Id.* at 24-26. Specifically, in a few cases, industry commissioned private safety reviews by FASEB. These reviews would involve published and peer-reviewed study reports. *Id.* at 24.

In 1974, the agency issued a further rule specifying criteria for GRAS status, and explained the difference between GRAS status and food additive petitions, and the procedures used in each.⁴⁶ FDA clarified that a “general recognition of safety” could be demonstrated by either scientific procedures or by experience based on common use in food before 1958. The agency emphasized that, in its view, “Congress intended the phrase ‘scientific procedures’ as used in section 201(s) of the act to have the same dimensions as the full reports of investigations required to prove the safety of a food additive under section 409 of the act.”⁴⁷

Thus, the FDA concluded that GRAS determinations “require the same quantity and quality of scientific evidence as is required to obtain approval of a food additive regulation for the ingredient.”⁴⁸ It based its interpretation on two prior Supreme Court decisions that required the same standard of scientific evidence for GRAS drugs as for new drug applications.⁴⁹ The agency also clarified that scientific evidence for GRAS status must be “widely disseminated” such that it becomes “common knowledge among such scientists.”⁵⁰ The scheme established in the 1970s was comprehensive; experts at the time believed that the new formal GRAS requirements limited the GRAS category to substances used prior to 1958 and meant that the “only mobility with respect to GRAS status is a loss of that status.”⁵¹

ii. The 1997 Proposed Rule

In 1997, FDA published a proposed rule that would create a new GRAS notification procedure to replace the GRAS affirmation process and make several smaller changes to the system. First, the 1997 proposal specifically emphasized that the *safety* standard for food additives and GRAS substances is the same, but that GRAS also requires *common knowledge* of the safety of a use or substance.⁵²

The 1997 proposal also suggested revising the requirements for the “common knowledge” element of GRAS. First, FDA proposed to broaden the description of common knowledge by expanding the types of technical evidence of safety that form the basis for a GRAS determination. Specifically, FDA proposed that “general recognition of safety through scientific procedures be based upon generally available and accepted scientific data, information, methods, or principles, which ordinarily are published.”⁵³ This proposal is a subtle but

⁴⁶ General Recognition of Safety and Prior Sanction for Food Ingredients, 39 Fed. Reg. 34,194, 34,194 (Sept. 23, 1974) (codified at 21 CFR § 121).

⁴⁷ *Id.* at 34,194.

⁴⁸ 21 U.S.C. § 321(s); 21 C.F.R. § 170.30(b).

⁴⁹ *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609 (1973); *Weinberger v. Bentex Pharmaceuticals, Inc.*, 412 U.S. 645 (1973).

⁵⁰ 39 Fed. Reg. at 34,194.

⁵¹ Fred H. Degnan, *FDA’S Creative Application of the Law* 25-26 (2d ed. 2006) (describing the 1974 proposal as a shift from industry GRAS standards to FDA’s standards for approval of food additive, thereby limiting the applicability of the GRAS exemption and formalizing the GRAS affirmation process).

⁵² 62 Fed. Reg. at 18,942 (“[A] GRAS substance is neither more safe nor less safe than an approved food additive.”).

⁵³ *Id.* For consistency, FDA also proposed to revise the definition of “scientific procedures” to include “scientific data, information, methods, or principles, which ordinarily are published.” *Id.*

significant revision to the prior regulations, which had provided that scientific procedures relied upon “shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data and information.”⁵⁴ The revision elevates the role of *unpublished* studies, data, information, and methods from mere corroboration to primary support.

Second, FDA sought to clarify the role of publication in satisfying the general recognition standard, explaining that publication is “usually necessary, but may not always be sufficient, to satisfy the common knowledge element of the GRAS standard.”⁵⁵ It also specified that the common knowledge element precludes a GRAS determination if the data and information evaluated by an expert panel are only available in files that are not publicly accessible.⁵⁶ As this document will demonstrate, this requirement for GRAS has largely been ignored in practice.

Finally, and most significantly, FDA proposed replacing the voluntary GRAS affirmation petition process with a voluntary notification procedure.⁵⁷ While the proposal was never finalized, the notification procedure has been in force as an interim procedure since it was proposed in 1997.⁵⁸ FDA provided three main justifications for replacing the prior system. The first rationale was its perception that the onerous GAP process was discouraging individuals from requesting affirmation of self-determined GRAS status.⁵⁹ The agency thus predicted that a simpler process would provide an incentive for manufacturers to inform FDA of their GRAS determinations, resulting in “increased agency awareness of the nation’s food supply and the cumulative dietary exposure to GRAS substances.”⁶⁰ Second, FDA predicted that the “streamlined” notification process would allow the agency to redirect its resources to GRAS substances “that are a priority with respect to public health protection” and to issuing industry guidance on food safety issues.⁶¹ Third, FDA explained its belief that because it was replacing one voluntary process (GAP) with another voluntary process, its proposal was “neutral” from a legal and regulatory perspective.⁶²

⁵⁴ 21 C.F.R. § 170.30(b).

⁵⁵ 62 Fed. Reg. at 18,943.

⁵⁶ *Id.* at 18,943. In responses to GRAS submissions, FDA has indicated that it prefers studies to be published and “available in the scientific literature for a ‘reasonable amount of time’ (at least several months) before relying on them to make a GRAS conclusion” in order to provide “evidence that there is agreement within the scientific community about the conclusions of the study that a substance is safe.” FDA correspondence regarding GRN 362 for L-Carnitine (on file with CSPI).

⁵⁷ 62 Fed. Reg. at 18,941 (to be codified at 21 C.F.R. § 170.36).

⁵⁸ *Id.* at 18,954. FDA included an “interim” notification process in the NPRM that would be used “between the time of publication of this proposal and any final rule based on this proposal.” The “interim” process simply directs manufacturers to use the notification process described in the proposed rule. *Id.*

⁵⁹ *Id.* at 18,941. As one law review article points out, the agency’s justification for its proposal is “ironic” given that “the burdens cited by the Agency that would prevent an individual from filing a petition fell largely on the Agency [as] the data and information submitted with the petition needed to be collected for an independent determination of GRAS status regardless of whether the information was submitted to the FDA.” Beyranevand, *supra* note 26, at 905.

⁶⁰ 62 Fed. Reg. at 18,941.

⁶¹ *Id.*

⁶² *Id.* at 18,951.

In lieu of the GAP process, under the 1997 proposal, any person may notify FDA that a proposed use of a substance is GRAS by submitting a “GRAS exemption claim.”⁶³ A GRAS exemption claim includes a “succinct” description of the substance, the applicable conditions of its use, and the basis for the GRAS determination (*i.e.*, through scientific testing or that it was commonly used in that manner in food prior to 1958).⁶⁴ It must include a statement that the information supporting the GRAS determination is available for FDA review and will be sent to FDA upon request; however, unlike the GAP process, the notification process does not require notifiers to submit supporting information with a GRAS notice.⁶⁵

Upon receiving a claim, FDA will inform the notifier in a letter of one of the following responses: (1) FDA has “no questions” (and therefore, it is implied – but not stated – that the substance may be used in food without further FDA review, though this is not a formal affirmation of GRAS status);⁶⁶ (2) the notice is insufficient; or (3) FDA has ceased to evaluate the GRAS notice at the company’s request.⁶⁷

FDA may question a notifier’s conclusion that a use of a substance is GRAS if the notice: (1) does not adequately establish technical evidence of safety; (2) lacks evidence that the knowledge of safety is generally available; (3) does not convince the agency that there is the

⁶³ *Id.* at 18,941.

⁶⁴ *Id.*

⁶⁵ *Id.*

⁶⁶ *Id.* at 18,938 (no questions letter “would not be equivalent to an agency affirmation of GRAS status because FDA would neither receive nor review the detailed data and information that support the GRAS determination”). For example, in a “no questions” response letter FDA issued regarding whey protein isolate and dairy product solids, FDA wrote:

Based on the information provided by ADPI in GRP 1G0371, as well as other information available to FDA, the agency has no questions at this time regarding ADPI's conclusion that whey protein isolate and dairy product solids are GRAS under the intended conditions of use. The agency has not, however, made its own determination regarding the GRAS status of the subject use of whey protein isolate and dairy product solids. As always, it is the continuing responsibility of ADPI to ensure that food ingredients that the firm markets are safe, and are otherwise in compliance with all applicable legal and regulatory requirements.

Agency Response Letter GRAS Notice No. GRN 000037 (Apr. 2000), <http://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm154133.htm> (last accessed March 3, 2015). Despite this express disclaimer and the clear language in the regulation, decision letters are still sometimes cited by companies as evidence of FDA clearance. Tom Neltner & Maricel Maffini, NRDC, *Generally Recognized as Secret: Chemicals Added to Food in the United States* 4 (Apr. 2014), available at <http://www.nrdc.org/food/files/safety-loop-hole-for-chemicals-in-food-report.pdf>; see also Erin Quinn & Chris Young, Why the FDA doesn't really know what's in your food, Center for Public Integrity (Apr. 14, 2015), [http://www.publicintegrity.org/2015/04/13/17112/why-fda-doesnt-really-know-whats-your-food?utm_source=feedburner&utm_medium=feed&utm_campaign=Feed%3A+publici_rss+\(The+Center+for+Public+Integrity+Latest+Stories\)](http://www.publicintegrity.org/2015/04/13/17112/why-fda-doesnt-really-know-whats-your-food?utm_source=feedburner&utm_medium=feed&utm_campaign=Feed%3A+publici_rss+(The+Center+for+Public+Integrity+Latest+Stories)) (quoting Neltner and Maffini saying that they have seen ingredient manufacturers hawk their additives as “FDA approved” or “approved by FDA procedures” even though “no questions” letters do not constitute actual approvals).

⁶⁷ Memorandum from Linda S. Kahl, Center for Food Safety and Applied Nutrition, to Docket No. FDA-1997-N-0020, Re: Substances that Are Generally Recognized as Safe (GRAS); Experience with GRAS Notices 10 (Nov. 2010); see also Neltner & Maffini, *supra* note 66, at 9.

requisite expert consensus about the safety of the substance for its intended use; or (4) is so poorly presented that the basis for a GRAS determination is not clear.⁶⁸ FDA can also question the claim if it is “aware of information that is not included in the notice but raises important public health issues.”⁶⁹

If FDA rejects a GRAS notice, it explains its safety concerns in a letter to the company and publishes the letter on the agency’s Web site. However, a company may withdraw the notice at any time and ask FDA to cease further review.⁷⁰ In this case, the agency does not publish the questions that prompted the agency’s concern and/or the company to withdraw its notice. Regardless (and remarkably), evidence shows that those or other companies may continue to market that substance for use in food, despite FDA’s questions about its safety.⁷¹

The current notification system represents an absolute nadir in FDA’s already-flawed implementation of the FAA and is illegal under the statute. The proposal’s notification process differs from the previous GAP process in that the notifier no longer must provide the detailed data and information that support the GRAS determination as part of the submission, and that FDA does not actually make a binding decision as to the GRAS status of the use of a substance in its response.⁷² Thus, unlike the GAP process, FDA does not assess the underlying support or issue a regulation affirming the GRAS conclusion made by the notifier. As a result, the notification process does not offer the protection from FDA enforcement provided by the GAP process.⁷³

Yet, both systems suffer from the same overarching deficiency in that they are completely voluntary. Both the GAP and notification process permit GRAS status to be determined by industry without any oversight or input from FDA. In other words, they allow industry to conduct what some have called a “secret GRAS” procedure as the sole prerequisite for introduction of a new use of a substance in food.⁷⁴ This lack of transparency and basic information prevents the entire food safety system from working as intended by Congress.

⁶⁸ 62 Fed. Reg. at 18,950.

⁶⁹ *Id.*

⁷⁰ *Id.* at 18,951.

⁷¹ Neltner & Maffini, *supra* note 66, at 9. Companies ask FDA to cease evaluations of their GRAS determinations with alarming frequency. A review of the list of GRAS notifications on FDA’s website indicates that 84 notifications have been withdrawn out of a total 562 submissions – 15% of the total number of notifications. GRAS Notices, <http://www.accessdata.fda.gov/scripts/fdcc/?set=GRASNotices> (last accessed 2/25/2015). This issue is discussed in further detail below.

⁷² 62 Fed. Reg. at 18,950.

⁷³ *Compare* IOM Workshop Summary, *supra* note 28, at 3 (describing GAP process as the “primary mechanism for manufacturers to protect themselves from FDA enforcement actions), *with* 62 Fed. Reg. at 18,950 (explaining that under proposed notification system, “FDA would not be in a position to affirm a notifier’s conclusion that a use of a substance is GRAS”).

⁷⁴ Neltner & Maffini, *supra* note 66, at 2-3 (noting that “Generally Recognized as SECRET” rather than “Generally Recognized as SAFE” is a better name for the GRAS loophole). However, even though the GAP process was voluntary, it appears that secret GRAS was much rarer under GAP than under the 1997 proposal. IOM Workshop Summary, *supra* note 28 at 26 (describing self-determination during the GAP years as “carr[ying] obvious regulatory risks”).

iii. Elements of the GRAS Standard

Through regulation, FDA has clarified that the safety standard for GRAS substances is the same as for food additives. For a substance to be GRAS, there must be technical evidence of safety (the “technical element”) along with the additional requirement that the safety of the substance be generally known and recognized (the “common knowledge element”).⁷⁵ To satisfy the technical element, there must be information about the substance establishing that its intended use is safe.⁷⁶

Again, FDA has defined “safe” or “safety” to mean that “there is a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use.”⁷⁷ When assessing the safety of *food additives*, Congress directed that certain factors must be considered:

- (A) the probable consumption of the additive and of any substance formed in or on food because of the use of the additive;
- (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.⁷⁸

As FDA has specifically directed that the safety standard for GRAS substances is the same as for food additives, the same factors must be considered for GRAS substances.⁷⁹ Thus, the technical element of a scientific procedure GRAS determination “must consider the probable consumption and cumulative effect of the substance in the diet.”⁸⁰

In addition to technical evidence of safety, GRAS substances must satisfy a “common knowledge” element. The “common knowledge” element includes two factors. First, the data and information necessary to establish the scientific evidence must be “generally available.”⁸¹ Second, there must be a basis to conclude that there is consensus among qualified experts about the safety of the substance for its intended use.⁸² This “consensus” does not require unanimity.

⁷⁵ 62 Fed. Reg. at 18,940 (“[A] GRAS substance is distinguished from a food additive on the basis of the common knowledge about the safety of the substance for its intended use rather than on the basis of what the substance is or the types of data and information that are necessary to establish its safety.”).

⁷⁶ 62 Fed. Reg. at 18,940.

⁷⁷ 21 C.F.R. § 170.3(i).

⁷⁸ 21 U.S.C. § 348(c)(5).

⁷⁹ 21 C.F.R. § 170.3(i) (defining safety under the statute as involving these three considerations).

⁸⁰ 62 Fed. Reg. at 18,944.

⁸¹ *Id.* at 18,940.

⁸² *Id.* at 18,940.

Generally, common knowledge is demonstrated through publication in a peer-reviewed scientific journal; however, under the agency's 1997 proposal, it may be established through other means, including "secondary scientific literature," an "expert panel" convened for this purpose, or opinions from authoritative scientific bodies.⁸³

iv. 2010 Reopening of Docket & Center for Food Safety Consent Decree

Although FDA never finalized the proposed rule, both the agency and the food industry have been operating under the proposed procedure as an interim procedure since 1997. Between February 1, 1998 and December 31, 2009, the Center for Food Safety and Applied Nutrition's (CFSAN) Office of Food Additive Safety (OFAS) received and filed approximately 26 GRAS notices per year.⁸⁴ It is unknown how many GRAS determinations were made by industry during that time without notice to the agency. Of the notices received, approximately 79 percent of GRAS notices came to closure with a "no questions letter," 5 percent of GRAS notices ended with an "insufficient basis letter," and 16 percent of GRAS notices concluded with a "cease to evaluate letter."⁸⁵

In 2010, FDA reopened the docket on the 1997 proposal in light of the length of time that had passed since the 1997 proposal.⁸⁶ In reopening the docket, the agency did not change the 1997 proposal, but specifically sought comment on certain aspects of the original proposal, including the common knowledge element, proposed definition of scientific procedures, and requirement of cumulative exposure estimates, among others.⁸⁷

In early 2014, the Center for Food Safety (CFS), an advocacy group, filed a lawsuit against FDA challenging the 1997 proposal and the agency's failure to finalize the rule.⁸⁸ In October 2014, FDA entered into a consent decree with CFS that calls for FDA to submit a final rule regarding GRAS for publication no later than August 31, 2016.⁸⁹ We thus submit this comment for FDA to consider as it prepares to finalize that final rule.⁹⁰

⁸³ *Id.* at 18,941.

⁸⁴ Kahl Memo, *supra* note 67, at 3.

⁸⁵ *Id.* at 10-11. For the "cease to evaluate" letters, the content of the notifier's letter requesting that OFAS cease to evaluate the notice and the content of OFAS's response varied and depended on the circumstances. *Id.* at 16.

⁸⁶ Substances Generally Recognized as Safe; Reopening of the Comment Period, 75 Fed. Reg. 81536, 81536 (Dec. 28, 2010).

⁸⁷ *Id.* at 81,536.

⁸⁸ Press Release, Center for Food Safety, Center for Food Safety Sues FDA Over Food Additives (Feb. 21, 2014), available at <http://www.centerforfoodsafety.org/press-releases/2924/center-for-food-safety-sues-fda-over-food-additives#>.

⁸⁹ *Center for Food Safety v. Burwell*, Case No. 1:14-cv-267-RC, Consent Decree, ECF No. 14-1 (Oct. 20, 2014).

⁹⁰ We urge FDA to consider these comments when the agency contemplates finalizing the rule in 2016, particularly as the agency's published deadline for finalizing the rule suggests ongoing consideration of the final rule at FDA and there is considerably more than a year's time between our submission of this comment and FDA's published calendar for a final rule. Agencies generally consider late-filed comments "to the extent practicable." *See, e.g.*, 69 Fed. Reg. 16,054 (March 26, 2004) (Department of Health and

III. The 1997 Proposal Violates the FAA.

The 1997 proposal is illegal under the FAA. Under it and the interim procedures now in place, companies may avoid the required statutory food additive petition process, and substances may be added to food without any real assurance of their safety.⁹¹

Rather than furthering the objective of the FAA, FDA's 1997 proposal – and prior agency actions – stymies it. Because FDA fails to effectively limit the substances that may fall within the scope of GRAS, virtually all new chemicals are added to the food supply by manufacturers using the GRAS exemption – even those that cannot meet the definition for general recognition of safety. Furthermore, the GRAS exemption essentially replaces the formal food additive petition process laid out in the FAA. This directly contradicts the statute, which designated the food additive petition process as the primary means to assure the safety of new substances added to the food supply.⁹²

In addition, FDA incorrectly interprets the FAA as imposing no obligation on firms to even *inform* the agency of any GRAS decisions.⁹³ Because industry is not currently required to notify FDA of new GRAS substances, FDA lacks a comprehensive catalog of such substances or their dietary exposure.⁹⁴ FDA therefore cannot police the border between food additives and GRAS substances, and neither manufacturers nor FDA can base GRAS determinations (or food additive petitions) on accurate exposure data and assess the cumulative effect of similar

Human Services will consider late-filed comments); 16 C.F.R. § 1021.12 (Environmental Protection Agency will consider late-filed comments “to the extent practicable” on Environmental Impact Statements); 79 Fed. Reg. 24,632 (May 1, 2014) (Department of Transportation); 78 Fed. Reg. at 70888 (Nov. 27, 2013) (Federal Railroad Administration); 79 Fed. Reg. 10760-01 (Feb. 26 2014) (Department of Homeland Security); 79 Fed. Reg. 45,146 (Aug. 4, 2014) (Federal Highway Administration); 69 Fed. Reg. 32,200 (June 8, 2004) (Department of Agriculture); 62 Fed. Reg. 24,614 (May 6, 1997) (Consumer Product Safety Commission); 61 Fed. Reg. 1,412 (Jan. 19, 1996) (Office of Management and Budget). CSPI, NRDC, and Consumers Union all previously commented during the open docket periods. These comments supplement our original submissions to reflect relevant and significant information that has emerged in the ensuing two decades since the rulemaking was proposed. Specifically, the Pew Charitable Trusts and NRDC have published significant studies on the deficiencies of the GRAS program since the close of the second comment period. This comment should also be considered in the interest of fairness – the 19-year gap between the proposal and the final rule creates space for an empirical assessment of how the proposal has or has not functioned – and much of our comment demonstrates that FDA's proposal has failed to meet the agency's stated goals in the NPRM or correct pre-existing inadequacies in FDA's oversight of the safety of GRAS substances, and in practice undermines the statutory goals set out by Congress.

⁹¹ To the contrary, this was the very assignment given to FDA by the law – the “Act to protect the public health by amending the FDCA to prohibit the use in food of additives which have not been adequately tested to establish their safety.” Food Additives Amendment of 1958, P.L. 85-929, 52 Stat. 1041 (1958).

⁹² Should industry complain that the food additive process is too burdensome, their problem is not with FDA, but with the design of the law in the FAA. FDA cannot and should not use this as an argument to circumvent clearly expressed Congressional intent.

⁹³ Pew Charitable Trusts, *Fixing the Oversight of Chemicals Added to Our Food* (Nov. 2013), at 1.

⁹⁴ GAO Report, *supra* note 37, at 33. Furthermore, FDA is not made aware of whether companies track the evolving scientific information regarding substances determined to be GRAS, further limiting its ability to make ongoing safety assessments. *Id.* at 25.

substances as required by law. Furthermore, as will be demonstrated below, companies base their GRAS determinations on stale, conflict-ridden, and often unpublished, non-peer-reviewed science. In sum, the proposed rule establishes no real oversight over the safety of GRAS substances, and thus achieves little regarding public health, in clear violation of the FAA.

As a result of these serious deficiencies, the current GRAS process as defined by FDA “frustrate[s] the policy that Congress sought to implement” in passing the FAA and is an unlawful abrogation of FDA’s responsibilities to protect the public health from both unsafe and unproven additives.⁹⁵ It is therefore contrary to the intent of Congress as “unambiguously expressed” in the FAA. If FDA were to finalize the 1997 rule as proposed, it would thus be unlawful under the statute.⁹⁶ In the alternative, even if the statutory language were held to be ambiguous, FDA’s interpretation is “inconsisten[t] with the design and structure of the statute as a whole,” and does not merit deference under *Chevron*.⁹⁷ Finally, if FDA were to finalize the rule as proposed without revision, it would be “arbitrary and capricious” under the Administrative Procedure Act for its failure to consider many manifest problems with the interim system, the flaws and predictable errors in the original proposal, and the evidence presented to the agency since 1997.⁹⁸

The illegality of the proposed rule is amply demonstrated in the following section by reference to the plain language and structure of the FAA and its legislative history. It is further confirmed by the comments already on the docket and through several case studies illustrating the practical flaws of the proposed system, which will be discussed in Sections IV and V. FDA is fully aware of this record of failure⁹⁹ and has an affirmative obligation to correct it in the final rule on GRAS.

a. The 1997 Proposal violates the FAA and does not merit judicial deference under the *Chevron* doctrine.

In light of the language, structure, and legislative history of the FAA, FDA’s interpretation of the GRAS exemption is unlawful and deserves no deference by the courts. Judicial review of FDA’s decisions is governed by *Chevron*’s two step analysis:

First, always, is the question whether Congress has directly spoken to the precise question at issue. If the intent of Congress is clear, that is the end of the matter;

⁹⁵ *Fed. Election Comm'n v. Democratic Senatorial Campaign Comm.*, 454 U.S. 27, 32 (1981).

⁹⁶ *Chevron v. Natural Resources Defense Council*, 467 U.S. 837, 842-43 (1984).

⁹⁷ *Util. Air Regulatory Grp. v. E.P.A.*, 134 S. Ct. 2427, 2442 (2014) (quoting *University of Tex. Southwestern Medical Center v. Nassar*, 133 S.Ct. 2517, 2529 (2013)).

⁹⁸ *Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43-44 (1983).

⁹⁹ Speaking to the New York Times in 2013, FDA’s Deputy Commissioner for Foods Michael Taylor acknowledged a need for the agency to revisit the FAA: “From our standpoint, we do need to look at whether this regime established by Congress almost 60 years ago gives us the information we need. It would be desirable for F.D.A. to have more information on products being added to food.” Stephanie Strom, *Drink Ingredient Gets a Look*, N.Y. Times, Dec. 12, 2012, www.nytimes.com/2012/12/13/business/another-look-at-a-drink-ingredient-brominated-vegetable-oil.html?_r=0.

for the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress. If . . . Congress has not directly addressed the question at issue, the court does not simply impose its own construction on the statute, as would be necessary in the absence of an administrative interpretation. Rather, if the statute is silent or ambiguous with respect to the specific issue, the question for the court is whether the agency's answer is based on a permissible construction of the statute.¹⁰⁰

In this case, FDA's interpretation of the statute does not merit deference at either step of the *Chevron* analysis. First, Congress has directly spoken to the question at issue. The GRAS category, as it is currently applied by FDA and the food industry, includes substances that are not "safe" or "generally recognized" as safe, and thus plainly contradicts Congress's "unambiguously expressed" intent under the FAA. Second, even if the statute were viewed as ambiguous, FDA's position should not receive deference as it is an impermissible construction of the law in light of "the broader context of the statute as a whole."¹⁰¹

i. The 1997 Proposed Rule is contrary to Congress's "unambiguously expressed" intent under the FAA.

Under the 1997 proposal, and prior decisions, FDA essentially cedes the regulation of food additives to industry by applying a reading of the GRAS exemption that allows industry to make secret GRAS determinations without meaningful limitations by the agency. As a result, there are few restrictions, in practice, on what qualifies as "generally recognized as safe," in plain violation of the statutory language. Because anything can be GRAS, the exemption has entirely overtaken the "food additive" petition process laid out in the FAA. This is plainly contrary to the structure of the law, which makes clear that Congress was establishing a premarket review process for substances added to foods. To ensure that the GRAS and "food additive" definitions have meaning, GRAS determinations cannot be secret. Furthermore, safety determinations under the FAA require exposure data, which cannot be supplied when industry and FDA are both unaware of uses and exposures of substances in the food supply.

1. The current scope of the GRAS exemption exceeds the plain language of the statute.

The text of the FAA shows that Congress intended to establish FDA oversight over new food additives to ensure their use was safe before they were consumed by the general public, exempting substances "generally recognized as safe." The plain words of the GRAS exemption indicate that it was intended to permit those uses of substances that were relatively well known, uncontroversial in light of then-current scientific data, and long used for that purpose, while still subjecting both unknown additives and potentially unsafe known additives to mandatory premarket testing. Instead, FDA has expansively interpreted "generally recognized as safe," and in so doing has both undermined the statutory food additive petition process and failed to meet its statutory obligations to ensure the safety of all substances added to the food supply.

