Regulation of Added Substances in the Food Supply by the Food and Drug Administration Human Foods Program

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The US food supply is increasingly associated with diet-related diseases, toxicity, cancer, and other health harms. These public health concerns are partly attributable to a loophole in federal law.

The Food and Drug Administration (FDA) evaluates the premarket safety of ingredients regulated as food additives but allows the food industry to self-regulate and determine which substances to classify as generally recognized as safe (GRAS) based on undisclosed data and conclusions that the FDA never sees. Furthermore, the FDA lacks a formal approach for reviewing food additives and GRAS substances already found in the food supply. Substances in the food supply thus include innocuous ingredients (e.g., black pepper), those that are harmful at high levels (e.g., salt), those that are of questionable safety (e.g., potassium bromate), and those that are unknown to the FDA and the public.

A recent court decision codified these gaps in the FDA's current approach, leaving states to try to fill the regulatory void. The FDA and Congress should consider several policy options to ensure that the FDA is meeting its mission to ensure a safe food supply. (*Am J Public Health*. Published online ahead of print August 8, 2024:e1–e10. https://doi.org/10.2105/AJPH.2024.307755)

The Food and Drug Administration's (FDA's) mission includes protecting the "public health by ensuring that foods are safe, wholesome, sanitary, and properly labeled."[1] Yet concerns have been raised that, because of weak statutory requirements, the FDA's interpretation of its authorities, and lack of sufficient funding, the FDA's oversight for ingredients in our food supply is inadequate to ensure a safe and wholesome food supply.[2–4]

The Federal Food Drug and Cosmetics Act (FDCA) distinguishes between—but does not clearly define—substances that are considered food additives and those that are deemed generally recognized as safe (GRAS). Both categories include complex chemical substances, but their regulatory frameworks are quite different. Food additives are subject to FDA premarket review because they are presumed to be unsafe. Consequently, foods containing food additives are considered adulterated unless the use of the substance complies with an FDA regulation prescribing the conditions of safe use.[5] By contrast, GRAS substances are presumed to be safe and thus exempt from such requirements. This exemption allows the food industry to define a wide array of new substances as GRAS and introduce them into the food supply without FDA or public knowledge of their existence, use, or safety.

A stark example of the FDA's regulatory gap was seen in October 2023, when California banned 4 substances from being used as ingredients in food sold or manufactured in the state.[6] These substances are banned in Europe because of their association with an increased risk of cancer and other health, behavioral, developmental, and reproductive harms.[6] A month later, the FDA proposed revoking the approved food additive status for 1 of the 4 substances banned in California: brominated vegetable oil (BVO).[7] BVO was considered GRAS decades ago.[7] In 1970, the FDA determined that BVO was no longer GRAS and designated it as an approved food additive.[7] After this reclassification, BVO remained in food products such as Gatorade and Mountain Dew, while science mounted questioning its safety. It was not until California banned BVO that the FDA

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announced it was taking action, leaving questions on how proactive the FDA is over ingredients already in the food supply.

Indeed, a 2021 court case, *Center for Food Safety v Becerra* (*Center for Food Safety*), highlighted that GRAS substances are not necessarily safe and that ingredients already in the food supply are not regularly reexamined for safety.[8] Although the FDA has clear authority to take postmarket action, the FDCA does not provide the FDA with a clear or well-resourced pathway to systematically review food additives or GRAS substances already in the food supply. As a result, foods contain ingredients that may be harmful in high doses (e.g., salt), are of questionable safety (e.g., nonnutritive sweeteners), or are unknown to the FDA or the public.

Concerns about ingredients in the US food supply have been increasing in recent years.[9] In 2022, at the FDA's request, the Reagan–Udall Foundation released a report noting the need for the FDA to adapt to a changing food supply, including increasing its oversight of the chemicals in food.[9] In response, the FDA announced a restructuring of its Human Foods Program to improve and coordinate its prevention and response activities. As part of these new efforts, in May 2023, the FDA announced that it was "embarking on a more modernized, systematic reassessment" of chemicals in the food supply "with a focus on postmarket review."[10] The proposed activities are crucial. However, the announcement raises questions about how the FDA will accomplish such an evaluation and, perhaps more critically, how ingredients make their way into the food supply in the first place and whether the FDA is aware of all of the ingredients that should be subject to this postmarket review.

