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

Re: Tool for the Prioritization of Food Chemicals for Risk Assessment; Request for Comments (Docket No. FDA-2025-N-1733-0001)

Dear Sir or Madam:

Thank you for the opportunity to comment on the Food and Drug Administration's (FDA's) Tool for the Prioritization of Food Chemicals for Risk Assessment ("Prioritization Tool").[1] As the Food Industry Association, FMI works with and on behalf of the entire industry to advance a safer, healthier, and more efficient consumer food supply chain. FMI brings together a wide range of members across the value chain — from retailers that sell to consumers, to producers that supply food and other products, as well as the wide variety of companies providing critical services — to amplify the collective work of the industry. More information about our organization is available at www.FMI.org.

FMI greatly appreciates the actions FDA has taken to date toward the development of an enhanced approach to conducting Post-Market Assessments of chemicals in food. We have been actively engaged throughout the process since the August 2024 publication of the FDA Discussion Paper outlining the proposed process and the September 25, 2025 Public Meeting hosted by FDA. To reiterate the oral comments we delivered at the Public Meeting, and the written comments we submitted to Docket No. FDA-2024-N-3609 (incorporated by reference herein), FMI and its members are committed to ensuring a safe food supply and we welcome FDA's efforts to engage in Post-Market Assessments of chemicals in food using an approach that is both transparent and grounded in sound science.

FMI supports having a basic framework for prioritizing chemicals for risk assessment, as it would enable the agency to evaluate how it will use its resources effectively and efficiently. At the same time, FMI would welcome additional detail and specificity regarding the agency's use of the Tool within the wider process for Post-Market Assessment, so it and other stakeholders can

[1] FDA Seeks Input on a New Method for Ranking Chemicals in Food for Post-market Assessments (June 18, 2025), available at https://www.fda.gov/food/hfp-constituent-updates/fda-seeks-input-new-method-ranking-chemicals-food-post-market-assessments.

fully understand how the process will work in practice and to ensure that the process is transparent, science-based, and applied consistently to maximize benefit for the U.S. consumer.

We offer below two general comments on the proposed Prioritization Tool before responding to the specific questions raised by the Agency:

- FMI Requests Additional Opportunity to Comment on the Prioritization Tool Once FDA Has Finished Developing the Revised Post-Market Assessment Framework:

As a threshold issue, because the details of the final Post-Market Assessment process are under development, there are open questions about the purpose and functionality of the Prioritization Tool. The Overview section of the Prioritization Tool paper states, "the systematic post-market assessment of food chemicals consists of the following steps: signal detection, triage, prioritization, scoping, scientific assessment (safety, risk, and/or hazard), risk management review, and risk management action," and that a "full description of the process will be published later this year." It is not clear, however, whether and to what extent the final process will retain elements from the framework outlined in the August 2024 Discussion Paper. For example, the August 2024 Discussion Paper contemplated both "focused" and "comprehensive" assessments, with the "prioritization" step occurring only for comprehensive assessments. It is not clear whether FDA intends to maintain the two types of assessments and, if so, where exactly the prioritization step will occur. Moreover, it is difficult, if not impossible, to determine whether the proposed Prioritization Tool is appropriate without understanding the criteria that will be used for the initial signal detection and triage steps. FMI appreciates the work FDA has done to develop the Prioritization Tool, yet FMI is not able to fully assess the purpose and effect of the tool without considering it within the proper context of the full Post-Market Assessment process. We therefore urge FDA to reopen the comment period for the Prioritization Tool once additional details of the post-market assessment process are made public.

- FDA Should Commit to Releasing the Prioritization Score Assessments and Conducting Timely Assessments of Prioritized Chemicals:

To reiterate FMI's prior written comments: clear and consistent communication to the public about any Post-Market Assessment action taken and what it signifies is necessary to convey potential risks effectively and to reassure consumers of the safety of our food supply. With respect to the Prioritization Tool, we ask FDA to commit to releasing the prioritization assessments and their scoring results for each chemical to which the tool is applied. This information – which would include the individual scores assigned to each criterion and the calculation performed to reach the Total Prioritization Score for each substance – will allow the public to understand why a substance was prioritized over another and will help further FDA's commitment to radical transparency. Moreover, once a chemical has been prioritized and identified for post-market review, conducting a timely assessment and publishing the

conclusions regarding the safety of the substance is critical for maintaining public confidence in the food supply.