¹⁰⁰ *Chevron*, 467 U.S. at 842-43.

¹⁰¹ *Robinson v. Shell Oil Co.*, 519 U.S. 337, 341 (1997).

Today, almost all new substances in the food supply are self-determined GRAS, even those that are lab-created chemicals, have no history of safe use in food, or are otherwise novel. It is clear from the language and structure of the FAA that the current scope of the GRAS category has expanded unrecognizably beyond the original intent of Congress. Both indicate that GRAS was never intended to apply to unknown and unproven substances. In fact, these substances were precisely the intended target of the “food additive” approval requirements under the law.

The plain meaning of the words “general recognition” indicates that the exemption was not intended to apply to novel or newly discovered substances known only to a few people. “General recognition” of safety necessarily implies an awareness of the substance in the scientific community. This obvious interpretation has been adopted by the courts and by FDA: both have construed the language as requiring an “expert consensus” based on “substantial evidence.”¹⁰² Such consensus is impossible to achieve if a chemical’s existence and use are unknown to the general scientific community (or the relevant segment of it) and to FDA, as “unawareness of a product among qualified experts precludes a finding of general recognition.”¹⁰³

Furthermore, courts have found that the substantial evidence required for a general recognition of safety “consists of adequate and well-controlled studies that must be *generally available* to the scientific community.”¹⁰⁴ Thus, prior judicial analysis of the plain language of the law indicates that the food additive GRAS exemption was not intended to apply to novel substances whose properties or safety are not widely known. Yet, as demonstrated by the case studies at section V *infra*, under the 1997 proposal, novel and unknown substances are designated as GRAS and bypass the statutorily intended food additive petition process – a stark divergence from the unambiguous language of the statute.

Moreover, because the 1997 proposal expands the technical evidence requirements for GRAS to include “scientific data and scientific information,” thereby virtually eliminating the requirement for peer-reviewed studies in deciding GRAS status, it broadens the description of “common knowledge” so as to make the provision meaningless. Because industry’s GRAS determinations are essentially unregulated, firms use their own employees, consultants, and

¹⁰² *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 632 (1973) (interpreting “generally recognized” language in the drug context); *United States v. An Article of Drug Consisting of 4,680 Pails, More or Less, Each Pail Containing 60 Packets, Etc.*, 725 F.2d 976, 985 (5th Cir. 1984) (“[G]eneral recognition’ requires a two-step showing: first, that there is general recognition in fact, *i.e.*, that there is an expert consensus that the product is effective; and second, that the expert consensus is based upon “substantial evidence” as defined in the Act and in FDA regulations.”); 62 Fed. Reg. at 18,939 (“To establish such recognition, the proponent must show that there is a consensus of expert opinion regarding the safety of the use of the substance.”).

¹⁰³ *United States v. Articles of Drug . . . Hormonin*, 498 F. Supp. 424, 431-32 (D.N.J. 1980) *aff’d sub nom. Appeal of Carnrick Labs., Inc.*, 672 F.2d 902 (3d Cir. 1981) and *aff’d sub nom. United States v. Articles of Drug*, 672 F.2d 904 (3d Cir. 1981).

¹⁰⁴ *United States v. An Article of Drug Consisting of 4,680 Pails*, 725 F.2d at 987 (emphasis added); *see also United States v. An Article of Drug . . . “Bentex Ulcerine”*, 469 F.2d 875, 880 (5th Cir. 1972) (observing that if a substance is generally recognized as safe, one would expect to “find in the medical literature over a period of years support for this premise from wide experimentation and study”).

experts to make safety decisions, resulting in ubiquitous conflicts of interest.¹⁰⁵ These determinations are often based on stale and unpublished, non-peer-reviewed science.¹⁰⁶ Such backroom determinations cannot meet any plain definition of “general recognition” of safety in the scientific community.

The statutory language also unambiguously indicates that a substance whose safety is seriously disputed among qualified experts cannot be GRAS.¹⁰⁷ FDA itself has acknowledged that “it is well settled that a mere showing that the use of a substance is ‘safe’ is not sufficient to exempt the substance from the [FAA’s] definition of “food additive.”¹⁰⁸ Instead, the substance must *also* be shown to be “generally recognized” as safe.¹⁰⁹ Again, both the agency and the courts have found that “general recognition” requires a “consensus of expert opinion” regarding the safety of the use of the substance.¹¹⁰

If a requirement for general consensus of safety among experts means anything at all, it must exclude any substances that an authoritative body of scientists has linked to adverse outcomes for human health, as it is self-evident that such substances cannot receive the benefit of a “general consensus” of opinion among experts knowledgeable about their safety.¹¹¹ Yet, under the current system, as demonstrated below, substances flagged as a risk to human health by authoritative bodies can be designated as GRAS, in violation of the unambiguous statutory language.

FDA’s current system places no meaningful limits on the scope of the GRAS exemption. As will be shown in the case studies, industry regularly designates novel and lab-created substances as GRAS, as well as substances whose safety has been questioned by authoritative

¹⁰⁵ See discussion of funding bias, *infra* at Section IV.b.

¹⁰⁶ *See id.*

¹⁰⁷ *United States v. Undetermined Quantities of Various Articles of Drug . . . Equidantin Nitrofurantoin Suspension*, 675 F.2d 994, 1000 (8th Cir. 1982) (finding “a genuine dispute concerning the safety and effectiveness of a drug product . . . precludes a finding of “general recognition”) (quoting *United States v. Articles of Drug (Hormonin)*, 498 F.Supp. at 431-32). This requires a comprehensive review of the literature, as FDA regulations specify that an assessment of the safety of a food substance generally involves an evaluation of information about its safety and functionality including *all* studies and tests of a food additive on animals and humans and all studies and tests of a food additives for identity, stability, purity, potency, performance and usefulness. 21 CFR Sec 171.1 (h(4)) (emphasis added).

¹⁰⁸ 62 Fed. Reg. at 18,939 (citing *United States v. An Article of Food * * * Coco Rico, Inc.*, 752 F.2d 11, 15 n. 4 (1st Cir. 1985)).

¹⁰⁹ *Id.* (citing *Coco Rico*, 752 F.2d at 15 n. 4); *see also United States v. Articles of Food and Drug * * * Coli-Trol 80*, 518 F.2d 743, 745 (5th Cir. 1975).

¹¹⁰ *Id.*; *see also United States v. Western Serum Co., Inc.*, 666 F.2d 335, 338 (9th Cir. 1982); *United States v. Articles of Drug * * * Promise Toothpaste*, 624 F. Supp. 776, 778 (N.D. Ill. 1985), *aff’d* 826 F.2d 564 (7th Cir. 1987); *United States v. Articles of Drug * * * Hormonin*, 498 F. Supp. 2d 424, 435 (D.N.J. 1980). Courts further found that even published data may not be sufficient to establish GRAS status unless they had been “collected” with regard to establishing the safety of a specific use and evaluated in the context of a scientific “peer review.” Degnan, *supra* note 51, at 27.

¹¹¹ Note that such substances would remain eligible for use in the food supply as additives approved at levels below which they pose a risk to human health under the food additive approval process, should the food industry be able to show they may safely used for some purposes and at some level in food.

bodies. FDA’s system thus permits GRAS determinations for substances that cannot meet any possible interpretation of the words “general recognition of safety.” As a result, FDA’s interpretation of the GRAS exemption is legally unacceptable: agencies do not have the power to “rewrite[e] unambiguous statutory terms.”¹¹²

2. FDA’s expansive interpretation of GRAS nullifies the statutory food additive petition process.

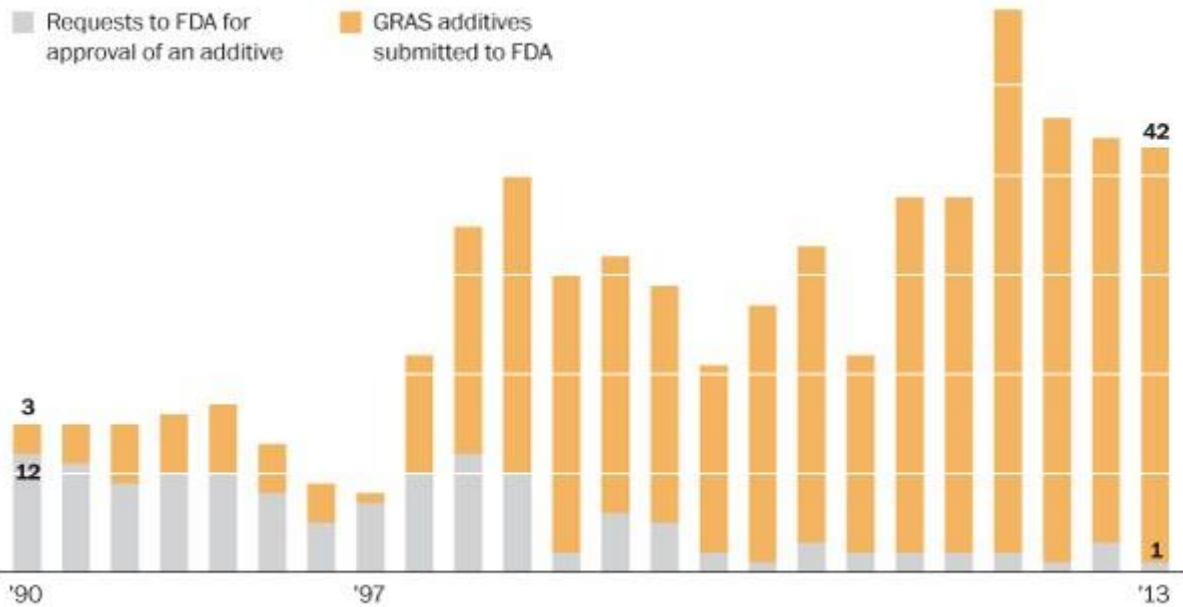
The effectively unlimited expansion of GRAS also violates the statute because it allows – and in fact *encourages*¹¹³ – unapproved food additives to masquerade as “GRAS” substances. The statutory design of the FAA makes clear that the food additive petition process was the primary process Congress intended to assure the safety of new and untested substances added to the food supply.¹¹⁴ Yet, because FDA has failed to sensibly limit the scope of the GRAS exemption, far more new substances added to food today bypass the formal food additive petition process than go through it, rendering the FAA’s food additive petition process virtually irrelevant.¹¹⁵

¹¹² *Util. Air Regulatory Grp. v. E.P.A.*, 134 S. Ct. at 2446.

¹¹³ The GRAS exemption – whether FDA is notified or not – is a far less labor-intensive process than the food additive petition process, which can sometimes take years to reach approval. Thus, it would be reasonable to conclude that it would be more attractive to industry – and the extreme decline in food additive petitions compared to GRAS notifications since 1997 (displayed in Washington Post graphic) indicates that this is in fact the case.

¹¹⁴ Should industry complain that the food additive process is too burdensome, their problem is not with FDA, but with the design of the law in the FAA. FDA cannot and should not use this as an argument to circumvent the clearly expressed Congressional intent.

¹¹⁵ See Comments by Lisa Lefferts, Center for Science in the Public Interest, quoting Tom Neltner, “Conflicts of Interest in Approvals of GRAS Additives: Out of Balance,” slides available at http://www.pewtrusts.org/~media/legacy/uploadedfiles/phg/content_level_pages/issue_briefs/PotentialCOfinGRASWorkshoppdf.pdf (“Over the past ten years, GRAS Notifications outnumber Food Additive Petitions by more than 14 to 1 for direct additives.”); see also IOM Workshop Summary, *supra* note 28, at 1 (“In the absence of timely approval, industry is likely to rely more heavily on the statutory exception for Generally Recognized As Safe (GRAS) substances to facilitate the marketing of new ingredients.”).



Source: Graphic by Kimberly Kindy and Cristina Rivero for the Washington Post, August 17, 2014.
 Data Sources: Natural Resources Defense Council, Food and Drug Administration, Center for Science in the Public Interest, Pew Charitable Trusts.

Thus, FDA’s expansive interpretation of the GRAS exemption allows substances that should be subject to the food additive petition process to bypass agency oversight, a stark nullification of the unambiguous statutory procedure laid out by Congress in the FAA. This is further exacerbated by the voluntary nature of the GRAS notification process, as “secret GRAS” prevents FDA from ensuring that “food additives” under the law are subject to the statutorily required preapproval process. For the “food additive” definition to have any meaning in practice, FDA must police the GRAS exemption to ensure that potentially unsafe additives are pretested for safety under the food additive petition (FAP) process as required by the statute – which it cannot do under a voluntary notification process.

The “secret GRAS” process also creates a perverse and undermining incentive: because industry does not ask for or receive explicit FDA approval, FDA may not be notified of substances that pose the most substantial risks to public health. As CSPI noted in its original comments on the proposed rule, “there will always be some companies who will never notify FDA of their GRAS self-determinations [and t]hose companies are the ones most likely to have self-declared substances as GRAS that may not actually be safe.”¹¹⁶ The voluntary notification system thus allows unapproved food additives that may in fact be the most dangerous to evade the regulatory process.

As a result of these deficiencies, in violation of any possible construction of the FAA, the GRAS exemption has completely overtaken the definition of “food additive.” The language and structure of the statute make clear that this interpretation could not have possibly been the intention of Congress in passing the FAA. Indeed, if Congress had intended the GRAS

¹¹⁶ CSPI Comment Re: Substances Generally Recognized as Safe; Proposed Rule Docket No. 97N-0103, July 16, 1997.

exemption to overtake the statutory food additive petition process, it would have said so, as Congress “does not . . . hide elephants in mouseholes.”¹¹⁷ Instead, FDA’s expansive interpretation of GRAS turns an exception into the dominant rule, in plain violation of Congress’s unambiguous intent.

3. “Secret GRAS” eviscerates the safety standard under the statute.

Under the “secret GRAS” system sanctioned by FDA under the current regulations, many “food additives” avoid the statutorily mandated food additive petition process, in plain violation of the statute. Moreover, because the current notification system is voluntary, FDA has limited oversight over these additives and is unaware of public exposures to and the use of an estimated 1,000 substances – so-called “secret GRAS.”¹¹⁸ This leaves the FDA, industry, and public unaware about uses of substances in foods and their exposure levels – yet analysis of such data is essential to making a determination of safety under the plain language of the FAA.

The FAA specifically dictates that FDA consider exposure and cumulative effects when determining the safety of food additives.¹¹⁹ To meet these requirements, FDA *must* be able to estimate what type of foods contain the substance and how much of the substance is likely to be in each type of food. If someone other than FDA has made a GRAS safety determination for the substance, the agency is obligated by subparagraph (A) to know about the exposure likely to result from that decision. If FDA is not notified of the decision (as is often the case under the current voluntary notification system), then neither FDA nor other manufacturers can estimate probable consumption as required by Congress. Instead, under the current system, multiple companies may privately conclude that an ingredient is safe at a specific level, while their combined uses actually result in unsafe exposure levels.¹²⁰ In other words, the express

¹¹⁷ *Whitman v. Am. Trucking Associations*, 531 U.S. 457, 468 (2001).

¹¹⁸ See Neltner, *supra* note 3, at 342; Neltner & Maffini, *supra* note 66, at 2.

¹¹⁹ 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;
- (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.

21 U.S.C. § 348(c)(5). This safety standard also applies to GRAS substances, which by regulation must meet the same standard for safety as that for food additives. 21 C.F.R. § 170.30(b). These requirements were also reiterated by Congress when it passed the Food and Drug Administration Modernization Act (FDAMA) in 1997, which specifically required consideration of criteria such as the probable consumption of such food contact substance and potential toxicity of the food contact substance in food contact substance notifications. Pub. L. 105–115, §309, 111 Stat. 2354 (1997) (codified at 21 U.S.C. § 348(h)).

¹²⁰ The Center for Public Integrity provided an effective illustration of this problem:

Consider how this could play out at a family’s breakfast table. A company might privately conclude that an ingredient is safe at a specific level in cereal. Another might do the same for its use in muffins. Ditto for a third company adding it to juices. A

requirements of the FAA for food additive petitions – and for GRAS under applicable interpretations upheld in the courts – cannot be met when notifications are voluntary.

In addition, to estimate the cumulative effect, Congress explicitly requires FDA to take into account “any chemically or pharmacologically related substance.”¹²¹ To meet this statutory requirement, the agency must know the chemical structure of all of the components of the additive in order to identify chemically-related substances. It must also know how the additive acts upon and affects the body, for example, the mechanism of action and physiological effect of the substance, in order to identify pharmacologically-related substances. Then, to assess the cumulative effects, FDA must know the *amount* of exposure, taking into account all chemically and pharmacologically-related substances. Only by knowing all of this could FDA – or another industry notifier for that matter – begin to consider the cumulative effect of the substance and chemically and pharmacologically-related substances and satisfy the express requirements of the statute.¹²²

The language and structure of the statute definitively show that the system Congress created in the FAA cannot function when such determinations are secret.¹²³ Thus, the voluntary nature of the notification system – “secret GRAS” – is illegal under the FAA. FDA itself has acknowledged that “it would be informative for FDA to have . . . at least an awareness of the existence of substances that are independently determined to be GRAS, even in the absence of a GRAS notice submitted by a company.”¹²⁴ FDA’s acknowledgement is a serious

family sitting down to a breakfast of all three foods could end up consuming much more of the ingredient than each company had anticipated.

Quinn & Young, *supra* note 66.

¹²¹ 21 U.S.C. § 348(c)(5).

¹²² For an example of how such a cumulative effect assessment would be conducted, *see generally* Maricel Maffini & Thomas Neltner, *Brain Drain: The Cost of Neglected Responsibilities in Evaluating Cumulative Effects of Environmental Chemicals*, *J. Epidemiol. Community Health* 1-4 (2014). In their analysis, they focus on chemicals likely to affect children’s brain development. They assembled a list from FDA’s own toxicology database that the agency noted as affecting the brain, hypothalamus (the part of the brain that interfaces with the endocrine system), or the thyroid. In the womb, the thyroid is essential for brain development. Even transient disruptions of the thyroid could interfere with fetal brain development in an inalterable manner. The list also included the results of the federal governments Tox21 *in vitro* testing program of chemicals that either inhibited or activated thyroid hormone receptors. FDA is active participant in the Tox21 program. Finally, it included pesticides that the European Food Safety Authority determined may harm the thyroid or the nervous system.

¹²³ This logic was also apparent to the U.S. Government Accountability Office when, in its 2010 report, it recommended:

To better ensure FDA's oversight of the safety of GRAS substances, the Commissioner of FDA should develop a strategy to require any company that conducts a GRAS determination to provide FDA with basic information—as defined by the agency to allow for adequate oversight—about this determination, such as the substance's identity and intended uses, and to incorporate such information into relevant agency databases and its public Web site.

GAO Report, *supra* note 37, at 34.

¹²⁴ Comments from the Food and Drug Administration *in* GAO Report, *supra* note 37, at 62. FDA has also acknowledged that it “cannot ensure that GRAS determinations that are not currently notified to FDA are rigorous, robust, or consistent with agency’s proposed criteria.” *Id.*; *see also* Kindy, *supra* note 5

understatement. Such awareness is not simply “informative,” it is *essential* for FDA to meet its statutory obligations. When FDA’s acceptance of “secret GRAS” is considered in light of its obligations under 21 U.S.C. § 348(c), it is clear that the FDA’s proposed rule is contrary to the unambiguously expressed intent of Congress under the FAA.

FDA’s current interpretation of the law allows an expansive interpretation of GRAS that contradicts the plain meaning of “general recognition of safety” and nullifies the statutory definition of “food additive.” Its secret nature permits unknown and unproven additives to bypass the statutorily mandated FAP process and makes it impossible for industry or the agency to obtain the exposure data necessary to meet the safety requirements in the law. While FDA has the power to resolve some questions left open by Congress in administering the law, it does *not* have the power to “rewrite clear statutory terms to suit its own sense of how the statute should operate.”¹²⁵ Thus, FDA’s actions are unlawful and due no deference, as FDA may not make “administrative constructions . . . contrary to clear congressional intent.”¹²⁶

ii. The 1997 Proposal is not based on a permissible construction of the FAA and therefore does not merit *Chevron* deference.

In the alternative, even if the statute were found to be ambiguous, FDA’s interpretation of the GRAS exemption still would not merit deference under *Chevron*. Where a statute is ambiguous, the question becomes whether the agency’s action is based on a permissible construction of the statute.¹²⁷ Thus, *even if* the FAA is considered ambiguous, FDA must still operate “within the bounds of reasonable interpretation.”¹²⁸ To be reasonable, the agency’s interpretation must account for both “the specific context in which . . . language is used” and “the broader context of the statute as a whole.”¹²⁹ A statutory “provision that may seem ambiguous in isolation is often clarified by the remainder of the statutory scheme . . . because only one of the permissible meanings produces a substantive effect that is compatible with the rest of the law.”¹³⁰

Applying this framework, FDA’s interpretation of its obligations under the statute is plainly unreasonable in light of the broader context of the statute as a whole. The FAA was intended to create a system of regulatory oversight over new and potentially unsafe substances added to foods: “An Act to protect the public health by amending the FDCA to prohibit the use in food of additives which have not been adequately tested to establish their safety.”¹³¹ FDA’s current interpretation of GRAS – that it permits a secret, virtually unlimited system of industry determinations – is plainly incompatible with the rest of the law, as it nullifies the premarket

(quoting FDA’s Michael Taylor: “We simply do not have the information to vouch for the safety of many of these chemicals[; w]e do not know the volume of particular chemicals that are going into the food supply so we can diagnose trends[; and w]e do not know what is going on post-market.”).

¹²⁵ *Util. Air Regulatory Grp. v. E.P.A.*, 134 S. Ct. at 2446.

¹²⁶ *Chevron*, 467 U.S. at 843.

¹²⁷ *Id.* at 842-43.

¹²⁸ *Arlington v. FCC*, 569 U.S. ___, 133 S.Ct. 1863, 1868 (2013).

¹²⁹ *Robinson.*, 519 U.S. at 341.

¹³⁰ *United Sav. Assn. of Tex. v. Timbers of Inwood Forest Associates, Ltd.*, 484 U.S. 365, 371 (1988).

¹³¹ Food Additives Amendment of 1958, Pub. L. No. 85-929, 52 Stat. 1041 (1958).

testing process and prevents FDA from exercising ongoing oversight of the safety of substances added to foods. Thus, while the words “generally recognized as safe” may have multiple possible constructions, when viewed in light of the statute as a whole, the 1997 proposal goes well beyond the “bounds of statutory authority”¹³² and FDA’s interpretation does not merit deference under *Chevron* step two.

1. In the FAA, Congress intended to establish a comprehensive regulatory scheme overseeing the safety of substances added to foods.

Under the 1997 proposal, FDA cedes far too much of its food additive oversight. The agency’s construction of the law is patently unreasonable in light of the purpose of the FAA, which was to create a comprehensive regulatory scheme overseeing the safety of all substances added to foods. When the FAA was passed, both lawmakers and leading scientists were deeply concerned about the food industry’s increasing use of untested food additives. The statute was a response to the lack of information about the possible chronic risks of existing and future food use chemicals.¹³³ The entire purpose of the bill, in the words of FAA-sponsor Congressman James Delaney of New York, was to change a system that made consumers “the guinea pigs for anything that comes on the market.”¹³⁴ He went on to remark at the congressional hearings on the bill, “I say that we are probably playing Russian roulette with some of these things. We just do not know. This bill simply provides for ordinary testing or pretesting before these new and untested chemicals are added to our food supply.”¹³⁵

¹³² *Arlington*, 133 S.Ct. at 1868.

¹³³ H. Rep. No. 82-2356, at 27 (1952).

¹³⁴ *Chemical Additives in Food: Hearings on H.R. 4475 Before the Subcomm. On Health and Sci. of the House Comm. On Interstate and Foreign Commerce*, 84th Cong., 2d Sess. 30 (1956). One of the main purposes of the legislation, according to the Report accompanying the House Bill, was “to protect the health of consumers by requiring manufacturers of food additives and food processors to pretest any potentially unsafe substances which are to be added to food.” H. Rep. No. 85-2284 (July 28, 1958). The second purpose was to “advance food technology by permitting the use of food additives at safe levels.” *Id.* This was a response to the previously existing law, which “entirely prohibit[ed] the use of these additives [even] at safe levels.” *Id.* While this purpose promoted the use of additives, to a degree, it was only the safe use thereof, as policed by adequate premarket assessment.

¹³⁵ *Id.* at 30 (1956). The select committee headed by Delaney had undertaken an inventory of chemicals then in use, and the legislation was intended to address the gaps in safety assessments. As Delaney noted, “there are approximately 276 chemicals being used in food today the safety of which has not been established to the satisfaction of many groups concerned with the health and safety of the public.” *Id.* at 29. In addition, concerns were being raised about “methods of processing” foods and the “chemical changes” they incurred in substances. *Id.* The need for a comprehensive regulatory scheme to address the gaps was emphasized throughout the hearings. For example, Rep. Delaney, who led a Congressional investigation of the use of chemicals in foods by a select committee in the 81st and 82nd Sessions of Congress, summarized the results of the select committee’s investigations for the record at the hearing, noting that “...the committee believed that the public is in need of protection against some irresponsible elements, as well as against the possible inadvertent mistakes of reputable food processors and the premature enthusiasms of chemical manufacturers.” *Id.* at 27.

Before the FAA was passed, FDA had only weak, post-market regulatory authority over chemicals added to food under the FDCA. Section 402(a) of the FDCA provided that a food shall be deemed adulterated if it “bears or contains any poisonous or deleterious substance which may render it injurious to health.”¹³⁶ To remove an additive from the market, FDA had to *prove* that a substance was poisonous or deleterious and could render the food injurious to health. Because of the substantial scientific support it would require to sustain such a finding, FDA could enforce this provision only after consumers were already exposed to its risks.¹³⁷ It could take years for FDA to obtain the requisite proof, during which time it could not keep the substance off the market or protect consumers.¹³⁸

The FAA was thus passed specifically to shift this burden from the agency to the industry – the new system “would put upon the processor rather than our Government the burden of proving that a newly discovered substance which a processor of foodstuffs proposes to add to the food we eat is safe.”¹³⁹ In addition, it would replace the existing system with a *premarket* review process overseen by FDA. Under the statute, a food additive could not be used unless and until the agency deemed it safe for the use proposed by the sponsor.¹⁴⁰ When reviewed in this context, it is clear that the GRAS exemption was not intended to upset this balance; rather, it provided additional flexibility so that FDA would retain authority over novel and risky substances, while allowing substances with an undisputed and generally known record of safety to be quickly cleared of concern and used.¹⁴¹

FDA’s conception of GRAS subverts the objectives of the FAA. Under the current system, almost all chemical additives are self-determined GRAS by the food industry and thereby bypass the food additive petition and premarket review process established by the FAA.¹⁴² Once a substance is determined to be GRAS by industry, it may immediately be marketed in foods without FDA’s approval or knowledge. In practice, FDA takes the position

¹³⁶ 21 U.S.C. § 342(a).