We set forth the history of the GRAS notification and food additive approval processes and examine the decision and implications of *Center for Food Safety*, which solidified the FDA's anemic GRAS oversight. (Color additives are treated under a different framework, and we do not address them.) We conclude with recommendations for future action for the FDA to achieve its duty of ensuring a safe food supply.

FOOD ADDITIVES AND GRAS SUBSTANCES

Congress passed the Food Additives Amendment of 1958 to establish a rigorous statutory scheme for the FDA to review and approve food additives before they go to market.[11] An entity seeking to introduce a food additive into the food supply petitions the FDA requesting that the FDA promulgate a regulation prescribing the conditions under which the substance may safely be used.[2,11] The FDA evaluates the petition in light of scientific data to determine whether the data demonstrate that the food additive is safe—using the standard of "a reasonable certainty of no harm"—for the proposed conditions of use.[12] If the FDA believes it is safe, it publishes a draft regulation in the Federal Register for public notice and comment.[2,12] Consequently, for food additives, the FDA must go through a full regulatory process that requires a transparent demonstration of safety before approval.

By contrast, the Food Additives Amendment of 1958 carved out GRAS substances as those that are "generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures" to be safe under the conditions of its intended use or, for a substance used in food before 1958, through experience based on common use in food (e.g., salt, pepper).[11] The separate designation for GRAS was designed to permit substances commonly used in food to remain in the food supply without the necessity of companies supplying evidence to prove safety and the FDA using its finite resources to review such data.[2] GRAS substances are thus explicitly exempted from food additive regulations and therefore the FDA's current premarket review process.

However, for the decade or so after passage of the Food Additives Amendment, the FDA exercised rigorous oversight over GRAS substances and published and updated a list of all existing and new substances considered GRAS in the Code of Federal Regulations.[13] But in 1972, the FDA began using a voluntary GRAS affirmation process in which manufacturers had the option to voluntarily submit a GRAS affirmation petition with data for FDA review.[2,13] When submitted, the FDA would publish a notice and request for comments and then issue its GRAS determination on the substance.[2] During this period, concerns arose about the safety of cyclamate salts, which were in the food supply. President Richard Nixon directed the FDA to review the safety of GRAS substances already in the food supply.[2] The FDA worked with an independent scientific organization to conduct a safety review of 422 substances from 1972 to 1982, but then the agency did not adopt the recommendations of the committee.[2]

In 1997 the FDA proposed a rule to replace the GRAS voluntary affirmation process with a voluntary notification process "whereby any person may notify the FDA of a determination that a

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particular use of a substance is GRAS."[14] Although the rule was not formally finalized until 2016, the FDA has operated under this proposed rule since 1997 (Table 1 provides a timeline of relevant activities).

Under the GRAS notification rule, manufacturers have the choice of either engaging in "self-GRAS" or submitting a notification. Through self-GRAS, a company is supposed to determine through their own internal research that an ingredient is GRAS, and then they can market the food with the ingredient without any notification to—or oversight by—the FDA.[15] Alternatively, companies can go through the more onerous process of submitting a GRAS notification to the FDA describing the substance, the applicable conditions of use, and the basis for the GRAS determination (i.e., common use in food or scientific procedures) before using the ingredient. The company then waits for the FDA to issue either a "no question letter" stating that it does not question the company's GRAS decision—allowing the company to go to market with this letter—or an "insufficient basis" letter—meaning the FDA finds insufficient information to substantiate the GRAS claim, suggesting the company can submit additional data.[16] If a company submits a GRAS notification but then chooses to withdraw it, the FDA issues a "cease to evaluate" letter, and the company can still go to market with the substance.[2,3]

Thus, in practice, a strong impetus exists for the food industry to self-GRAS so it can manufacture and market food products with new substances without ever notifying the FDA of either its determination or the research underlying its determination that the substance is safe.[2,3,16] Moreover, if the food industry actually notifies the FDA that it considers a new substance to be GRAS, the FDA does not need to engage in its own research to confirm the industry's conclusions or the ingredient's safety.[16]