Additionally, as an overarching comment about the structure of the Prioritization Tool, we urge FDA to reconsider the inclusion of non-scientific "Other Decisional Criteria" in its current form in the Prioritization Tool. We believe it is important for the Agency to address external concerns that have the potential to undermine confidence in the post-market assessment process and, more broadly, the safety of the food supply chain. However, we have significant concerns with the proposed "Other Decisional Criteria" as drafted, which we address in detail in our answer to Question 2(b).

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FMI's responses to FDA's specific questions for comment follow.

1. **The purpose of the Post-market Assessment Prioritization Tool is to assist in making decisions about which chemicals, including both intentionally added substances and unintentional contaminants in food, are a priority to review. Is the modeling approach we proposed appropriate for this purpose? If not, please explain your reasoning and provide alternatives for FDA to consider. Please be specific and provide references, as appropriate.**

As discussed above, it is not possible to determine whether the proposed approach is appropriate without understanding where the prioritization step falls within the overarching Post-Market Assessment process and the criteria for the preceding steps of signal detection and triage.

As noted in our prior comments, FMI suggests that the post-market assessment work should primarily focus on intentionally added substances, while contaminants should continue to be managed through existing initiatives, such as FDA's *Closer to Zero* program in the case of toxic elements. Chemical contaminants typically are unavoidably present in food and are subject to different exposure scenarios, risk assessment methodologies and risk management strategies than intentionally added substances that have been subject to pre-market review. If the combined approach is maintained, the overarching Post-Market Assessment framework and elements of the Prioritization Tool may need to be modified. For example, contaminants typically have hazard properties greater than intentional additives; however, their exposure is typically much lower. As the prioritization scheme is designed on hazard criteria (not risk) it will prioritize contaminants over intentional additives, irrespective of risk or ability to mitigate such risk. FDA should ensure that the prioritization process considers that unintentional substances have not gone through "pre-market" review the way other substances have, and adjust the prioritization process accordingly, if needed.

Although not directly relevant to the prioritization step, the risk assessment and risk management approaches that are appropriate for unintentional contaminants are different from

those that are appropriate for intentionally added substances. It is pivotal for FDA to consider the nuances required for the different substances when developing the risk assessment methodologies and risk management strategies that will be employed as part of the larger Post-Market Assessment framework.

2. **The draft Post-market Assessment Prioritization Tool currently includes four Public Health criteria and three Other Decisional criteria.**
    a. **Are the four Public Health criteria appropriate for the purpose of the tool? If not, please explain what changes might be considered and why.**

Although FMI generally supports the four Public Health criteria (Toxicity, Change in Exposure, Susceptible Subpopulation, and New Scientific Information), we believe there are opportunities to refine the descriptions for the "change in exposure" and "susceptible subpopulation" criteria, and offer comments on the "new scientific information" criterion below. We address the Toxicity Rubric in more detail in response to Question #3.

- The "*change in exposure*" criterion considers the question: "Have there been changes in exposure since the last assessment, such as level (e.g., above regulatory level), consumption (e.g., consuming populations, amount consumed, products consumed, how prepared), production volumes, and/or conditions of use?" We are concerned that because the "Change in Exposure" criterion does not explicitly consider estimated cumulative exposure, it does not facilitate a risk-based prioritization. Section 409(c)(5) of the Federal Food, Drug, and Cosmetic Act requires that FDA make food additive safety determinations based upon 1) the probable consumption of a food additive or constituent, 2) *the cumulative effect of such additive in the diet* (emphasis added), and 3) safety factors that are generally recognized as appropriate for the use of animal experimentation data.[2] Accordingly, the Agency's safety assessments of food chemicals must consider the dietary exposure of a food additive as a component of the prioritization and risk assessment.

  Since 1958, FDA has operated under the tenet of toxicology that "the dose makes the poison." For example, the preamble to the 1997 Proposed Rule to amend 21 C.F.R. § 170.30 includes this foundational principle as an example of a "common scientific principle" that underlies a determination that a substance is safe when present in food at certain levels even if it exhibits toxicity when present at higher levels.[3] An increase in

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[2] Although "other relevant factors" may be considered, FDA "shall consider" the factors listed here. FFDCA § 409(c)(5).

