U.S. FOOD & DRUG ADMINISTRATION

Human Foods Program

Tool for the Prioritization of Food Chemicals for Post-Market Assessment

1. OVERVIEW

In August 2024, the U.S. Food and Drug Administration (FDA) published a discussion paper on the development of an enhanced systematic process for the post-market scientific (risk and safety) assessment of chemicals in food, including food additives; color additives; generally recognized as safe (GRAS) substances (including GRAS substances that have not been notified to FDA); food contact substances; and chemicals that are present as unintentional contaminants. 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. A full description of the process will be published later this year and will describe each of these steps within the context of the systematic post-market assessment process. This document focuses on FDA's proposed method of prioritizing chemicals identified for post-market assessment using existing information about the food chemical. FDA seeks to develop a science-based, data-driven, systematic, and reproducible process for the prioritization of chemicals in food that are candidates for post-market assessments. In 2023-2024, FDA developed and piloted a draft prioritization tool for that purpose. The pilot was used to evaluate the prioritization approach, including details such as scoring criteria, and determine whether this method was suitable for future prioritization of chemicals for review. Internal review supported the pilot approach. Based on results from the pilot and stakeholder input, FDA updated the prioritization tool. The details of the updated prioritization tool are described in the following sections. Specific questions for public comment can be found in Section 4 below.

The Post-market Assessment Prioritization Tool focuses on potential risk to public health (risk ranking) and also includes other decisional considerations, using a Multi-Criteria Decision Analysis (MCDA) method. Subject Matter Experts (SMEs) from a variety of disciplines within FDA's Human Foods Program (HFP) will use the prioritization tool to score a set of criteria evaluating candidate chemicals in food for priority for further review. From the individual criterial scores, an overall score is determined. In our MCDA method, the higher the total score, the higher the priority of that chemical for post-market assessment.

For Public Health criteria, a chemical that would receive the highest score is one for which:

- The chemical may produce severe health effects (e.g., cancer, cardiovascular toxicity);
- Dietary exposure to the chemical has increased;
- The chemical is found in or could potentially be present in food intended for vulnerable subpopulations (e.g., infants); and
- Newly available information, data, or science indicates a potentially high impact on the conclusions of the previous assessment of the chemical.

For Other Decisional criteria, a chemical that would receive the highest score is one for which:

- There is high attention (e.g., Congressional and/or national news media coverage) on this chemical, multiple organizations monitoring it, and/or multiple stakeholder groups active in setting standards;
- Multiple other governmental agencies are making decisions or taking action on this chemical; and
- Not assessing this chemical could result in the public losing confidence in the safety of the U.S. food supply.

The methodology presented below will be refined in response to public comment and external peer review, and is part of a broader systematic post-market assessment process.[1] The prioritization tool is also intended to work in association with FDA's surveillance and signal detection tools,[2] which will assist in generating an inventory of candidate chemicals for prioritization. The score a chemical receives and the ultimate position of that chemical in the prioritized list provided by the Post-market Assessment Prioritization Tool is *not* an evaluation as to whether that chemical poses a public health risk. The potential impact to public health of exposure to any chemical through food is determined during the pre- and post-market risk/safety assessment processes. The Post-market Assessment Prioritization Tool is intended to prioritize chemicals in food for post-market assessments and will be used to support Agency resource allocation for that purpose.

2. ACTIVITIES ASSOCIATED WITH DEVELOPING AND IMPLEMENTING THE POST-MARKET ASSESSMENT PRIORITIZATION TOOL

Activities associated with developing and implementing the tool are summarized below. These activities are intended to ensure credibility and utility of the tool, as well as to enhance transparency of the process.

2.1 Post-market Assessment Prioritization Tool Development

2.1.1 The prioritization tool was initially developed and piloted in 2023-2024. Using lessons learned from the pilot, input from the public following the September 2024 public meeting, and internal review, the prioritization tool was updated.

2.1.2 The updated prioritization tool will undergo external review including an opportunity for public comment followed by external peer review in compliance with the Information Quality Act in fiscal year 2025.

