CENTER FOR Science IN THE Public Interest
Your Food and Health Watchdog

January 21, 2025

Jim Jones
Deputy Commissioner for Human Foods
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Development of an Enhanced Systematic Process for the Food and Drug Administration's Post-Market Assessment of Chemicals in Food; Public Meeting; Request for Comments (Docket FDA-2024-N-3609)

Dear Deputy Commissioner Jones,

The Center for Science in the Public Interest (CSPI) respectfully submits these comments regarding the FDA's public meeting held on September 25, 2024, titled "Development of an Enhanced Systematic Process for FDA's Post-Market Assessment of Chemicals in Food" and the associated discussion paper. We appreciate the opportunity to present our perspective in written comments here and in the oral comments we presented at the public meeting.

The FDA's existing system for post-market assessments puts consumers at unnecessary risk from unsafe food chemicals, allowing harmful substances to remain in use long after evidence of harm emerges. The FDA's proposal for an enhanced post-market framework, while a step forward, is critically deficient in detail and fails to maximize scientific rigor, transparency, and public health protection, leaving us with limited confidence that the new system will provide consumers the protections they deserve.

CSPI is an independent consumer advocacy organization that envisions thriving communities supported by equitable, sustainable, and science-based solutions advancing nutrition, food safety, and health. We have worked since 1971 to improve the public's health through better nutrition and safer food. We do not accept corporate donations.

Post-market safety assessment of food chemicals is an essential function of the FDA, and thus CSPI supports the agency's commitment to systematically evaluating the safety of food chemicals and performing oversight activities to address safety concerns with such chemicals. The FDA's recent public meeting (1), the publication of the agency's discussion paper (2), and the creation of the list of select chemicals under review by the FDA (3) mark important first steps toward that goal.

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At the FDA's public meeting, we were struck by the agreement among the diverse stakeholders, including the FDA, that this new framework should be rigorously scientific, reliant on high-quality data, and have a high degree of transparency and public engagement throughout the process. Further, the diverse stakeholders collectively expressed a need for clarity in the criteria the FDA will use in prioritizing chemicals for post-market assessment and determining the type of assessment (focused versus comprehensive) it will perform. Finally, there appeared to be general agreement that the FDA needs additional resources to develop and implement a framework that fulfills these goals. Considering the agreement on these points, CSPI encourages the FDA to refine its proposed framework to better maximize rigor, data quality, transparency, and public engagement, and we also hope that the FDA will continue working with Congress to identify solutions to its resource shortfall.

In these comments, we provide our perspective and recommendations to help the FDA's post-market assessment framework maximize the protection of public health, transparency, and public engagement.

In **Section I** of this comment (beginning on page 3), we describe our recommendations:

- **A. Develop and Implement a Detailed Methodology**: The FDA should develop, publish, and implement a detailed methodology for assessing the safety of food chemicals in a post-market setting to ensure that these assessments are rigorously scientific, systematic, objective/unbiased, and consistent/reproducible.
- **B. Prioritize the Riskiest Chemicals First**: The FDA should reframe its proposed system to begin with risk-based prioritization of chemicals using currently available information to ensure that existing concerns with specific food chemicals are addressed in a timely manner, rather than waiting for new/emerging information to come to light to trigger a review.
- **C. Establish Clear Criteria for Selecting Focused vs. Comprehensive Assessments**: The FDA should revise its focused assessment process by prescribing the criteria that will be used to determine when a focused assessment is more appropriate than a comprehensive assessment. Decisions made within the focused assessment process should still be based on the total weight of evidence rather than considering new information in isolation.
- **D. Improve Data Quality**: The FDA should commit to taking proactive steps to improve the quantity and quality of hazard and exposure data available for chemicals under evaluation. The agency should publicly specify what those steps are. The FDA should develop a process for acquiring information relevant to the risk assessment and risk management processes for both focused and comprehensive assessments.
- **E. Enhance Focus on Public Health Protection**: The FDA should exclude non-risk factors (e.g., cost, feasibility) from its risk assessments, thereby helping ensure that public health protection is the primary factor driving decision-making.
- **F. Reform GRAS to Reduce the Burden on the Post-market System and Facilitate Better Surveillance**: The FDA should commit to revisiting its GRAS regulations and announce a timeline for notice and comment rulemaking on GRAS reform. New regulations should ensure that GRAS determinations and supporting documentation are made public and are reviewed by the FDA. Until that reform is enacted, the FDA should

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develop a robust surveillance system for identifying previously unknown GRAS substances and establish a method for using that surveillance system to evaluate GRAS status and identify substances lacking sufficient data.

- **G. Rigor and Transparency**: The FDA should make additional revisions to its proposed system to promote rigor and transparency. We recommend that the FDA specify in its methodology how it will evaluate data from observational studies. We suggest that the FDA establish, publicize, and routinely update a timeline for completing each specific post-market assessment, and that the agency develop a centralized database for publishing its completed assessments. We also recommend that all comprehensive assessments and some focused assessments be subjected to external peer review.
- **H. Include Assessment of Dietary Ingredients and Chemicals Added to Supplements in the Framework**: The FDA should explicitly include dietary ingredients and other chemicals used in dietary supplements in the scope of its enhanced post-market assessment framework.