[3] 62 Fed. Reg. 18942 (April 17, 1997). Other FDA publications demonstrate the Agency's ratification of this principle and historical deference to it when determining the amount of attention a certain food chemical should receive. *See* U.S. Food and Drug Admin., *Guidance for Industry: Summary Table of Recommended Toxicology Testing for Additives Used in Food* (June 2006) https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-summary-table-recommended-toxicological-

exposure on its face, without taking into account estimated cumulative exposure, does not necessarily warrant a high score for prioritization. In other words, although exposure might double in a certain scenario, estimated cumulative exposure might still be extremely low, such that a high score is not warranted. Therefore, we recommend that FDA revise the Public Health criteria to include estimated cumulative exposure. FMI does not recommend conducting a formal or rigorous determination of a food chemical's dietary intake (CEDI), but rather that FDA identify general estimates of cumulative exposure based on existing data that can be used to conduct a "mini" risk assessment to provide a science-based approach to prioritization.

Additionally, the scoring rubric assigns a score of "9" if the "exposure has considerably increased because data indicate considerably higher levels of the chemical OR found in food(s) highly consumed OR considerable increase in production volume of the chemical." FMI is concerned that there is a lack of data necessary to evaluate changes in exposure based on the current language. Moreover, these descriptions are not necessarily relevant to whether there has been a change in the exposure to a chemical and some descriptions present the risk that the Prioritization Tool will conflate prevalence data with exposure data. For example, an increase in production volume of a chemical alone does not mean that the chemical in question is being used in food products. Additionally, a chemical that is found in "highly consumed foods" could be present at extremely low levels that would not change the overall level of exposure. Together, these factors do not necessarily mean that there has been an increase in the actual intake of the chemical through food.

FMI therefore urges FDA to specify that changes in production volume should only be used for chemicals that utilize exposure estimation methods based on volume (e.g., Maximized Survey-Derived Daily Intake). Otherwise, we urge FDA to eliminate consideration of "production volumes" and whether the chemical is "found in food(s) highly/moderately/not often consumed" from the description and scoring considerations for "change in exposure." Instead, the criterion should be tied to a consumer's actual estimated exposure to the food chemical.

We provide additional comments on the scoring approach for "change in exposure" in response to Question 3, below.

- The "*susceptible subpopulation*" criterion is described as "Chemical is found (e.g., using label information from Mintel or another consumer-packaged goods database or FDA monitoring systems) or could potentially be present (e.g., occurs naturally, is introduced or formed during manufacturing, or based on proposed intended uses or technical effects) in food specifically intended for susceptible subpopulations." FMI urges FDA to

testing-additives-used-food, which takes into account cumulative human exposure when calculating levels of concern.

more clearly define "susceptible subpopulation," which the paper currently defines as "e.g., infants." We propose that the term refers to children up to three years of age (consistent with the Codex definition of young child). We do not believe there is value in including other potentially sensitive subpopulations within the definition (e.g., pregnant women) as foods generally are not specifically formulated to be eaten by such subpopulations.

- The *"new scientific information and potential impact*" criterion considers whether there is new scientific information available (e.g., new toxicity or adverse health effect data or studies; improvement in detection methods or limits; new data or studies on biopersistence) that would impact or change the conclusions of the previous assessment. We ask FDA to clarify that the agency will consider only high-quality, peer-reviewed, scientific studies as part of its evaluation of new scientific information and potential impact. A transparent scheme should be used to systematically weigh 'new evidence' such that prioritization is based on the likelihood that there is an adverse effect that has not previously been accounted for.

b. Are the three Other Decisional criteria appropriate for the purpose of the tool? If not, please explain what changes might be considered and why.