Another result of the self-GRAS allowance is that a company may self-GRAS an ingredient that otherwise should be considered a food additive subject to the FDA's premarket oversight. Therefore, numerous ingredients that should be appropriately regulated as food additives are likely in the food supply through the self-GRAS mechanism. Indeed, research published by Neltner et al. found that between 1990 and 2010, an estimated 1000 manufacturer ingredient-safety decisions were never reported to the FDA or the public.[17] An industry panel of experts (known as a "GRAS panel") determined an additional 2702 ingredients to be GRAS.[15] Since this review was completed back in 2011, there are likely numerous more ingredients in the food supply that have never been reviewed by the FDA and that are of unknown safety to the FDA and the public.

CENTER FOR FOOD SAFETY V BECERRA

After the FDA finalized its GRAS rule in 2016, nonprofit organizations sued the FDA, arguing that the rule violates the FDCA and that the agency abdicated its responsibility to ensure a safe food supply and unlawfully delegated its duties to the food industry through the self-GRAS mechanism.[8] In 2021, a federal district court upheld the FDA's final rule in *Center for Food Safety*, finding that the FDA did not unlawfully delegate its authority over food safety to private parties and that the rule does not violate the FDCA.[8]

According to the court, because the FDCA is "silent" on the question of whether GRAS notifications must be mandatory, the FDA's allowance for voluntary notification was a reasonable interpretation of the statute.[8] The court thus deferred to the FDA's interpretation of its authority under what is called the *Chevron* doctrine, which is when a court provides deference to an agency's interpretation of its own authority under an ambiguous statute.[8] The court reasoned that because the FDCA sets forth a rigorous scheme for food additive approvals—and GRAS substances were specifically exempt from that scheme—it was within the FDA's authority to adopt a voluntary notification system for GRAS substances.[8]

In terms of the self-GRAS determinations themselves, the court explained that self-GRAS conclusions must be based on "the same quantity and quality of scientific evidence as is required to obtain approval of a food additive," which is "based upon the application of generally available and accepted scientific data, information, or methods" or "common knowledge throughout the scientific community."[8] However, it found that this requirement does not translate into a need for self-GRAS determinations to be based on published studies, nor are companies required to publicly disclose the basis for their self-GRAS decisions.[8] The court highlighted that the FDA retains the postmarket power to disagree with manufacturers' self-GRAS determinations and bring enforcement actions.[8]

Yet, as the plaintiffs noted, the FDA's ability to bring postmarket enforcement is complicated by the voluntary GRAS notification process, which allows industry to add new substances to food without the FDA's knowledge. The FDA is thus hindered from using its

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TABLE 1— Timeline of Key Actions Related to the US Food and Drug Administration's Generally Recognized as Safe and Food Additive Substances Regulations