¹³⁷ H. Rep. No. 85-2284, at 1 (1958) (“To prove an untested substance poisonous or deleterious may require approximately 2 years or more of laboratory experiments with small animals and during this period the Government cannot prevent the use of such a substance in food.”).

¹³⁸ *Id.*

¹³⁹ S. Rep. No. 85-2422, at 3 (1958). Despite numerous bills on the topic, the chairman of the Health and Science Subcommittee opened the hearings in the House by stating, “There is basic agreement among proponents of this legislation with regard to the need for additional legislation. The industries concerned – those who manufacture the chemicals in question and those who use them in connection with food products – and the Government agencies are in agreement that an advance determination by the Government as to the acceptability of a chemical in connection with foods is desirable from the point of view both of the industries concern, the Government and the consumer.” *Chemical Additives in Food: Hearings on H.R. 4475 Before the Subcomm. On Health and Sci. of the House Comm. On Interstate and Foreign Commerce*, 84th Cong., 2d Sess. 1-2 (1956).

¹⁴⁰ S. Rep. No. 85-2422, at 2 (1958) (“The processor who wants to add a new and unproven additive [must] accept the responsibility . . . of first proving it to be safe for ingestion by human beings.”).

¹⁴¹ Beyranevand, *supra* note 26 at 895.

¹⁴² Pew Charitable Trusts, *supra* note 4, at 1; Post Graphic at p. 21 *supra*.

that it then must demonstrate the substance is *not* safe in order to revoke its GRAS status, and any safety review is postmarket.¹⁴³

Thus, the regulatory process FDA invented in its 1997 proposal for GRAS substances returns us, practically speaking, to a pre-FAA world – a world in which the burden of proof was on FDA and safety review occurred *after* substances were already marketed to consumers. The fact that FDA has allowed this shift in the burden of proof¹⁴⁴ violates the FAA, which was expressly intended to shift the burden *from* FDA onto additive manufacturers to prove a substance is safe.¹⁴⁵ For this reason, the GRAS system is “inconsisten[t] with the design and structure of the statute as a whole,” and is therefore an illegal interpretation of the FAA.¹⁴⁶

Far from furthering the statutory purpose of the FAA, FDA’s GRAS system does essentially nothing to protect the public from unsafe substances added to foods. The FAA, by its plain meaning and structure, was meant to create a regulatory system to ensure the safety of substances added to foods through required premarket testing and expanded FDA oversight. However, under the 1997 proposal, the voluntary GRAS notification system places FDA in a

¹⁴³ Toni Clarke, *FDA Considering Revamping Food Additive Rules Amid Growing Safety Concerns*, Huffington Post, Aug. 7, 2013, http://www.huffingtonpost.com/2013/05/07/food-additives-rules-fda-safety-concerns_n_3229755.html (“Our system really puts the onus on us to prove harm,” FDA Commissioner Margaret Hamburg said at the Reuters Health Summit in New York. “It’s perhaps a time to look at what the legal framework looks like and what opportunities there are now to ask and answer questions in new ways because of advances in science and technology.”).

¹⁴⁴ This is at least how it has been interpreted by industry. *See, e.g.*, Comment of Grocery Manufacturers of America re: Tentative Determination Regarding Partially Hydrogenated Oils; Request for Comments and for Scientific Data and Information (March 2014), at 7 (“[To revoke GRAS status,] FDA bears the burden of demonstrating that there exists a severe conflict among experts with respect the safety of the challenged use of a substance.”)

¹⁴⁵ *See* S. Rep. No. 85-2422, at 3 (1958). Indeed, another clear theme of the hearings was that the law was intended to shift the burden of proof regarding the safety of additives to the regulated industry and off the FDA. Rep. Dies asked Rep. Delaney: “This would shift the burden to the industries to have the pretesting done?” Rep. Delaney responded, “At least to show that they have made tests to prove that they are not toxic, to the satisfaction of the Food and Drug Administration.” *Chemical Additives in Food: Hearings on H.R. 4475 Before the Subcomm. On Health and Sci. of the House Comm. On Interstate and Foreign Commerce*, 84th Cong., 2d Sess. 30 (1956). Rep. Delaney also quoted from the findings of the select committee regarding the views of a food industry representative, Dr. R.C. Newton, Vice President of Swift & Co., who, citing the risks to the reputations of companies from a “disaster,” noted that the current burden of proof rested with FDA, and stated that “[a] simple change in the law to place the burden of proof on the prospective user, for example, of the chemical, is essentially all that is needed.” The select committee’s investigation headed by Rep. Delaney emphasized this overarching purpose as well in its conclusion, proposing “that the public is entitled to greater protection with respect to foods it must necessarily consume; and that such protection is not afforded by existing legislation under which the Government may take no action until after the food has been placed upon the market and injury may have occurred.” *Id.* at 31.

¹⁴⁶ *Nassar*, 133 S. Ct. at 2528-29; *see also Fed. Election Comm’n v. Democratic Senatorial Campaign Comm.*, 454 U.S. 27, 32 (1981) (finding that “administrative constructions of the statute, whether reached by adjudication or by rule-making,” must be rejected where they are “inconsistent with the statutory mandate or . . . frustrate the policy that Congress sought to implement.”)

quasi-regulatory role that Congress never intended.¹⁴⁷ While the system allows industry to submit notifications to FDA, the agency does not accord its own action any regulatory or clearance status for the safe use of the substance.

Where FDA does raise real safety questions, manufacturers are permitted to withdraw their notifications, and still may market the substances in question. The notification system also gives producers little inducement to notify FDA in the case of potentially dangerous substances, as it would invite regulatory scrutiny without much benefit for industry (as FDA never actually attests to a determination of GRAS).¹⁴⁸ Thus, the 1997 proposal actually *decreases* FDA oversight over the most critical decisions impacting public safety, frustrating the “policy that Congress sought to implement.”¹⁴⁹ It therefore does not merit deference.

2. FDA’s current interpretation of GRAS is unreasonable in light of the purpose of the FAA.

FDA’s current expansive interpretation of GRAS, which has overtaken the “food additive” definition under the law, is plainly unreasonable in light of the purpose and history of the FAA (as well as the statutory language, as discussed above). The legislative history indicates that Congress intended the GRAS exemption to be used only where the probable consumption of a substance was widely known and its safety publicly and clearly understood. FDA’s current interpretation of GRAS directly conflicts with this intent.

The FAA was enacted in response to a 1952 Congressional Committee Report that recommended amending the FDCA to require that chemicals used in foods be subject to the same safety standards as those required for new drugs.¹⁵⁰ The Committee Report found that only about half of the 840 chemicals used in food were considered safe, and concluded that the existing law failed to provide adequate safety assurances for food additives.¹⁵¹ At that time, new drugs required premarket testing and FDA approval, while new food additives did not.¹⁵² The FAA was thus passed to “prohibit the use in food of additives which have not been adequately tested to establish their safety.”¹⁵³ Representative Delaney specifically stated, when describing the scope of the law, “I am talking of new and unused and untested chemicals and this bill requires, to get down to the basic point, that when a chemical is added there be sufficient testing

¹⁴⁷ In the words of James O’Reilly, a professor of food and drug law at the University of Cincinnati College of Law, this system amounts to “a balloon in the shape of a regulator. We have the appearance that there’s a regulator protecting us, but there’s not.” Quinn & Young, *supra* note 66.

¹⁴⁸ Compare IOM Workshop Summary, *supra* note 28, at 3 (describing GAP process as the “primary mechanism for manufacturers to protect themselves from FDA enforcement actions), with 62 Fed. Reg. at 18,950 (explaining that under proposed notification system, “FDA would not be in a position to affirm a notifier’s conclusion that a use of a substance is GRAS”).

¹⁴⁹ *Fed. Election Comm’n*, 454 U.S. at 32; see also *Util. Air Regulatory Grp. v. E.P.A.*, 134 S. Ct. at 2442 (2014) (quoting *Nassar*, 133 S.Ct. at 2529) (agency interpretation “‘inconsisten[t] with the design and structure of the statute as a whole’ does not merit deference”).

¹⁵⁰ H. Rep. No. 82-2356, at 27 (1952); Lars Noah & Richard A. Merrill, *Starting from Scratch?: Reinventing the Food Additive Approval Process*, 78 B.U. L. Rev. 329, 336 (1998).

¹⁵¹ Beyranevand, *supra* note 26, at 893.

¹⁵² Noah & Merrill, *supra* note 149, at 336–37.

¹⁵³ Pub. L. No. 85-518, 72 Stat. 1784 (1958).

so that the Food and Drug Administration is satisfied that it does not contain elements that are not harmful to the human system.”¹⁵⁴

Recognizing that it would be impractical to require pre-market evaluation for innocuous substances that had long been used in foods or were well known to be safe, Congress included an exemption for substances with a well-recognized track record of safety. The law therefore required premarket evaluation for safety with respect to additives that were not “generally recognized among competent experts as having been adequately shown to be safe under the conditions of their intended use,” or “generally recognized as safe” (“GRAS”).¹⁵⁵

The GRAS exemption was narrowly tailored to achieve the aforementioned goal: it did not exempt *all* substances in current use, as this would not have achieved the purpose of ensuring the safety of all additives used in foods. Instead, it was understood at the time that the pretesting requirement would deal “mostly with new additives and more occasionally with old ones” and that the status of *any* substance – including GRAS substances – could always change in light of updated science.¹⁵⁶ Through the FAA, Congress sought to establish a comprehensive, far-reaching regulatory scheme overseeing all substances added to foods – rather than applying only to a small subset of additives. In other words, contrary to FDA’s current application, GRAS was truly intended to be an exception to the FAP process, not the primary practice.

The legislative history also indicates that GRAS was meant to have a narrow construction. The “generally recognized” clause was copied verbatim from the new-drug law provision already in force under the original FDCA.¹⁵⁷ Under the FDCA, the term “new drug” means “any drug . . . the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof.”¹⁵⁸ Any manufacturer of a new drug – one not “generally recognized . . . as safe” – must file an application for approval to FDA before delivering or distributing the drug in interstate commerce.¹⁵⁹

In the new-drug context, the “generally recognized . . . as safe” language has never been interpreted to allow industry-made safety determinations for novel pharmaceuticals – and had not been at the time of the FAA’s enactment. The FAA’s use of the FDCA’s new drug language is a clear indication that the GRAS exemption for food additives was intended by Congress to

¹⁵⁴ *Chemical Additives in Food: Hearings on H.R. 4475 Before the Subcomm. On Health and Sci. of the House Comm. On Interstate and Foreign Commerce*, 84th Congress, 2d Sess. 28 (1956).

¹⁵⁵ 21 U.S.C. § 321(s).

¹⁵⁶ Charles Wesley Dunn, Initial Comments—for Food Law Institute, 13 *Food Drug Cosm. L.J.* 743, 744 (1958); 104 *Cong. Record*, 85th Cong, 2d Sess. 17412, 17420 (Aug. 13, 1958) (Letter from John L. Harvey, Deputy Commissioner of FDA) (explaining that later scientific developments could always change GRAS status to food additive status).

¹⁵⁷ The language is also used in the Pesticide Residues Amendment of 1954. Pub. L. No. 83-518, 68 Stat. 511 (1954) (codified at 21 U.S.C. 346a(a)), repealed and replaced by Food Quality Protection Act of 1996, Pub. L. No. 104-170, 11 Stat. 1489 (1996).

¹⁵⁸ 21 U.S.C.A. § 321.

¹⁵⁹ 21 U.S.C.A. § 355.

function similarly.¹⁶⁰ Indeed, the new-drug language is repeatedly referenced throughout the Congressional hearings on the FAA. For example, when discussing the GRAS exemption at the Congressional hearings, a representative from the Grocery Manufacturer of America noted that the vagueness of the GRAS language would not be problematic because “as the new drug section experience suggests, unless the one using the ingredient is absolutely certain, the risk of criminal penalties will result in his asking the FDA whether it thinks a new ingredient falls within the act or is general[ly] recognized as safe.”¹⁶¹ This suggests that, in the new-drug context, the industry would decline to invoke the GRAS exemption except in the very clearest circumstances for fear of FDA’s strict enforcement.

The Congressional hearings on the FAA indicate that Congress assumed that the same process would occur in the food additive context.¹⁶² However, because FDA enforcement in the food additive space is virtually nil (due to inadequate resources, a self-created lack of information about industry practices on GRAS substances, and FDA’s failure to hold GRAS notifications to the safety standards applied for food additives), the GRAS exemption for food additives has never been limited by industry fears of prosecution in the way it was and always has been for new drugs.¹⁶³ Instead of noticing this critical distinction in practice and addressing it by narrowing the exemption appropriately to reflect Congress’s intent, FDA has ignored the difference, and even worsened it, through its failure to enforce the law with penalties for violators or to adequately police the substances permitted to be self-declared as GRAS by industry. In the food area, in stark contrast to drugs, FDA’s interpretation of the GRAS exemption has blown a hole in the law sufficient to undermine its clearly stated intent.

That GRAS was intended to be narrowly construed is amply supported by testimony from the congressional hearings. During the Congressional hearings on the bill, a statement by William Goodrich, then-Assistant General Counsel for FDA, regarding the “generally recognized” language, demonstrates the intended scope of the GRAS exemption:

¹⁶⁰ *Chemical Additives in Food: Hearings on H.R. 4475 Before the Subcomm. On Health and Sci. of the House Comm. On Interstate and Foreign Commerce*, 84th Congress, 2d Sess. 203-205 (1956). (George P. Larrick, Commissioner of FDA, describing agency’s experience applying GRAS exception for drugs).

¹⁶¹ *Food Additives: Hearings Before the Subcomm. On Health and Sci. of the House Comm. On Interstate and Foreign Commerce*, 85th Cong. 213 (1957) (Testimony of Charles Wesley Dunn, on behalf of GMA).

¹⁶² *Id.*

¹⁶³ FDA’s policing of GRAS substances is exceedingly rare. While a procedure exists for citizens to petition the removal of an additive’s GRAS status, this process is also nonfunctional; of the 11 citizen petitions submitted to the agency between 2004 and 2008, FDA has decided on the validity of these concerns in only one case. Nine of these 11 petitions raised specific concerns about the safety of GRAS substances. For example, a 2006 petition cited studies linking diacetyl (a GRAS substance used in microwave popcorn) to severe respiratory reactions. Nine years later, FDA has still not responded to this petition, and diacetyl remains both “GRAS” and on the market. GAO Report, *supra* note 37, at 23. The remaining citizen petitions involved milk protein concentrate, partially hydrogenated vegetable oils, aluminum-based food additives, salt, carbon monoxide gas in fresh meat packaging, carbon monoxide gas in fresh tuna packaging, diacetyl, iodized salt, monosodium glutamate, carrageenan and similar substances, and stevia extracts. *Id.*

Mr. GOODRICH. The point of the general language is to avoid pretesting of things like table salt. We have to have the law like that.

Mr. DIES. He would be perfectly safe in putting out table salt.

Mr. GOODRICH. Because it is generally recognized.¹⁶⁴

At the same hearings, then-Commissioner of the FDA George P. Larrick testified similarly:

We believe only those chemicals should be automatically exempted from the new law which are recognized among competent experts as safe for their intended use. This would make it unnecessary, for example, to do studies on table salt, but would not approve the continued use, without scientific proof of safety, of the synthetic emulsifiers now widely used in some fabricated foods.¹⁶⁵

The testimony at the hearings clearly shows that the GRAS exemption was meant to be limited to substances considered at that time to be both safe and uncontroversial. The hearings also indicate clearly that novel chemical additives could never be GRAS because they have not been used for an adequate amount of time for their safety to be generally recognized. For example, a representative from the adhesive industry testified that, “it is certainly true that no new substance can qualify as being used to a material extent or for a material length of time, which is the ordinary or usual connotation of the words ‘generally recognized.’”¹⁶⁶ In other words, novel chemical additives could never be GRAS because their very novelty makes a broad scientific consensus impossible to achieve.

The food industry’s own interpretation of their legal obligations under the Act indicates that they also shared this understanding of the statutory language. At the hearings, a representative from several major food industry groups (including the American Bakers Association, the Grocery Manufacturers Association, and the National Restaurant Association) declared industry’s support for the bill and issued the following principles:

- We believe *every substance not represented by long usage in the human diet should be subject to question as an ingredient in food*, and that this question

¹⁶⁴ *Chemical Additives in Food: Hearings on H.R. 4475 Before the Subcomm. On Health and Sci. of the House Comm. On Interstate and Foreign Commerce*, 84th Cong., 2nd Sess. 227 (1956) (Testimony of William Goodrich, Assistant General Counsel for FDA). Note that the safety of salt was then considered uncontroversial; yet sodium in the diet may not be GRAS for all current uses. See *Petition to Revoke the GRAS Status of Salt*, submitted by CSPI to FDA Nov. 8, 2005, *available at* http://www.cspinet.org/new/pdf/fda_salt_petition.pdf. This highlights the need for FDA’s active reassessment of the safety of additives as required under the law.

¹⁶⁵ *Chemical Additives in Food: Hearings on H.R. 4475 Before the Subcomm. On Health and Sci. of the House Comm. On Interstate and Foreign Commerce*, 84th Cong., 2nd Sess. 197 (1956) (Testimony of FDA Commissioner George P. Larrick).

¹⁶⁶ *Id.* at 151 (Statement of John A. Gosnell, on behalf of the Adhesives Manufacturers Association of America).

should be resolved by adequate animal experimentation to prove that its use in food does not present a hazard to public health.

- We believe *every new substance proposed for use in human food should be subjected to adequate pretesting* by the manufacturer or user of the substance and that such pretesting should be required by law.
- We believe it to be a proper function of government to control those factors which may affect adversely public health. Therefore, we believe *the results of animal experimentation in pretesting new substances proposed for use in food should be reviewed and approved by the Food and Drug Administration before the substance is allowed to be used in food sold to the public.*¹⁶⁷

Thus, even in the view of the *regulated industry*, the pretesting and FDA approval requirements under the food additive petition process were intended to apply to all novel chemical additives – or in their words, “substances not represented by long usage in the human diet.” It is exceedingly clear from the legislative history that novel chemical additives were never intended to fall within the GRAS exemption of the FAA.¹⁶⁸ Indeed, FDA itself has more recently recognized that novel additives warrant greater caution in toxicological testing than known ones.¹⁶⁹ The fact that the current system permits unknown and unproven substances to be self-determined GRAS is an unreasonable interpretation of the statute in light of the original purpose of the GRAS exemption and the overall purpose of the FAA.

3. “Secret GRAS” undermines the purpose of the FAA and prevents the statute from working as Congress intended.

Finally, the legislative history makes clear that Congress, in passing the FAA, intended FDA to monitor the long-term effects of additive exposure in order to identify and address less obvious risks. However, the lack of transparency under “secret GRAS” makes it difficult or impossible for FDA to perform this critical task. Such review is also hampered because FDA lacks basic, comprehensive data on the public’s exposure to chemicals that would allow it to

¹⁶⁷ *Id.* at 58 (Statement of Howard O. Hunter, President of the American Institute of Baking, Appearing for Various Food Industry Associations) (emphasis added).

¹⁶⁸ See Noah & Merrill, *supra* note 149, at 337 (finding that the legislative history of the FAA demonstrates that “food processors and ingredient suppliers accepted the need for some method of premarket FDA review of novel ingredients in processed food”).

¹⁶⁹ U.S. Food and Drug Administration, *Guidance for Industry: Summary Table of Recommended Toxicological Testing for Additives Used in Foods* (June 2006), at n.2, <http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm054658.htm#ftn2> (last accessed 3/3/15) (“Minimum toxicological testing recommended to support the safety of a novel additive might include studies generally recommended for a Concern Level III additive, irrespective of its chemical structure and exposure.”); see also U.S. Food & Drug Administration, *Guidance for Industry: 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* 14 (June 2014), available at <http://www.fda.gov/downloads/Cosmetics/GuidanceRegulation/GuidanceDocuments/UCM300927.pdf>, federal register notice at 79 Fed. Reg. 36,533 (June 27, 2014) [hereinafter “Nanotech Guidance”].

connect trends in the food supply to trends in public health.¹⁷⁰ Quite simply, FDA’s proposed rule makes it impossible for the agency to do its job under the FAA, which clearly contemplated ongoing FDA oversight and reassessment of all substances in food. The “secret GRAS” permitted by the voluntary notification process is therefore unlawfully “incompatible” with “the substance of Congress’ regulatory scheme,” and does not warrant *Chevron* deference.¹⁷¹

The legislative history clearly demonstrates that Congress intended FDA to be aware of *all* substances added to foods, including those properly determined to be GRAS. Before 1958, FDA could already police poisonous additives and adulterants. In passing the statute, Congress was giving FDA increased control over additives in order to address less obvious or immediate risks presented by such substances, such as potential carcinogenicity.¹⁷² In other words, Congress was “not so much concerned with the acutely toxic compounds, whose harmfulness can readily be detected, as with those chemicals which may produce harmful effects only after being ingested for months or perhaps for years.”¹⁷³ Instead, Congress was “most interested in . . . the residuary toxicity that is found in many of the[] chemical additives” that may not be “apparent [for] a day, or 2 days, or a week” after exposure.¹⁷⁴

Moreover, the legislative history underscores that Congress meant for FDA to ensure the safety of *all* substances – even those found initially to be safe that presented later problems or substances that are adverse to health over the life of a human. As Congresswoman Leonor Sullivan, of Missouri’s 3rd District, clarified during the hearings:

Mrs. SULLIVAN. Am I correct that while the bill primarily deals with new chemical additives, it does not preclude the Food and Drug Administration from moving against existing additives if they have evidence to question their safety?

Mr. HARRIS. Yes; I will say that the gentlewoman is correct in her statement.¹⁷⁵

¹⁷⁰ Kindy, *supra* note 5 (quoting FDA’s Michael Taylor: “We do not know the volume of particular chemicals that are going into the food supply so we can diagnose trends.” “We do not know what is going on post-market.”).

¹⁷¹ *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 156 (2000).

¹⁷² *See, e.g.*, Food Additives Amendment of 1958, P.L. 85-929, 52 Stat. 1041 § 409(c)(3)(A) (1958) (“[N]o additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal[.]”).

¹⁷³ *Chemical Additives in Food: Hearings on H.R. 4475 Before the Subcomm. On Health and Sci. of the House Comm. On Interstate and Foreign Commerce*, 84th Cong., 2d Sess. 27 (1956) (Testimony of Representative Delaney, quoting committee report).

¹⁷⁴ *Id.* at 29.

¹⁷⁵ 104 Cong. Record, 85th Cong, 2d Sess. 17,412, 17,421 (Aug. 13, 1958).

Representative Delaney similarly stated his view that, “if a chemical is harmful, even if it has been used over a period of time, . . . it should be rejected.”¹⁷⁶ Rather, “[t]he criterion should always be: ‘Is this chemical safe for public consumption.’”¹⁷⁷

At the same time, the FDA Deputy Commissioner made clear that the agency believed even the most innocuous GRAS substances would be subject to its ongoing oversight. In a letter to Congress, the Deputy Commissioner elucidated that the GRAS exemption was not a grandfather clause; rather, “if later developments show that a substance previously considered safe because of common use in food were, in fact, subject to question and not generally recognized as safe, then the substance would become subject to the definition of a food additive and would have to be cleared under the procedures of the proposed law.”¹⁷⁸

The FAA thus intended to require ongoing FDA oversight over all chemicals added to foods. GRAS status was never intended to be a permanent or true “grandfather clause,” as that would defeat the food safety purpose of the statute.¹⁷⁹ Instead, Congress was clear that the status of any substance could always change in light of updated science. Indeed, Congress recognized that while most additives are not chronically dangerous to consumers, it needed a system of oversight that could ensure the safety of all substances, particularly those to which consumers are exposed at low doses over long periods of time. Without such ongoing oversight, there would be no way to identify latent effects linked to the food supply or their source. To perform such oversight, as intended by Congress, FDA must be informed about what is in our food – and therefore “secret GRAS” cannot possibly be a legal interpretation of the statute in light of its overarching purpose.

FDA recognizes to this day that the FAA imposes an obligation on the agency to reassess the GRAS status of substances when new evidence of harm is produced. Current FDA regulations state that “[n]ew information may at any time require reconsideration of the GRAS status of a food ingredient.”¹⁸⁰ FDA recently reaffirmed this position in its tentative determination regarding the GRAS status of PHOs, published in the Federal Register in 2013.

¹⁷⁶ *Chemical Additives in Food: Hearings on H.R. 4475 Before the Subcomm. On Health and Sci. of the House Comm. On Interstate and Foreign Commerce*, 84th Cong., 2d Sess. 28 (1956).

¹⁷⁷ *Id.* at 31.

¹⁷⁸ 104 Cong. Record, 85th Cong, 2d Sess. 17412, 17420 (Aug. 13, 1958) (Letter from John L. Harvey, Deputy Commissioner of FDA). This contrasts with the prior-sanctioned clause, which functions more like a true grandfather clause. In order to reverse a prior sanction, the FDA must meet the adulteration standard under the FDCA. 21 C.F.R. § 181.1(b) (“Based upon scientific data or information that shows that use of a prior-sanctioned food ingredient may be injurious to health, and thus in violation of section 402 of the Act, the Commissioner will establish or amend an applicable prior sanction regulation to impose whatever limitations or conditions are necessary for the safe use of the ingredient, or to prohibit use of the ingredient.”).

¹⁷⁹ Frederick H. Degnan, *Rethinking the Applicability and Usefulness of the GRAS Concept*, 46 Food Drug Cosm. L.J. 553, 554 (1991) (citing *Chemical Additives in Food: Hearings on H.R. 4475 Before the Subcomm. On Health and Sci. of the House Comm. On Interstate and Foreign Commerce*, 84th Cong., 2d Sess. 28 (1956)).

¹⁸⁰ 21 C.F.R. § 170.30(k)(1) (2012).