FMI supports and appreciates FDA's recognition of the need to consider both scientific data with policy considerations for Prioritization. We understand the purpose of including the Other Decisional criteria is to provide a means for ensuring public confidence not only in the regulatory process, but more importantly, in the food supply. When the public raises concerns about a particular chemical found in food to the point that it could lead to disruptions in the food supply chain, it is FDA's duty to respond by evaluating whether there is a scientific basis to support those concerns that would trigger Agency action, or to otherwise reassure the public, and U.S. trading partners, of the safety of how the chemical of potential concern is found in food. However, FMI is concerned that the three Other Decisional criteria, as they are currently defined, scored, and weighted, are not appropriate for the purpose of the tool, as they could erroneously stigmatize substances that remain safe for use in foods and may undermine the scientific principles that serve as the foundation of the Post-Market Assessment process. Additionally, FDA has stated that the Post-Market Assessment process will include a signal monitoring and surveillance stage. External stakeholder activity and/or other government decisions likely would be captured through this process, presenting the possibility that these factors could be counted multiple times during the assessment. Finally, and perhaps most importantly, assigning a numerical score to inherently subjective criteria could lead to inconsistent results and confusion among the public and regulated industry. We first provide comments on the criteria as currently proposed and then offer an alternative framework.

<u>Current Other Decisional Criteria</u>:

The Prioritization Tool includes three Other Decisional criteria: external stakeholder activity/attention, other government decisions, and building public confidence. We share our feedback on each criterion below:

- External Stakeholder Activity/Attention: With respect to the first criterion, although activity by/from external groups or organizations could be relevant to evaluating public interest in a given chemical, the Prioritization Tool does not adequately define which "organizations" or "stakeholder groups" would be considered as part of the assessment. Furthermore, a chemical could receive a score of "9" due to "high attention raising concerns" based on "social media coverage" or if there are "multiple organizations watching this." Not only are these scoring considerations vague, but they risk placing unreasonable weight on a (potentially unfounded) "high attention raising concern" regarding a given chemical or ingredient that has been amplified through unverified social media channels.

- Other Government Decisions: The second criterion concerns whether there has been action by other governmental agencies. FMI is concerned that action by an international or even state agency could be entirely irrelevant to whether a chemical presents a safety concern that would trigger the need for a Post-Market Assessment by FDA. For example, a decision from an international partner could be based on hazard-only frameworks or precautionary principles that differ from FDA's risk-based approach and using consumption and population data that are not relevant to the United States. Furthermore, there may be instances where another government's decision is not based on science at all, but rather driven by politics. Although recent regulatory action by other regulatory bodies could drive public interest in a given chemical, it is important to recognize that such action does not necessarily signal a change in the safety risk presented by the chemical.

- Building Public Confidence: Ensuring consumer confidence in the U.S. food supply is an important factor in post-market assessments. The description asks "[i]f a post-market assessment is not conducted, what potential impact may that have on public confidence in the safety of the U.S. food supply?" FMI believes this is not only relevant to consumer trust, but also to the integrity of the food supply chain. The post-market assessment process is an important mechanism for ensuring continuity of the food supply and minimizing avoidable food chain disruptions that could result from lapses in consumer confidence.

Furthermore, by assigning equal weighting to the quantitative Public Health Criteria and inherently qualitative Other Decisional Criteria, the Prioritization Tool risks distorting consumer and agency understanding of the single Prioritization Score attributed to a single chemical. As structured, this will not meet the FDA mission of protecting public health due to conflation of criteria not related to factual health risk. Therefore, we recommend the FDA consider adopting an alternative framework that accounts for public interest in a chemical, while still separating

science-based and policy-based considerations. Below are three options that FDA could consider in further discussions with industry and stakeholders, which could help mitigate the concerns discussed above. These are meant to serve simply as examples for FDA's consideration and we believe further discussion on this topic is warranted.

Option 1:

One way the Agency could achieve this is by eliminating the "Other Decisional Criteria" completely and base the Total Prioritization Score on the four Public Health Criteria. FDA then would use "Building Public Confidence" as an accelerating factor to rank substances after the Public Health Criteria have been applied. FDA could adapt elements of the Other Decisional Criteria to frame this question as follows: *"If a post-market assessment is not conducted, would it significantly impact public confidence in the safety of the U.S. food supply and/or the stability of the food supply chain?"*

If the agency concludes the answer is "Yes," the accelerating factor could be used to prioritize a chemical that otherwise would not have been prioritized based solely on its public health score. FDA would be required to document and publish as part of the Total Prioritization Score the extent to which the Building Public Confidence factor influenced the prioritization of a chemical for Post-Market Assessment, including identifying the specific factors the agency considered in reaching its conclusion. Such an approach would allow for the overall Total Prioritization Score to be based exclusively on scientific factors, while allowing the agency the ability to address the subjective criteria that drive public interest and public confidence in the food supply in a transparent way.