1958	Congress passes the Food Additives Amendment of 1958, establishing the current framework for food substances that are GRAS or food additives
1961	FDA amends its regulations to include a list of food substances that are GRAS under certain conditions of use
1969	FDA removes cyclamate salts from its GRAS list as a result of safety questions
1969	President Nixon directs the FDA to make a critical evaluation of the safety of GRAS food substances
1970	FDA starts its critical review of the GRAS process and finds it to be resource intensive
1972	FDA conducts rulemaking to establish the affirmation process to affirm the GRAS status of substances that are subject to GRAS review
1977	FDA approves caffeine as a GRAS substance when used in cola-type beverages at 0.02%
1978	CSPI submits a citizen petition to the FDA requesting it to revoke the GRAS status of salt
1982	FDA holds "GRAS Safety Review of Sodium Chloride" and declines to regulate salt using its GRAS/food additive authority but announces its policy of encouraging food manufacturers to voluntarily reduce sodium in processed foods and notes that it is proposing a sodium-labeling regulation
1984	FDA proposes and finalizes labeling regulations to define terms such as "sodium free," "low sodium," and "reduced sodium," among other acts (effective July 1, 1986)
1990	Congress passes NLEA, which requires the disclosure of the nutrition facts label and ingredient list on packaged food
1993	FDA promulgates regulations to carry out the NLEA
1996	FDA promulgates a regulation affirming high fructose corn syrup is GRAS
1997	FDA proposes a rule to replace the GRAS affirmation process with a GRAS notification process and starts functioning under this proposed rule
2003	FDA promulgates a final rule requiring trans fatty acids be declared in the nutrition facts label of foods (effective January 1, 2006)
2004	CSPI submits a citizen petition to the FDA to revoke the GRAS status of PHOs and declare PHOs as food additives
2005	The IOM suggests limiting consumption of artificial trans fat to as low as possible
2005	CSPI submits a citizen petition to the FDA requesting it revoke the GRAS status of salt
2007	FDA holds a public hearing on CSPI's 2005 petition requesting it to revoke the GRAS status of salt
2009	Fred A. Kummerow, trans fat researcher, submits a citizen petition to the FDA requesting the FDA ban partially hydrogenated fat from the food supply
2010	The IOM issues a report on strategies to reduce sodium in the food supply, which includes a recommendation that the FDA use its GRAS regulatory authority to mandate limits on the amount of sodium allowed in food
2010	The US Government Accountability Office releases a report criticizing the FDA's 1997 proposed GRAS rule
2013	FDA makes a preliminary determination that the trans fats generated from PHOs are no longer GRAS
2013	CSPI submits a citizen petition to the FDA to ensure the safe use of "added sugars" using the FDA's authority over GRAS substances
2014	FDA promulgates a proposed rule to revise the nutrition facts label to include an "added sugar" disclosure among other updates
2015	FDA promulgates its final determination that PHOs are no longer GRAS
2016	FDA promulgates final rule updating the nutrition facts label to include "added sugar" among other updates (compliance set for 2018 for large manufacturers and 2019 for small manufacturers)
2016	FDA finalizes its 1997 GRAS notification rule
2017	Nonprofit consumer and environmental protection organizations file a lawsuit challenging the FDA's final GRAS notification rule
2018	FDA denied a petition by Grocery Manufacturers Association to allow PHOs as a food additive
2021	The US District Court for the Southern District of New York upholds the FDA's voluntary GRAS notification rule in *Center for Food Safety v Becerra*
2021	FDA establishes "Voluntary Sodium Reduction Goals," which provide voluntary sodium reduction targets
May 2022	US Senator Markey introduces the bill Ensuring Safe and Toxic-Free Foods Act of 2022 to address deficiencies in the FDA's GRAS notification procedure; bill fails to pass
July 2022	FDA Commissioner Robert Califf requests that the Reagan–Udall Foundation convene an independent expert panel to conduct a comprehensive evaluation of the FDA Human Foods Program to strengthen the FDA's food regulatory role
September 2022	The White House holds the Conference on Hunger, Nutrition, and Health
December 2022	The Reagan–Udall Foundation issues its report *Operational Evaluation of the FDA's Human Foods Program*
December 2022	FDA issues guidance document "Best Practices for Convening a GRAS Panel"

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TABLE 1— Continued

January 2023	FDA announces the proposed restructuring of its Human Foods Program
October 2023	California bans 4 substances permitted to be in food by the FDA (red dye no. 3, potassium bromate, brominated vegetable oil, and propylparaben) from being used as an ingredient in food sold or manufactured in California
November 2023	FDA announces its proposal to revoke the approved food additive status of brominated vegetable oil
November 2023	US senators Edward J. Markey (D, MA) and Cory Booker (D, NJ) announce the introduction of the bill Ensuring Safe and Toxic-Free Foods Act of 2023
March 2024	FDA announcement that it would conduct postmarket review of 21 chemicals in the food supply

Note. CSPI = Center for Science in the Public Interest; FDA = US Food and Drug Administration; GRAS = generally recognized as safe; IOM = Institute of Medicine; NLEA = Nutrition Labeling and Education Act of 1990; PHO = partially hydrogenated vegetable oil.