In **Section II (**beginning on page 15), we respond to the questions posed by the FDA in its discussion paper.

In **Section III** (on page 18), we provide concluding remarks.

I. Detailed Comments on FDA Discussion Paper & Recommended Revisions to the Proposed Framework

A. Develop and Implement a Detailed Methodology

While understanding that the discussion paper is perhaps a preliminary, high-level summary of the framework, its lack of specificity and detail precludes us from understanding whether the new framework will be adequately systematic, rigorous, and transparent. Providing greater detail on methods will help ensure that the assessments conducted under this framework are rigorously scientific, systematic, objective/unbiased, and consistent/reproducible.

> **Recommendations**: The FDA should develop, publish, and implement an explicitly detailed methodology as part of its enhanced post-market review framework. The framework should prescribe how the agency will systematically identify, evaluate, and integrate all available evidence—including evidence published before and after the last FDA assessment of the chemical, human epidemiological evidence, evidence from "new approach methodologies," and unpublished data.
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> This method should use modern scientific approaches for evidence evaluation and integration, perhaps based on the U.S. National Toxicology Program (NTP) Office of Health Assessment and Translation (OHAT) *Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration* (4).

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The method should outline how the FDA will take into consideration the cumulative effects from chemically and pharmacologically related substances, as required by federal statute (5).

The FDA's detailed methodology should be subjected to interagency review, including the FDA's partner agencies involved in toxicological research and chemical risk assessment and regulation (e.g., the Environmental Protection Agency [EPA], Centers for Disease Control and Prevention [CDC], National Institutes of Health [NIH], and NTP), as well as external peer review. The FDA should also provide an opportunity for the public to provide input.

Because each individual chemical or class of chemicals can present unique challenges, we recognize that some degree of flexibility must be built into the FDA's methodology. Similarly, we recognize that scientific practices and principles shift over time, meaning the FDA must retain the ability to revise its methods to adapt to shifting science. The FDA should not refuse to establish a detailed methodology on account of these issues, however.

Recommendations: When deviating from the detailed method due to a chemical-specific issue, the FDA should describe in detail what deviations were made and explain why those deviations were necessary when it publishes its draft and final assessments. Substantive permanent revisions to the methodology should go through an open revision process involving public input and external peer review.

The discussion paper notes that the FDA will consider populations/subpopulations of concern, but does not specify these subpopulations, how subpopulations will be identified, or how their unique concerns will be considered.

Recommendations: The FDA should always consider infants, children, and people who are pregnant as unique subpopulations of concern given that these are developmental stages associated with greater susceptibility to toxic effects.

To whatever extent is possible, the FDA should prespecify its approach for identifying and considering additional subpopulations as part of each post-market assessment. Based on existing or novel exposure analyses, the FDA should identify sociodemographic groups that are disproportionately exposed to toxic chemicals via the diet or otherwise (e.g., Nguyen et al. 2020 identified racial differences in hazardous chemical exposures among women in the U.S. (6)) and give these groups unique consideration with respect to their potentially different susceptibility to adverse effects from food chemical exposures as a result of their overall burden of exposures.

B. Prioritize the Riskiest Chemicals First

The proposed system is framed as a forward-looking process that—once implemented—would monitor for new information and emerging concerns and then prioritize chemicals for post-market assessment based on that information. In effect, if the FDA implements this system by the

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end of 2025, as intended, it appears that post-market assessments would only be triggered by information published thereafter (i.e., in 2026 and beyond). It seems that the FDA is operating under the assumption that its existing post-market processes and systems sufficiently identified and responded to concerns that arose previously, allowing the agency to focus entirely on reacting to new information and concerns. This assumption, however, is flawed because the FDA itself acknowledges that there are problems with the agency's existing post-market assessment processes. Deputy Commissioner Jones at the public meeting said:

> "We have not had a robust Post-Market Assessment program here at FDA. This is largely because there's no statutory requirement for FDA's post-market review…As such, given our limited resources, the agency has not established a systematic process to ensure that our original determination of safety held up over time. Until now, we have taken an ad hoc approach to post-market safety by monitoring the literature and engaging with national and international counterparts to review emerging data as they become available."

Indeed, if there were no problems with the existing system, the FDA would not be undertaking this effort to enhance that system. CSPI has been calling on the FDA to reform its approach to post-market assessment of food chemical safety for years—and we have repeatedly petitioned the agency to take regulatory action against unsafe chemicals in recent years—precisely because the FDA has not suitably addressed all concerns raised about the safety of chemicals in our foods. There are numerous instances where, in our opinion, the FDA failed to respond appropriately to new information relevant to the safety of food chemicals in recent years.

For example, the FDA has yet to publicly acknowledge or respond to a 2021 assessment of synthetic dyes by California's Office of Environmental Health Hazard Assessment (OEHHA) that concluded that synthetic food dyes "can cause or exacerbate neurobehavioral problems in some children" (7). This was a peer-reviewed systematic review of the human, animal, and mechanistic evidence that explicitly called into question the validity of the existing Acceptable Daily Intake values set by the FDA for these dyes. This should have triggered a thorough FDA review and a public response. In verbal communications with us, the FDA claimed that it has reviewed the OEHHA report, but the FDA's website on food dyes does not acknowledge that OEHHA performed this assessment or the conclusions it reached (8), leaving external stakeholders and the public with no understanding of whether or how the FDA took the OEHHA assessment into consideration.

