Environmental Working Group Comment on the FDA's Development of an Enhanced Systematic Process for the Food and Drug Administration's Post-Market Assessment of Chemicals in Food

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Thank you for the opportunity to provide feedback on the FDA's "Discussion Paper: Development of an Enhanced Systematic Process for the FDA's Post-Market Assessment of Chemicals in Food" and public meeting on the critical issue of post-market reassessment of food chemicals.

The current food chemical regulatory system is broken. The FDA's reorganization and the FDA's commitment to standing up a review program represent a unique and unprecedented opportunity to fix the system. It is crucial that the FDA creates a strong, credible post-market review process to ensure that food chemicals are assessed rigorously and transparently and pose a reasonable certainty of no harm to consumers.

There are thousands of chemicals in food and food contact materials, many of which were approved decades ago and have not been meaningfully re-evaluated, despite new evidence of potential harm. When the FDA does reassess an ingredient for safety, often it does so without an opportunity for public input or opportunity to read the science behind the FDA's decisions. Alarmingly, some chemicals have never been reviewed by the FDA at all because companies exploited the Generally Recognized as Safe, or GRAS, loophole to bypass FDA pre-market review. A recent EWG analysis found that 99 percent of new food chemicals have come onto the market through the GRAS loophole, rather than through the FDA's pre-market petition process.[1] EWG's analysis was limited to substances with submitted GRAS notices, but because notice is voluntary, there is another universe of GRAS chemicals that EWG, the public, and the FDA is unaware of. This secrecy makes it possible for substances like tara flour, a substance self-affirmed as GRAS without notice to the FDA, to sicken hundreds of people before the FDA was able to act.[2]

Therefore, it's no surprise that consumer perception of the safety of the additives in our food supply is the lowest it has been in decades.[3] And it's no surprise that states have stepped in to

[1] Olivia Backhaus and Melanie Benesh, *EWG Analysis: Almost All New Food Chemicals Greenlighted By Industry, Not the FDA*, Env't Working Grp. (April 13, 2022), https://www.ewg.org/news-insights/news/2022/04/ewg-analysis-almost-all-new-food-chemicals-greenlighted-industry-not-fda.
[2] Food and Drug Admin., FDA Update on the Post-Market Assessment of Tara Flour (May 15, 2024), https://www.fda.gov/food/hfp-constituent-updates/fda-update-post-market-assessment-tara-flour.
[3] International Food Information Council, *IFIC Spotlight Survey: American Perceptions of Food Safety*, Food Insight (Sept. 19, 2024), https://foodinsight.org/ific-survey-food-ingredient-safety/

fill the gaps and protect consumers from harmful chemicals in food. Nearly a dozen states introduced legislation addressing food chemicals of concern in 2024.[4]

To restore trust and adequately protect the public from toxic substances in food, the FDA must establish a transparent, scientifically rigorous post-market review process with clear deadlines. To do so, the FDA must:

- Create a system for prioritizing chemicals of concern
- Take a proactive approach to reviewing chemicals of concern
- Conduct comprehensive risk assessments
- Look at a range of endpoints and data sources when prioritizing and assessing chemicals
- Create a transparent process with opportunities for peer review and public comment
- Restrict a substance whenever there is not a reasonable certainty of no harm
- Keep risk assessment and risk management decisions separate
- Close the GRAS loophole

The FDA should proactively prioritize chemicals of concern for reassessment

The FDA's current proposal frames the process as one that looks forward, focusing on monitoring for emerging problems. However, this is a reactive approach, not a proactive one. There is an existing body of scientific evidence reflecting safety concerns for some chemicals used in food. To identify these chemicals, the FDA should create a system of prioritization.