postmarket authority for substances that are unknown to it. Finally, the court agreed that the plaintiffs' "legitimate concerns" about potential industry conflicts of interest "may be valid," but the FDCA was also silent on this issue, so the FDA was not required to address potential conflicts of interest for self-GRAS reviews.[8]

The plaintiffs also argued that the FDA's GRAS rule contravenes the FDCA's Delaney Clause. The Delaney Clause, incorporated into the FDCA by the Food Additives Amendment of 1958, explicitly requires the FDA to ban food additives that are found to cause or induce cancer in humans or animals.[18] The FDA successfully argued that "the Delaney Clause governs food additives, not GRAS" substances.[8] Although the court agreed that GRAS substances linked to cancer are exempt from the FDA's premarket review, the court noted that "inherent in the GRAS Rule are criteria that would likely prevent a carcinogenic substance from being deemed GRAS," because it would not be generally recognized as safe.[8] However, without required premarket notification, this may be difficult for the FDA to ensure in practice.

In assessing the reasonableness of the FDA's interpretation of the statute, the court noted approvingly that the number of GRAS notifications the FDA receives since amending its rule in 1997 had increased.[8] The court cited FDA data showing that under the previous voluntary affirmation process, the FDA received approximately 8 GRAS affirmation petitions per year between 1987 and 1996 but approximately 34 per year between 1997 and 2015.[8] However, these numbers are complicated by an obvious fact: the denominator of new substances added to the food supply each year is unknown. Moreover, as Neltner et al. found, only a small percentage of all GRAS substance determinations actually ever cross the FDA's desk.[17] Given the advances in food-processing technologies, it seems plausible that the increase in filings is explained by a growing number of new substances being developed each year.[8]

Lastly, the court agreed with the FDA that it could choose, as it did, to not require GRAS substance notification because a mandatory system would consume the FDA's resources.[8] Indeed, a more robust system would require Congress to dedicate additional resources to the FDA—something Congress has historically failed to do.[9] In conclusion, the court did not find that the FDA's GRAS rule supports the safety of the food supply but that the rule did not violate the FDCA despite the safety concerns raised by the plaintiffs.

IMPLICATIONS

Even before the FDA finalized its GRAS rule, it was aware of gaps in its oversight highlighted by the *Center for Food Safety* plaintiffs. In 2010, the US Government Accountability Office (GAO) released a report determining that the FDA's oversight process does not "ensure the safety" of new GRAS substances or those based on previous GRAS determinations.[19] The report recommended that the FDA strengthen its GRAS oversight, including by developing strategies to require companies to provide the FDA with basic information about GRAS substances and to minimize the potential for conflicts of interest in companies' self-GRAS determinations. The GAO also recommended that the FDA create a more systematic mechanism to review and reconsider existing GRAS determinations.[19] The FDA issued guidance documents clarifying its thinking on several issues in this report[20]; however, in 2016 the FDA chose to finalize its GRAS notification rule without modifying it in accordance with GAO recommendations. Thus, the problems the GAO identified remain.[3]

As a result of the FDA's GRAS rule, and the supportive ruling in *Center for Food Safety*, the food industry is free to self-determine the GRAS status of a

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substance and add that substance to food products without notifying the FDA or the public. Although some food companies may choose to undertake the voluntary public notification process to obtain the "no question" letter from the FDA, a company that seeks to maintain confidentiality over its proprietary information (or does not wish to bring attention to a new substance it has added) will choose to self-GRAS.

The FDA has reminded companies that choose to self-GRAS that they must still have the data to support their safety decisions or they will be noncompliant. Even with such data, very real concerns about conflict of interest remain. Neltner et al. found that of the 451 GRAS notifications voluntarily submitted to the FDA between 1997 and 2012, 100% of them were decided by people with a conflict of interest, including employees of—or consulting firms selected by—the manufacturers themselves or by a GRAS panel with conflicts of interest.[21] A subsequent 2023 analysis of these GRAS panels found that food industry GRAS panels are made up of experts whose income is derived from GRAS panel participation.[22] The authors identified 7 people (all with financial conflicts of interest) who essentially determine the safety of GRAS ingredients in our food supply by serving on the majority of self-GRAS determination panels.[22]