As another example, the FDA's website currently provides a one-paragraph response to an evaluation by the European Food Safety Authority (EFSA) on the safety of the color additive, titanium dioxide (9), and the FDA also provided a similar statement to the Titanium Dioxide Manufacturers Association (TDMA) (10). The EFSA assessment in question was a 130-page document, plus appendices, that concluded that titanium dioxide could not be considered safe when used in food based on a systematic review of the evidence (11). In its brief communications, the FDA claims that it evaluated the EFSA assessment and reached the opposite conclusion (i.e., that titanium dioxide is safe in food when used in accordance with current U.S. federal regulations). EFSA's evaluation warrants a thoroughly detailed response from the FDA in

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which the agency describes the approach it used to identify, evaluate, and weigh the evidence and explains clearly how the FDA reached a different conclusion. Without such a response, external stakeholders cannot audit the quality of review that the FDA performed and thus can only have limited trust in its outcome.

Thus, de facto reliance on prior post-market assessments is not appropriate. If the new framework fails to reckon with the existing "signals" and instead waits for new signals, chemicals with known or suspected safety concerns will remain in use, perpetuating a fundamental problem with the FDA's existing (flawed) post-market system.

> **Recommendations**: The FDA should not assume that (1) its existing monitoring system reliably identified all relevant signals that emerged previously, (2) that assessments completed under the existing system meet the standards for rigor and transparency that the FDA is striving to establish under its enhanced system, and (3) that all concerns that arose previously have been adequately addressed.
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> The FDA's post-market framework should begin with risk-based prioritization of chemicals using the existing body of evidence, including human, animal, and mechanistic evidence. Evidence of adverse effects in human studies should be given higher weight. Substances that pose severe (life-threatening or otherwise irreversible) adverse health risks should be prioritized. The FDA should address existing signals and prioritize chemicals accordingly while also monitoring for future signals, which can be used to re-prioritize as needed. The fact that the FDA has completed a post-market assessment for a specific chemical under its existing (flawed) system should not preclude the agency from ranking that substance highly and scheduling a new post-market assessment for that substance under the new framework.
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> The FDA should utilize existing authoritative resources to streamline its prioritization process, which could include hazard and risk classifications and assessments by the NTP, EPA, other national authorities (e.g., the EFSA, Health Canada), international authorities (e.g., World Health Organization [WHO], the International Agency for Research on Cancer [IARC], the Joint Food and Agriculture Organization/WHO Expert Committee on Food Additives [JECFA]), and state agencies (e.g., the California Proposition 65 list).

The discussion paper does not specify if or how the public will be notified of the outcome of the agency's prioritization process, and it does not indicate that the public will have an opportunity to provide input on the prioritization process.

> **Recommendations**: The FDA should solicit public input on the prioritization process and provide opportunities for stakeholders to nominate chemicals for assessment in a process different from and more streamlined than formally petitioning the agency. The FDA should open dockets and request information on the chemicals it prioritizes, including data on safety and current uses for the chemicals.

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C. Establish Clear Criteria for Selecting Focused vs. Comprehensive Assessments

We recognize that the FDA needs a system for responding quickly and efficiently to more trivial issues, but we have major concerns with the focused assessment process the FDA intends to use. Our primary concerns with the focused assessment center on the decision-making process for whether a substance will be subjected to a focused or comprehensive assessment. The discussion paper generally fails to explain the criteria that will be used for any decision point in the proposed framework, and this is true of the focused versus comprehensive decision point. Detailed criteria are especially important in this case given the major differences between the focused and comprehensive assessment processes.

It seems that the FDA intends to use focused assessments in response to a diverse spectrum of signal types, ranging from signals arising from social media to the publication of new scientific information, but the agency has not clearly defined the bounds of that spectrum. We would agree that focused assessments are appropriate when the agency needs to quickly respond to the more trivial matters that arise frequently in the popular press or social media or similar signals.

Decisions made within the focused assessment process should be based on the weight of evidence. Thus, focused assessments are likely to be most appropriate for the evaluation of new evidence when the agency has recently completed a comprehensive assessment. In such a case, the new evidence can be easily integrated into the existing body of evidence and conclusions. Studies that replicate the design and results of studies that have previously been evaluated by the FDA as part of a comprehensive safety assessment, for example, are probably appropriate candidates for evaluation under the focused assessment process. Studies with novel designs or different results are likely to require deeper analysis and might not be appropriately addressed by a focused assessment. If the new study is inferior in quality to studies in the existing body of evidence such that it is unlikely to influence prior conclusions, a focused assessment might be appropriate. We suspect that these are the sorts of considerations that the FDA intends to make as part of the Triage and Fit For Purpose processes briefly described in the discussion paper, but the discussion paper lacks clarity and specificity on these matters.

Since the FDA intends for focused assessments to be less resource-intensive and faster than comprehensive assessments, we are concerned that the FDA may be tempted or pressured to use a focused assessment when a comprehensive assessment is more appropriate. Indeed, there is evidence that the agency has already misused its intended focused assessment process.