There, the agency noted:

Importantly, the GRAS status of a specific use of a particular substance in food is time-dependent. That is, *as new scientific data and information develop about a substance or the understanding of the consequences of consumption of a substance evolves, expert opinion regarding the safety of a substance for a particular use may change such that there is no longer a consensus that the specific use is safe.* The fact that the status of a substance under section 201(s) of the FD&C Act may evolve over time is the underlying basis for FDA’s regulation at § 170.38, which provides in part that FDA may, on its own initiative, propose to determine that a substance is not GRAS. (See generally 36 FR 12093 (June 25, 1971) (issuance of 21 CFR 121.3, the predecessor of § 170.38)). Further, as stated previously, history of the safe use of a substance in food prior to 1958 is not sufficient to support continued GRAS status if new evidence demonstrates that there is no longer expert consensus that an ingredient is safe.¹⁸¹

Although FDA acknowledges that it is required under the FAA to make an ongoing review of GRAS substances to ensure they are still safe in the face of updated science and exposure, its current GRAS proposal fails to create a system in which the agency is made aware of all the substances it should be monitoring. Without knowing what is in our food, FDA cannot perform the job given to it by Congress. Without information on substances and their dietary exposure, FDA is incapable of measuring the more long-term, or more subtle, health effects that led Congress to pass the FAA. Instead, FDA’s regulatory regime can only respond either to acute risks or chronic risks with an obvious connection to a well-known source.¹⁸² By ensuring that it is ignorant of the composition of the food supply, the agency has handicapped itself and its policing of the safety of substances in food contrary to the original intent of the FAA.

As a result of this lack of information and oversight, FDA rarely actually reconsiders the GRAS status of substances in light of new safety concerns – for example, the agency has *never* revoked the GRAS status of any substance approved through the petition affirmation process, nor has it retracted a “no questions” letter since 1997.¹⁸³ This is likely in part because FDA, in its

¹⁸¹ *Tentative Determination Regarding Partially Hydrogenated Oils; Request For Comments And For Scientific Data And Information*, 78 Fed. Reg. 67,169, 67,170 (Nov. 8, 2013) (emphasis added).

¹⁸² FDA acknowledged that chronic risks are notoriously difficult to connect to a source: “Currently, the legal system does not ensure the optimum level of safety for foods because consumers who become ill often do not know the reason for, or source of, their illness. Even in cases where consumers are aware that their illness was contracted from a specific food, it is often difficult to determine who is ultimately responsible for their illness, since the particular source of contamination is not known in many circumstances.” U.S. Food and Drug Administration, Preliminary Regulatory Impact Analysis for the proposed rules on Foreign Supplier Verification Programs (Docket No. FDA-2011-N-0143) and Accreditation of Third-Party Auditors/Certification Bodies to Conduct Food Safety Audits and to Issue Certifications (Docket No. FDA-2011-N-0146) under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601-612), the Unfunded Mandates Reform Act of 1995 (Public Law 104-4), and the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520) 3-4 (2013), *available at* <http://www.fda.gov/downloads/AboutFDA/.../EconomicAnalyses/UCM363286.pdf>.

¹⁸³ GAO Report, *supra* note 37, at 22. This in spite of the fact that safety concerns have arisen regarding many GRAS substances, such as parabens, salt, and sugar used in sugar-sweetened beverages.

own words, “do[es] not know the volume of particular chemicals that are going into the food supply so [it] can diagnose trends,” and it “do[es] not know what is going on post-market.”¹⁸⁴ As a result, FDA lacks the data it would need to sensibly prioritize a public health approach and assess overall exposure of particular chemicals or classes of chemicals – it does not have the information it needs to form intelligent hypotheses about health trends and dietary exposure.¹⁸⁵ Merely according final rule status to the proposal would similarly fail to enable the agency to accomplish its statutory assignment to track the safety of substances on scientific or public health grounds.¹⁸⁶

Contrary to public expectations and its Congressional assignment to assure the safety of the food supply, FDA has failed to meet its *legal* obligations under the FAA – and has proposed continuing in that state, with weakened reporting and oversight. To perform its responsibilities under the law, FDA *must* be informed of GRAS substances in use.¹⁸⁷ Without information about a chemical’s identity and toxicology, dietary exposure, and proposed use, FDA cannot assess its health consequences over long periods of time – or even determine when and which substances warrant review.¹⁸⁸ Thus, so long as “secret GRAS” is allowed, FDA cannot meet its obligation to ensure the safety of substances added to foods as required by the FAA.

¹⁸⁴ Kindy, *supra* note 5 (quoting Michael Taylor).

¹⁸⁵ The relevance of this is obvious. Post-market review cannot be sufficient when FDA has no means to link public health trends to substances present in the food supply. Under the current system, FDA is woefully unable to explore links between dietary exposure and outcomes. For example, recent research points to the origins of childhood obesity as an outcome of the dynamic interplay of genetic, behavioral, and environmental factors, with a compelling body of evidence suggesting that environmental exposures affect a child’s risk of obesity. See Institute of Medicine, *Examining a Developmental Approach to Childhood Obesity: The Fetal and Early Childhood Years: Workshop in Brief 1* (March 2015), available at http://www.nap.edu/openbook.php?record_id=21716. IOM, along with other partners, recently convened a two-day workshop on the links between dietary exposure of additives and obesity, which FDA did not participate in. See *id.* Without information about exposure and cumulative effects, FDA cannot even begin to form appropriate questions about long-term exposure that Congress was so concerned about when it passed the FAA in 1958 – and therefore fails to meet its obligations under the statute.

¹⁸⁶ For example, a recent study questioning the safety of emulsifiers – a substance with a very high exposure in the food supply – illustrates the type of safety concern that Congress intended FDA monitor when it passed the FAA. See Benoit Chassaing et al., *Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome*, *Nature* 519, 92-96 (Feb. 2015), <http://www.nature.com/nature/journal/v519/n7541/full/nature14232.html>.

¹⁸⁷ Notably, both President Nixon and the FASEB committee presumed that the FAA permitted FDA to conduct a comprehensive assessment of the safety of GRAS substances, as reflected by the comprehensive review initiated during the 1970s. See *supra* at 8.

¹⁸⁸ 21 C.F.R. § 170.3(i). FDA told GAO that it maintains a database called the Priority-Based Assessment of Food Additives (PAFA), containing administrative, chemical, and toxicological information about food ingredients, including GRAS substances, in order to prioritize substances for assessment. However, FDA could not provide any examples of a reconsideration of a GRAS substance derived from use of this database. GAO Report, *supra* note 37, at 21. Regardless, this database is unlikely to include GRAS substances that FDA has never been notified about, further illustrating the need for required notification, as discussed *infra*.

Commenters have noted that the legislative history of the FAA shows that “industry and agency witnesses alike assumed that a manufacturer had the opportunity to make its own GRAS determinations”¹⁸⁹ – thus arguing that the FAA allows for the present “secret GRAS” system. However, *independent* GRAS is not the same as *secret* GRAS. Even if independent GRAS determinations are legal under the FAA, this does *not* mean that industry determinations totally supplant FDA’s regulatory authority. FDA still has the responsibility, under the FDCA and the FAA, to ensure the safety of all substances in the food supply. As a result, FDA has the obligation to enact a regulatory scheme that allows it to meet its statutory mandate. As the foregoing makes clear, FDA can only achieve its responsibilities when it is informed about the composition of the food supply. Thus, the language of the FAA does not authorize independent determinations to be made in secret or on insufficient evidence.

FDA has indicated that it does not believe it has the authority to require mandatory notification of GRAS determinations.¹⁹⁰ However, this is plainly not the case. Nowhere in the statute does it say that FDA may not require such notification. Instead, the purpose of the statute indicates that Congress intended FDA to have oversight over all substances added to foods. This includes the authority to develop a regulatory program to ensure the purposes of the law are met; in other words, “[FDA] is not merely an implementer of law, but an architect of the law as well.”¹⁹¹

Again, while the language of the statute does not foreclose the possibility of independent industry GRAS determinations, this does not usurp FDA of its authority (and obligation) to oversee the safety of such substances. Indeed, FDA has frequently policed GRAS in the past, by issuing regulations narrowing and defining its scope.¹⁹²

In addition, in the 1997 proposal, it suggested that it would perform random audits in order to ensure that GRAS determinations were made properly – a further indication that FDA recognizes its own authority to regulate industry-made GRAS designations, and to assert enforcement powers necessary to achieve its statutory and regulatory goals. It is unreasonable to think that a program of random audits would be a sufficient or appropriate use of agency resources where mere notification by industry would allow much more efficient allocation of agency enforcement resources. Indeed, the secrecy of the current program means that the audits would be truly random, and could not be targeted in any systematic way. Moreover, FDA and the industry cannot meaningfully assess cumulative exposure and therefore the possible harm of exposure. Mandatory notification is simply a more practical and efficient means of accomplishing the same goal, and is therefore an implied authority under the FAA.

¹⁸⁹ Degnan, *Rethinking the Applicability and Usefulness of the Gras Concept*, *supra* note 179, at 560.

¹⁹⁰ GAO Report, *supra* note 37, at 19 (in response to GAO questions, “FDA officials stated that the agency would have to seek authority from Congress in order to require all companies to inform it of their GRAS determinations.”).

¹⁹¹ IOM Workshop Summary, *supra* note 28 at 4.

¹⁹² *See, e.g.*, 23 Fed. Reg. at 9,512 (“In general, any substance added to a food which has no history of common use as a food ingredient, should be regarded as a substance that is not generally recognized as safe unless it has been scientifically tested and shown to be safe.”)

FDA also has ample implied authority to address the statutory goals by requiring mandatory notification. Section 701(a) of the FDCA vests the Secretary with the authority to issue regulations for the efficient enforcement of the Act.¹⁹³ Under this section, FDA may issue regulations in order to “effectuate a congressional objective expressed elsewhere in the Act.”¹⁹⁴ Even narrowly construed, this plainly gives FDA the authority to police the line between GRAS and food additives to ensure that all food additives are subject to the statutory petition process required in the Act.

Moreover, because a primary objective of the FDCA is the enhancement of public health, the FDA’s rulemaking authority under Section 701(a) “has been broadly construed to uphold a wide variety of assertions of regulatory power” and is valid so long as it is reasonably related to an authorized regulatory objective.¹⁹⁵ The objectives of the FAA in ensuring the safety of all substances added to foods, codified as part of the FDCA, can only be achieved if exposure and safety data are available and current for all substances added to foods. Thus, under 701(a), FDA has the authority to require notifications, as a comprehensive inventory of substances added to foods is an essential predicate to achieving its responsibilities under the FAA.

Indeed, courts interpreting 701(a) have evaluated practical enforcement considerations to determine their role in carrying out the statutory scheme.¹⁹⁶ In this case, FDA can only fulfill its statutory obligations under the FAA if it is informed about usage and exposure of all substances added to foods – thus, required notification would plainly be proper in order to “effectuate a congressional objective” under the FAA. In fact, the lack of notification actually *prevents* effective enforcement of FDA’s statutory obligations to consider exposure and cumulative effects in making safety determinations. To keep such data current, companies must notify FDA (and thereby each other) of their use of such substances.

Thus, FDA has both the authority – and a clear obligation – to issue regulations requiring public and ongoing notification of all GRAS determinations.¹⁹⁷ FDA’s program permitting

¹⁹³ 21 U.S.C. 371(a) (“The authority to promulgate regulations for the efficient enforcement of this chapter, except as otherwise provided in this section, is vested in the Secretary.”).

¹⁹⁴ *Association of American Physicians and Surgeons, Inc. v FDA*, 226 F. Supp. 2d 204 (D.D.C. 2002) (citing *Pharm. Mfrs. Ass’n. v FDA*, 484 F. Sup. 1179, 1183 (D. Del. 1980) (upholding FDA regulation requiring doctors to distribute information about estrogen-containing drugs to patients to whom the drugs were prescribed because it was related to FDCA objective that consumers receive facts material to consequences that may result from pharmaceuticals).

¹⁹⁵ See *Pharm. Mfrs. Ass’n*, 484 F. Supp. at 1183; see also *U.S. v. Nova Scotia Food Products*, 568 F.2d 240, 246 (2d Cir. 1977) (finding that enforcement-related regulations are valid so long as they are reasonably related to the purposes of the enabling legislation). In addition, in its final rule implementing the seafood HACCP requirements, FDA broadly interpreted its authority under 701(a) as allowing it to require record maintenance and access as effectuating a congressional objective to ensure safe conditions in processing. See Degnan, *FDA’s Creative Application of the Law*, *supra* note 51, at 60.

¹⁹⁶ See *Nat’l Confectioners Ass’n v. Califano*, 569 F. 2d 690, 693 (D.D.C. 1978) (finding that encoding and recordkeeping requirements appropriately assisted the FDA in fulfilling its statutory mandate to provide remedies for any adulterated foods present in interstate commerce, such as through product recalls).

¹⁹⁷ The FDA recently recognized such an authority when it included recordkeeping requirements for recipes under the nutrition facts labeling proposed rulemaking. In the proposal, FDA found that “[t]he

“secret GRAS” is therefore unreasonable in light of the statute as a whole, and does not merit deference. Even if a court were to conclude that the agency’s prior interpretation of the law had once been permissible, upon this record, as demonstrated below, it is no longer a reasonable interpretation by FDA of its obligations.¹⁹⁸

Congress’s purpose in passing the FAA was clear: to establish a comprehensive regulatory scheme to protect the health of consumers from potentially unsafe substances added to foods. The 1997 proposal, which all but eliminates the last shreds of FDA oversight, cannot possibly achieve the objectives of the statute. Thus, in light of the purpose of the statute and FDA’s responsibility to oversee the safety of all substances, the agency’s interpretation of GRAS is unlawfully “inconsistent with the statutory mandate” laid out in the FAA, and does not merit deference under *Chevron*.¹⁹⁹

b. If FDA were to finalize the 1997 rule as proposed, it would be “arbitrary and capricious” under the Administrative Procedure Act.

Finally, if FDA were to finalize the 1997 rule as proposed, this would be unlawfully arbitrary and capricious under the Administrative Procedure Act. An agency rule is “arbitrary and capricious” if an agency has “relied on factors which Congress has not intended it to consider” or “entirely failed to consider an important aspect of the problem.”²⁰⁰ In this case, the proposed rule has been in effect for nearly 20 years and FDA is fully aware that it is not functioning as the agency intended, much less achieving the purposes of the FAA. Thus, if FDA were to finalize the rule unchanged, it would be arbitrary and capricious due to a clear failure to “consider an important aspect of the problem” under *State Farm*.²⁰¹

The FDA’s rationale for creating the GRAS notification process was that the onerous GAP process was discouraging individuals from requesting affirmation of self-determined GRAS status.²⁰² The agency predicted that a simpler process would provide incentive for manufacturers to inform FDA of their GRAS determinations, resulting in “increased agency awareness of the nation’s food supply and the cumulative dietary exposure to GRAS

authority granted to FDA under sections 701(a), 403(q), 403(a)(1) and 201(n) of the FD Act not only includes authority to establish records requirements, but also includes access to such records. Without such authority, the nutrient declarations for these specific nutrients that FDA has determined are necessary to assist consumers in maintaining healthy dietary practices under section 403(q)(2)(A) of the FD Act are, practically speaking, not enforceable.” *Food Labeling: Revision of the Nutrition and Supplement Facts Labels*, 79 Fed. Reg. 11,880, 11,884 (2014).

¹⁹⁸ The fact that FDA has long misinterpreted its obligations under the FAA does not change this, as the Supreme Court has made clear that even “longstanding agency interpretations must fail to the extent they conflict with statutory language.” *Pub. Employees Ret. Sys. of Ohio v. Betts*, 492 U.S. 158, 171, 109 S. Ct. 2854, 2863, 106 L. Ed. 2d 134 (1989). Moreover, the 1974 Rulemaking and prior actions by the Nixon Administration clearly demonstrate that FDA long viewed its authority over GRAS as permitting, perhaps even necessitating, the agency to compile a comprehensive inventory of all GRAS substances.

¹⁹⁹ *Fed. Election Comm’n.*, 454 U.S. at 32 (explaining that courts must reject administrative rulemakings “that are inconsistent with the statutory mandate or frustrate the policy that Congress sought to implement”).

²⁰⁰ *Motor Vehicle Mfrs. Ass’n of U.S., Inc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983).

²⁰¹ *Id.* at 43-44.

²⁰² 62 Fed. Reg. at 18,941.

substances.”²⁰³ FDA also predicted that the “streamlined” notification process would allow it to redirect its resources to GRAS substances “that are a priority with respect to public health protection” and to issuing industry guidance on food safety issues. Finally, it stated that because both the GAP and notification procedures were voluntary, the substitution would be “neutral” from a legal and regulatory perspective.²⁰⁴

The interim system has been in force since 1997 and ample evidence demonstrates that it has not performed as the agency intended. While FDA predicted that the new system would encourage greater reporting to the agency, it overlooked a crucial fact: the notification system actually gives industry *less* inducement to notify FDA in the case of potentially dangerous substances, because notice would invite regulatory scrutiny without concrete benefit for industry (because FDA never actually attests to a determination of GRAS, as it did under the GAP process).

At the same time, the interim rules have led to a dramatic shift away from the food additive petition process, which has been functionally abandoned since the notification process debuted. Thus, it is simply not the case that the 1997 proposal is “neutral.” Instead, FDA has taken a program with considerable propensity to tolerate abuse and made abuse the norm, the very “opposite of what the oversight law intended.”²⁰⁵

Before the notification system went into effect, independent GRAS existed, but occurred only “occasionally.” Even in such cases, manufacturers would reportedly commission semi-public safety reviews by reputable scientific organizations.²⁰⁶ But rather than improving this situation, the 1997 proposal has led to decreased transparency in the underlying science. As FDA’s Michael Taylor noted, “the law was meant to increase public scrutiny of additive safety by encouraging companies to publish their science in academic journals.”²⁰⁷ Instead, since 1997, the bulk of GRAS determinations have been made by expert panels without peer-reviewed publication.²⁰⁸

²⁰³ *Id.*

²⁰⁴ *Id.* at 18,951.

²⁰⁵ Kindy, *supra* note 5 (quoting Michael Taylor).

²⁰⁶ IOM Workshop Summary, *supra* note 28, at 24; *see id.* at 25 (describing private GRAS reviews as “occasional”). In addition, the FEMA process appears to have changed significantly in the wake of the 1997 proposal. Originally, FEMA contracted with FDA to publish safety data underlying GRAS determinations for flavorings. These reviews were published on a period basis during the 1970s and formed the basis for the GRAS affirmation (GRASa) Program, which operated from 1975-1985. Following the GRASa Program, there was an extreme decline in GRAS determinations for flavorings; however, in the wake of the 1997 proposal, “there has been a significant increase in the number of substances GRASed annually” by FEMA. *See* R.L. Smith et al., *GRAS Flavoring Substances* 24, Food Technology 46-48 (June 2009).

²⁰⁷ Kindy, *supra* note 5.

²⁰⁸ Kahl Memo, *supra* note 67, at 5 (“In practice, approximately one half of the GRAS notices filed by OFAS during the interim period included the findings of a panel of individuals who evaluated the data and information that were the basis for the notifier’s GRAS determination. In most cases, these findings were included as a report in the GRAS notice but were not published in peer-reviewed journals. In most cases, OFAS responded to a GRAS notice containing the findings of a GRAS panel with a “no questions letter”).

Thus, it is clear under the 1997 proposal, FDA has failed to increase its awareness of substances in the food system, their safety, and their dietary exposure.²⁰⁹ While the rate of GRAS notifications is higher than that of GAP submissions, FDA remains totally unaware of an estimated 1,000 substances currently added to foods. Because FDA is not notified about a majority of GRAS substances nor their dietary exposure, the agency cannot rationally prioritize its resources to address substances of public health concern (another purported justification in the proposal). To finalize the proposed rule when it has not realized FDA's justifications for proposing it, and has in fact resulted in changes for the worse, would be indubitably "arbitrary and capricious."

There is also considerable evidence before the agency, as detailed in the next section, about the failures of the system under the proposal and why it does not achieve the purposes of the FAA. These failures were also raised by comments to the docket when the comment period was reopened in 2010, over ten years after the interim system went into effect, and by an internal review of FDA's own experience with the program.²¹⁰ It is also evidenced by the myriad examples, provided below, of "GRAS" substances that are, properly considered, a food additive – whether because they are novel, of questionable safety, or because their safety is not generally recognized – and by the high number of GRAS notifications that are withdrawn before FDA can publish its concerns regarding the industry's notice. The fact that "food additives" and substances of questionable safety are regularly introduced into the food supply via the GRAS system – rather than the scheme statutorily mandated by Congress – demonstrates that the proposed rule does not meet the requirements of the FAA. Instead, as explained above, the 1997 proposal undercuts the statutory objectives of the Act.

In sum, if FDA were to finalize the current proposed rule without revision, it would disregard the fact that the system has prevented the statutory food additive petition process from working as intended, has eviscerated the definitions of "safety" and "general recognition" thereof under the statute, and has prevented effective FDA oversight of both food additives and GRAS substances. It would thus plainly be "arbitrary and capricious" in violation of the Administrative Procedure Act.

IV. Previous comments and studies in this docket demonstrate that the proposed notification system does not achieve the purposes of the FAA.

The serious defects in the process described above were raised by an in-depth 2010 GAO Report, in six peer-reviewed studies performed by the Pew Charitable Trusts,²¹¹ other reports by Pew, and in the prior comments on this proposed rulemaking; these reports are in the docket and FDA is well aware of them.²¹²

²⁰⁹ GAO Report, *supra* note 37, at 13 ([W]ithout overseeing all companies' GRAS determinations, FDA is less informed about the nation's food supply and consumers' cumulative dietary exposure to GRAS substances – both of which were viewed by FDA as beneficial potential outcomes of its 1997 proposal.)

²¹⁰ See generally Kahl Memo, *supra* note 67.

²¹¹ Four of which were published in the journal for the food industry's professional society, the Institute of Food Technologists.

²¹² Indeed, FDA reopened the docket in 2010 in response to the GAO report.

a. A Key GAO Report found that FDA’s current GRAS system fails to ensure safety of substances used in food as required by the FAA.

In 2010, GAO reviewed the GRAS program to determine the extent to which FDA’s oversight of new GRAS determinations helps ensure the safety of these substances and the continued safety of existing GRAS substances.²¹³ The results of GAO’s review were unambiguously abysmal. GAO found that FDA’s GRAS process failed to meet the purposes of the FAA in the same respects that we highlight in these comments; specifically, that FDA’s oversight process “does not help ensure the safety of all new GRAS determinations,” and that the agency is not “systematically ensuring the continued safety of current GRAS substances” – the central purpose of the FAA.²¹⁴

GAO found FDA’s oversight process deficient because under the voluntary notification system, FDA reviews only the GRAS determinations that companies *choose* to submit. Thus, FDA’s role is limited because “the agency generally does not have information about other GRAS determinations companies have made [as] companies are not required to inform FDA of them.”²¹⁵ Because notification is not required, industry applies an expansive interpretation of GRAS that allows many food additives to avoid the regulation required by the FAA. GAO expressed a particular concern about the safety of imported food products, noting that GRAS substances may be manufactured anywhere in the world, and companies need not identify this information as part of their GRAS determinations.²¹⁶ The report also noted that this lack of transparency makes FDA less informed about the nation’s food supply and cumulative dietary exposure to GRAS substances. As a result, it is difficult for FDA to ensure the safety of GRAS substances over time, a major concern of the legislators who passed the statute.²¹⁷

Based on all of these deficiencies, GAO concluded that, “[b]ecause of the difficulty of identifying GRAS substances as the source of food safety problems after they have entered the food supply, FDA’s oversight of their safety would be improved if companies were required to make the agency aware of their GRAS determinations.”²¹⁸ GAO recommended that FDA improve the system in many of the same ways that we recommend below, including that FDA reassess the safety of GRAS substances in a more systematic manner.

GAO also found that FDA “has not taken certain steps that could help ensure the safety of GRAS determinations,” such as issuing industry guidance on how to document GRAS determination or monitoring companies to ensure that such determinations are made

²¹³ GAO Report, *supra* note 37, at 1.

²¹⁴ *Id.*

²¹⁵ *Id.*

²¹⁶ *Id.* at 13-14.

²¹⁷ *Id.* at 12 (“Once a GRAS substance has entered the marketplace, FDA would find it difficult to identify that substance as the potential source of a food safety problem, especially if FDA is unaware that the substance has been determined to be GRAS. Food products may contain numerous ingredients, including GRAS substances, making it difficult, if not impossible, for public health authorities to attribute a food safety problem to a specific GRAS substance.”)

²¹⁸ *Id.* at 12.

appropriately.²¹⁹ It recommended that FDA issue guidance on how to better document GRAS determinations and develop a strategy to minimize the potential for conflicts of interest in companies' GRAS determinations. Last, it urged the agency to issue regulations requiring any company that conducts a GRAS determination to provide FDA with basic information – as defined by the agency to allow for adequate oversight – about this determination, such as the substance's identity and intended uses, and to incorporate such information into relevant agency databases and its public website.

b. The Pew Charitable Trusts's studies found that FDA does not ensure the safety of new and existing additives as required by statute.

In 2010, the Pew Charitable Trusts, a nonprofit, non-governmental organization, launched a food additives project to evaluate the federal regulatory program overseeing food additives.²²⁰ Its research, focused on the overall regulatory system, evaluated FDA's ability to fulfill its statutory obligation under the FAA to protect public health from unsafe chemicals intentionally added to foods. The study involved experts from industry, academia, government agencies, and public interest organizations. Like GAO, Pew concluded that the GRAS system is plagued with systemic problems that prevent FDA from ensuring the use of food additives is safe.²²¹

Pew's main critique was that, although FDA is supposed to make safety determinations after considering cumulative effects of safety and exposure, it cannot do its statutorily required job given that it has not been notified of: (1) an estimated 1,000 chemicals currently allowed in food (secret GRAS); (2) actual usage for both these chemicals *and* the toxicologically related chemicals it actually knows about; and (3) studies that suggest previously unknown health effects.²²² Because FDA lacks basic information needed to assess the safety of the thousands of chemicals that have been cleared for use in food by industry, it only evaluates the safety of the additives it happens to be aware of, through a program that is neither systematic nor scientific.²²³

Pew discovered that, as a result of this lax oversight, industry employs inadequate science in its GRAS determinations. Pew found that most GRAS substances are not tested for safety in accordance even with FDA's most limited testing recommendations.²²⁴ For example, agency guidance indicates that chemicals intentionally added to food should be fed to laboratory animals to identify potential harmful effects, but Pew found that in the majority of cases, industry-determined GRAS chemicals did not undergo any of this very basic type of testing.²²⁵ In

²¹⁹ *Id.* at 1.

²²⁰ Pew Charitable Trusts, *Food Additives Project*, <http://www.pewtrusts.org/en/archived-projects/food-additives-project> (last accessed Feb. 23, 2015).