The court in *Center for Food Safety* focused on the FDA's postmarket authority as a safeguard to self-GRAS. However, the FDA has revoked the GRAS status of substances very few times, likely in part because of the lack of a resourced and robust systematic process for the FDA to conduct a postmarket review of GRAS substances or food additives. For example, the FDA's inventory of postmarket determinations that the use of a substance is not GRAS includes only 14 substances for which GRAS status has been revoked.[23] Yet, this database is incomplete, as it excludes 4 examples of GRAS revocations mentioned in the FDA's 2015 Federal Register entry when it revoked the GRAS status of partially hydrogenated vegetable oils (PHOs).[24]

The FDA's treatment of PHOs exemplifies its ability to exercise postmarket authority over GRAS ingredients. Scientific literature on the health harms of industrially produced trans fat from PHOs began accumulating in the 1950s.[25] In the early 1990s, a seminal editorial identified a significant association between trans fat consumption and heart disease among more than 100 000 US women, and growing experimental evidence documented harmful effects of trans fat on blood cholesterol concentrations.[25] In 2005, the Institute of Medicine (IOM; now the National Academies of Sciences, Engineering, and Medicine) issued a report identifying the health harms of PHOs and recommending reduced consumption. Citizens' petitions were filed with the FDA in 2004 and 2009. Despite this strong evidence that there was no longer a consensus among qualified experts that PHOs were generally recognized as safe, the FDA did not alter the GRAS designation but merely required the disclosure of trans fat on the nutrition facts label, effective 2006.[26]

It was not until 2013 that the FDA proposed revoking the GRAS status of PHOs, a rule that was not finalized until 2015 and did not go into effect until 2018.[24] This example highlights the extensive weight of science and time required for the FDA to remove a previous GRAS designation from an industrially produced food ingredient, illustrating the barriers the FDA faces in its ability to exercise postmarket authority for a known substance even when there is clear information questioning its safety.

POSTMARKET REVIEW OF CHEMICALS IN FOOD

In March 2024, the FDA announced that it identified 21 chemicals in the food supply for which it would conduct postmarket review.[27] However, only a few of these chemicals are food ingredients. Moreover, this is only a small fraction of the thousands of food additives, GRAS-affirmed ingredients, and—especially concerning—self-GRAS ingredients now in the US food supply.

Notably, the FDA has not proposed to reevaluate or conduct postmarket review of common GRAS-designated substances that may be safe at low levels but unsafe when added at high levels. This is true even when the current GRAS approval is level specific. For example, in 1977, the FDA approved caffeine as a GRAS substance when used in cola-type beverages at 0.02%.[28] Currently, caffeine is added to energy drinks at levels far exceeding this GRAS tolerance level, with resulting hospitalizations and even deaths among children and adults.[28] Yet, the FDA has not acted on caffeine in energy drinks even though the FDA regulates the use of GRAS substances, meaning the FDA can set limits on the amount of caffeine in energy drinks.

Similarly, given the documented health harms of excess added salt and sugar in the food supply,[29] there is a public health need for the FDA to conduct a postmarket review of the health implications of high levels of added salt and sugar. The Center for Science in the Public Interest unsuccessfully petitioned the FDA to revoke salt's GRAS status in 1978 and again in 2005.[30]

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In 2010, the IOM issued a report on strategies to reduce sodium in the US food supply that included a recommendation that the FDA use its food regulatory authority to mandate limits.[31] Ralston Aoki et al. suggested compelling strategies for the FDA to implement the IOM's sodium recommendations by classifying and regulating sodium as either GRAS or a food additive with safe harbor provisions or specific regulations for use.[32]