Option 2:

Alternatively, FDA could consider assigning a numerical value to the "Building Public Confidence" factor, as currently outlined in the paper, and including it in the overall Total Prioritization Score. Under this proposal, there would be 5 criteria: the 4 Public Health Criteria and 1 Building Public Confidence" factor.

Option 3:

Additionally, FDA could consider a letter-based system to represent the "Other Decisional Criteria", as proposed by other industry groups in their comments[4]. To separate science-based and policy-based considerations, the letter-based system (e.g. A, B, or C) would be appended to the numerical score derived from the "Public Health" criteria (e.g. 4.3A, 4.3B, 4.3C). By visually separating the scientific assessment and the broader contextual considerations of the Prioritization Tool, this format would prevent

[4] See comments from the Food Packaging Coalition.

the public from misinterpreting a single numerical score as a purely science-driven ranking.

Under this system:

"A" could indicate high external visibility or urgency, such as when a chemical is in the national spotlight, has drawn attention from senior leadership (e.g., the HHS Secretary or FDA Commissioner), or has been the subject of recent regulatory action by other regulatory bodies.
"B" could reflect moderate attention, such as limited media coverage or stakeholder interest without direct regulatory or political engagement.
"C" could denote minimal or no external attention.

We believe an alternative approach could allow the ultimate list of chemicals for review to be steered by sound scientific principles, while also allowing FDA to respond to public interest in a chemical by evaluating and, if appropriate, reaffirming the safety of a substance in a timely manner. As we have stated in other sections, clear and transparent communication to address consumer concerns regarding the safety of chemicals and the outcome of any post-market assessments is essential to ensuring public confidence in the food supply. If FDA chooses to maintain its current approach, we urge the agency to consider revising the Other Decisional Criteria to address the concerns raised above.

3. **The draft scoring definitions for all criteria were developed to consider the expected variability in the types and extent of data available for the wide variety of food chemicals that may be considered for review.**
    a. **Given this context, are the scoring definitions for the Public Health criteria appropriate for the purpose of the tool?**
        i. **Are the definitions appropriately defined? If not, please describe changes that might be considered and why.**
        ii. **The toxicity criterion described in Section 3.1.1 considers data for seven different toxicity data types and the score assigned reflects the highest toxicity data type score from the toxicity rubric, which is described in Appendix A Table A1. Is this the most appropriate strategy for assigning a toxicity criterion score? If not, please explain your reasoning and provide alternatives for FDA to consider. Please be specific and provide references, as appropriate.**

FMI believes the scoring definitions for "change in exposure" and "toxicity" could both benefit from additional clarity and refinement.

- **Change in Exposure**: In addition to our comments discussed in response to Question #2 above, which recommend that FDA include an estimated cumulative exposure criterion, FMI is concerned that the change in exposure criterion uses vague descriptions such as "considerably" increased (to merit a score of 9), or "moderately" increased (to merit a

score of 5), that do not correspond to defined scientific standards. We urge FDA to provide clearer definitions and quantitative metrics for how this criterion is scored. For example, FDA could base the scoring on whether the magnitude of exposure has increased such that new toxicity endpoints are relevant to the estimated exposure, and thus directly represent the change in risk resulting from the change in exposure.

- **Toxicity:** The "Toxicity" criterion considers seven different data types: acute toxicity; carcinogenicity/mutagenicity/genotoxicity; developmental and reproductive toxicity; neurotoxicity; other organ-specific toxicity; immunotoxicity; and bioaccumulation/biopersistence. Although we generally support the proposed Toxicity Rubric, we do offer the following recommendations for refinement:

    - Scoring System: All of the toxicity data types except for carcinogenicity/mutagenicity/genotoxicity assign a high score of "9" to a chemical if there is "evidence" of the relevant toxicity in humans. We urge FDA to revise this standard to specify what type of "evidence," including the weight and degree of uncertainty of that evidence, would merit a high score. Specifically, FMI recommends that a high score will be assigned only if the "weight of the evidence" indicates toxicity in humans.