During the public meeting, the FDA presented a memo on the safety of erythritol that the agency drafted in response to the publication of a new study (12). That study, Witkowski et al. 2023, was a human study that suggested that erythritol might increase the risk of major adverse cardiovascular events. The agency described its assessment of this new evidence as an example of how focused assessments might occur under the proposed framework. The memo lacked details necessary to understand how, upon considering the new evidence, the FDA determined that erythritol is safe. The memo states that the "purpose of this memo is to summarize the key findings presented in the paper, placing into context the implications of this study with

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previously published toxicological data on erythritol." Yet, it is unclear how the agency defined, searched, and reviewed the existing body of evidence and integrated the new study into that body of evidence. The memo states there is a need for additional studies to clarify uncertainties and fill gaps but makes no mention of whether or how the FDA intends to actively seek these data. This memo seemingly was not subjected to any external review. In our opinion, given the novelty of the results, the fact that Witkowski et al. was a human study, the complexity of the issue, the severity of the health outcome, and the potential for controversy, a focused assessment without external engagement was not appropriate in this case.

Recommendations: As part of its detailed methodology, the FDA should explicitly detail the criteria it will use in determining when it will conduct a focused assessment versus a comprehensive assessment, particularly in response to the publication of new scientific evidence. Factors that the FDA might consider in establishing these criteria include: whether the agency has recently completed a comprehensive assessment; whether the new study replicates studies already evaluated by the FDA (either in design or results); study quality relative to the existing body of evidence; complexity of the scientific or regulatory issues; severity of the health outcome in question; and potential for public controversy. Decisions made within the focused assessment process should be based on the total weight of evidence and single studies should not be assessed in isolation.

We suggest that focused assessments never be used in response to the following (i.e., these should always prompt comprehensive assessments):

- New evidence from well-designed human studies (including clinical and epidemiological studies), systematic reviews/meta-analyses, adverse event reports, or other sources that suggest a food chemical is causing harm in the human population, particularly if the risk is high either in severity or magnitude; in establishing its criteria, the FDA should specify clearly how it will classify a study as "well-designed;"
- New evaluations by other authorities, especially evaluations that challenge the safety assessments that serve as the basis of existing U.S. authorizations or GRAS determinations;
- New evidence from well-designed animal studies identifying a previously unknown hazard or better characterizing a known hazard.

We provide the above as examples. The agency might further identify categories of information that should always prompt comprehensive assessments, and if so, the agency should specify what those categories are.

D. Improve Data Quality

It is impossible for the FDA to confidently establish safety without high quality hazard and exposure data. The FDA should take active steps to improve data quality on adverse effects from, and exposure to, food chemicals. Yet, it is unclear from the discussion paper the extent to which improving data quality is a goal of this framework. If the agency has a separate process whereby it will seek to improve data quality, it should indicate that.

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Exposure data are necessary for a risk assessment, but there is often a lack of high-quality, recent, generalizable exposure data for food chemicals. Consider aspartame, for example, which is regarded by the FDA as one of the more widely studied food additives (13). In 2024, though, Riess et al. published estimates of aspartame exposure in the U.S. using a novel method for estimating food additive exposures that linked consumer purchase data (acquired from NielsenIQ Homescan), ingredient label information from the U.S. Department of Agriculture (USDA) Branded Food Products Database (BFPD), consumption data from the National Health and Nutrition Examination Survey (NHANES), and aspartame use levels from the published literature, ingredient statements, patents, or calculations based on its sweetness relative to sucrose (14). Previously, Chazelas et al. developed a method for estimating dietary exposures to food additives among participants in the French NutriNet-Santé cohort study that combined 24-hr dietary recall records, ingredient presence/absence information from a combination of governmental and private (paid) databases, and quantitative composition data from laboratory testing or usage levels in food categories as reported/specified by EFSA or the Codex General Standard for Food Additives (15). This method was then used to assess aspartame exposure in the NutriNet-Santé cohort in 2022 (16, 17). Thus, even for one of the most widely studied additives, our understanding of quantitative exposure has been limited until recently.

Notably, both of these recently developed exposure estimation methods rely on ingredient declarations. Considering that there are categories of food chemicals for which declaration by name on the ingredient list is not required—specifically, flavors and spices (18), certain color additives (19), and incidental additives (20)—these methods are not able to be applied to all categories of substances intentionally added to foods. Similarly, these methods could not be readily applied to food contact materials or contaminants because these do not appear on ingredient lists. The FDA has developed methods for estimating exposures to certain chemical contaminants of foods that use the agency's Total Diet Study (21), but the scope of chemical contaminants measured by the Total Diet Study is limited (22).