Instead of exercising its postmarket regulatory authority, the FDA has focused on labeling and voluntary targets for sodium.[32,33] The FDA's proposed voluntary sodium reduction goals provide carefully determined levels across 163 categories of commercially processed packaged and prepared foods, each based on amounts already present in multiple products in each category.[34] The FDA could use these evidence-based levels as the basis for a determination that foods that exceed these limits are no longer considered GRAS. In addition, evidence exists that current levels of salt added to certain products far exceed the amount reasonably acceptable under conditions of "good manufacturing practice."[35] Good manufacturing practices require that the "quantity of the substance added to food does not exceed the amount reasonably required to accomplish its intended physical, nutritive, or other technical effect in food."[35] This violation of good manufacturing practice has been empirically demonstrated by widely varying sodium contents of otherwise very similar food items.[34]

FUTURE DIRECTIONS

The FDA recognizes its authority to conduct postmarket review and reclassification of GRAS substances found to "produce not just cancer but any disease or disability"[24(p34654)] to regulate them as food additives. Yet, the sheer number of GRAS substances and food additives to be reviewed, combined with the lack of knowledge about the existence of self-GRAS ingredients, insufficient resources, and documented time delays for well-supported action, renders reliance on postmarket authority an ineffective and unreliable method for ensuring a safe food supply. The FDA is only starting to use its postmarket powers to review a tiny number of ingredients in the food supply, even though evidence of harm has been present for decades.

Our analysis indicates that a new framework is needed to assess the safety of GRAS substances and food additives. This could include (1) a new, mandatory premarket GRAS notification or public affirmation process aligned with continued use of the mandatory food additive premarket review process; (2) user fees for the FDA to be able to engage in robust premarket review of GRAS substances and food additives; (3) a new framework for regular, robust, and transparent postmarket FDA review of both GRAS substances and food additives currently in the food supply; and (4) additional resources allocated by Congress. Table 2 sets forth recommendations for action by Congress and the FDA to help achieve these goals.

In the background of these recommendations was the expectation that in June 2024, the US Supreme Court would overturn the *Chevron* doctrine—which it did. The *Chevron* doctrine provided judicial deference to agencies' interpretation of their own authorities. This may result in huge swaths of regulatory actions subject to judicial review without the benefit of such deference, rendering courts the final arbiter of whether Congress granted an agency the authority in question. Based on the issues we have identified, the FDA could still take the position of requiring premarket review of all GRAS substances—a position it mentioned it would consider during its 2016 rulemaking based on implicit authority it acknowledged possessing.[36,37] However, the court's finding in *Center for Food Safety* that the FDCA is "silent" on the FDA's premarket GRAS authorities and the FDA's position that it lacks express statutory authority to require companies to submit GRAS notices leaves questions on how courts would interpret a reverse in the FDA's position absent congressional action indicating that Congress disagrees with the FDA's position or the court's decision in *Center for Food Safety*.

Congressional action would shield the FDA from lawsuits by food industry entities claiming the FDA does not have authority for mandatory GRAS review. The growing evidence for the harms of ultraprocessed foods[38]—a category defined in particular by the presence of industrial compounds added for functional purposes—may provide additional impetus for both Congress and the FDA to act. Congress could revise the Food Additives Amendment of 1958 to require the FDA use a methodologically sound premarket approval or required notification process with transparent data based on publicly available research for GRAS substances. Separately, Congress should provide meaningful new resources to the FDA for both pre- and postmarket review efforts, coupled with a user fee program created by Congress, as it did for tobacco, or negotiated by the FDA with food companies, as it did for drug regulation (Table 2).

In November 2023, Senators Edward J. Markey (D, MA) and Cory Booker (D, NJ) introduced the Ensuring Safe

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TABLE 2— Recommendations to Strengthen the FDA's GRAS and Food Additive Processes to Protect the Food Supply