      Additionally, for the developmental and reproductive toxicity (DART), neurotoxicity, and other organ-specific toxicity data types, FDA proposes to use a scoring system that would assign a "high" score for all chemicals with a repeat dose no-observed-toxicity level of < 250 mg/kg bw/day. However, using a toxicological end point of < 250 mg/kg bw/day would capture a large number of food chemicals, making prioritization challenging if not impossible. Rather, for these toxicity data end points, FMI recommends that FDA adapt the Toxic Substances Control Act (TSCA) score ranking for existing oral exposure data.[5]

      We believe that this will provide a more scientifically sound and refined list of chemicals that would present the type of toxicity concerns that would merit prioritization.

    - Animal and Human Studies: Several of the toxicity data types include end points based on animal studies. However, animal studies require interpretation as to their relevance to humans. When considering end points based on animal studies, we urge FDA to clarify in the Toxicity Rubric that the animal data considered will be limited to animal studies that have high likelihood of being applicable to humans and that human studies corroborated with data from animal and other studies will be weighted highest. Moreover, when evaluating human studies, we urge FDA to clarify that it will give greater weight to

[5] *See* TSCA Work Plan Chemicals: Methods Document Table 1.

randomized controlled trials, intervention studies, metanalyses and systematic reviews thereof where there is a plausible causation, rather than correlative data.

- Acute Toxicity: We recommend removing "acute" toxicity from the data types considered in the Toxicity Rubric. The inclusion of acute toxicity data in the Prioritization Tool is not appropriate, given the tool's intended purpose and scope. Acute toxicity data, which typically reflect short-term effects from high-dose exposures, do not accurately represent the chronic, low-level exposures that are more relevant to food safety assessments. FDA should instead handle observed acute toxicity to a food chemical through its inspection, enforcement, and recall operations, not through a post-market review prioritization process. Food chemicals fit for the post-market review process will generally be present in the diet at levels significantly below acute toxicity thresholds.

  If FDA chooses to retain the "acute" toxicity data type, we urge FDA to provide clarification regarding what would be considered a "poisoning" or "adverse event" that could trigger a "high" score.

- Carcinogenicity/mutagenicity/genotoxicity: A "high" score of "9" is assigned for carcinogenicity/mutagenicity/genotoxicity with a finding that either (1) the substance is classified as GHS 1A, 1B, GHS2, or by an authoritative entity as a probable or likely carcinogen (any route) in animal or human; or (2) the weight of evidence (in vitro, animal, or human) supports that the substance is genotoxic mutagenic or carcinogenic. We urge FDA to eliminate the first "classification" endpoint and consider only the "weight of the evidence" in making this scoring decision. Indeed, this would be in line with how the Toxicity Rubric approaches the "moderate" and "low" scores for this data type, which only use "weight of the evidence" standards. It should be noted that criteria such as those employed within the GHS are intended to help manage bulk chemicals and incorporate both non-threshold and threshold effects related to exposure scenarios that are not relevant for foods. If FDA chooses to retain the classification consideration in the final Prioritization Tool, we urge FDA to more clearly define what would be considered an "authoritative entity" under the Toxicity Rubric and provide justification for the use of specific chemical classification schemes.

- Neurotoxicity: With respect to the consideration of neurotoxicity in the overall Toxicity Rubric, most substances lack formal neurotoxicity studies such as an OECD 424 study. Neurotoxicity is, however, incorporated in various other more common studies such as sub-chronic studies and reproductive toxicity studies. The FDA should clarify how neurotoxicity potential will be evaluated under the prioritization tool, including the possible subdivision for substances that have some coverage of neurotoxicity potential even if not identified in a dedicated study.

- Bioaccumulation/biopersistence: The end points identified for the Bioaccumulation/biopersistence data type covers several elements related to how the human body processes and metabolizes substances, beyond just questions of bioaccumulation and biopersistence. We therefore recommend revising the name of this data type to Toxicokinetics or Absorption, Disposition, Metabolism, Elimination (ADME). Additionally, We would recommend a clarification that a high score will be reserved for chemicals that are absorbed and resistant to catabolism or likely to be consumed before there is complete elimination of the previous consumption event.

b. Are the scoring definitions for the Other Decisional criteria appropriate for the purpose of the tool?

i. Are the definitions appropriately defined? If not, please describe changes that might be considered and why.