²²¹ Pew Charitable Trusts, *supra* note 93, at 6.

²²² *Id.* at 7.

²²³ *Id.* at 8.

²²⁴ *Id.* at 9 n.72; Thomas G. Neltner et al., *Data gaps in toxicity testing of chemicals allowed in food in the United States*, 42 *Reproductive Toxicology* 85, 88 (2013).

²²⁵ Neltner et al., *supra* note 224, at 90. In this report, Pew researchers found that less than 38% of FDA-regulated additives have a published feeding study (the first test a scientist would do to evaluate the safety of a chemical additive). For direct additives, only 21.6% have the feeding studies necessary to estimate a

addition, Pew found that less than 38% of FDA-regulated additives have a published feeding study.

Pew also found that FDA's food additive (and GRAS) toxicology requirements were severely out-of-date.²²⁶ According to FDA's own scientists, advances in science have not been incorporated into FDA's practices, and the safety assessments currently used were developed in the 1950s without sufficient updates.²²⁷ In the words of one FDA scientist, "[FDA] ha[s] not tried to make [its] safety factor approach current with science."²²⁸ Many of the scientific deficiencies found in the 1982 report by FDA's Select Committee on GRAS Substances (SCOGS) persist, remaining unresolved to this day.²²⁹ In particular, Pew found that FDA's food additive and GRAS toxicology requirements were insufficient with regard to the following areas:

- **Behavioral Effects.** FDA has failed to establish adequate testing standards to assess the impact of additives on behavior. This puts the agency behind the U.S. Environmental Protection Agency (EPA) and developed countries in the Organization for Economic Cooperation and Development, which adopted such methods and standards years ago.²³⁰
- **Endocrine systems.** FDA has failed to identify standards and methods for how to evaluate additives for potential endocrine disruption. Again, FDA is well behind EPA in developing such practices.²³¹
- **Vulnerable Subpopulations.** FDA has failed to require consideration of additive exposure to vulnerable subpopulations. Currently, its regulations only consider infants. Pew recommends that this consideration be extended to pregnant women, children, and those with hypersensitivity to certain substances, for example.
- **Absorption, distribution, metabolism, and excretion data.** FDA currently allows safety determinations to be made for chemicals without the data crucial to understanding how humans process such chemicals, such as absorption, distribution, metabolism, and excretion (ADME) data.

safe level of exposure, and only 6.7% have reproductive or developmental toxicity data in FDA's database. *Id.* at 88-90.

²²⁶ Maricel V. Maffini, Heather M. Alger, Erik D. Olson & Thomas G. Neltner, *Looking Back to Look Forward: A Review of FDA's Food Additives Safety Assessment and Recommendations for Modernizing its Program*, 12 *Comprehensive Reviews in Food Science and Food Safety* 439, 449 (2013) (finding that FDA's food additives program has "not kept pace with the scientific developments of the last 20 y[ears]"). This is supported by FDA's own recent internal review of the agency's process for food additives. See U.S. Food and Drug Administration, *OFVM Report of the CFSAN Chemical Safety Assessment Review Working Group*, Appendix A at 11 (Apr. 2014).

²²⁷ See U.S. Food and Drug Administration, *OFVM Report of the CFSAN Chemical Safety Assessment Review Working Group*, *supra* note 226, Appendix A at 11 ("Our conservative approach to food safety or assessing the safety of food additives is also a weakness in a way because the safety factors that we rely on when doing a safety assessment were developed in the early to mid 50's. They are based on the science and policy of that day. Since then they really have not been changed.").

²²⁸ *Id.* at 12.

²²⁹ Maffini et al., *supra* note 226, at 449.

²³⁰ Pew Charitable Trusts, *supra* note 4, at 10; Maffini et al., *supra* note 226, at 450.

²³¹ Pew Charitable Trusts, *supra* note 4, at 10; Maffini et al., *supra* note 226, at 450.

Thus, Pew concluded that as a result of the minimal FDA oversight and scientific standards for GRAS, these substances are not subject to adequate testing to ensure their safety for use in the food supply.

Pew also found that the lack of FDA oversight results in rampant conflicts of interest between industry and the experts making GRAS determinations. The organization reviewed the industry's GRAS notifications from 1997 to 2012 and found that "financial conflicts of interest in these decisions are ubiquitous."²³² The Pew report relied on criteria developed by the Institute of Medicine in 2009, which identified a framework to assess the severity of conflicts of interest.²³³ Applying this framework, Pew concluded that a manufacturer's employee would have the greatest likelihood of favoring a food substance as GRAS, while a member of a standing expert panel selected by an independent third party would be least likely to do so.

Applying these standards to the 451 GRAS notices voluntarily submitted to the FDA between 1997 and 2012, Pew found that 22.4% were made by an employee of an additive manufacturer, 13.3% were made by an employee of a consulting firm selected by a manufacturer, and 64.3% were made by an expert panel selected by the manufacturer or a consultant to manufacturer.²³⁴ When manufacturers convened an expert panel, the panels were small, typically only three people, all handpicked by the manufacturer or its hired consultant.²³⁵

Pew also found considerable overlap among the expert panels – at least 10 individuals served on 27 or more panels, while one person served on 128 panels (of the total 290 panels involved in GRAS determinations).²³⁶ In *no* case did a manufacturer use a standing expert panel selected by an independent third party – the method Pew found least likely to involve a conflict of interest short of FDA review. Thus, it is apparent that the current notification process does little or nothing to curb conflicts of interest in GRAS determinations. In addition, there is no basis to assume that the decisions withheld from agency review are better in terms of conflicts of interest present in the determination process – in fact, they are likely worse.

Recognizing the significance of this problem, Pew drafted guidance on avoiding conflicts of interest in GRAS evaluations and submitted it to the current docket on September 4, 2013.²³⁷ This guidance incorporated input from multiple reviewers and stakeholders in a public August 2013 workshop of experts, advocates and industry participants. Relying in part on FDA's Guidance for the Public, FDA Advisory Committee Members, and FDA Staff on Procedures for

²³² Thomas G. Neltner et al., *Conflicts of Interest in Approvals of Additives to Food Determined to Be Generally Recognized as Safe*, 173 JAMA Intern. Med. 2032, 2035 (2013).

²³³ Institute of Medicine (US) Committee on Conflict of Interest in Medical Research, Education, and Practice, *Conflict of Interest in Medical Research, Education and Practice* (Bernard Lo & Marilyn Field, eds. 2009).

²³⁴ Neltner et al., *Conflicts of Interest*, *supra* note 232, at 2034.

²³⁵ *Id.* at 2035.

²³⁶ *Id.* at 2035.

²³⁷ The Pew Charitable Trusts, *Draft Guidance for Industry on Selection of Experts Conducting "Generally Recognized as Safe" (GRAS) Evaluations*, submitted to Docket No. FDA—1997—N—0020, Substances Generally Recognized as Safe; Reopening of the Comment Period (Sept. 4, 2013).

Determining Conflict of Interest and Eligibility for Participation in FDA Advisory Committees, Pew recommended that:

- 1) Conflicts of interest should be disclosed to FDA for its review; and
- 2) An expert should not be permitted to conduct a GRAS evaluation if he or she would be ineligible to serve on an FDA advisory committee without an agency waiver due to disqualifying financial interests.

Since the FDA Guidance is primarily focused on financial factors, Pew identified several additional factors that should be considered, drawn from similar policies adopted by food industry groups and regulators.²³⁸ The draft notes that it “implements several of the U.S. GAO’s recommendations from 2010 regarding the GRAS program.”²³⁹

As part of the review process for the draft guidance, Pew requested feedback from workshop participants and outside reviewers (all submitted to the docket along with the draft guidance). Some of these reflections are plaintive appeals for additional clarity from FDA from scientists and practitioners.²⁴⁰ Lisa Lefferts, a Senior Scientist for CSPI, noted several other

²³⁸ In particular, the Draft Guidance prompts the manufacturer or end user to answer four questions to evaluate whether the expert is qualified by scientific training and experience to evaluate whether a use of a food substance may qualify for the GRAS exemption and provides additional detailed guidance for evaluating responses for each question: 1) Does the expert have the necessary expertise? 2) Is the expert too close to the issue to objectively assess the consensus of the scientific community? 3) Is the expert disqualified because of serious financial conflicts of interest from exercising independent judgment? 4) Are there non-financial conflicts of interest that need to be considered? *Id.* at 9.

²³⁹ *Id.* at 3.

²⁴⁰ For example, Nancy Rachman, a regulatory scientist with experience conducting risk assessments for food additives and other chemicals, noted the following issues related to GRAS determinations:

- 1) “In addition to managing the potential for expert bias due to COI... two other aspects of any regulatory process ... are important for confidence in any decision: communication and transparency... and steps to ensure the consistency and integrity of the scientific basis for decisions. The less transparent a decision is, including its process and scientific basis, the greater the concern about the potential for COI [conflicts of interest] will be. GRAS has real transparency challenges...the food science, food toxicology and food regulatory community (including FDA) have not done an adequate job of explaining some important aspects of GRAS.”
- 2) “The concept of ‘general recognition’ could be made much more transparent. It has always been clear to me as a regulatory specialist and GRAS practitioner that an integral component of ‘general recognition’ is the use of well-established and accepted safety evaluation/risk assessment approaches to the selection, analysis, interpretation and combining/weighting of evidence... Those requirements and procedures are well established lore within the food science, food toxicology and food law community, and reputable practitioners adhere to them. It would help improve GRAS transparency if FDA would consolidate the various GRAS interpretive guidance materials it has made available into a more comprehensive, ‘user-friendly’ and transparent format.”

Comments from Nancy J. Rachmann, GRAS consultant, to Tom Neltner, on *Draft Guidance for Industry on Selection of Experts Conducting “Generally Recognized as Safe” (GRAS) Evaluations* 1-2 (Aug. 21, 2013).

important aspects of the workshop’s presentations, including the following information that was presented:

“A financial interest does not have to be great for the influence to be undue. Indeed, social science research suggests that gifts of small value may influence decisions. It also suggests that influence may operate without an individual being conscious of it.”²⁴¹

Because conflicts of interest are not a problem of “deliberate corruption, but of subconscious bias,”²⁴² the social science research suggests that the only effective way to mitigate conflicts of interest is to “realign incentives to eliminate conflicts.”²⁴³ For this reason, mechanisms that create functional independence in researchers and their research outcomes – such as separate funding – are recommended. Lefferts pointed out that other research-based food regulators, such as those in Europe, require public disclosure of conflicts, and that requirements for conflicts should be stricter than those for advisers of FDA given GRAS reviewers’ critical role in determining the public’s exposure to ingredients. Moreover, Lefferts suggested that proving an actual conflict of interest should not be necessary; instead, the presence of a potential conflict should be “sufficient to raise questions about the integrity of the process and undermine public confidence” in the safety of GRAS substances.²⁴⁴

Due to weak scientific requirements, nonexistent conflicts of interest standards, and insufficient FDA oversight, the GRAS system does nothing to ensure the actual safety of industry-determined GRAS substances. Pew concluded that these various deficiencies prevent FDA from being able to oversee the safety of chemicals added to food as required by law.

c. Previous comments on this docket agree that the GRAS notification system fails to ensure safety of substances added to food as required by the FAA.

Several consumer advocacy organizations submitted similar critiques as the GAO and Pew in their comments on this proposal. Comments identified the lack of required notice, and corresponding unavailability of necessary exposure data and scientific support, as the primary weaknesses of the proposal, because they allow unapproved additives to avoid the review required by the FAA. Thus, FDA is well aware of the problems with the 1997 proposal and it would be arbitrary and capricious to finalize the rule as proposed.²⁴⁵

In a 2011 comment, Food & Water Watch urged FDA to adopt all of the recommendations in the GAO report and condemned the proposed rulemaking as inadequate, observing that the 1997 proposed rule falls short of what is necessary for adequate review and that its “scope is inappropriately narrow [because it o]ffers only minor tweaks to a voluntary system that does not offer real protection to consumers or an opportunity to participate in the

²⁴¹ Comments from Lisa Lefferts, Senior Scientist, CSPI, to Tom Neltner, on *Draft Guidance for Industry on Selection of Experts Conducting “Generally Recognized as Safe” (GRAS) Evaluations* (Aug. 1, 2013).

²⁴² *Id.*

²⁴³ *Id.*

²⁴⁴ *Id.*

²⁴⁵ *Envtl. Integrity Project v. E.P.A.*, 425 F.3d 992, 996 (D.C. Cir. 2005).

process before substances are used.”²⁴⁶ Consumers Union commented in opposition to the proposed notification system, because it fails to “ensure the safety of all substances added to food,”²⁴⁷ which is the FDA’s statutory obligation under the FAA.

As Consumers Union noted, because “companies can make their own determination that a substance is GRAS, not tell the FDA of that decision, and then start adding that substance into food and selling it to consumers, . . . the system allows for potentially dangerous substances to enter the food supply, without FDA’s knowledge or supervision.”²⁴⁸ As the International Center for Technology Assessment (ICTA) pointed out in its 1997 comments on the proposed rulemaking, the proposed notification system actually “reduce[s] the incentive for producers to notify FDA, because notification would invite regulatory scrutiny without requiring the FDA to attest to a determination of GRAS.”²⁴⁹

ICTA also pointed out that the lack of public notification prevents third parties (such as consumer protection groups, competing companies, or scientific organizations) from being able to alert FDA to potentially harmful substances in the food supply. Under the 1997 proposal, “[t]he agency is essentially privatizing all new food additive data, an arbitrary and capricious action which clearly contradicts Congressional goals of creating direct public oversight of the food additive process.”²⁵⁰ As a result, the system fails to protect the safety of the food supply and is a failure of FDA’s statutory obligations. Thus, to ensure the safety of all substances added to food, as is the FDA’s responsibility, commenters contend that “companies, at a minimum, should be required to notify FDA of any GRAS determinations they make.”²⁵¹

Several groups expressed concerns about the fact that the current system does not make dietary exposure estimates possible, which impedes an adequate finding of safety under the law. NRDC, in its comment, recommends that GRAS safety determinations include published exposure assessments.²⁵² Food & Water Watch stated that companies should be required to submit exposure data in their GRAS determinations so that industry, FDA, and citizens can make a comprehensive assessment of the safety of substances.²⁵³

Finally, commenters noted that the “general recognition” standard for GRAS status is significantly underdeveloped. As ICTA stated in its comments, “in yet another blow to food safety oversight, the agency proposal broadens the description of ‘common knowledge’

²⁴⁶ Food & Water Watch, *Comment on Docket No. FDA—1997—N—0020, Substances Generally Recognized as Safe; Reopening of the Comment Period 1* (March 28, 2011).

²⁴⁷ Michael Hansen, *Comments of Consumers Union on Food and Drug Administration (FDA) Proposed rule on Substances Generally Recognized as Safe; Reopening Comment Period Docket No. FDA—1997—N—0020 1* (March 28, 2011).

²⁴⁸ *Id.* at

²⁴⁹ International Center for Technology Assessment, *Comments Concerning Docket No. 97 N-0103 “Substances Generally Recognized As Safe” 2* (July 16, 1997).

²⁵⁰ *Id.* at 3.

²⁵¹ Hansen, *supra* note 247, at 1.

²⁵² Natural Resources Defense Council, *Comment on Docket No. FDA-1997-N-0020, Role of exposure assessment in general recognition of safety and related issues 2* (Aug. 28, 2014).

²⁵³ Food & Water Watch, *supra* note 246, at 3.

requirements so as to make the provision virtually meaningless.”²⁵⁴ For example, the technical evidence requirements for the GRAS determinations have been expanded from “studies” to include “scientific data and scientific information,” thereby “de-emphasizing and virtually eliminating the requirement for peer-reviewed studies in deciding GRAS status.”²⁵⁵ This severely weakens the “general recognition” requirement under the statute, as peer-reviewed and published studies provide the expert and objective reviews essential for a “general recognition of safety” finding. The commenters therefore emphasized the need to restore the centrality of published, peer-reviewed scientific support in GRAS determinations.

Commenters also recommended that GRAS notices include information demonstrating the independence of experts who generate data or analysis and that FDA should require submitters to include a comprehensive discussion of information that may be inconsistent with a GRAS conclusion.²⁵⁶ Without such requirements, any substance could masquerade as GRAS, even one without an adequate record of safety. As the examples in the next section show, this is in fact the case under the current system.

V. Case Studies: Many supposed “GRAS” substances today are in fact unapproved food additives, in clear violation of Congressional intent under the FAA.

The 1997 proposal prevents FDA from being able to fulfill the regulatory role intended by Congress because it leaves FDA without the information and oversight capability it needs to ensure safety. The massive (and illegal) inadequacies of the current proposed GRAS system mean that, in practice, many substances determined GRAS by industry are actually unapproved food additives that FDA fails to adequately regulate or oversee under the statutorily required FAP process. Even when a substance’s safety is questioned by independent experts commissioned by the agency itself – as in the case of the SCOGS committee recommendations in 1982 that FDA ignored, discussed above – it may be marketed to consumers without going through the food additive petition process. Furthermore, because notifications are not required, secret industry GRAS designations are made without the information on exposure and cumulative effects that should be necessary to make such a determination.

The following section provides several current examples of how the 1997 proposal fails to meet the requirements of the FAA: (1) the results of a FOIA request performed by CSPI with regard to caffeine and caffeinated products; (2) a survey of withdrawn GRAS notifications; (3) an FDA response letter on taste modifiers; (4) FDA’s lack of control regarding the possible use of nanotechnology in the food supply; (5) several flavorings determined to be GRAS despite being found carcinogenic by authoritative bodies; and (6) industry-determined GRAS substances of dubious safety, such as Quorn-brand products. These case studies are only a small sampling of how the 1997 proposal prevents effective regulation of substances added to foods and thus directly contravenes the FAA.

²⁵⁴ International Center for Technology Assessment, *supra* note 249, at 3.

²⁵⁵ *Id.*

²⁵⁶ See Food & Water Watch, *supra* note 246; Hansen, *supra* note 247.

a. The GRAS status of caffeine illustrates how current system impedes informed and consistent GRAS determinations.

As the GAO and Pew studies and other comments on the docket noted, the 1997 proposal makes meaningful oversight over substances added to foods impossible. This problem is starkly illustrated by the GRAS status of caffeine. Although caffeine is limited in cola-type beverages to 72 milligrams per 12 ounces in a GRAS regulation,²⁵⁷ caffeine is a product that industry has self-determined to be GRAS – or even used without self-determining that it is GRAS – for many other novel applications, even while it poses safety risks to consumers. FDA cannot effectively regulate industry’s new and increased uses of caffeine under the current system because it lacks information, such as exposure data, required to make ongoing assessments of safety.²⁵⁸

Caffeine added to foods and beverages has been linked in FDA’s own data to serious adverse effects for consumers. In response to a FOIA request, CSPI found that between January 1, 2004, and March 10, 2014, FDA received 276 reports of adverse events associated with energy drinks containing added caffeine.²⁵⁹ Thirty-four of those incidents resulted in death, often due to heart failure. Of the remaining reports, 42 involved life-threatening injuries, 82 involved injuries that were characterized as “serious,” 115 resulted in hospitalization, 15 resulted in disability, and one resulted in miscarriage.²⁶⁰ Consumers reported experiencing high blood pressure, convulsions, paralysis, and brain damage due to lack of oxygen.²⁶¹ These risks were particularly acute in vulnerable populations such as teenagers, perhaps due to their comparatively lower body weights and inexperience with caffeine consumption.²⁶²

²⁵⁷ 21 C.F.R. § 182.1180.

²⁵⁸ Given that companies’ GRAS determinations are kept secret from the public and FDA, we rarely have access to a range of self-determinations made for different uses of a substance by a wide swath of companies. Because FDA requested and received this information for caffeine, and it became available to CSPI through a Freedom of Information Act (FOIA) request, the use of caffeine in foods and beverages presents a compelling case study in the failures that attend the FDA’s current policy permitting secret GRAS determinations.

²⁵⁹ Results of CSPI FOIA Request, FOI 14-17 Report, Center for Food Safety and Applied Nutrition Adverse Event Reporting System (CAERS) Reports Allegedly Related to Multiple Energy Drinks, available at <http://cspinet.org/images/foia-energy-drinks.pdf>.

²⁶⁰ *Id.*

²⁶¹ *Id.*

²⁶² Anais Fournier, a 14-year-old girl, died from a cardiac arrhythmia due to caffeine toxicity after consuming a Monster energy drink while she was at the mall with her friends. Autopsy Report of Anais Fournier, Age 14, Hagerstown Maryland Resident Who Died After Consuming Monster Energy Drink. The death of a 19-year-old in California and the brain damage suffered by an Oklahoma 16-year-old have also been linked to the consumption of Monster beverages. James Mulcahy & Kevin A. Adams, *Monster Beverage Company —A Case Study of Vertical Distribution Landmines*, Mulcahy LLP, <http://mulcahyllp.com/firmnews/practicenews/monsterbeveragecompanyacasestudyofverticaldistributionlandmines.html>. Additionally, government records show that two 25-year-olds and an 18-year-old died in Canada, possibly because of their consumption of either Monster or Red Bull beverages. *Energy drinks suspected to have caused deaths of 3 Canadians*, Toronto Star, Nov. 18, 2012, http://www.thestar.com/news/canada/2012/11/18/energy_drinks_suspected_to_have_caused_deaths_of_3_canadians.html. And while energy drinks and other products with added caffeine are oftentimes marketed to athletes, a case report indicates that a 28-year-old man consumed three energy drinks and five

These reports demonstrate that the consumption of foods and beverages with added caffeine may have dangerous effects, and in June 2013, FDA requested information from companies that had self-determined the GRAS status of caffeine in their products. FDA asked each company how it had determined that its products and proposed uses met the standards for GRAS. The companies' responses relating to their self-determinations of GRAS status expose glaring inconsistencies and deficiencies in their determinations, and provide a stark indication that industry self-determined GRAS does little to ensure the safety of the food supply. This sorry record – almost by itself – demonstrates the need for required notification and recordkeeping, along with better-defined requirements for the science and exposure data necessary to sustain a GRAS determination. Despite the discrepancies, we are unaware of any action taken by FDA to date to enforce GRAS obligations for these companies or revoke the GRAS determinations regarding these uses of caffeine.

The industry's GRAS responses indicate a desperate need for commonly agreed-upon, accurate, and updated exposure data – all information necessary for the FAA to function as intended. When considering worst-case scenarios for ingestion of caffeine, many of the companies assumed unrealistically low levels of exposure. Jelly Belly, for instance, noted exposure levels resulting from just two to three servings of its “Extreme Sports Beans” (caffeinated jelly beans),²⁶³ even though the product is sold in units that contain 24 packaged servings and has an appearance that a consumer could easily confuse with non-caffeinated candy.

More troublingly, the companies fail to adequately consider whether consumers have already ingested caffeine from other sources, as would be required for a meaningful assessment of the cumulative effect of the substance. It is well within the realm of possibility to imagine a situation in which a consumer drinks a coffee before consuming a large quantity of caffeinated jelly beans, for instance. Consumption from several products would represent the upper level of caffeine exposure presented by a product, but none of the companies that responded to FDA's request for information factored in caffeine exposure from other sources when considering worst-case exposure scenarios.²⁶⁴ In fact, Jelly Belly specifically (and appallingly) stated that other sources of caffeine need not be considered because consumers would replace their other sources of caffeine with their beans. The company's self-serving, illogical, and empirically unsupported assumptions should be plainly insufficient to support a GRAS finding.

hours later lost consciousness while playing basketball. He was hospitalized and after three days died following sudden cardiac arrest. S. Avci, R. Sarikaya & F. Buyukcam, *Death of a Young Man after Overuse of Energy Drink*, 31 Am. J. Emergency Med. 1624 (2013).

²⁶³ Letter from John Di Giusto, General Counsel, Jelly Belly Candy Company, to Michael Landa, Director, Center for Food Safety and Applied Nutrition (June 24, 2013) (on file with CSPI).

²⁶⁴ This ignores FDA's guidance for intake estimates of direct additives, which requires the petition process to consider “[a]ny anticipated increase in consumption from its petitioned use(s), if the food additive is also a naturally occurring material. The concentration of the additive occurring naturally in food(s) and an estimate of the level of consumption of the food(s) should be provided.” U.S. Food and Drug Administration, *Guidance for Industry: Recommendations for Submission of Chemical and Technological Data for Direct Food Additive Petitions* (March 2009), available at <http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm124917.htm#intake>.

The responses that companies submitted to FDA regarding 90th percentile intake of caffeine reveal further discrepancies and inadequacies with regard to exposure estimates and the need for accurate exposure data. Kraft, for instance, assumed 90th percentile consumption levels ranging from 2.3 mg/kg/day to 5.2 mg/kg/day, which in a 70 kg person would amount to 161 to 364 mg of caffeine.²⁶⁵ In contrast, Pepsi assumed 90th percentile caffeine levels at 392 mg per day for adults over 20 and Coke cited a 90th percentile of 406.3 mg per day for adults over 18 in its self-determination.²⁶⁶ Monster assumed an even higher 90th percentile intake of 8.6 mg/kg, or 600 mg/day for a 70 kg person.²⁶⁷ In addition, Monster noted that per capita intake of caffeine is approximately 300 mg/day,²⁶⁸ which is significantly higher than the lower range of 90th percentile consumption assumed by Kraft. Monster was also the only company that mentioned 90th percentile caffeine intake for adolescents, which it stated to be less than 225 mg.²⁶⁹

These significant discrepancies in the most basic assumptions needed for a safety assessment reveal that GRAS – even industry-determined GRAS – cannot work when companies do not share information with FDA and each other. The chaos that results indicates that some companies lack the updated and accurate exposure data necessary to make a GRAS determination, and will tailor core scientific assumptions that are critical to public health to meet their own perceived needs.

The data sources companies rely upon are also cause for concern. Jelly Belly, for instance, examined outdated caffeine consumption data from nearly 60 years ago.²⁷⁰ Many of the companies relied on data from foreign markets, where consumption trends may differ from those in the United States. Monster cited a survey conducted by researchers at Penn State University²⁷¹ that found that four percent of Americans who consume caffeine consume energy drinks.²⁷² This rate is higher than rates found in studies cited by both Monster and Rockstar

²⁶⁵ Letter from Kraft Foods Group, Inc., to Michael Landa, Director, Center for Food Safety and Applied Nutrition 9 (Aug. 5, 2013) (on file with CSPI).