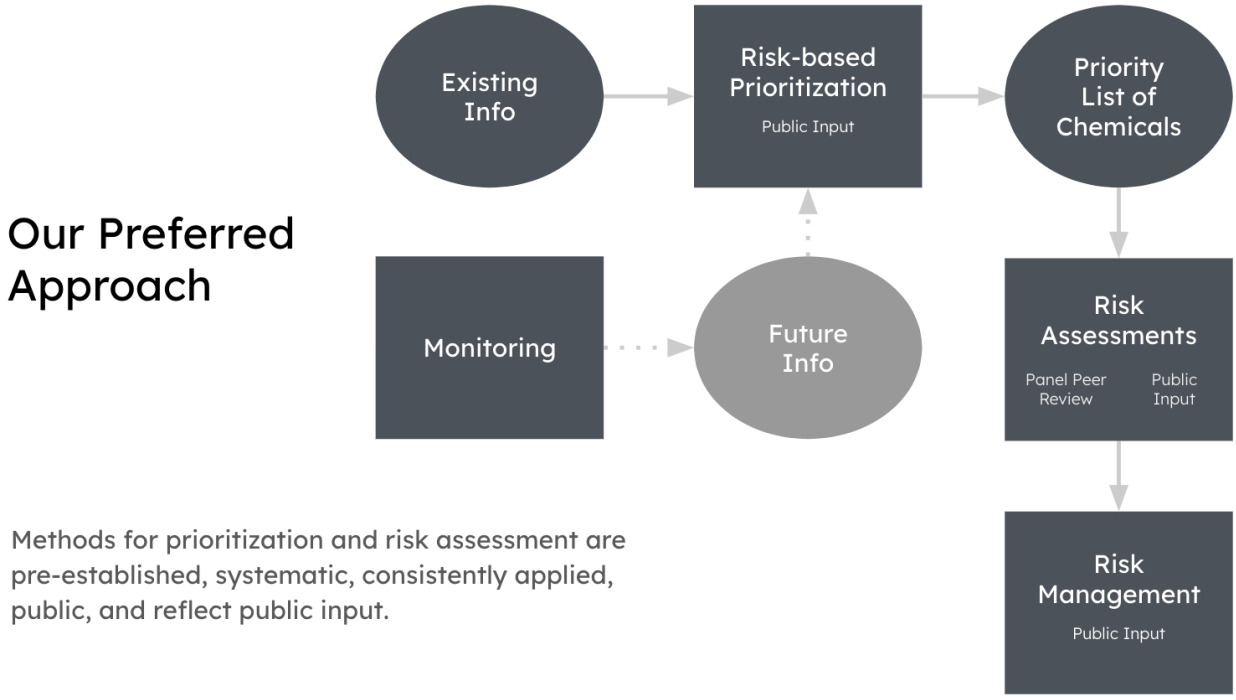
The FDA should prioritize chemicals based on existing data and known health risks before initiating risk assessments. The prioritization process should be systematic, transparent, and public, with clear, pre-established criteria for evaluating the relative risks of various substances.

The discussion paper describes the proposed FDA process as signal monitoring → triage → fit for purpose decision making. While the FDA should be monitoring emerging science, it should not wait for new information to act on chemicals, especially those that are already known to pose risks. Instead, the FDA should create a transparent and proactive process to actively prioritize chemicals for review. Prioritization may include signal monitoring, but should also include reviews of the existing literature, identification of chemicals on authoritative lists, and regulatory status in other jurisdictions. The FDA can then triage its review of existing information alongside the signals received. The list of chemicals the FDA identifies as priorities should be

[4] Iris Myers, *Interactive Map: Tracking Food Chemical Regulation in the U.S.*, Env't Working Grp. (April 4, 2024), https://www.ewg.org/news-insights/news/2024/04/interactive-map-tracking-food-chemical-regulation-us.

public. The public should also have the opportunity to weigh in on chemicals that the FDA should add to the prioritization list and which chemicals the FDA should select for review.

Here is what that process might look like,[5] and how it might fit into a larger review process:



Candidates for Prioritization

The FDA's process for prioritization should be based on hazard, emphasizing chemicals linked to the most significant outcomes including carcinogens, concern for children's health like reproductive or developmental effects, immunotoxicants, endocrine disruptors, neurotoxicants, obesogens, chemicals causing irreversible organ toxicity, and chemicals linked to chronic disease. The FDA should also prioritize chemicals that are biopersistent or have been detected in biomonitoring programs.

It should not be difficult for the FDA to compile an initial list of chemicals to prioritize. There are several pending petitions before the FDA on food chemicals including PFAS, BPA, titanium dioxide, BHA, lead solder, and three carcinogenic solvents. These pending petitions, many of which have been pending for years, are a logical starting place. The FDA can also identify

[5] This graph was also included in the presentation made by Melanie Benesh and Thomas Galligan at the September 25, 2024 FDA meeting on post-market review of chemicals.

chemicals by cross referencing chemicals used in food in the U.S. with lists of substances of concern such as[6]:

- Chemicals known to the State of California to cause cancer or reproductive toxicity that are listed pursuant to the Safe Drinking Water and Toxic Enforcement Act of 1986 (Chapter 6.6 (commencing with Section 25249.5 of Division 20)).
- Chemicals classified by the European Union as carcinogens, mutagens, or reproductive toxicants pursuant to Category 1A or 1B in Annex VI to Regulation (EC) 1272/2008.
- Chemicals included in the European Union Candidate List of Substances of Very High Concern in accordance with Article 59 of Regulation (EC) 1907/2006 on the basis of Article 57(f) for endocrine disrupting properties.
- Chemicals for which a reference dose or reference concentration has been developed based on neurotoxicity in the federal Environmental Protection Agency's Integrated Risk Information System.
- Chemicals that are identified as carcinogenic to humans, likely to be carcinogenic to humans, or as Group A, B1, or B2 carcinogens in the federal Environmental Protection Agency's Integrated Risk Information System.
- Chemicals included in the European Chemicals Agency Candidate List of Substances of Very High Concern in accordance with Article 59 of Regulation (EC) 1907/2006 on the basis of Article 57(d), Article 57(e), or Article 57(f) of Regulation (EC) 1907/2006 for persistent, bioaccumulative and toxic, or very persistent and very bioaccumulative properties.
- Chemicals that are identified as persistent, bioaccumulative, and inherently toxic to the environment by the Canadian Environmental Protection Act Environmental Registry Domestic Substances List.
- Chemicals classified by the European Union in Annex VI to Regulation (EC) 1272/2008 as respiratory sensitizer category 1.
- Group 1, 2A, or 2B carcinogens identified by the International Agency for Research on Cancer.
- Neurotoxicants that are identified in the federal Agency for Toxic Substances and Disease Registry's Toxic Substances Portal, Health Effects of Toxic Substances and Carcinogens, Nervous System.
- Persistent bioaccumulative and toxic priority chemicals that are identified by the federal Environmental Protection Agency National Waste Minimization Program.
- Reproductive or developmental toxicants identified in Monographs on the Potential Human Reproductive and Developmental Effects published by the federal National Toxicology Program, Office of Health Assessment and Translation.
- Chemicals identified by the federal Environmental Protection Agency's Toxics Release Inventory as Persistent, Bioaccumulative and Toxic Chemicals that are subject to reporting

[6] Note many of these chemicals are included as "designated lists" identifying potentially hazardous chemicals in California's Cleaning Products Right to Know Act of 2017. *See* S.B. 258, the Cleaning Products Right to Know Act of 2017, https://leginfo.legislature.ca.gov/faces/billNavClient.xhtml?bill_id=201720180SB258.

under Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986 (42 U.S.C. Sec. 11001, et seq.).
- Chemicals that are identified as known to be, or reasonably anticipated to be, human carcinogens by the federal National Toxicology Program.

While prioritization should be primarily concerned with health hazard considerations, the FDA can also look at exposure and biomonitoring data from the Total Diet Study and NHANES to further prioritize chemicals that may be especially prevalent in the diet or marketed to vulnerable populations like children.

After the FDA prioritizes a chemical, most of the time it should then pursue a comprehensive review to ensure it adequately captures risk and can take action to mitigate any risks across different conditions of use.

Focused Reviews May Overlook Crucial Evidence

The discussion draft devotes significant time to distinguishing between focused and comprehensive reviews of chemicals. However, to ensure that chemicals pose a reasonable certainty of no harm, comprehensive reviews should be the default. Focused reviews could lead to the neglect of important scientific data if they fail to consider the full body of evidence. There is a lack of clarity in the discussion draft regarding when the FDA will opt for a focused review versus a comprehensive review. The FDA states that it may opt for a focused review if it identifies a "single new small study on a chemical."[7] But to reach reliable, credible safety conclusions, that study must be contextualized in the total body of evidence, especially if the FDA has not meaningfully assessed the safety of a chemical in many years, which is likely the case for many chemicals of concern.

However, if new evidence of harm emerges for a particular use or condition of use of an ingredient, a focused review may be appropriate to quickly restrict that use or condition of use so that consumers are not harmed while a longer, more comprehensive review is ongoing. However, if a focused review identifies the need to quickly restrict a particular use, the FDA should *also* conduct a more comprehensive review to determine if other uses or conditions of use also need to be updated to ensure the chemical poses a reasonable certainty of no harm. In other words, FDA restrictions following a focused review should be an interim step while the FDA completes a more comprehensive review.