> **Recommendations**: The FDA should engage in efforts in collaboration with academic, governmental, industry, and independent researchers to adapt existing exposure estimation methods (e.g., those recently published by Chazelas et al. and Riess et al.) or to develop new methods for improving exposure assessments. As part of these efforts, the FDA should specifically work with USDA and industry to improve the BFPD to ensure that the database accurately reflects the current U.S. packaged food market. Similarly, the FDA should collaborate with the CDC to improve NHANES data collection as needed to facilitate easier estimation of food chemical consumption. Improving the quality of both BFPD and NHANES will enable both agency and non-agency scientists to continue improving exposure estimates and refining estimation methods.
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> The FDA should consider expanding the Total Diet Study to include other chemical contaminants in food (e.g., per- and polyfluoroalkyl substances [PFAS], other persistent organic pollutants, acrylamide, and polycyclic aromatic hydrocarbons) and generally work in collaboration with diverse stakeholders to increase testing of foods for toxic elements and these other chemical contaminants in order to facilitate improved exposure estimation.

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The FDA should revise its ingredient labeling regulations to require specific disclosure of all flavors, spices, color additives, and incidental additives used in foods (see CSPI's 2024 report, *Hidden Ingredients*, for additional details and policy recommendations (23)).

In addition to high-quality exposure data, the FDA needs high-quality hazard data for its risk assessments. While the FDA currently recommends animal and in vitro tests for assessing food chemical safety (24), human data provide the most directly relevant hazard information for evaluating human health risks. Yet, as with exposure data, there is a notable lack of high-quality human hazard data for many food chemicals.

Recommendations: The FDA should engage in, and support, research efforts to improve the quantity and quality of data on human health effects related to food chemical exposures, especially including human randomized controlled trials and longitudinal studies, as appropriate, because these will provide the highest-quality and most useful data.

The FDA should continue to improve its adverse event reporting portal to make it easier for consumers to submit reports, revise the portal as needed to ensure that the data collected are useful for hazard identification, and conduct an educational campaign to ensure that consumers are aware that this portal is available and encourage them to use it (25).

The FDA should also work to utilize disease registries, hospital records, electronic health records, wearables, meal-tracking apps, and digital surveillance tools (e.g., monitoring trends in Google searches and social media) to identify health effects associated with dietary exposures to food chemicals.

Recognizing that generating high-quality human data will take years or decades, the FDA must also take steps to ensure the quality of animal and in vitro evidence. We are aware that the FDA currently provides guidance to industry on recommended testing for food chemicals, with recommendations based on structurally predicted toxicity and anticipated exposure (24), as well as guidance to industry on toxicological principles for the safety assessment of food ingredients (this guidance is known as the "Redbook" and primarily outlines animal testing protocols) (26). However, neither of these guidances are binding and neither has been updated in more than 15 years. These guidances, therefore, are not sufficient to ensure that the animal and mechanistic data available is of sufficient quality to produce reliable risk assessments, especially for GRAS substances that never undergo FDA review and of which the agency may be unaware.

Recommendations: The FDA should establish a mandatory approach to data collection and testing to replace its guidance on recommended tests. In establishing this mandatory approach, the FDA could take into consideration chemical structure and likely exposure as its current testing guidance does. If the agency determines it lacks authority to establish a mandatory approach, it should request it from Congress.

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For substances intentionally added to food or food contact materials, when data are severely lacking to the point that the FDA is unable to complete an assessment of whether there is a reasonable certainty of no harm, the FDA should consider revoking authorizations or GRAS status until deficiencies are rectified.

The FDA should modernize the Redbook, taking into consideration recommendations made by CSPI and others in response to the FDA's 2014 public meeting and solicitation of written comments (27, 28) as well as principles and practices currently employed by other agencies (e.g., the NTP, EFSA, EPA, IARC, and JECFA).

In setting data and testing requirements, the agency should specify what data are needed to facilitate identification and consideration of subpopulations of concern.

The discussion paper does not indicate that the FDA will request stakeholder information at any point in the focused assessment process or before the risk management step in the comprehensive assessment process, which could deprive the agency of information it needs to consider. Ideally, rather than requesting such information, the FDA would compel industry stakeholders to supply the agency with important information such as unpublished safety data resulting from industry-sponsored studies and data on use levels in foods.

Recommendations: The FDA should develop a process for acquiring information relevant to the risk assessment and risk management processes for both focused and comprehensive assessments. If the FDA determines it currently lacks sufficient authority to compel industry to supply such information, it should ask Congress to grant that authority.

E. Enhance Focus on Public Health Protection

Recent actions by the FDA raise concern about the way the agency takes industry's interests into consideration and balances those against public health protection. Specifically, when the FDA proposed action levels for lead in certain categories of juice and prepared baby foods, the FDA evaluated the current level of lead contamination in products on the market and proposed action levels that 90-95% of products could already achieve (i.e., only the 5-10% most contaminated products would be eliminated from the market) (29, 30). CSPI critiqued this achievability-first approach in two sets of comments made to the agency, detailing how this approach is fundamentally backward and misses critical opportunities to maximize public health benefit (31, 32). We urged the FDA to set initial levels based on what is needed to protect public health and then to make any adjustments based on achievability. We are concerned that the FDA might adopt an approach in its enhanced post-market framework that is similarly deferential to industry.

Recommendations: The FDA's risk assessments should only include data relevant to health and safety, not non-risk factors like cost, feasibility, and availability of alternatives. When managing risk, the FDA's top priority should be protecting public health, not minimizing impacts on industry or prioritizing industry achievability.

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In the Triage section of its discussion paper, the FDA indicates that at this step it will conduct a preliminary impact assessment.