²⁶⁶ Letter from Rene Lammers, Chief Science Officer, PepsiCo, to Michael Landa, Director, Center for Food Safety and Applied Nutrition 2 (Aug. 1, 2013) (on file with CSPI); Letter from Rhona Applebaum, Vice President and Chief Science & Health Officer, The Coca Cola Company, to Michael Landa, Director, Center for Food Safety and Applied Nutrition (Aug. 1, 2013) (on file with CSPI).

²⁶⁷ Letter from Miriam Guggenheim, Counsel to Monster Beverage Company, to Michael Landa, Director, Center for Food Safety and Applied Nutrition 6 (June 24, 2013) (on file with CSPI).

²⁶⁸ *Id.*

²⁶⁹ *Id.* at 7. Adolescents are a vulnerable population when it comes to caffeine. *See Scientific Report of the 2015 Dietary Guidelines for Americans Committee* 8-9 (Feb. 2015) (“The marketing and availability of high-caffeine beverages and products is on the rise. Unfortunately, only limited evidence is currently available to ascertain the safety of high caffeine intake (greater than 400 mg/day for adults and undetermined for children and adolescents) that may occur with rapid consumption of large-sized energy drinks. Limited data suggest adverse health outcomes, such as caffeine toxicity and cardiovascular events.... Limited or no consumption of high caffeine drinks, or other products with high amounts of caffeine, is advised for children and adolescents.”).

²⁷⁰ Letter from John Di Giusto, *supra* note 263.

²⁷¹ D.C. Mitchell, et al., Supported by Washington (DC): International Life Sciences Institute, *Beverage Caffeine Intakes in the U.S.* (2013) [Poster presented at EB 2013 in Boston, ASN Meeting, April 22, program number: 848.12, abstract number: 7769].

²⁷² Letter from Miriam Guggenheim, *supra* note 267, at 7.

based on Canadian consumption. One such study mentioned by the companies found that only 1.5 percent of Quebecois teenagers consumed energy drinks daily,²⁷³ while another found that only one percent of Quebecois teenagers reported daily energy drink consumption – while small in order, one of these estimates is fifty percent higher than the other, which would alter the estimate significantly.²⁷⁴

The fact that the companies made such disparate and often outdated exposure assessments demonstrates that safety determinations for GRAS may not be based on accurate or updated data – which is hardly surprising given that the current system does not require submission of exposure data. The current GRAS system fails to ensure that such information is – or even can be – taken into account by companies when determining whether use of a given substance is safe. Accurate exposure data could only be obtained if companies are required to submit GRAS notifications along with the most accurate possible updated exposure estimates, and FDA engages in an iterative process with companies to standardize such estimates, as it does for food additive petitions (which must meet identical requirements related to probable consumption and exposure).

Due to FDA’s failure to develop any regulatory definition of “harm,”²⁷⁵ the submissions also fail to seriously consider important risks associated with the intended use of caffeine. For example, while the companies consider lethal doses in their GRAS determinations, the amount of caffeine known to produce non-permanent harm, such as anxiety, nausea, and sleeplessness – which are less severe but still significant – received scant attention. The possibility for non-fatal side effects, for instance, is not even addressed in Jelly Belly’s response. Kraft’s response notes that consumption of an entire bottle its MiO caffeine concentrate would result in exposure of approximately 1,000 mg of caffeine; according to Kraft’s own assessment, this amount presents a reasonable likelihood of adverse effects in children.²⁷⁶ But Kraft disregards this danger and instead assesses its product according to the more serious but less-likely-to-occur possibility that it might cause a severe adverse event, which Kraft defines as one “requiring medical intervention to manage, mitigate or prevent progression to a life-threatening situation.”²⁷⁷ This means that, in the absence of a regulatory definition of harm, industry has literally defined “GRAS” as anything that will not kill you – a grossly insufficient standard to protect public health.

Red Bull and Rockstar similarly devote negligible attention to the risk of harm in their responses. Pepsi and Coke acknowledge the potential for caffeine to cause anxiety and sleep

²⁷³ Institut de la Statistique du Quebec, *Frequence de consommation habituelle de certaines boissons sucrees, eleves du secondaire*, Tableau A3.2, L’Enqu~te quebecoise sur la sante des jeunes du secondaire 2010-2011: TOME 1: Le visage des jeunes d’aujourd’hui: leur santti physique et leurs habitudes de vie (2012).

²⁷⁴ Reseau du sport etudiant du Quebec, *Enquete Quebecoise sur le Marketing de la Malbouffe: 10 000 Jeunes se Prononcent!* (2011).

²⁷⁵ Maffini et al, *supra* note 226 at 441.

²⁷⁶ Letter from Kraft Foods Group, *supra* note 265, at 8. (Noting that the probability of adverse side effects is considered “low-medium” for ingestion rates between 500 and 1,000 mg of caffeine and “medium” for rates between 1,000 and 1,500 mg). This contrasts with the DSM-5 which states that caffeine intoxication can occur “with low doses (e.g., 200 mg) in vulnerable individuals such as children, the elderly, or individuals who have not been exposed to caffeine previously.”).

²⁷⁷ *Id.*

disturbance but dismiss these concerns, citing studies that show that caffeine use is self-limiting, although consumers would inevitably suffer adverse effects before deciding to limit their intake.²⁷⁸ And Monster, though it mentions the potential behavioral effects of caffeine on children in passing, ultimately disregards them. The current system ignores the potential effects of chronic and sustained exposures, in clear violation of the FAA's original intent to address effects beyond acute toxicity.²⁷⁹

The potential for adverse effects is an especially glaring omission considering that teenagers are the most frequent users of energy drinks and adverse effects are more likely to occur in consumers who are caffeine-naïve and have lower body weights.²⁸⁰ It shows the need for scientific requirements regarding vulnerable populations, as recommended by the Pew studies. As Monster notes in its response, a study of caffeine-naïve children found that ingestion of less than 50 mg of caffeine per day produced effects such as restless behavior and difficulty sleeping.²⁸¹ More pointedly, the varying definitions and lack of clarity point out an urgent need for FDA to clarify the definition of harm in its final rule.²⁸²

Moreover, the responses demonstrate that the voluntary nature of the current regime permits industry self-determinations to ignore the applicable scientific requirements for GRAS. For example, the Jelly Belly submission indicates that it based its GRAS finding for Extreme Sports Beans on the “common use” of caffeine before 1958. In its submission, Jelly Belly stated that no further scientific assessment was required because caffeine was in common use before the FAA.²⁸³ However, the interim rule clearly states that it is the *nature* of the use, not the mere use of the substance in foods, which confers eligibility for the GRAS exemption based on use before 1958. Thus, an “evaluation of whether an additional use of a substance that is GRAS through experience based on common use in food is also GRAS requires a scientific procedures GRAS determination when *the use in question* was not common prior to January 1, 1958.”²⁸⁴ As caffeine was not used as an additive in jelly beans before 1958, Jelly Belly's GRAS determination must be based on scientific evidence, not common use. However, as the current system is voluntary, companies often fail to follow applicable regulations and employ adequate science.

The responses also confirm the potential for conflicts of interest in GRAS determinations flagged by Pew. Kraft, for instance, used an in-house toxicologist to conduct the company's determination, who singlehandedly determined that 60 mg of caffeine per 8-ounce serving was

²⁷⁸ Letter from Rene Lammers, *supra* note 266, at 18; Letter from Rhona Applebaum, *supra* note 266.

²⁷⁹ Even the SCOGS, back in 1982, recognized the potential risks of caffeine. The majority conclusion was that FDA should issue an interim food additive regulation requiring commitment, within a stated period, that necessary testing would be undertaken (the substance continuing as GRAS during completion of tests and evaluation of the results). The minority conclusion would require that safe conditions of use be established. Select Committee on GRAS Substances, *Insights on food safety evaluation* 50, 52 (1982).

²⁸⁰ F. Castellanos & F. Rapoport, *Effects of caffeine on development and behavior in infancy and childhood: a review of the published literature*, 40 *Food & Chemical Toxicology* 1235-1242 (2002).

²⁸¹ *Id.*

²⁸² Maffini et al., *supra* note 226, at 441 (noting that the lack of definitions of “harm” or “adverse effects” in FDA rules and public guidance documents makes system unpredictable and difficult to administer).

²⁸³ Letter from John Di Giusto, *supra* note 263.

²⁸⁴ 62 Fed. Reg. at 18950 (emphasis added).

GRAS, even though that is 25% higher than the amount determined by FDA to be GRAS when used in a cola beverage.²⁸⁵ Monster also made its own GRAS determination, and later hired consultants to prepare a safety assessment “(t)o help ensure the independence of the GRAS determination.”²⁸⁶ The rest of the companies commissioned consulting firms and toxicologists. This financial relationship presents a conflict of interest because scientists may feel pressure to reach favorable conclusions for the companies that employ them.²⁸⁷ These conflicts of interest undercut the integrity of the determinations and underlying scientific assessments.

The industry’s limited assessment of adverse health effects and vulnerable subpopulations, insufficient attention to updated science, use of woefully dated and incomplete exposure assessments, and rampant conflicts of interest all demonstrate that the GRAS system as it currently operates does not achieve the purposes of the FAA.

b. Scores of withdrawn GRAS notifications illustrate how the GRAS notification system fails to ensure the safety of substances used in the food supply.

As explained above, companies will sometimes withdraw their GRAS notifications rather than waiting for FDA’s response to their submissions. Typically, if FDA has raised safety questions about a substance, a company will withdraw its notification, and FDA will subsequently disclose only that it has ceased to evaluate the GRAS notice at the company’s request, without publishing the concerns that might have led to this request. Companies ask FDA to cease evaluations of their GRAS determinations with alarming frequency. A review of

²⁸⁵ 21 C.F.R. § 182.1180 (caffeine up to a level of 0.02 percent (200 ppm) is generally recognized as safe (GRAS) for use in cola-type beverages).

²⁸⁶ Letter from Miriam Guggenheim, *supra* note 267, at 1.

²⁸⁷ Recent research has documented significant effects related to funding bias in the outcomes of studies, and industry sources of funding for research have been found to have significant impacts on outcomes of studies. See, e.g., A. Lundh et al., *Industry Sponsorship and Research Outcome*, The Cochrane Collaboration (2013) (finding in a review of 48 papers on drugs and medical devices, that “industry sponsored drug and device studies are more favorable to the sponsor’s products than non-industry sponsored drug and device studies due to biases that cannot be explained by standard risk of bias assessment tools.”); Lenard Lesser, Cara Ebbeling, et al., *Relationship between Funding Source and Conclusion among Nutrition-Related Scientific Articles*, 4 PLoS Med 41-46 (2007) (finding that studies sponsored exclusively by food/drinks companies were four to eight times more likely to have conclusions favorable to the financial interests of the sponsoring company than those which were not sponsored by food or drinks companies); Anke Huss et al., *Source of Funding and Results of Studies of Health Effects of Mobile Phone Use: Systematic Review of Experimental Studies*, 115 Env. H. Persp. 1-4 (Jan. 2007) (finding that studies of the health effects of cellular telephone use that were “funded exclusively by industry ... were least likely to report a statistically significant result.”); Paul Ridker & Jose Torres, *Reported Outcomes in Major Cardiovascular Clinical Trials Funded by For-Profit and Not-for-Profit Organizations, 2000-2005*, 295 JAMA 2726 (May 17, 2006) (finding that recent cardiovascular trials funded by for-profit organizations are more likely to report positive findings than trials funded by non-for-profit organizations: while non-profits’ studies favored new treatments in 49 percent of case, studies funded by for-profits favored new treatments in 67 percent of studies, and approximately the same results held when only randomized trials were considered).

the list of GRAS notifications on FDA's Web site indicates that 84 notifications have been withdrawn out of a total 562 submissions – 15% of the total number of notifications.²⁸⁸

Withdrawal of notifications, conducted under the terms of FDA's 1997 proposal, seriously undercuts what little oversight FDA previously had retained over the GRAS process. In many of these cases, FDA identifies serious concerns about a company's GRAS notification, yet a company is allowed to continue marketing and selling its product for consumption, without publication of the agency's concerns for public or third-party review.²⁸⁹

In 2014, NRDC made a FOIA request for communications between FDA and the manufacturers behind 16 withdrawn GRAS notifications, to ascertain the types of concerns that would prompt manufacturers to ask the agency to stop reviewing a GRAS notice. In its review of the FOIA documents, NRDC found that FDA does review notifications and ask tough questions. When a notification raises serious safety concerns, FDA tells the company that it will reject a notice if it is not voluntarily withdrawn. The company may then withdraw the notification and use the product anyway, without any online publication of FDA's concerns.²⁹⁰ In such a case, both the public and other manufacturers are deprived of important information that might affect future decisions.

In a 2014 report, NRDC described several chemicals that have been used in foods after manufacturers withdrew their GRAS notifications in response to FDA's questions. For example, epigallocatechin-3-gallate (EGCG) is a chemical used in beverages. Its manufacturer declared the chemical GRAS despite evidence that it may cause leukemia in fetuses, and short-term study results showing that it affected the thyroid, testis, spleen, pituitary, liver, and gastrointestinal tract.²⁹¹ The notice also did not explain potentially dangerous interactions with sodium nitrite, a common preservative, or with acetaminophen, a common ingredient in over-the-counter painkillers. A company has submitted and withdrawn GRAS notices for EGCG twice. Despite

²⁸⁸ U.S. Food and Drug Administration, *GRAS Notices*, <http://www.accessdata.fda.gov/scripts/fdcc/?set=GRASNotices> (last accessed Feb. 25, 2015). In the FDA experience memo, spanning the period from 1998-2009, FDA estimates that 16% of notices are withdrawn. See Kahl Memo, *supra* note 67, at 10.

²⁸⁹ Neltner & Maffini, *supra* note 66, at 9. This report provides the following quote from an email procured from the FOIA request:

The next day, [notifier] called and asked whether [notifier] would have an option to withdraw the notice rather than receive a letter that the notice did not provide a basis for a GRAS determination. I replied that this was an option. On September 4, [notifier] asked whether [notifier] could still sell its [name] product if it withdrew its GRAS notice.

Consistent with my response to her earlier question about marketing [name], I said yes.

Id. at 3 (quoting FDA officer summarizing telephone conversations with manufacturer regarding its GRAS notice review).

²⁹⁰ *Id.* at 9. An FDA reviewer stated that FDA "cannot require anything, as this is a voluntary program and we don't want to frighten anyone away." *Id.*

²⁹¹ U.S. Food & Drug Administration, GRAS Notice Inventory, GRN No. 225 and NRDC, Main FDA Response to FOIA regarding GRN No. 225 (2014), www.nrdc.org/food/files/chemicals-in-food-FOIA-Main.pdf.

the red flags identified by FDA, other companies still use EGCG in their products: NRDC identified 25 food products with EGCG as a named ingredient.²⁹²

Gamma-amino butyric acid (GABA) is a neurotransmitter that was self-determined GRAS by industry for use in beverages, chewing gum, coffee, tea, and candy. GABA was declared GRAS despite the fact that estimated exposures were in excess of what the manufacturer considered safe. In addition, the submitter relied on unpublished safety studies, and failed to consider existing exposures.²⁹³ When FDA identified these concerns, the company withdrew its notice. While the company told NRDC that it would not market the product for use in food, it continued to use the ingredient in dietary supplements. NRDC also identified five food products marketed by other companies with GABA as a named ingredient, including bottled tea and nutrition bars.²⁹⁴

Sweet lupin protein, fiber, and flour have been declared GRAS by an Australian firm for use in baked goods, dairy products, gelatin, meats, and candy, despite concerns that the chemicals could cause allergic reaction in people with peanut allergies.²⁹⁵ In communications with the firm, FDA noted that a warning label would be insufficient to alert consumers to this risk, and the company withdrew its GRAS notification. Despite FDA's concerns, sweet lupin is listed as an ingredient in more than 20 food products, none of which include a warning for those with peanut allergies.²⁹⁶ These products are likely marketed by other companies who have not been alerted to FDA's concerns, as they are not publicized under the current system.

Finally, theobromine was declared GRAS by a U.S. company for use in bread, cereal, beverages, chewing gum, tea, soy milk, gelatin, candy, and smoothies, despite having an estimated consumption rate that was more than five times the safe consumption level reported by the company's consultant. On top of this already considerable cause for alarm, the notification did not provide explanations for various safety concerns raised by animal testing of theobromine, including testicular degeneration and delayed bone formation.²⁹⁷ Nevertheless, NRDC found that theobromine was a named ingredient in more than 20 food products, including isotonic waters, nutrition bars, and diet foods.²⁹⁸

These examples show that even when the GRAS process is theoretically “working” – when FDA actually receives and reviews GRAS notifications – it does little to actually ensure the safety of our food supply. Manufacturers are permitted to withdraw their notifications and

²⁹² Neltner & Maffini, *supra* note 66, at 9.

²⁹³ U.S. Food & Drug Administration, GRAS Notice Inventory, GRN Nos. 257 and 259, and NRDC, Main FDA Response to FOIA regarding GRN Nos. 257 and 259 (2014), www.nrdc.org/food/files/chemicals-in-food-FOIA-Main.pdf.

²⁹⁴ Neltner & Maffini, *supra* note 66, at 9.

²⁹⁵ FDA, GRAS Notice Inventory, GRN Nos. 262, 263, and 264, and NRDC, Main FDA Response to FOIA regarding GRN Nos. 262, 263, and 264 (2014), www.nrdc.org/food/files/chemicals-in-food-FOIA-Main.pdf.

²⁹⁶ Neltner & Maffini, *supra* note 66, at 10.

²⁹⁷ FDA, GRAS Notice Inventory, GRN No. 340, and NRDC, Main FDA Response to FOIA regarding GRN No. 340 (2014), www.nrdc.org/food/files/chemicals-in-food-FOIA-Main.pdf.

²⁹⁸ Neltner & Maffini, *supra* note 66, at 10.

continue to use the product despite legitimate concerns raised by FDA. Moreover, the ingredients may be marketed by other companies – and, in fact, because FDA’s concerns are not published, the third-party companies may never know about the safety questions raised by the agency. This means that FDA’s process does nothing to prevent unsafe products from entering the food supply or being adequately labeled. This demonstrates both the vacuity of the proposal’s process for GRAS and the importance of making GRAS notifications both required and public. In addition, the fact that *significant* safety concerns have been raised in the scientific community regarding these substances means that they should not be able to use the GRAS process in the first place.

c. The current GRAS system permits novel “food additives” to bypass the statutory food additive process.

We have identified many examples of novel and/or questionable substances that cannot meet any possible interpretation of the “GRAS” language in the FAA, but nonetheless have apparently been self-determined GRAS by industry, rather than going through the statutory FAP process.

i. Taste Modifiers

As described above, the FAP process was intended to apply to novel, unfamiliar additives – as these substances could not have a track record of safety necessary to qualify as “GRAS.” Yet, under the current system, many novel substances are used in foods without a FAP. For example, in 2013, CSPI wrote to FDA seeking information about the labeling requirements for a novel group of substances known as “taste modifiers,” including, specifically, 4-amino-5,6-dimethylthieno[2,3-d]pyrimidin-2(1H)-one & hydrochloride salt and 3-[(4-amino-2,2-dioxido-1H-2,1,3-benzothiazin-5-yl)oxy]-2,2-dimethyl-N-propylpropanamide. The presence of these chemicals is not obvious from food labels because the food industry claims – wrongly in our view – that they are encompassed by the labeling term “artificial flavors,” despite the manufacturer’s acknowledgment that they do not have any taste of their own. Therefore, their use in the food supply – and the extent of this use – is a mystery to consumers.

FDA is apparently content to let it remain mysterious. In response to CSPI’s letter on taste modifiers (two years after receipt), FDA wrote that the substances in question had been determined GRAS by industry, that the manufacturer had not submitted any information on the substances to FDA, and therefore FDA had not conducted an evaluation of the substances.²⁹⁹ These types of chemicals, 4-amino-5,6-dimethylthieno[2,3-d]pyrimidin-2(1H)-one & hydrochloride salt and 3-[(4-amino-2,2-dioxido-1H-2,1,3-benzothiazin-5-yl)oxy]-2,2-dimethyl-N-propylpropanamide, which were lab-created to modify how humans perceive flavors, plainly constitute the kind of “newly discovered substances” that Congress was contemplating when it passed the FAA. That such complex, novel compounds have been self-determined as GRAS illustrates how industry uses the GRAS exemption to circumvent the food additive petition process required by Congress. Furthermore, the fact that their toxicology, use, and exposure levels are not publicly known should preclude any possible “general recognition”

²⁹⁹ Letter from Yinqing Ma, Center for Food Safety and Applied Nutrition, U.S. Food & Drug Administration, to Michael F. Jacobson, Executive Director, CSPI (Feb. 9, 2015) (on file with CSPI).

of their safety, as required by the statute and FDA regulations. Their industry-determined GRAS status is conclusive proof that the current system is not working as intended by Congress.

ii. Nanomaterials

In addition to taste modifiers, we have concerns – shared by GAO – about nanomaterials being used in the food supply without FDA oversight. Nanomaterials are another example of a novel food additive that may masquerade as GRAS rather than being approved via the statutory food additive petition process. Engineered nanomaterials are created through nanotechnology – the manipulation of materials at a molecular scale that enhances the resulting nanomaterials’ physical properties.³⁰⁰ While the underlying chemical structure of a substance is not changed by the engineering process, its physical properties may change. As GAO noted in its 2010 report, nanotechnology presents potential challenges to the regulation of food safety because companies may conclude that their engineered nanomaterials are GRAS without informing FDA.³⁰¹

Since the GAO report was issued in 2010, FDA has issued a *voluntary* guidance on nanotechnology in food ingredients, suggesting that such products are ineligible for self-determined GRAS,³⁰² however, this guidance is not binding.³⁰³ Furthermore, because all GRAS notifications are voluntary, FDA has no way of knowing the full extent to which engineered nanomaterials have entered the U.S. food supply, despite the fact that they are precisely the type of “food additives” warranting pre-market testing contemplated by Congress in passing the FAA.

In its guidance, FDA notes that it would be “prudent” for manufacturers to consult the agency on changes in manufacturing processes that include “novel” and “emerging” technologies such as nanotechnology (which, according to FDA, results in “new properties not seen in traditionally manufactured food substances”³⁰⁴). While the agency fails to *require* consultation,³⁰⁵ FDA clearly understands the risks of allowing the industry to experiment on the public, stating: “[t]he consequences (to consumers and to the food industry) of broadly distributing a food substance that is later recognized to present a safety concern have the potential to be significant.”³⁰⁶ This is precisely the concern that drove Congress to enact the FAA in the first place – and is therefore yet another stark illustration of how the statutory food

³⁰⁰ GAO Report, *supra* note 37, at 2.

³⁰¹ *Id.* at 26.

³⁰² Nanotech Guidance, *supra* note 169.

³⁰³ As the guidance indicates: “[i]t does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations.” *Id.* at 1. It further provides that “FDA’s guidance documents, including this guidance, do not establish legally enforceable responsibilities. . . . The use of the word *should* in Agency guidelines means that something is suggested or recommended, but not required.” *Id.* at 6. As there are no “statutes or binding regulations” specific to nanotechnology and FDA has interpreted its own obligations on the safety of additives and GRAS so haphazardly, as above, this text in this context is essentially meaningless.

³⁰⁴ *Id.* at 14.

³⁰⁵ *Id.* at 5.

³⁰⁶ *Id.*

additive petition process has been undone by FDA’s interpretation of its obligations under the law.

Nanotechnology also reveals the limitations of FDA’s current scientific standards for testing of GRAS substances. Nanomaterials may have a unique effect on the human body, as changes in the “physical and chemical properties of a food substance can affect its bioavailability through altered absorption, distributions, metabolism and excretion of the substance in the body [and] affect the level at which toxic effects may occur,” including such changes as “particle size.”³⁰⁷ FDA concedes that its standard toxicological guidance may not address “known toxicological endpoints” that are a concern for some compounds or class of compounds, and states that “in such cases, it is the responsibility of chemical manufacturers and food industry end users to develop appropriate protocols to address particular safety issues” and that “historically, such persons have been advised” to consult FDA.³⁰⁸ In short, nanotechnology clearly alters the metrics for risks to human health, and FDA’s current scientific standards do not address some of these new and emerging risks.

FDA’s analysis makes that clear that particular testing to measure the impacts of nanotechnology would be needed to assure the safety of such substances.³⁰⁹ Specifically, due to the variability shown in a body of research regarding the toxicology of nanotechnology, particular kinds of *in vitro* tests would be required to validate the results of safety testing for nanomaterial foods substances.³¹⁰

In the guidance, the agency states that it has not to date received GRAS affirmation petitions or notices for any uses of nanomaterials in food, but that where “safety questions are raised that experts would need additional data to resolve and such data are not generally recognized, the criteria for GRAS would not be satisfied for the use of such food substances.”³¹¹ The agency further stated that it was not aware of any food substances intentionally engineered on the nanometer scale “for which there are generally available safety data sufficient to serve as the foundation for a determination that the use of a food substance is GRAS.”³¹²

³⁰⁷ *Id.* at 13.

³⁰⁸ *Id.*

³⁰⁹ *Id.* at 15 (“The variation in biological activity that may result from engineering food substances in the nanometer range may raise questions about the applicability of traditional safety tests for these materials. Thus, as with any studies to support the safety of food substances, studies to establish the safety of food substances manufactured using nanotechnology *should have been* appropriately validated for these materials. Notably, variability has been reported when traditional toxicity tests have been used to assess nanomaterials. Because of this variability, and because the physiochemical properties of an individual nanomaterials may require adjustment to a particular assay, validation (single and/or multi-laboratory) of traditional *in vitro* toxicity tests will ensure that the results are meaningful and appropriate to the safety assessment of the nanomaterial food substance. FDA anticipates that method validation for nanomaterial food substances would include parameters such as accuracy, precision, sensitivity, specificity, repeatability and biological relevance.”)

³¹⁰ *Id.*

³¹¹ *Id.* at 15-16.

³¹² *Id.*

Thus, FDA is suggesting that nanomaterials cannot be GRAS – a stunningly logical conclusion, under the law – but it is doing so in a nonbinding guidance in the context of a program that requires *no notice* to FDA of the use of any substance self-determined by the food industry to be GRAS. This development is so far outside the contemplation of the FAA that it is a farce built upon a fallacy. In fact, the agency currently has no way of knowing whether nanotechnology is being used in food; even after issuance of its guidance, these substances could be in the food supply and FDA would never know. Most troublingly, the guidance from FDA likely (and foreseeably) undermined the agency’s ostensible purpose: by signaling that expensive additional testing sensitive to the risks of nanotechnology would be required to demonstrate the safety of a nanotech food substance in any notification to the agency, FDA ensured that any use of such substances would remain a food industry secret.