Focused reviews must be transparent and publicly available and should include, at a minimum, the FDA's review of the existing science, health concerns and uses identified, the studies considered, and the basis for the FDA's conclusions.

Criteria for Risk Assessments

[7] U.S. Food and Drug Administration, Discussion Paper: Development of an Enhanced Systematic Process for the FDA's Post-Market Assessment of Chemicals in Food, at page 4 (2024), https://www.fda.gov/media/180942/download.

Risk assessments must be based on high-quality hazard and exposure data and consider the full body of evidence, including cumulative and synergistic effects of chemicals. If high-quality data is unavailable, the FDA should take immediate steps to improve data collection efforts, including as part of the prioritization process, before the FDA initiates the risk assessment. Risk assessments should be peer reviewed by an unbiased, unconflicted external review panel.

The purpose of a risk assessment must be to determine if a chemical poses a reasonable certainty of no harm. The FDA cannot reach this conclusion without high-quality hazard and exposure data, and without conducting a comprehensive, weight-of evidence assessment that incorporates all sources of information including in vitro data, animal data, and human data. FDA risk assessments must also consider the cumulative effects from any chemically and pharmacologically similar chemicals,[8] and the FDA should provide more information about how it plans to do that, including by responding to a citizens petition on cumulative effects that has been pending since 2020.[9] When data gaps exist, a chemical generally will not be able to meet the "reasonable certainty of no harm" standard. Risk assessments must also only consider data relevant to health and safety. Non-risk factors like the cost and the availability of alternatives must not factor into the risk assessment, as these are risk management considerations.

The FDA should adopt self-imposed concrete deadlines to complete risk assessments to ensure that reviews happen efficiently and do not drag on for years or decades while the public is exposed to potentially harmful chemicals. These deadlines should be no longer than three years, which is a realistic timeframe for these assessments. The Environmental Protection Agency has three years to complete risk assessments on prioritized chemicals under the Toxic Substances Control Act, and those assessments consider the safety of dozens, or even hundreds, of potential uses of a chemical.[10] By contrast, the FDA risk assessments will be far narrower in scope which should allow the FDA to complete assessments more quickly.

FDA Assessments Should be Transparent and Scientifically Rigorous

The FDA should strive to make the review process, from prioritization to risk assessment and management, transparent and open to public input. Risk assessments should be externally peer reviewed by unconflicted experts. And stakeholders should have the opportunity to comment on the prioritization and risk assessment process, the FDA's list of chemicals to prioritize, risk assessments, and risk management decisions. The FDA should publish all findings in detail, including any studies included or excluded from the FDA's assessment. The FDA should also

[8] 21 U.S.C. § 348(c)(5)

[9] Env't Defense Fund et al., Citizens petition requesting that FDA define key terms essential to consider the cumulative effect of a food additive, food contact substance, generally recognized as safe substance, or color additive, taking into account any chemically- or pharmacologically-related substances in the diet, when assessing safety as required by law (Sept. 23, 2020), https://blogs.edf.org/health/wp-content/blogs.dir/11/files/2020/09/Additives-Cumulative-Effects-Citizen-Petition-FINAL-9_23_20.pdf?_gl=1*1gx1oi7*_gcl_au*OTI2MzYxNTYyLjE3MzY1Mjg2MTM.*_ga*NDUzNzExMTAyLjE3MzY1Mjg2MTE.*_ga_2B3856Y9QW*MTczNzUxNzQ5Ny4yLjAuMTczNzUxNzQ5OS41OC4wLjA.*_ga_Q5CTTQBJD8*MTczNzUxNzQ5Ny4yLjAuMTczNzUxNzQ5OS41OC4wLjA..

[10] 15 U.S.C. 2605(b)(4)(G)

be transparent about who is deciding which chemicals to review, conducting the risk assessments, and making risk management decisions.

The FDA Must Restrict a Substance Whenever There is Not a Reasonable Certainty of No Harm

Once the risk assessment is complete, the FDA must take swift action if the safety of a chemical is in doubt. If the agency finds that a chemical no longer meets the standard of "reasonable certainty of no harm," it must take action—even if harm has not yet been conclusively proven.