Please see our response to Question #2, above for FMI's comments on revising the Other Decisional criteria category and its scoring definitions.

ii. FDA is exploring quantitative and qualitative methods to help inform the scoring of the 'building public confidence' criterion (Section 3.2.3) such as conducting public sentiment analysis (e.g., utilizing natural language processing). How might such tools or the information they provide be incorporated into this criterion? What additional strategies and metrics could FDA consider?

FMI urges FDA to limit its use of natural language processing and any other Artificial Intelligence (AI) tools to the signal monitoring and/or triage phase of the Post-Market Assessment process. To the extent any AI models are used with the Prioritization Tool, FDA should develop a governance review process for the use of AI to ensure there is no bias, appropriate data is assessed, and that the assessment could be corroborated by experts.

4. The prioritization methodology includes weighting factors.

a. FDA is considering equal weighting among the Public Health criteria and (separately), among the Other Decisional criteria for the Post-market Assessment Prioritization Tool.

i. Should different weights be applied to the Public Health criteria when determining the Total Public Health Criteria Score? If so, please specify the weighting scheme that might be considered and why.

ii. Should different weights be applied to the Other Decisional Criteria when determining the Total Other Decisional Criteria Score? If so, please specify the weighting scheme that might be considered and why.

b. **FDA is considering equal weighting among the Total Public Health Criteria Score and the Total Other Decisional Criteria Score to determine the overall Post-market Assessment Prioritization Score.**
    i. **Should different weights be applied when determining the overall Post-market Assessment Prioritization Score? If so, please specify the weighing scheme that might be considered and explain why it would be more appropriate than equal weighting.**

With respect to the Public Health Criteria, FMI does not agree with FDA's proposal for equal weighting among the four Public Health criteria and urges FDA to provide greater weight to the Toxicity criterion, as well as providing weight to the new estimated cumulative exposure criterion, we proposed above when combined with the toxicity criteria. If the Agency proceeds without weighting Toxicity in concert with an estimated cumulative exposure-based factor, FDA risks prioritizing and thus evaluating the safety of trace food chemicals with public health risks that are theoretical.

As discussed in response to Question #2, above, FMI recommends the FDA consider adopting an alternative framework that accounts for public interest in a chemical, while still separating science-based and policy-based considerations. We believe an alternative approach could allow the ultimate list of chemicals for review to be steered by sound scientific principles, while also allowing FDA to respond to public interest in a chemical by evaluating and, if appropriate, reaffirming the safety of a substance in a timely manner. As we have stated in other sections, clear and transparent communication with the public about the reasons a chemical is prioritized or deprioritized and the outcome of the post-market assessment process is essential to ensuring public confidence. If FDA chooses to maintain its current approach, we urge the agency to consider revising the Other Decisional Criteria to address the concerns raised above.

5. **The draft toxicity rubric uses traditional toxicity data (in vivo, as well as limited in vitro such as for genotoxicity), human health outcomes (e.g., adverse event reports), and epidemiological data for determination of the toxicity criterion score within the Public Health criteria. Considering that the prioritization process is not a comprehensive review, please address the following questions.**
    a. **How might FDA incorporate information from new approach methodologies (NAMs) into the toxicity rubric?**
        i. **Are there specific NAMs (e.g., systems biology, engineered tissues, artificial intelligence, in vitro, microphysiological systems, or other alternative data or modeling tools) that would be most appropriate for use in the toxicity rubric? If so, please explain which NAM(s) would be most appropriate and why.**
        ii. **Given that a single NAM is not expected to be a one-to-one replacement for a traditional in vivo toxicity test, how can the strengths and limitations of each NAM be appropriately considered if it is incorporated into the toxicity rubric?**

NAMs can be used to either predict what may be observed in traditional toxicology studies, or they may provide data which cannot be obtained from traditional studies. In a limited number of situations to-date, groups of NAMs may also be used as an alternative to traditional studies. FMI supports utilizing NAMs, when such data are available, and are likely to be appropriate to informing on hazard, within the Toxicity Rubric. However, the weight of such evidence needs to be considered separately for each chemical and effect under investigation. It is interesting to reflect that NAM data could be used in a screening manner to establish a priority list of substances for further review in similar manners to those that have been used by, amongst others, the EPA and Health Canada. For example, NAMs could be used to extract bioactivity data for food substances from large programs such as ToxCast and Tox21 to calculate percentiles of points of departure from which reverse dosimetry could be undertaken using high-throughput toxicokinetic models to generate oral equivalent doses (OEDs). Such OEDs could then be compared with exposure estimates as part of a 'mini risk assessment' which could be an additional criterion. In practice, risk characterization could then be performed using both traditional in vivo studies and NAMs, which could be particularly beneficial for substances with limited in vivo data available. FDA also could consider the strengths and limitations of each NAM through the use of automated quality appraisal of non-guideline in vitro studies.[6]