However, FDA’s invocation of a limitation on GRAS based on an assessment of risks and the inadequacy of data sufficient for a general safety is instructive. It shows a way forward, should the FDA finally breathe meaning and life into its moribund authorities. The fact that FDA limits, in its guidance, the eligibility of nanotech food substances for a GRAS designation is good precedent for an appropriate additional narrowing of GRAS eligibility with binding rules that bring the program in line with both historical indicators of Congressional intent and the clear statutory design.³¹³

d. The lack of appropriate limits on “GRAS” designations allows substances whose safety is questioned in the scientific community or unsupported by the scientific literature to impermissibly bypass the food additive process.

By the plain language of the statute, a substance whose safety has been questioned by the scientific community cannot be “generally recognized as safe.” However, we are aware of many cases of allegedly GRAS substances whose safety has been seriously questioned by the scientific community or is unsupported by the scientific literature. These examples demonstrate that the 1997 proposal allows industry to make GRAS designations for substances whose safety is not “generally recognized” by experts – in plain violation of the FAA. These substances, by definition, should not fall within the GRAS exemption and, because of questions about their safety raised in the scientific community, should only be approved for use in food via the congressionally mandated food additive petition process. Instead, their GRAS status illustrates how the system permits substances whose dangers have been recognized by authoritative bodies, or whose safety has not been demonstrated by science, to bypass the statutory system without FDA’s knowledge or approval.

i. Flavorings

³¹³ FDA made similar findings in a nonbinding industry guidance regarding substances added to beverages and dietary supplements. *See* U.S. Food and Drug Administration, *Guidance for Industry Considerations Regarding Substances Added to Foods, Including Beverages and Dietary Supplements 5* (Jan. 2014) (stating that it was “concerned that some of the novel substances that are being added to conventional foods . . . may cause the food to be adulterated because these added substances may not be GRAS for their intended use and are not being used in accordance with a food additive regulation prescribing conditions of safe use”).

Many flavorings have been determined to be GRAS by industry despite the formal designation of a government authority that they induce cancer when ingested by man or animal. Most of these GRAS determinations were originally made in the 1960s, and were not reassessed when later scientific studies revealed the problems. For example:

- 2-Phenylphenol/*o*-Phenylphenol was determined as GRAS for use as a seasoning or flavoring,³¹⁴ despite being declared a carcinogen by California Prop 65 in 2000.³¹⁵
- Quinoline was determined GRAS in 1975 for confectionary and baked goods, puddings, meats, and soups.³¹⁶ In 2001, EPA IRIS found it likely to be carcinogenic in humans, echoing California Prop 65's finding that it was carcinogenic in 1997.³¹⁷ Industry did eventually remove the GRAS designation for quinoline, but not until late 2014, nearly two decades after the Prop 65 finding.³¹⁸
- Trans,trans-2,4-hexadienal was found to be GRAS in 1974 and 2003;³¹⁹ IARC found it possibly carcinogenic to humans in 2012.³²⁰

It is unknown how many dangerous or carcinogenic substances have been self-determined as GRAS without any notification to FDA or the public.

³¹⁴ FEMA Expert Panel and Staff (P. Newberne, R.L. Smith, J. Doull, V.J. Feron, I.C. Munro, P.S. Portoghese, W.J. Waddell, B.M. Wagner, C.S. Weil, T.B. Adams and J.B. Hallagan), GRAS Flavouring Substances 19 (FEMA No. 3906-3963), Food Technology, Vol. 54, No. 6, (June 2000).

³¹⁵ California Office of Environmental Health Hazard Assessment (OEHHA), *Chemicals Listed Effective August 4, 2000 as Known to the State of California to Cause Cancer: o-Phenylphenol* (2000), available at http://oehha.ca.gov/prop65/out_of_date/800Not.html.

³¹⁶ B.L. Oser and R.A. Ford on behalf FEMA Expert Panel, *Recent Progress in the Consideration of Flavouring Ingredients Under the Food Additives Amendment, GRAS Substances* (FEMA No. 3445-3476), Food Technology, Vol. 29, No. 8 (Aug. 1975).

³¹⁷ EPA IRIS, *Quinoline* (CASRN 91-22-5), <http://www.epa.gov/iris/subst/1004.htm> (last accessed 2/21/15); OEHHA, *Evidence On The Carcinogenicity Of Quinoline And Its Strong Acid Salts* (1997), available at www.oehha.ca.gov/prop65/hazard_ident/pdf_zip/quinolin.pdf.

³¹⁸ *FEMA Upgrades GRAS Interim List, Removes Quinoline* (Nov. 2014), <http://connection.ebscohost.com/c/articles/98900741/fema-updates-gras-interim-list-removes-quinoline>.

³¹⁹ B.L. Oser and R.A. Ford on behalf FEMA Expert Panel, *Recent Progress in the Consideration of Flavouring Ingredients Under the Food Additives Amendment: 8. GRAS Substances*, (FEMA No. 3424-3444), Food Technology, Vol. 28, No. 9 (Sept. 1974); FEMA Expert Panel (R.L. Smith, S.M. Cohen, J. Doull, V.J. Feron, J.I. Goodman, L.J. Marnett, P.S. Portoghese, W.J. Waddell, B.M. Wagner, and T.B. Adams), *GRAS Flavouring Substances 21* (FEMA No. 4024-4068), Food Technology, Vol. 57, No. 5 (May 2003).

³²⁰ IARC, *2,4-Hexadienal*, IARC Monograph – Volume 101-012, 391-405 (2012), available at <http://monographs.iarc.fr/ENG/Monographs/vol101/mono101-012.pdf>.

Equally worrying, many industry-made GRAS determinations are based entirely on unpublished safety data. For example, in 2013, the Flavor and Extract Manufacturers Association (FEMA) issued GRAS determinations for four new flavorings:

- FEMA GRAS No. 87: *trans*-6-Octenal (also known as (*E*)-6-Octenal or (*E*)-Oct-6-enal)
- FEMA GRAS No. 4798: 2-(((3-(2,3-Dimethoxyphenyl)-1*H*-1,2,4-triazol-5-yl)thio)methyl)pyridine (also known as 2-((5-(2,3-Dimethoxyphenyl)-2*H*-1,2,4-triazol-3-ylthio)methyl)pyridine or Pyridine, 2-(((3-(2,3-dimethoxyphenyl)-1*H*-1,2,4-triazol-5-yl)thio)methyl))
- FEMA GRAS No. 4802: (S)-1-(3-(((4-amino-2,2-dioxido-1*H*benzo[*c*][1,2,6]thiadiazin-5-yl)oxy)methyl) (also known as piperidin-1-yl)-3-methylbutan-1-one)
- FEMA GRAS No. 4809: 2-(4-Methylphenoxy)-*N*-(1*H*-pyrazol-3-yl)-*N*-(thiophen-2-ylmethyl)acetamide (also known as *N*-(1*H*-pyrazol-5-yl)-*N*-(thiophen-2-ylmethyl)-2-(ptolyloxy)acetamide)

When nonprofit groups sought data on these new substances, the organizations found *no* relevant published safety data, toxicology data, or exposure data.³²¹ When the groups asked FEMA for published data on the four substances, it responded that there was none.³²² This practice of relying on unpublished data cannot meet any definition of “general recognition” of safety. As FDA is aware, FEMA fails to apply the published safety data requirement to their GRAS determinations.³²³ That a trade group can further enlarge the already-oversized GRAS loophole to extend to substances that have been labeled by scientific experts as known hazards to human health is only more evidence that FDA’s current practices are profoundly inadequate under the law.

ii. Mycoprotein (“Quorn”)

Mycoprotein is another example of a novel substance that poses obvious and evident risks to consumers, yet was permitted to bypass the food additive petition process (and be marketed to consumers) due to FDA’s overexpansive conception of GRAS. The case of mycoprotein also illustrates the need for a more reaching definition of harm, to ensure that GRAS determinations consider vulnerable subpopulations and effects that disrupt the ordinary routines of consumers, rather than considering only acute health risks or irreversible harm.

³²¹ Letter from NRDC, CSPI, CFS, Center for Environmental Health, and Environmental Working Group to Michael Taylor Re: Flavors and FEMA GRAS Program (Sept. 18, 2014) (on file with CSPI).

³²² *Id.* It did, however, offer to make 7,000 pages of unpublished data available to NRDC for a processing fee of over \$1,000.

³²³ Letter from NRDC, CSPI, CFS, Center for Environmental Health, and Environmental Working Group to Michael Taylor, Deputy Commissioner for Foods, FDA, Re: Flavors and FEMA GRAS Program (Sept. 18, 2014), at Appendix C (on file with CSPI).

Mycoprotein is a manufactured form of fungus that is the base of Quorn-brand meat and poultry substitutes. The ingredient was developed in the United Kingdom and originally marketed there in 1985. Marlow, the manufacturer of Quorn foods petitioned the FDA in 1986 to approve mycoprotein as a food additive. However, because the FDA never reached a final decision on that petition, in 2001 the manufacturer notified FDA that, consistent with the FDCA, it had concluded that mycoprotein was GRAS. The notice was supported by an analysis by a panel of “experts” convened by Marlow. In 2002, FDA issued a “no questions” letter in response to the GRAS notice,³²⁴ but has never formally approved the product as a food additive.³²⁵

Despite its supposed GRAS status, adverse effects associated with Quorn are frequent. An analysis of 2,007 adverse reaction reports and previously published papers found that the “mycoprotein” in Quorn-brand meat substitutes causes food intolerances and allergic reactions. Gastrointestinal (GI) symptoms, including vomiting and diarrhea, typically occurred 1–3 hours after consumption of the product.³²⁶ Symptoms ranged from mild nausea to vomiting severe enough to warrant medical attention.³²⁷ Some consumers “said they broke out in hives and had breathing difficulties – anaphylactic reactions.”³²⁸ The GI episodes associated with Quorn were described as “violent”; victims “would vomit so hard it could break the blood vessels in their eyes.”³²⁹ It is not known if the reactions are due to food allergies, intolerances, or both. The analysis also found that the “mycoprotein” in Quorn-brand meat substitutes caused apparent allergic reactions within 4 hours in 312 people. One of those individuals died after eating a Quorn food.

In addition, a double-blind, placebo-controlled study conducted in 1977–78 by the developer of mycoprotein, found that nine of 200 people who were fed mycoprotein two times in

³²⁴ Letter from Alan M. Rulis, Director, Office of Food Additive Safety, Center for Food Safety and Applied Nutrition, FDA, to Stuart M. Pape, Attorney for Marlowe Foods (Jan 7, 2002), *available at* <http://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm154623.htm>.

³²⁵ The no questions letter suggests that the GRAS notice replaced the food additive petition: In 1986, when Marlow submitted FAP 6A3930, most of the data and information that Marlow relies on to conclude that the intended use of mycoprotein is safe were not generally available to the public. Given the circumstances in 1986, there was no basis at that time to consider whether the intended use of mycoprotein could be GRAS. In contrast, at the present time most of the data and information that Marlow relies on to conclude that the intended use of mycoprotein is safe are generally available to the public. In addition, these data and information have been reviewed by a panel of individuals that Marlow considers qualified by scientific training and experience to evaluate the safety of substances added to food. Given the circumstances at present, FDA has no questions about Marlow's view that mycoprotein is GRAS under the conditions of its intended use.

Id. The regulatory timeline for Quorn is an explicit example of how industry-made GRAS designations have entirely replaced the statutory food additive petition process.

³²⁶ Michael F. Jacobson, Janna dePorter, & Qian Yuan, *Food Intolerances or allergic reactions linked to Quorn-brand foods* (forthcoming).

³²⁷ *Id.*

³²⁸ Kindy, *supra* note 5 (quoting Michael Jacobson).

³²⁹ *Id.*

each of four weeks suffered GI symptoms that appeared to be due to mycoprotein, including five “minor” symptoms and four “more severe” (mostly violent vomiting, difficulty breathing, severe abdominal pains) or a rash, while only one out of 100 people fed a control food reported significant symptoms.³³⁰

These reports and studies raise real questions about whether Quorn is safe for use in foods as an additive at all – particularly as it is a non-essential product. However, whether or not these adverse effects should prevent its use in foods altogether, it is clear that they raise sufficient questions about the safety of Quorn to preclude any general consensus or “general recognition” of safety in the scientific community and thus should have been subject to the full food additive petition process. As with caffeine, the GRAS status of Quorn also demonstrates the need for FDA to provide a definition of “harm” that takes less-serious, but still disruptive, effects into account when reviewing the GRAS designation of substances added to foods.

VI. In finalizing the rule, FDA must limit the categories of substances eligible for GRAS determinations and set clearer requirements for the scientific standards.

As the foregoing makes clear, FDA cannot legally finalize the rule as proposed, as it violates Congress’s unambiguous intent of the FAA and would be arbitrary and capricious under the APA in light of the substantial evidence already before the agency. Instead, FDA must revise its proposal and reopen the docket in order to establish a meaningful regulatory system that accomplishes the requirements of the FAA as intended by Congress.

Specifically, FDA must strengthen its oversight of substances added to foods in two major respects. First, FDA must limit the GRAS safety determinations with binding standards and establish an effective enforcement regimen for such standards. Under the current scheme, the GRAS exemption has nullified the food additive petition process under the FAA and rendered the law toothless. To fix this, the current rulemaking should delimit eligibility for GRAS and set clearer requirements for the “general recognition of safety” standard to ensure that “food additives” are subject to the requirements of the FAA.

Second, FDA must make GRAS notifications both mandatory and public. Due to missing data on the composition of the food supply, neither FDA nor the food industry can actually conduct the safety evaluations required by the law for both GRAS substances and food additives. It should also establish a requirement for updated GRAS notifications to monitor the use of chemicals in the food supply, so that the agency, industry and public can use common exposure baselines for chemicals and classes of chemicals.

a. FDA should limit the GRAS concept as Congress intended.

First, FDA must address the limits on GRAS in its rulemaking. The 1997 proposal has nullified the food additive regulatory system under the FAA by allowing GRAS to overtake the “food additive” definition. FDA should narrow the GRAS exemption by issuing a final rule,

³³⁰ R.H.M. Research Limited, *Large scale volunteer trial on mycoprotein (A3/5) (1977)*; R.H.M. Research Limited. *Supplementary studies on subjects who consumed A3/5 mycoprotein in a large scale volunteer trial conducted November/December 1977 (1978)* (Documents on file at the FDA).

binding on future GRAS determinations, that: (1) GRAS cannot apply to novel ingredients since a scientific consensus has not yet developed; (2) GRAS cannot apply to substances flagged as a risk to human health by authoritative scientific bodies; (3) GRAS status must be based on a regulatory definition of “harm,” to be developed by FDA; (4) GRAS determinations must be based on published and peer-reviewed science; (5) GRAS must be evaluated based on adequate science for the chemicals being assessed and their anticipated maximum exposure levels; and (6) GRAS must be determined by experts without conflicts of interest.

i. GRAS cannot apply to novel ingredients since a scientific consensus regarding their safety has not yet developed.

As detailed above, the legislative history of the FAA unambiguously indicates that the GRAS exemption was never intended to apply to novel or “newly discovered” substances. FDA has an affirmative obligation to more narrowly define the scope of the GRAS exemption going forward in order to ensure that all novel food additives are subject to the food additive petition process as intended by Congress in passing the FAA. Neither the existing nor the proposed regulations delineate this category; to maintain consistency with the statute, FDA must promulgate a final rule making clear that novel substances cannot be self-determined GRAS.³³¹ As noted above, courts interpreting an identical legal standard in the drug context have drawn this self-evident and obvious conclusion.³³² To meet the “general recognition of safety” standard in the FAA, GRAS chemicals must be familiar substances whose safe use in the food supply is generally known and well established.

ii. GRAS cannot apply to substances flagged as risks to human health by authoritative scientific bodies or questioned in the scientific community.

In addition to excluding novel additives from the GRAS exemption, FDA must further define the extent of scientific agreement required to meet the GRAS standard. FDA and the courts have interpreted the FAA to require a high level of scientific consensus for a GRAS determination.³³³ However, such consensus has not been required in practice. The standard is a

³³¹ For example, Canada defines a “novel food” in its regulations, in part, as “(a) a substance, including a microorganism, that does not have a history of safe use as a food; (b) a food that has been manufactured, prepared, preserved or packaged by a process that (i) has not been previously applied to that food, and (ii) causes the food to undergo a major change. . . .” C.R.C., c. 870 § B.28.001.

³³² See, e.g., *United States v. An Article of Drug . . . "Bentex Ulcerine"*, 469 F.2d 875, 880 (5th Cir. 1972) (observing that if a substance is generally recognized as safe, one would expect to “find in the medical literature over a period of years support for this premise from wide experimentation and study”); *United States v. Articles of Drug . . . Hormonin*, 498 F. Supp. 424, 431-32 (D.N.J. 1980) *aff'd sub nom. Appeal of Carnrick Labs., Inc.*, 672 F.2d 902 (3d Cir. 1981) and *aff'd sub nom. United States v. Articles of Drug*, 672 F.2d 904 (3d Cir. 1981) (finding that “unawareness of a product among qualified experts precludes a finding of general recognition”).

³³³ 21 C.F.R. 170.30(a) (1997) (GRAS “requires common knowledge about the substance throughout the scientific community knowledgeable about the safety of substances directly or indirectly added to food”); *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 632 (1973) (interpreting “generally recognized” language in the drug context to require “expert consensus” based on “substantial evidence”); *United States v. An Article of Drug Consisting of 4,680 Pails, More or Less, Each Pail Containing 60*

general recognition of safety by competent scientists; a substance cannot possibly be GRAS if it has been identified as harmful by authoritative entities within the scientific community.

In the 1997 proposal, FDA explains that “general recognition” requires consensus in the scientific community without “severe” conflict.³³⁴ This suggests that the “general recognition” standard is not merely whether a scientist compensated by the food industry decides that something is safe; instead, to be GRAS, the safety of a substance is demonstrated by general agreement among the scientific community.³³⁵ To that end, FDA must issue a rule stating that the GRAS exemption cannot apply to any substance whose safety has been called into question by expert authorities. This is essentially a self-executing requirement under the law, regardless of FDA’s role.³³⁶ The statute does not require any agency review or pronouncements on the matter; it simply is the case that GRAS eligibility is unavailable for substances that lack a consensus of safety among knowledgeable experts.

However, given the decades of agency neglect of this clear statutory principle, FDA should acknowledge this limitation explicitly and make clear its meaning: if certain authoritative bodies,³³⁷ such as the U.S. Environmental Protection Agency, the Institute of Medicine, the European Food Safety Authority, the National Toxicology Program, the International Agency for Research on Cancer, or the State of California (or other state authorities), have declared a substance to be a hazard to human health or a carcinogen, the substance cannot be self-determined GRAS, as such a conclusion is definitive proof of serious discord among “knowledgeable experts” and constitutes an absence of a “general recognition” of safety.³³⁸

This does not mean that an additive flagged by an authoritative body is automatically barred from use in foods; it would simply fall within the definition of a food additive under the statute as not GRAS and need to go through the formal food additive petition process to be approved for use in food. This would narrow the GRAS exemption as intended by the statute without requiring additional work by FDA in evaluating the safety of the most-disputed, and potentially dangerous, substances being proposed for entry into the food supply. It would also

Packets, Etc., 725 F.2d 976, 985 (5th Cir. 1984) (“[G]eneral recognition’ requires a two-step showing: first, that there is general recognition in fact, i.e., that there is an expert consensus that the product is effective; and second, that the expert consensus is based upon “substantial evidence” as defined in the Act and in FDA regulations.”); *United States v. Undetermined Quantities of Various Articles of Drug . . . Equidantin Nitrofurantoin Suspension*, 675 F.2d 994, 1000 (8th Cir. 1982) (finding “a genuine dispute concerning the safety and effectiveness of a drug product . . . precludes a finding of “general recognition”) (quoting *United States v. Articles of Drug (Hormonin)*, 498 F.Supp. at 431-32).

³³⁴ 62 Fed. Reg. at 18939

³³⁵ *Id.*

³³⁶ Neal Fortin, *PHOs: Illegal Additives Since 2005*, Food Technology, Nov. 2014, at 92.

³³⁷ FDA has already acknowledged, in the 1997 proposal, the role such bodies can play in *supporting* a GRAS finding. 62 Fed. Reg. at 18941. They should have equal force in disproving a general recognition of safety.

³³⁸ Indeed, FDA has already acknowledged safety conclusions in its decisions in the past, including its proposal to de-GRAS trans fat, which relied on an Institute of Medicine analysis on PHOs. 78 Fed. Reg. at 67,169. FDA concluded that the IOM’s questioning of the safety of PHOs meant that the substance was no longer “generally recognized as safe” in the scientific community. *Id.* FDA should formalize this practice in a final rulemaking.

immediately and definitively bring the intended and much-needed lucidity to the regulatory scheme. For clarity (rather than because it is statutorily required), FDA should also maintain and publish a regularly updated list of bodies and determinations that it explicitly incorporates into this standard and invite the public to submit additional bodies and determinations for its list.

iii. FDA must provide a definition of what constitutes “harm” to human health.

Safety is defined in the regulations as “a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use.”³³⁹ However, there is no corresponding definition of what may be considered “harmful.”³⁴⁰ The examples of mycoprotein and caffeine illustrate an immediate need for a definition of harm that protects vulnerable subpopulations and encompasses transient effects that disrupt the ordinary routines of consumers. The definition of harm should not be interpreted narrowly to mean only effects that require medical intervention. Instead, the definition should include both transient and permanent effects, as well as acute and chronic effects.

Whether or not such adverse effects should prevent use of a substance in foods, it is clear that they raise sufficient questions to preclude a general consensus or “general recognition” of safety in the scientific community. Thus, by failing to define “harm” under its regulations, FDA has provided an additional means of abusing the GRAS concept. FDA should issue a definition of harm that ensures that effects which are transient or affect only vulnerable subpopulations are taken into account when determining the GRAS designation of substances added to foods.

iv. GRAS determinations cannot be based on unpublished research and must instead be based on peer-reviewed, published science.

FDA should also clarify the standard for “general recognition,” to help industry identify the types of substances that cannot fall within the category. General recognition of additive safety requires consensus in the scientific community. Such consensus is impossible to achieve if a chemical’s use is unknown to the scientific community and to FDA. Thus, the general recognition standard necessarily requires a basis in peer-reviewed and published science.³⁴¹ Under the previous regulations, “[g]eneral recognition of safety through scientific procedures shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data and information.”³⁴² The 1997 proposal expanded the language to include “generally available and accepted scientific data, information, methods, or principles, which

³³⁹ 21 C.F.R. § 170.3(i).

³⁴⁰ Beyranevand, *supra* note 26, at 889.

³⁴¹ *United States v. An Article of Drug Consisting of 4,680 Pails*, 725 F.2d at 987 (finding that the substantial evidence required for a general recognition of safety “consists of adequate and well-controlled studies that must be *generally available* to the scientific community”).

³⁴² 21 C.F.R. § 170.30.

ordinarily are published.”³⁴³ This revision elevates unpublished studies from corroboration to primary support.³⁴⁴

To meet the requirements of general recognition, FDA must take steps to ensure that all GRAS determinations are based on published and peer-reviewed studies. That recommendation is supported by comments in the docket submitted by other interest groups; for example, NRDC noted the need for published toxicological and exposure data in making GRAS determinations.³⁴⁵ Thus, in its final rule, FDA should restore the pre-1997 requirements for actual studies, both toxicological and exposure, to support GRAS determinations, and the primacy of published studies in furnishing sufficient evidence. This proposal could be accomplished on the current docket, as FDA’s proposal has been opposed by commenters, and returning to the pre-1997 standard would therefore be a “logical outgrowth” of the pending proposal.³⁴⁶

v. GRAS must be evaluated based on adequate science for the chemical being assessed.

FDA must also strengthen the evidentiary requirements for GRAS determinations. As FDA states in its existing regulations, the standard of safety for GRAS substances is identical to the standard that applies to food additives.³⁴⁷ Therefore, a manufacturer’s decision must be consistent with the food additive regulations and comply with FDA’s guidance on food additive testing, including the Redbook and other relevant sources from the agency. However, this is not the case in practice.

Under FDA guidance, safety evaluations for chemicals added directly to food³⁴⁸ involve assigning the substance to a Concern Level (i.e., low (I), intermediate (II) or high (III)) based on the substance’s toxicological potential predicted from its chemical structure and an estimation of cumulative human exposure.³⁴⁹ Yet, according to Pew, only 1 percent of GRAS notifications even identified a concern level, and most GRAS substances are not tested for safety even with

³⁴³ 74 Fed. Reg. at 18960.

³⁴⁴ This is illustrated by the FEMA letter, which notes that the GRAS determinations for four flavorings made in 2013 were based on no published studies, exposure data, or toxicological data. Letter from NRDC, CSPI, CFS, Center for Environmental Health, and Environmental Working Group to Michael Taylor, Deputy Commissioner for Foods, FDA, Re: Flavors and FEMA GRAS Program (Sept. 18, 2014), at Appendix B (on file with CSPI).

³⁴⁵ NRDC Comment, *supra* note 252, at 2; *see also* International Center for Technology Assessment, *supra* note 249, at 3 (noting need for peer-reviewed published studies).

³⁴⁶ *Env’tl. Integrity Project v. E.P.A.*, 425 F.3d 992, 996 (D.C. Cir. 2005) (“An agency’s proposed rule and its final rule may differ only insofar as the latter is a ‘logical outgrowth’ of the former.”).

³⁴⁷ 21 C.F.R. § 170.30(b) (GRAS status based on scientific procedures “require[s] the same quantity and quality of scientific evidence as is required to obtain approval of a food additive regulation for the ingredient.”).

³⁴⁸ This does not include indirect additives such as those used in packaging.

³⁴⁹ Food and Drug Administration, *Guidance for Industry: Summary Table of Recommended Toxicological Testing for Additives Used in Food* (June 2006), available at <http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm054658.htm>.

FDA's lowest concern level testing recommendations.³⁵⁰ FDA must thus emphasize that the science underlying GRAS safety determinations must be the same as for food additives, and that it will evaluate submissions on this basis.

In addition, as detailed above, FDA's standards for evaluating the safety of additives are severely out of date. In its final rule, FDA must require testing for potential endocrine disruption, behavioral effects, and developmental neurotoxicity, and include additional safety requirements for vulnerable subpopulations (such as infants, pregnant women, the elderly, people with compromised immune systems, diabetes, alcoholism, or food sensitivities, among others). FDA must also require absorption, distribution, metabolism, and excretion (ADME) assessments. These standards should be based on the Redbook and other governmental guidance on modern risk assessment principles and updated on a regular basis to ensure that they track contemporary scientific knowledge. FDA should also provide a clear guide for how to assemble and evaluate the scientific evidence underlying a GRAS determination.

vi. GRAS determinations must be made by experts without conflicts of interest.