Recent FDA decisions suggest that the FDA has been taking the opposite approach, assuming that a chemical is safe unless the FDA can show that it's not. For example, when the FDA completed a focused review of erythritol in 2023, the FDA acknowledged "conflicting results" from health studies on the substance, including "papers that suggest elevated circulating erythritol levels are associated with type II diabetes and coronary heart disease."[11] But the FDA goes on to conclude that "the observational studies… are incapable of establishing causation" and that further study is needed to "help to clarify whether circulating erythritol levels are a biomarker of cardiovascular and metabolic disease or actively contributing to the pathogenesis of these diseases."[12] In this case, the FDA was unable to conclude with reasonable certainty that there is no harm from erythritol, but declined to take action until it can establish "causation."

This is in contrast to other jurisdictions like the European Union. For example, the European Food Safety Authority, or EFSA, determined in 2021 that titanium dioxide can no longer be considered safe in food. EFSA reached that decision because it "could not exclude genotoxicity concerns after consumption of titanium dioxide particles. After oral ingestion, the absorption of titanium dioxide particles is low, however they can accumulate in the body."[13] EFSA did not conclude that titanium dioxide is definitely unsafe, but instead took a precautionary approach, finding that because of the chance for bioaccumulation and genotoxicity, the agency could not be certain of no harm. The FDA appears to disagree with EFSA's assessment, stating on a webpage that "FDA did not identify concerns related to potential genotoxicity based on the data available and noted that TiO2 did not cause cancer in National Toxicology Program (NTP) carcinogenicity studies."[14] However, the FDA has not made public its scientific assessment of

[11] Memorandum, An evaluation of the article "The artificial sweetener erythritol and cardiovascular event risk" by Witkowski et al., Nat Med. 2023 Mar;29(3):710-718., at page 6 (June 15, 2023), https://www.fda.gov/media/182122/download?attachment.
[12] *Id.* at 6-7.
[13] European Food Safety Authority, Titanium Dioxide: E171 No Longer Considered Safe When Used as a Food Additive, (May 06, 2021), https://www.efsa.europa.eu/en/news/titanium-dioxide-e171-no-longer-considered-safe-when-used-food-additive
[14] Food and Drug Admin, Titanium Dioxide as a Color Additive in Foods, https://www.fda.gov/industry/color-additives/titanium-dioxide-color-additive-foods (last updated March 04, 2024).

titanium dioxide, and has not yet responded to a pending petition on titanium dioxide filed in 2023,[15] making it difficult to know the scientific basis for the FDA's conclusions.

FDA's approach is also contrary to the clear language of the safety standard and the legislative history of the Food Additives Amendment. For example, a 1952 report to the House of Representatives from the Select Committee to Investigate the Use of Chemicals in Food and Cosmetics decried the inadequacy of the law to address the chronic risks from chemicals in food. The Select Committee report and its findings was an important precursor to the development of the Food Additives Amendment that passed in 1958. The Select Committee report makes clear that the FDA had failed to address the safety of food chemicals, in part, because the FDA had a legal burden of showing a chemical is unsafe before being able to take regulatory action. The report argues that the burden should shift away from the government showing harm, and should instead be placed on the food and chemical companies to show safety. The report clarifies that when there are doubts about safety, the product shouldn't be in commerce.

> Section 402(a)(1) declares a food to be adulterated if it bears or contains any poisonous or deleterious substance which may render it injurious to health. This provision places on the Government the burden of proving by a preponderance of the evidence, in a court of law, that a chemical added to food is harmful. In some instances, the Government does not possess the necessary proof of hazard, although doubt as to safety may exist. In other instances, the government secures the necessary proof, but only after injury has occurred.
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> Thus, if a chemical is used on or incorporated into a food without adequate toxicity testing, as a practical matter the government is frequently helpless and the consumer unprotected. If there is no evidence available as to the toxic nature of the substance, the Government cannot produce evidence in court to sustain its burden of proof. In such a situation, the Government may be compelled to undertake the burden of conducting chronic toxicity studies. Such experimental work may require years for completion. Meanwhile, the manufacturer may continue to market its product unmolested despite possible subtle damage to the health of the consumer.[16]

These ideas were backed up by the FDA commissioner at the time, George Larrick, who testified before a Congressional committee in 1958 and argued that . In his submitted statement, Commissioner Larrick explained:

> Some witnesses suggest that the expression "safe for use" be defined to mean that a chemical is safe when it is reasonably probable that it can be used under the conditions of its intended use without rendering the food in or on which it is used injurious to health. We do not want to feed chemically treated food to our children if the only assurance we

[15] Filing of Color Additive Petition From Environmental Defense Fund, et al.; Request To Revoke Color Additive Listing for Use of Titanium Dioxide in Food, 88 Fed. Reg. 27818 (May 03, 2023).