> **Recommendations**: The FDA should clearly specify whether "impact" means public health impact, market/economic impact, both, or some other impact. Importantly, even if a preliminary impact assessment takes into consideration market impacts, ultimately the decision as to whether to initiate a post-market assessment should be based on risk and the public health need.

F. Reform GRAS to Reduce the Burden on the Post-market System and Facilitate Better Surveillance

Even as the FDA works to improve its post-market assessment activities, many new food chemicals are coming to market without FDA oversight due to the GRAS exemption and the FDA-designed voluntary GRAS notification procedure. Companies are making safety decisions in secret and may well be failing to fulfill their obligations to rigorously assess the safety of food chemicals prior to use. This loophole undermines the FDA's efforts to ensure that the chemicals in our foods are safe before coming to market. It creates situations where the FDA only acts after consumers have been harmed and then deprives the agency of information necessary for conducting post-market surveillance and safety assessments. The FDA does not know which chemicals are on the market or whether the underlying data demonstrate their safety.

When asked at the public meeting how the FDA plans to identify and evaluate the safety of GRAS substances not known by the agency, Dr. Kirk Arvidson, the FDA's Chief of the Scientific Development Branch, Office of Food Additive Safety, stated:

> "[FDA began] developing a number of tools, both in information technology as AI and machine learning-based approaches such as the WILEE horizon scanning tool for signal detection and the FoodTrak food labels database. We can use those in our monitoring and surveillance of the food supply. These tools can be used to identify new ingredients through the signal detection tools that WILEE has and monitor for trends in the food supply."

Let us state the obvious: the surveillance system described by Dr. Arvidson is an after-the-fact attempt to compensate for the faulty GRAS process, a process that has been made worse by the FDA itself. In 1997, although not compelled to do so by law, the FDA proposed regulations that allowed companies to self-affirm the GRAS status of new chemicals and introduce them to market without telling the FDA, and the agency finalized those regulations in 2016 (33, 34). The FDA thereby created a system that allows these substances to enter the market secretly and is now attempting to develop another system to identify those same chemicals. It is clearly in the agency's best interest to reform the entire system.

> **Recommendations**: The FDA should commit to revisiting its GRAS regulations and announce a timeline for notice and comment rulemaking on GRAS reform. New

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regulations should ensure that GRAS determinations and supporting documentation are made public and are reviewed by the FDA.

Until a pre-market GRAS notification and substantiation requirement is enacted, the FDA should publish the methods it is using for conducting surveillance for unknown GRAS substances. Such a system should be designed to identify substances as soon as possible after market entry and should not rely solely on outbreaks, adverse event reports, or other indicators of harm. The FDA should regularly publish on its website the identities of new GRAS substances it finds via these surveillance efforts.

According to the FDA's regulations, for a general recognition of safety to exist, the underlying data and information must be publicly available (34), and as such FDA experts responsible for ensuring food chemical safety and the public should be able to access that information and data.

Recommendations: When the FDA identifies a previously unknown GRAS substance, it should request data from the companies using or marketing the substance. If those companies fail to provide a timely and scientifically adequate response, and the FDA is unable to independently locate sufficient data establishing GRAS status in the scientific literature or elsewhere in the public domain, the agency should reach a de facto conclusion that the substance is not GRAS. The FDA should then seek to revoke GRAS status, prioritizing substances for which a safety signal has been identified.

There is recent precedent for the agency reaching a "not GRAS" conclusion due, at least in part, to a lack of adequate data. The FDA's 2024 scientific memorandum on the regulatory status of tara flour stated, "Due to the lack of adequate data and information in the scientific literature to support the safe use of tara flour in food, [the Division of Food Ingredients] is unable to conclude that the addition of tara flour to food meets the statutory criteria for classification as GRAS" (35). The FDA's investigation into tara flour was spurred by an outbreak of liver injuries and other adverse events associated with foods containing tara flour, and these adverse events seemingly also informed the "not GRAS" determination. Nonetheless, the lack of adequate data was clearly a driving factor for the FDA's "not GRAS" conclusion. Under our proposed approach, combined with the FDA's new surveillance tools, the agency might have identified the lack of data for tara flour sooner, potentially even before the outbreak began. Furthermore, we hope and anticipate that, within our proposed system, companies would be further encouraged to preemptively provide GRAS determinations to the FDA and to better publicize the data supporting their GRAS determinations.

G. Rigor and Transparency

In the FDA's memorandum on erythritol, the agency said, "…there is an inherent limitation of observational studies to establish causation," and later in reference to the recent study by Witkowski et al., "…the observational studies in this paper are incapable of establishing causation" (12). Observational studies can provide strong evidence of causation between exposures and effects in the human population when they are well-designed and executed, especially when combined with mechanistic data. In many cases, observational studies may be

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the only human evidence available for food chemicals. All study designs, including observational studies, have inherent strengths and limitations which must be carefully considered when conducting a weight-of-evidence analysis.

> **Recommendation**: The FDA's methodology should specify how it will evaluate observational evidence alongside other human, animal, and mechanistic evidence in an integrative weight-of-evidence approach that considers the strengths and limitations of each study design comprehensively.