The GRAS exemption is meant to apply only where there exists a "consensus" among scientists that the use is generally recognized as safe. Under the 1997 proposal, companies can demonstrate this "consensus" in a variety of ways, such as scientific review articles, expert panels, reports by authoritative bodies, or by some combination of these methods. Problematically, the 1997 proposal treats industry-funded "expert panels" as the equivalent of more public and inherently credible forms of assuring safety, such as determinations by authoritative bodies and peer-reviewed published articles. As a result, food manufacturers often make GRAS safety decisions by relying solely or mainly on their own experts, despite the inherent conflicts of interest.³⁵¹

FDA has not issued any guidance to minimize potential for conflicts of interest for companies to help ensure that the members of their expert panels are independent in their determinations of GRAS status.³⁵² Furthermore, because FDA does not require companies to

³⁵⁰ For example, agency guidelines say that chemicals intentionally added to food should be fed to laboratory animals to identify potential harmful effects, but Pew found that in the majority of cases, industry-determined GRAS chemicals did not undergo this very basic type of testing. Neltner et al. *Data gaps*, *supra* note 224, at 90; *see also* McQuate & Kraska, *supra* note 6 ("The Redbook identifies many tests that may be needed to assess the safety of a food additive; however, most new food ingredients that have successfully emerged from GRAS notifications do not have the full complement of tests presently prescribed by the Redbook.").

³⁵¹ Elizabeth Weise, *Experts who decide on food additives conflicted*, USA Today, Aug. 18, 2013, <http://www.usatoday.com/story/news/nation/2013/08/07/food-additives-conflict-of-interest/2625211/> ("The companies hire a consulting firm to get experts for them and then the experts review the information that's available and then they write a letter to FDA saying this additive should be considered GRAS," says Marion Nestle, a professor of nutrition at New York University. "There are whole companies that are in the business of recruiting scientists to sign off on these things," she says. "That was one of the amazing findings of this paper.")

³⁵² GAO Report, *supra* note 37, at 14.

provide information about independence in their GRAS notices, FDA “does not know whether the determinations of companies’ expert panels are arrived at independently.”³⁵³

FDA regulations also state that GRAS “may be based only on the views of experts qualified by scientific training and experience to evaluate the safety of substances directly or indirectly added to food.”³⁵⁴ However, the agency has never explained how to identify the pool of potential experts that represent the scientific community and ascertain whether they are “qualified” to evaluate the safety of a substance’s use in food.

Thus, the current system thus provides no assurances the safety of GRAS substances are actually “common knowledge,” as required by law – and conflicts of interest are ubiquitous.³⁵⁵ As FDA’s Michael Taylor acknowledged to *The Washington Post* in August 2014, saying with regard to a company’s self-determination of EGCG’s safety (see, *infra*, at 55):

“This is the opposite of what the over[s]ight [sic] law intended,” the FDA’s Taylor said. “Although informing the FDA is voluntary,” he said, “the law was meant to increase public scrutiny of additive safety by encouraging companies to publish their science in academic journals.” . . . “The assessments need to be based on publicly available information where there is agreement among scientists,” he said. “It has got to be more than three employees in a room looking at information that is only available to them.”³⁵⁶

This 1997 system does not ensure that so-called GRAS substances are actually “generally recognized” as safe under the law. This is inconsistent with published case law on the identical standard in the drug context, which states that the evidence required for a general recognition of safety “does not consist of the expressed opinions of experts hired to testify on behalf of one party or the other.”³⁵⁷

The agency has indicated an interest in undertaking such a review of policy on conflicts.³⁵⁸ Rather than issuing more toothless voluntary guidance, however, FDA should publish its policy as part of a binding rule. The issue is central to the credibility of GRAS determinations and deserves treatment as such.

As mentioned in the GAO report, the devastating review by Pew of conflicts issues, and by other commenters to this docket, the notion that regulated industry is well equipped to undertake an objective scientific study of the very products it is seeking to bring to market is

³⁵³ *Id.* at 15.

³⁵⁴ 21 C.F.R. § 570.30.

³⁵⁵ GAO Report, *supra* note 37, at 15 (noting that the small community of experts means that panels inevitably have corporate or financial affiliations that could bias their decisions).

³⁵⁶ Kindy, *supra* note 5.

³⁵⁷ *United States v. An Article of Drug Consisting of 4,680 Pails*, 725 F.2d at 987.

³⁵⁸ McQuate & Kraska, *supra* note 6 (noting that FDA indicated a commitment to issuing guidance on conflicts of interest by end of 2014).

naïve at best and dangerous to consumers at worst.³⁵⁹ Recent research documents significant effects related to funding bias in the outcomes of studies, and industry sources of funding for research have been found to have significant impacts on outcomes of studies.³⁶⁰ Bias is apparent not only in outcomes, but in the myriad decisions that go into the categorizations and questions asked, and the multiple other informed judgments that shape study design.³⁶¹

This is a particular problem with regard to the secret GRAS process. Funding bias is both inescapable and utterly unchecked in such a system. For these reasons, it is incumbent upon the agency to craft a system of oversight for GRAS self-determinations that does the most it can do, given the industry's clear interests and its role as a source of funding for these studies, to counteract the funding bias that would otherwise undermine the integrity of the GRAS program.

Pew, with input from multiple reviewers and stakeholders in a public August 2013 workshop of experts, advocates and industry participants, drafted guidance on avoiding conflicts of interest in GRAS evaluations and submitted it to the current docket on September 4, 2013.³⁶² We recommend that FDA adopt the suggestions from the Pew guidance document submitted to this docket in 2013 as a binding final rule.³⁶³ These measures, made enforceable and with the agency's active oversight, would help to ensure that experts have necessary expertise, are sufficiently removed from the issue to ensure objective assessment of scientific consensus, and do not have financial or non-financial conflicts of interest.

We further recommend that FDA require any company that conducts a GRAS determination to provide FDA and the public with critical information about the experts who participated in making the determination, their sources, and their findings, as well as compensation arrangements. The need for this part of the final rule is articulated by other comments on the docket, which asserted that GRAS notices should include information demonstrating the independence of experts who generate data or analysis underlying the GRAS finding, as well as the Pew guidance draft.³⁶⁴

In addition, FDA must establish an active role in monitoring and evaluating the sufficiency of steps taken to address conflicts of interest in GRAS determinations. As noted above, the literature on funding bias is clear and shows the skewing effect of funding relationships upon outcomes; the current GRAS system is far worse than the research on general bias, which concerns peer-reviewed, published study outcomes, and demonstrably rife with both actual and potential conflicts. FDA therefore should develop objective measures for bias in

³⁵⁹ GAO Report, *supra* note 37, at 34 (calling on FDA to “[m]inimize the potential for conflicts of interest in companies’ GRAS determinations, including taking steps such as issuing guidance for companies on conflict of interest and requiring information in GRAS notices regarding expert panelists’ independence”)

³⁶⁰ See sources cited *supra* note 287.

³⁶¹ David Michaels, *It's Not the Answers That Are Biased, It's the Questions*, The Washington Post, July 15, 2008, <http://www.washingtonpost.com/wp-dyn/content/article/2008/07/14/AR2008071402145.html>.

³⁶² Pew Charitable Trusts, *Draft Guidance for Industry*, *supra* note 237.

³⁶³ *Id.*

³⁶⁴ Food & Water Watch, *supra* note 246, at 3; Hansen, *supra* note 247, at 5.

outcomes based on the funding bias literature, monitor conflicts in GRAS determinations to assess such bias, and publish its findings in a public report.

Should adoption of a binding, mandatory regime of disclosure and substantive checks on conflicts prove to be insufficient to address bias in outcomes, FDA must develop a more proactive approach to preventing predictable conflicts of interest. Either through its existing regulatory authority or by soliciting authority from Congress, it should establish a group of credentialed and independent expert reviewers for GRAS notifications, funded by pooling industry user fees, and base GRAS determinations on their reviews. *Ex parte* communication and funding between the pool of experts and the food industry should be barred. As the Pew report identifies, this is the gold standard for safety. There is considerable doubt that any industry-funded process – however well monitored by FDA – could produce unbiased scientific determinations sufficient to assure public safety.

b. FDA must require public notice of GRAS determinations to assure that the burdens of general recognition and ongoing assessment of safety are met.

Even these appropriate limits on the GRAS category will not provide meaningful protection to the public health unless FDA is notified about such substances. In addition to limitations on what may be found GRAS, FDA must make changes to the system to facilitate ongoing assessment and oversight over existing GRAS substances as intended by Congress under the FAA. To achieve these ends, FDA must: (1) make GRAS notifications mandatory; (2) require public notice of all GRAS determinations; (3) require regular submission and public notice of updated and public exposure assessments; and (4) require documentation and recordkeeping of GRAS determinations.

i. To achieve Congress’s intent under the FAA, GRAS notifications must be mandatory.

Under FDA’s proposed notification system, a majority of “food additives” are never declared to the agency. Without knowledge of “GRAS” substances currently in use, FDA cannot execute its ongoing oversight over substances added to foods as intended by Congress in passing the FAA. Moreover, no “general recognition of safety” standard can be satisfied where exposure data is unknown.

As detailed above, Congress intended FDA to undertake an ongoing review of all substances added to foods to ensure they remained safe in the face of updated science and exposure.³⁶⁵ Congress was clear that GRAS status could always change in light of new information on safety and risks. Moreover, the legislative history of the FAA indicates that this

³⁶⁵ 104 Cong. Record, 85th Cong, 2d Sess. 17412, 17420 (Aug. 13, 1958) (Letter from John L. Harvey, Deputy Commissioner of FDA) (explaining that “if later developments show that a substance previously considered safe because of common use in food were, in fact, subject to question and not generally recognized as safe, then the substance would become subject to the definition of a food additive and would have to be cleared under the procedures of the proposed law”). This has been recognized by FDA in its regulations, which state that [n]ew information may at any time require reconsideration of the GRAS status of a food ingredient.” 21 C.F.R. § 170.30(k)(1) (2012).

was precisely the type of oversight role that Congress intended FDA to develop – to monitor the potential risks related to long-term exposure of substances added to foods. However, the lack of required notification under the current system makes this, practically speaking, impossible, as FDA is only made aware of substances when and if industry chooses to submit a voluntary notification.

Moreover, even with respect to GRAS substances about which industry has notified the agency, FDA is unable to assess the risks because it is unaware of actual usage and exposure, of studies and adverse events that indicate possible (and previously unknown) adverse health impacts, or of data for classes of chemicals or chemicals that act similarly in the body. Because FDA lacks basic information needed to assess the safety of thousands of chemicals currently used in food, it cannot fulfill its statutory obligation to make ongoing reevaluations of the safety of such substances.

FDA’s proposal for a voluntary notification system certainly allows the agency to review some GRAS determinations; however, because it is not mandatory, this review is limited. FDA generally will not be alerted to “secret” GRAS substances in the marketplace or their dietary exposure.³⁶⁶ This means that once a secret GRAS substance has entered the marketplace, FDA would find it difficult to identify that substance as the potential source of a food safety problem.³⁶⁷ By making GRAS notifications voluntary, FDA is “relinquishing a vital component of its important role in food safety oversight [and] creating a situation in which public oversight of food additives is virtually impossible.”³⁶⁸

The lack of notification also makes it difficult or impossible for FDA to make ongoing safety assessments. FDA has claimed at times that it can address safety concerns that arise post-marketing by responding to concerns raised by the public or industry. In theory, information brought to the agency’s attention could prompt the agency to reconsider the safety of a GRAS substance, as it has done with PHOs. However, this mechanism fails under the current system in several respects. First, it is entirely reactive – safety is only assessed after a danger has arisen and the public has already been exposed to its risks. This is directly contrary to the purpose of the law, which was intended to fix a system in which risks could only be identified after substances were already sold to consumers. Second, industry and the public cannot alert FDA to safety concerns when they are not aware of those concerns themselves. This is particularly problematic given that these ingredients may or not be listed on labels (or listed under unfamiliar names), making it difficult for anyone to link their exposure to adverse effects.

We thus agree with GAO’s conclusion that “FDA’s oversight of additive safety would thus be improved if companies were required to make the agency aware of their GRAS

³⁶⁶ For example, officials representing one international marketer of food indicated the company makes about 5 GRAS determinations each year without notifying FDA. These are usually new uses of substances that have been deemed GRAS for other uses. In another case, a company began marketing a purified version of stevia, a plant-based sweetener, as a GRAS substance before submitting a notice to FDA and before FDA had indicated it had no questions about other GRAS notices related to stevia. GAO Report, *supra* note 37, at 12.

³⁶⁷ *Id.* at 12.

³⁶⁸ International Center for Technology Assessment, *supra* note 249, at 1.

determinations” because it would provide FDA with at least some information about GRAS substances to help with investigations of food safety problems that may arise after such substances have already been marketed.³⁶⁹ Consumers Union similarly found that “companies, at a minimum, should be required to notify FDA of any GRAS determinations they make.”³⁷⁰ We urge the FDA to heed our concerns, shared by the GAO and Consumers Union, and make GRAS notifications mandatory. Only mandatory notification would enable FDA to meet its obligations under the FAA to maintain ongoing oversight over GRAS substances in order to ensure their continuing safety in the face of developing science and exposure levels.

ii. Mandatory notifications must include accurate and current exposure data.

Under the current regulations, GRAS status based on scientific procedures “require[s] the same quantity and quality of scientific evidence as is required to obtain approval of a food additive regulation for the ingredient.”³⁷¹ The 1997 proposal clarified that a GRAS substance is “neither more safe nor less safe than approved food additives.”³⁷² For food additives, “safe or safety” means “a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use.”³⁷³ In making this determination, the agency must consider the probable consumption of the substance and its cumulative effect in the diet, taking into account any chemically or pharmacologically related substance or substances in such diet.³⁷⁴

The law, regulations, and guidance make clear that a GRAS determination requires an exposure assessment based on the probable consumption of the substance and its cumulative effects. As risk a function of both hazard and exposure, any “general recognition of safety” cannot be determined without knowledge of exposure. However, without required notice of GRAS determinations, the probable consumption of the substance and its cumulative effects cannot be measured by experts, industry, or FDA – and the safety of the substance cannot be “generally recognized.” To achieve the requirements and purpose of the statute, FDA and industry must be able to estimate dietary exposure for all GRAS substances.

Thus, FDA must require companies to publicly submit exposure data along with their GRAS determinations. A finding of general recognition of safety requires consensus in the scientific community based on accurate toxicology and exposure data, including natural exposure. General awareness of the substance and its exposure can only be achieved when FDA is notified by industry about the use and existence of GRAS substances, and their overall dietary exposure. To facilitate accurate exposure data and ongoing safety reassessments, FDA also must require companies to regularly update their exposure assumptions in light of new information and to assert under law that no new scientific information or adverse events reported by

³⁶⁹ GAO Report, *supra* note 37, at 12.

³⁷⁰ Hansen, *supra* note 247, at 1.

³⁷¹ 21 C.F.R. § 170.30(b).

³⁷² 62 Fed. Reg. at 18942.

³⁷³ 21 C.F.R. § 170.3(i).

³⁷⁴ 21 U.S.C. § 348(c)(5); 21 C.F.R. § 170.3(i).

consumers related to that substance have come to light, particularly with regard to potential health harms.³⁷⁵

This requirement is supported by prior comments to the docket. For example, NRDC recommends that a GRAS safety assessment include published exposure assessments.³⁷⁶ Food & Water Watch states that companies should be required to submit exposure data in their GRAS determinations so that industry, FDA, and citizens can make a comprehensive assessment of the safety of substances.³⁷⁷ In its final rule, FDA should also outline a mechanism the agency will employ to corral and standardize exposure estimates for GRAS substances that are of potential public health concern.

Finally, FDA should require notifiers to provide regular updates of exposure and safety data. Under the current regulations, “FDA does not know to what extent, or even whether, companies track evolving scientific information about substances they have determined to be GRAS.”³⁷⁸ FDA should thus require companies to periodically update their exposure assumptions in light of new information in the database and to assert under law that no new scientific or consumer safety information related to that substance has come to light. In particular, FDA should require submitters to disclose adverse studies and information in GRAS notifications as the regulations specify that an assessment of the safety of a food substance involves “an evaluation of information about its safety and functionality including *all* studies and tests of a food additive on animals and humans and all studies and tests of a food additives for identity, stability, purity, potency, performance and usefulness.”³⁷⁹

iii. Mandatory GRAS notifications must be public.

In addition to requiring submission of notification and exposure data, FDA should also require public notice of all GRAS notifications and the information provided therein. GRAS determinations made without notice to the agency (of which there are many) remain outside a third party’s independent evaluation, because they are not made aware of its use or existence. Academic experts, consumer groups, and scientific organizations do and should play an important role in helping FDA oversee the safety of GRAS ingredients; indeed, independent scientific research has contributed to FDA’s reconsideration of GRAS substances in the past.³⁸⁰ As GAO noted, “without knowledge of companies’ GRAS determinations, third parties, such as the ones that have filed citizen petitions in the past, do not have the opportunity to investigate the

³⁷⁵ This requirement should apply to food additive petitions as well as GRAS notifications, for related reasons.

³⁷⁶ NRDC Comment, *supra* note 252, at 2.

³⁷⁷ Food & Water Watch, *supra* note 246, at 3.

³⁷⁸ GAO Report, *supra* note 37, at 25. For example, representatives of one company told GAO that while they review the status of their GRAS ingredients and keep up with the scientific literature, they do not generally share these finding with FDA. *Id.*

³⁷⁹ 21 C.F.R. § 171.1 (h(4)).

³⁸⁰ GAO Report, *supra* note 37, at 24. In addition, third party information may affect FDA decisions on the GRAS notifications it *does* receive; under the proposed regulations, FDA may question a GRAS notification if it is “aware of information that is not included in the notice but raises important public health issues.” 62 Fed. Reg. at 18,950.

potential health effects of such GRAS substances, leaving an additional gap in the oversight of their continued safety.”³⁸¹

As the ICTA pointed out in its 1997 comments, the current system “mak[es it] virtually impossible for the public to fill the gaps left by the agency’s abdication of oversight review.”³⁸² With “no easily accessible collection of data made available to the public,” making it difficult for FDA, additive manufacturers, and public interest groups to monitor food safety. Furthermore, given the lack of information provided to FDA, FOIA requests will yield limited information because relevant documents remain with the producers. This is illustrated by CSPI’s FOIA requests with regard to taste modifiers and caffeine. For taste modifiers, FDA was unable to provide any information for some substances, and extremely limited information on the others. Regarding caffeine, the only reason CSPI could obtain any information at all was because FDA had conducted its own inquiry. The companies had not submitted any GRAS determination data voluntarily. This is particularly troubling given FDA’s insistence that it makes GRAS reassessments in response to concerns raised, in part, by the public interest community.³⁸³ Thus, to facilitate ongoing oversight over GRAS substances, FDA must require industry to submit public notice of its GRAS determinations and exposure data in its final rule.

FDA should also require companies to maintain active and accurate registrations for GRAS substances in a public database in order to better track exposure data. This proposal is supported by GAO, which recommended in its report that FDA issue regulations requiring any company that conducts a GRAS determination to provide FDA with basic information about this determination, such as the substance’s identity and intended uses, and to incorporate such information into relevant agency databases and its public Web site. Such public, consolidated disclosures will enable FDA, GRAS notifiers, and the interested public to assess the safety of new GRAS chemicals and proposed food additives based on accurate and current cumulative exposure estimates.

iv. FDA should require manufacturers to maintain proper documentation to support their GRAS determinations.

In its 1997 proposal, FDA stated that it would be prudent for companies to maintain documentation of their GRAS determinations and suggested that FDA would monitor compliance by conducting random audits of data and information maintained by the companies.

³⁸¹ GAO Report, *supra* note 37, at 24. Even when outside groups are made aware of GRAS substances and call attention to safety concerns, FDA has failed to respond to such concerns. While FDA claims that information brought to its attention could prompt the agency to reconsider the safety of a GRAS substance, it has historically not responded to the concerns of individuals and consumer groups. For example, FDA has largely not responded to the concerns raised through 11 citizen petitions submitted between 2004 and 2008. Nine of these 11 petitions raised specific concerns about the safety of GRAS substances or the way they are used in food. As of 2012, FDA had only responded to 3 of these petitions – all denials. Monica Eng, *Citizen complaints not addressed by FDA*, Chicago Tribune (Aug. 25, 2012), http://articles.chicagotribune.com/2012-08-25/health/ct-met-food-ingredients-popcorn-20120825_1_microwave-popcorn-fda-citizen-petitions.

³⁸² International Center for Technology Assessment, *supra* note 249, at

³⁸³ GAO Report, *supra* note 37, at 21.

In practice, FDA has never conducted such audits and thus has no way of ensuring that industry conducts proper recordkeeping.³⁸⁴ Moreover, FDA has never explained what the proper level of documentation would be.³⁸⁵ In finalizing the rule, FDA should develop criteria for the required documentation underlying industry GRAS determinations. As FDA indicated an intention to conduct random audits in the 1997 proposal, specifying rules for documentation would be a reasonable outgrowth of the proposed rule. In addition, the agency should renew its commitment to random auditing to ensure that companies maintain proper recordkeeping practices, and that company records reflect data in FDA notifications.

c. FDA's Final Rule should outline a comprehensive safety program.

In addition to fixing the process for GRAS substances moving forward, FDA must address the secret GRAS determinations it has illegally permitted to enter the food supply. To that end, it must bring them out of the shadows and classify them. There are many possible ways to address the data gaps that FDA has created – and allowed industry to create – since 1997 and prior. The food industry, recognizing the system's clear weaknesses, has begun its own approach, including developing a database, compiling safety information, and developing standards.³⁸⁶ However, the law requires FDA to assure the safety of the food supply, and it is both technically feasible and legally imperative that it take charge of any such endeavor. To demonstrate that fixing the program is both possible and desirable, we propose some steps below that the agency could take. We anticipate that development of a remedial program will be a public process, and welcome ideas that assure public safety and secure the goals of the law.

To address the holes in the current system, FDA's final rule should require submissions of GRAS self-determinations in a reasonable time, with penalties for noncompliance, from all food chemical manufacturers and food industry end users regarding their heretofore secret GRAS self-determinations. These submissions should include the toxicological and exposure data underlying these determinations. FDA should review the sufficiency of this documentation and terminate the GRAS status of facially inadequate notifications, after a reasonable back-and-forth with submitters, referring them instead, if appropriate, to the food additive petition process.

For substances in the current GRAS notifications database, FDA should require submitters of substances that withdrew notices, or received an "insufficient basis" letter from the agency, to notify FDA by a date certain about their use of that substance or other self-determined GRAS substances and to submit appropriate documents regarding their safety determinations. For submitters that received a "no questions" letter, FDA could prompt submitters to fill any needed data gaps in submissions by a date certain to align submissions with the revised documentation requirements. Previously completed GRAS affirmation or food additive petitions should also be updated by companies according to the new documentation requirements.

All of these data should be incorporated into a modernized, centralized database. FDA should also incorporate the data into a centralized data management system, such as the Chemical Evaluation and Risk Estimation System (CERES), and use these databases to prioritize

³⁸⁴ *Id.* at 17.

³⁸⁵ *Id.*

³⁸⁶ *See* note 6 *supra*.

toxicology and exposure data gaps and safety concerns, as it indicated it would do in the 1997 proposal. Once it has acquired use and exposure data, FDA will be able to identify and respond to potential safety issues, including the long-term effects of substances and the potential cumulative impacts of substances in combination with each other.

Most critically, the agency's rulemaking could create and publish for comment a system of risk-based review priorities for a combined database of GRAS and food additives. This would, as the 1997 rule promised, direct FDA's application of resources to the riskiest substances in the food supply and equip the agency to assess the factors directed in the statute to determine safe use. FDA should address the concern levels as follows:

- For substances or uses above a specified risk concern level, based on the database, FDA should clarify that the substance or use is not GRAS and require the notifier to use the food additive petition process.
- For classes of GRAS chemicals that pose risks to human health when their use exceeds a certain level above current exposure, FDA should use the data to assess and harmonize exposure levels as required by the law, for agency and industry use in notifications. FDA should ask the food industry to submit an updated, but simplified, set of data that would be needed to compute cumulative effect and probable consumption levels for those substances, if the agency lacks such data. FDA should compute naturally occurring exposures as well. These estimates should also be subject to public comment. Should overall exposure exceed a specified level of concern, FDA should open a public rulemaking on the GRAS status of that chemical or class of chemicals.
- Finally, for the lowest risk substances, FDA should compile and publish an updated list of clearly non-hazardous GRAS substances based upon its review of ingredient lists and industry and public submissions.

In addition, FDA should develop specific standards with regard to substances with novel toxicology or that pose unique risks, for example, substances whose effects are not linear to dose (such as endocrine disruptors), that pose specific concerns for vulnerable subpopulations, or that pose risks in combination with other chemicals. The final rule should establish particular testing requirements for such substances, as appropriate.

The database of secret GRAS substances and supporting documentation, like the GRAS notification and affirmation processes, should be published, so that the public may assist the agency in prioritizing the investigation of chemicals according to the exposure and risks to public health, as the law intended. To keep these determinations current, FDA should ask for ongoing public comments on which currently listed substances on GRAS lists are potentially hazardous and should be reassessed. FDA should also assign a schedule for expiration of substances and require renewal of notifications on an appropriate and periodic basis.

VII. Conclusion: FDA Can and Should Solve the GRAS Problem

The 1997 proposal undermines the goal of the FAA: to protect public health. It fails to ensure the safety of new or existing GRAS substances and allows food additives masquerading as GRAS to avoid the agency's oversight. FDA's current system for GRAS is thus an abrogation of its responsibilities under the FAA, and undermines consumer confidence in food additive safety. If FDA were to finalize the rule as proposed, it would be a failure of its statutory responsibilities; it must instead take this opportunity to revise the proposal in order to create a regulatory system that meets the requirements under the statute.

Taken together, the changes we urge would transform the GRAS system from badly broken to functional. FDA's regulation of GRAS has waxed and waned since the 1958 Amendment, and our proposal provides an effective, even elegant, solution. Independent determinations of the safety of substances in the food supply would remain, but would come out of the shadows into the public eye, where they belong. By reasserting its legitimate power over the scope and substance of safety determinations with reasonable definitions and requirements, FDA could restore the rightful position of GRAS in the statutory scheme and reestablish public confidence in the agency's oversight. These changes would accomplish what FDA hoped for – and failed to achieve – in its 1997 proposal. More importantly, they would equip the agency with tools to effectively monitor public exposures and to analyze evolving questions impacting public health in real time and proactively, just as Congress intended.