[16] H.R. Rep. No. 82-2356 at 22.

> have is that it is reasonably probable that the added chemicals will not cause harm. We want to know that it has been established convincingly that the added chemicals will not harm the youngsters and we believe the average mother in the United States today wants and deserves that same assurance. We think it would be poor public health protection to allow poisons in food solely on a showing that it is reasonably probable that they will not cause trouble.[17]

The FDA Must Keep Risk Assessment and Risk Management Decisions Separate.

As the FDA reevaluates the safety of chemicals in food, it's critical that the agency maintain separate processes for evaluating the risks of chemicals and managing the risks from those chemicals. Different staff should work on the assessments and regulations to ensure that non-risk factors do not influence the risk assessor's interpretation of the science.

The approach outlined in the FDA's discussion paper would not make the FDA's scientific assessment available until *after* the FDA has discussed risk management options. Instead the FDA should make the scientific assessment available as soon as it is complete and has undergone peer review. If the FDA waits until risk management options have already been discussed, there is a risk that those regulatory considerations could influence the content and outcome of the scientific assessment, which should be purely based on health factors.

When updating regulations for a food chemical, risk management must prioritize public health over industry interests and ensure that there's a reasonable certainty of no harm to the public from any continued use of the chemical.

Reform the GRAS Process

Finally, we urge the FDA to make long-overdue reforms to the Generally Recognized As Safe (GRAS) program. The GRAS system relies largely on post-market enforcement. Critically, because GRAS decisions can be made without FDA notification, the FDA may not even know when a GRAS substance is being used in a product or what health effects may be associated with that chemical. As a result, harmful chemicals may remain in food products and the FDA may only take action once significant consumer harm has occurred. For example, several students were hospitalized or died[18] before the FDA warned that caffeinated alcoholic

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[17] *Food Additives: Hearings Before the H. Comm. on Interstate and Foreign Commerce*, 85th Cong., 447, 456 (1957-58) (statement of George P. Larrick, Commissioner, Food and Drug Administration).

[18] *See, e.g.*, Kim Murphy, Four Loko incident in Washington state raises alarm about caffeinated alcoholic drinks, L.A. Times (Oct. 27, 2010), https://www.latimes.com/archives/la-xpm-2010-oct-27-la-na-blackout-in-a-can-20101027-story.html; Makers of Four Loko Sued After Teen's Death, CBS News (May 19, 2011), https://www.cbsnews.com/chicago/news/makers-of-four-loko-sued-after-teens-death/.

beverages were not GRAS.[19] Hundreds of people were sickened after consuming tara flour, but it still took the FDA nearly two years to clarify that tara flour was not GRAS.[20]

The FDA must enforce greater transparency in the GRAS process to avoid future tragedies. The FDA should ensure that companies cannot make secret GRAS determinations, should restrict the use of GRAS for novel ingredients, should enforce the recent guidance on conflicts in GRAS panels, should actively try to identify secret GRAS chemicals in the market, and aggressively take action when substances are used despite known risks. The FDA should include GRAS substances in its reassessment process and revoke status whenever there is not general recognition of safety, meaning a reasonable certainty of no harm.

Conclusion

Setting up a post-market review program is critical to fulfilling the FDA's mission to ensure that food and food packaging chemicals in the U.S. are safe. But to be credible, any review program must be based on rigorous scientific review that is systematic and objective, consistent and reproducible, transparent and public, unbiased, and protective of public health. This system must also be proactive about reassessing chemicals of concern, rather than simply waiting for and responding to signals as they emerge.

Americans have been waiting for decades for the FDA to address toxic chemicals in food. The FDA should move swiftly to develop and implement a framework that ensures the safety of the food supply. In the meantime, states should continue their efforts to protect consumers from unsafe food chemicals.

Thank you for considering these comments. We look forward to further opportunities to engage with the FDA on this important issue.

[19] Food and Drug Admin., Update on Caffeinated Alcoholic Beverages (Nov. 24, 2010), https://wayback.archive-it.org/7993/20161024020218/https://www.fda.gov/NewsEvents/PublicHealthFocus/ucm234900.htm.
[20] Food and Drug Admin., FDA Update on the Post-Market Assessment of Tara Flour (May 15, 2024), https://www.fda.gov/food/hfp-constituent-updates/fda-update-post-market-assessment-tara-flour.