Recommendations	Suggested Actions[a]	Alternative Actions[b]
Appropriations	Congress should allocate sufficient appropriations to the FDA's Human Foods Program, especially to oversee the safety of ingredients in the US food supply.	Congress should increase appropriations specifically to support the FDA's current (and additional more robust) premarket authorities and postmarket review of substances in the food supply.
User fees	Congress should establish a user fee program for the FDA to complete premarket review of food additives. Congress should establish a user fee program for the FDA to complete premarket review of GRAS substances if or when authorities are changed to require mandatory premarket review for GRAS substances.	FDA should negotiate a user fee program to complete premarket review of food additives and—if authorities are changed to require mandatory premarket review for GRAS substances—GRAS substances. Industry will oppose the FDA-negotiated user fees unless they benefit industry, in this case by ensuring premarket review is more efficient and timely.
Premarket review food additives	FDA should maintain premarket review of food additives.	
Premarket review of GRAS substances	Congress should amend the Food Additives Amendment of 1958 to require a mandatory premarket GRAS review process whereby data are submitted to the FDA for review before a company can market the ingredient. This is consistent with the method proposed in the bill Ensuring Safe and Toxic-Free Foods Act of 2023.[39]	FDA should promulgate regulations requiring premarket review (through notification or affirmation) for GRAS substances. If the FDA does not do full premarket review, it should at least promulgate regulations to review substances premarket to determine whether they can go through GRAS designation or must go through food additive review.
Distinguishing food additives from GRAS substances	Congress should amend the Food Additives Amendment of 1958 to better define GRAS substances and more clearly distinguish between GRAS and food additives so that substances that should rightly be food additives are required to go through the approval process.	FDA should promulgate regulations to clarify the distinction between GRAS substances and food additives.
Conflict-free GRAS determinations	FDA should require all GRAS determinations and panels to be free from conflicts of interest and follow best practices for convening GRAS panels. This includes prohibiting people with industry-related conflicts of interest from serving as experts on GRAS review panels,[39] ensuring GRAS panel members have appropriate and balanced expertise,[40] requiring public data and information to form the basis of GRAS review, and limiting the data provided to a GRAS panel to public information (e.g., not allowing trade secret information).[39]	Congress should mandate that GRAS panels are conflict-free.
Robust and systematic postmarket review	FDA should create a robust and systematic postmarket review process to reevaluate substances previously determined to be GRAS and approved food additives, with scheduled rereview time frames (building substantially on the process it announced in March 2024). FDA should undertake these systematic reviews on a regular basis.	Congress should require the FDA to create a robust procedure to systematically and regularly review the safety of approved food additives, substances previously determined to be GRAS by industry, and substances that went through a previous FDA GRAS affirmation or notification process.
Prohibit harmful substances from receiving or maintaining a GRAS designation	FDA should act to prohibit substances that show evidence of carcinogenic, reproductive, developmental, or metabolic toxicity from receiving GRAS designation or maintaining GRAS designation if postmarket evidence of this arises.[39]	Congress could authorize the FDA to fine or otherwise penalize food manufacturers that self-GRAS and market a substance without sufficient premarket evidence to ensure absence of such harms.
Transparency	Congress should require the food industry to identify all GRAS substances they have determined are safe through the self-GRAS process. FDA should disclose a list of all known GRAS substances in the food supply on its Web site. FDA should also post a clear list or database of all substances for which GRAS status has been revoked or limited.	
Reevaluating GRAS substances associated with health harm at high levels of consumption	FDA should develop and implement a framework to reevaluate the GRAS status of current levels and uses of added caffeine, sodium, and sugar, which are associated with health harms at high levels. FDA should consider imposing limits as part of the good manufacturing practices required for use of those substances.	

Note. FDA = US Food and Drug Administration; GRAS = generally recognized as safe.
[a]Recommended actions are those that have the most evidence or for which the actor (Congress or the FDA) has the most authority to act on that issue.
[b]Alternative actions are those that should be implemented if the recommended action is not implemented.

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and Toxic-Free Foods Act, which would address some of the gaps left in the wake of the FDA's current interpretation of its regulatory authority over GRAS substances.[39] Key points in this bill include requiring FDA premarket review of GRAS substances, reducing conflicts of interest in GRAS panels,[40] improving the FDA's postmarket review to reevaluate substances already in the food supply, and prohibiting carcinogenic substances and substances with evidence of reproductive or developmental toxicity from receiving GRAS designation.[39]

Our analysis demonstrates the very real challenges of the FDA's current framework for evaluating and regulating substances added to food products. Several policy pathways are available for Congress and the FDA to rectify these challenges and provide resources to the FDA to protect public health in the United States with a robust framework to ensure the safety of our food supply. AJPH

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