The FDA's discussion paper does not describe how the agency will set timelines for the completion of assessments or communicate those timelines to the public.

> **Recommendations**: We recognize that each assessment will be unique and, as such, the FDA will not be able to establish a standard timeframe for completing all reviews, but the FDA should establish an intended timeline for assessing each substance, publish those timelines on the agency website, and update them regularly to track progress in completing its assessments. This will allow all stakeholders to better anticipate when the FDA action will occur and be prepared to provide useful input.

The FDA's discussion paper does not propose a centralized channel for communicating the outcomes of its assessments to the public. Currently, the FDA's post-market safety activities are communicated to the public through a number of channels, including Federal Register publications, guidances, agency webpages, and peer-reviewed journals. The FDA lacks a centralized and transparent resource consolidating the scientific safety assessments and risk management decisions it makes for food chemicals. This stands in contrast to other U.S. and international authorities, including the EPA,[i] NTP,[ii] EFSA,[iii] and JECFA.[iv] The disparate avenues the FDA currently uses to disseminate its assessments provide varying degrees of detail, transparency, rigor, and safeguards against bias and conflicts of interest, with peer-reviewed journals typically offering the highest degree of these qualities.

> **Recommendations**: The FDA should detail its plans for finalizing and publishing the outcomes of its reassessments. The FDA should establish a centralized, publicly available database for its evaluations.

Peer-review is an essential facet of scientific evaluation.

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[i] The EPA's Integrated Risk Information System (IRIS) catalogues toxicity values for health effects resulting from chronic exposure to chemicals as determined by the agency (https://www.epa.gov/iris).
[ii] The NTP publishes the U.S. Department of Health and Human Services Report on Carcinogens, which compiles cancer hazard classifications made by the program (https://ntp.niehs.nih.gov/whatwestudy/assessments/cancer/roc). NTP also publishes information from its testing program in a publicly accessible database on the program website (https://ntp.niehs.nih.gov/whatwestudy/testpgm/substance-search).
[iii] In the EU, scientific assessments on the safety of food chemicals as well as guidelines for assessing safety are published in the EFSA Journal (https://efsa.onlinelibrary.wiley.com/journal/18314732).
[iv] The WHO maintains a publicly available database on its website of JECFA evaluations, including detailed toxicological monographs (https://apps.who.int/food-additives-contaminants-jecfa-database/).

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Recommendations: The FDA should subject comprehensive assessments to peer review by panels of external/independent unconflicted experts. The FDA could consider creating and using a subcommittee of the FDA Food Advisory Committee to facilitate peer-review of its post-market assessments. There will likely be situations in which focused assessments should also be subjected to external peer-review; thus, the FDA should specify how it will determine when a focused assessment will undergo peer-review.

H. Include Assessment of Dietary Ingredients and Chemicals Added to Supplements in the Framework

Much of the foregoing discussion applies equally to dietary supplements and dietary ingredients. The FDA regulates dietary supplements as foods, many substances used in supplements are also used in conventional foods, and the GRAS process is one mechanism by which new dietary ingredients enter the supplements market, meaning the dietary ingredients and other substances added to supplements are food chemicals (36-38). Furthermore, many of the entries in the FDA's current list of substances deemed "not GRAS" by the agency are, or were, commonly used in products marketed as dietary supplements—examples include Ginkgo biloba, melatonin, kava, tianeptine, cannabidiol, and delta-8 tetrahydrocannabinol (39). However, the discussion paper does not mention dietary ingredients or dietary supplements, leaving it unclear whether the FDA intends this framework to apply to dietary ingredients and dietary supplements.

Recommendations: The FDA should explicitly include dietary ingredients and other chemicals used in dietary supplements in the scope of its enhanced post-market assessment framework. If needed, the FDA should specify in its detailed methodology for post-market assessment how the agency's approach to assessing risk and safety for these substances or products will differ from that for other food chemicals.

II. Responses to FDA's Questions

1. **When and how should the FDA engage the public on post-market assessments?**

We provide recommendations pertaining to public/external engagement in Section I of these comments (see pages 4, 6, 10-11, and 12-15).

2. **Is the frequency and mechanisms of the envisioned public engagement described in Section V of [the FDA's discussion paper] appropriate? If not, please provide alternative areas for engagement/communication, additional information that you believe should be shared publicly, and rationale for the change**.

We provide recommendations pertaining to public/external engagement in Section I of these comments (see pages 4, 6, 10-11, and 12-15).

3. **Should the FDA integrate an advisory committee review into our post-market assessment process? If yes, at what stage, and what should the committee's role be?**

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We would like the FDA to subject its entire enhanced framework, including methodologies, as well as all comprehensive assessments and some focused assessments to peer review. This could take the form of the Food Advisory Committee, but there may be other suitable formats. We make recommendations on this issue in Section I of these comments (see pages 4 and 15).

4. **Are the Fit for Purpose Decision Tree questions in Section III of [the FDA's discussion paper] appropriate? If not, what questions would you add or how would you modify the questions to be more appropriate to the task?**

The Fit for Purpose section of the FDA's discussion paper is simply a list of questions with no indication of how answers to those questions will impact decision making. In addition to the lack of detailed criteria, we have concerns with several of the questions.