Nevertheless, we urge FDA to confirm that any NAMs that are used in the Toxicity Rubric have been appraised for methodological quality, fit for purpose, the doses utilized are applicable to human exposure, and are considered within the context of the overall weight of the evidence. We also acknowledge that a one-to-one replacement may not be scientifically supported at this time and support a use of a suite of assays or NAMs (e.g., adverse outcome pathways) that lead to a strong weight of evidence.

b. Threshold of Toxicological Concern (TTC) approaches can be used to assess the toxicity of chemicals that lack sufficient safety data and have low dietary exposures. Although the Cramer classification scheme has historically been used in TTC approaches, FDA has recently developed the Expanded Decision Tree (EDT) that assigns chemicals to one of six EDT classes. How might such tools or the information they provide be incorporated into the toxicity rubric?

FMI agrees that Threshold of Toxicological Concern (TTC) approaches can be useful as a prioritization metric, whereby chemicals with exposures below the relevant TTC threshold are considered a lower priority for follow-up. This may be of limited benefit to narrowing down lists except for substances in food contact materials and food flavoring. We also recommend that

[6] Blümmel T, Rehn J, Mereu C, Graf F, Bazing F, Kneuer C, Sonnenburg A, Wittkowski P, Padberg F, Bech K, E leftheriadou D, van der Lugt B, Kramer N, Bouwmeester H, Dobrikov T 2024. Exploring the use of Artificial Intelligence (AI) for extracting and integrating data obtained through New Approach Methodologies (NAMs) for chemical risk assessment. EFSA supporting publication 2024: 21(1):EN-8567. 400 pp. doi:10.2903/sp.efsa.2024.EN-8567.

FDA consider formal inclusion of read-across to address gaps in available data in cases where toxicity data are available for structurally-related chemicals.

We also appreciate FDA releasing the revised EDT on July 30.[7] We understand the Agency will release additional information and hold listening sessions to receive input from stakeholders. We look forward to the opportunity to learn more and provide our feedback on the tool, and how it may be utilized in the Post-Market Assessment process, as more information becomes available.

Given the limited amount of time between the EDT's release and the comment deadline for the Prioritization Tool, we are not in a position to provide substantive comments on the utility of the tool. Moreover, FDA's release of the revised EDT so close to the comment deadline for the Prioritization Tool reinforces the importance of a second opportunity for stakeholder input on the Prioritization Tool once all information related to the Post-Market Assessment program has been made available.

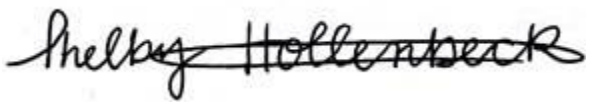
6. **Do you have any additional comments? Please share them in your review.**

According to the paper, Human Foods Program (HFP) Subject Matter Experts (SMEs) from a variety of disciplines will be responsible for scoring each criterion for each chemical in the inventory "according to their respective areas of expertise." FMI agrees that FDA should leverage the deep and varied expertise of its workforce in the prioritization process. Due to the inherently scientific nature of the Post-Market Assessment process, the SMEs who will be responsible for scoring must have the necessary scientific foundation and/or board certifications to effectively evaluate the public health criteria.

* * *

FMI greatly appreciates the opportunity to provide comments on the Development of an Enhanced Systematic Process for the FDA's Post-Market Assessment of Chemicals in Food. We look forward to further dialogue and collaboration with the agency and would be pleased to provide any further information that would be helpful to the agency.

Sincerely,



Shelby Hollenbeck, PhD

[7] FDA Releases New Tool for Toxicity Screening of Chemicals in Food (July 30, 2025), available at https://www.fda.gov/food/hfp-constituent-updates/fda-releases-new-tool-toxicity-screening-chemicals-food?utm_medium=email&utm_source=govdelivery.

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