We would argue that, in principle, resource requirements should not dictate the level of review a substance gets. If resource availability is preventing the FDA from completing the type of assessment the agency deems scientifically necessary, more resources should be sought rather than selecting a less resource-intensive assessment or foregoing the assessment entirely.

This question: "Is there scientific consensus and/or strong weight of evidence about the substance suggesting its potential to impact the prevailing conclusion of reasonable certainty of no harm under the conditions of use in food?" is concerning. It seems to imply that there could be instances where the FDA chooses not to conduct a review, instead deferring to its prior conclusions or deferring to assessments by other agencies or industry without critical evaluation, effectively accepting those assessments at face value. In our opinion, this would not be appropriate. While we support the agency in streamlining its processes, completing reviews efficiently, and avoiding duplicative efforts, prevailing conclusions can be wrong or influenced by bias. Moreover, consensus can shift over time as new evidence emerges and scientific understanding evolves. The FDA should independently verify the validity of any prevailing conclusion and very rigorously assess potential bias and conflicts of interest in doing so.

5. **Is the Prioritization of Risks scheme the FDA outlines in Section IV of [the FDA's discussion paper] appropriate for ranking food chemicals, (including contaminants, food ingredients, and those substances used in contact with food) for post-market assessments? If not, please explain why and how you would modify the Prioritization of Risks scheme. Please provide supporting rationale for the changes.**

We are supportive of the FDA prioritizing based on risk using a quantitative or semi-quantitative approach. However, we would need a much greater degree of specificity regarding this methodology before we can specifically endorse the proposed Multi-Criteria Decision Analysis (MCDA).

We are tentatively supportive of the FDA adapting the EPA's approach to chemical prioritization (40) and the FDA's risk-ranking model for traceability (41) for this purpose. Both of these existing frameworks are risk-based and have features that the FDA should retain in its MCDA,

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but both also contain features that are not relevant for the FDA's post-market assessment of food chemical safety (e.g., some aspects of the FDA risk-ranking model for traceability are specific to microbial contamination). Therefore, we ask the FDA to explicitly detail how it will adapt these approaches in the development of its MCDA.

Public engagement is a key aspect of both of those frameworks that the FDA should retain. The FDA subjected its risk-ranking model for traceability to extensive external review, including public comment and peer review; the FDA should similarly subject its forthcoming MCDA to external peer review by independent, unconflicted experts and invite public comment.

The EPA's approach excludes consideration of cost and non-risk factors, and it specifies that absence of sufficient data results in a substance being designated as high priority (i.e., there is a baseline assumption of high risk). The FDA should similarly exclude non-risk factors from consideration in its prioritization process (and in its risk assessment process, as discussed in Section I.E. of these comments beginning on page 11). Furthermore, FDA should also consider adopting an approach where inadequate data leads to revocation of GRAS status or authorization, as we discussed in Section I of these comments (see pages 11 and 13).

The EPA's method gives preference to chemicals that are carcinogenic, have high acute/chronic toxicity, bioaccumulate, or are biopersistent. The FDA's risk-ranking model for traceability uses a four-level rating system for hazard severity with a score associated with each: 0 = no known adverse health consequences (not a hazard), 1 = Moderate hazard: not usually life threatening; no sequelae; normally short duration; symptoms self-limiting; can be severe discomfort; transient effects, resolved with little or no medical intervention, 3 = Serious hazard, for general or susceptible population: incapacitating, but not usually life threatening; sequelae infrequent; moderate duration, 9 = Severe hazard, for general or susceptible population: life threatening or substantial chronic sequelae; long duration; death or death likely to occur. In describing the MCDA in the discussion paper, the FDA states that, among other factors, a substance associated with potentially life-threatening health effects would likely receive a higher score in the risk-based prioritization system the FDA intends to use. We suggest that, in addition, substances causing or linked to non-life-threatening yet severe, irreversible adverse health effects (e.g., developmental neurotoxicity, reproductive toxicity) also be prioritized, comparable to the risk-ranking model. Substances that bioaccumulate or that are biopersistent should also be prioritized, similar to the EPA's method. Evidence of adverse effects in human studies should also be given higher weight.

One key downside to the EPA's approach is that designations are dichotomous (i.e., chemicals are either high- or low-priority, with no ranking) and not quantitative. The FDA intends to deviate from this and instead take a semi-quantitative approach and rank chemicals based on risk, which we support.

We agree with the FDA's intent to prioritize substances for which exposure or production has increased and substances that may specifically affect vulnerable subpopulations.

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We look forward to reviewing and commenting on a more detailed description of the FDA's MCDA.

6. **Is the FDA's two-pronged approach of Focused Assessments and Comprehensive Assessments appropriate to assess public health risks of chemicals in food? If not, please explain why and provide an alternative process, including rationale for such alternative(s).**

This approach could be appropriate, but only with major revisions to the framework overall and to the focused assessment process specifically. See our detailed comments and recommendations in Section I of these comments (see pages 7-8, 11, and 15).

III. Concluding Remarks

We appreciate the FDA's commitment to enhancing its post-market assessment system for food chemical safety, and its consideration of our comments. We look forward to seeing how this framework develops and its eventual implementation.

Sincerely,

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