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[1] https://www.fda.gov/food/hfp-constituent-updates/fda-hold-public-meeting-development-enhanced-systematic-process-fdas-post-market-assessment; https://www.fda.gov/food/food-chemical-safety/list-select-chemicals-food-supply-under-fda-review

[2] FDA intends to use a variety of approaches, including well-established machine learning techniques, to ingest large volumes of publicly available data and synthesize useful information, including information about chemicals in food.

2.1.3 The prioritization tool will be further updated, as needed, considering public comments and the external peer review.

2.2 Implementation of the Post-market Assessment Prioritization Tool to Provide a Prioritized List of Chemicals for Post-Market Assessment

The first step of implementation is the development of an inventory of chemicals to be prioritized, based on FDA's surveillance and signal detection. Next, HFP SMEs will score each criterion for each chemical in the inventory according to their respective areas of expertise. The scores for each criterion will be used to derive a total risk score for each chemical and a rank. Risk managers, with leadership input from HFP and the U.S. Department of Health and Human Services (HHS), will use the ranked list to inform identification of priority chemicals for assessment.

3. DESCRIPTION OF THE POST-MARKET ASSESSMENT PRIORITIZATION TOOL

3.1 Public Health Criteria

The Post-market Assessment Prioritization Tool considers decisional criteria in two categories: risk to public health and interest in a food chemical by the public and other food safety regulators (see Section 3.2 Other Decisional Criteria). The Public Health criteria include information on the toxicity of a food chemical, how much of the food chemical is consumed (e.g., change in exposure), consideration of susceptible populations who may consume the food chemical, and impactful new scientific information. Taken together, high scores in these criteria would increase the priority of a food chemical for post-market assessment. In other words, if a food chemical is found to have concerning toxicity signals, impactful new scientific information, significant increases in dietary exposure since the last assessment, and/or a likelihood of consumption by vulnerable subpopulations (e.g., infants), FDA would prioritize that food chemical over food chemicals with lower scores in these criteria.

3.1.1 Toxicity:

- The toxicity criterion is scored by utilizing a toxicity rubric that consists of seven different data types: acute toxicity; carcinogenicity/mutagenicity/genotoxicity; developmental and reproductive toxicity; neurotoxicity; other organ-specific toxicity; immunotoxicity; and bioaccumulation/biopersistence (See Appendix A, Table A1). The rubric incorporates elements of the U.S. Environmental Protection Agency's (EPA) data-driven criteria for evaluation of toxicity[3] while also considering the wide variety of chemicals found in food.
- Each chemical receives a score for each of the seven data types in the rubric (i.e., information for all data types is sought). Similar to the EPA's approach, the highest score a chemical receives for any single toxicity data type becomes its score for the toxicity

[3] Toxic Substances Control Act (TSCA) Work Plan Chemicals: Methods Document

criterion in the Post-market Assessment Prioritization Tool (See below and Appendix A, Table A2).

Highest toxicity data type score from the rubric	Toxicity criterion score
High (9)	9
Moderate (5)	5
Low (1)	1

- Note: The evaluation of potential toxicity of a food chemical using the toxicity rubric and its ultimate toxicity criterion score should not be considered a comprehensive safety assessment.

3.1.2 Change in exposure:

Description	Scoring
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?	9 = 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; 5 = Exposure has moderately increased because data indicate somewhat higher levels of the chemical OR found in food(s) moderately consumed OR moderate increase in production volume of the chemical; 3 = Not previously assessed by FDA OR unable to assess change in exposure since the last assessment due to insufficient information; 1 = Exposure has not changed because data indicate similar levels of the chemical OR found in food(s) not often consumed OR limited, decreased, or no increase in production volume of the chemical

3.1.3 Susceptible subpopulation:

Description	Scoring
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.	9 = Yes 5 = Unknown 1 = No

3.1.4 New scientific information and potential impact:

Description	Scoring
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? If yes, what is the potential impact?	9 = Yes, new scientific information available with potential high impact; 5 = Yes, new scientific information available with potential moderate impact; 3 = Yes, new scientific information available with potential low or uncertain impact; 1 = No new scientific information available

3.2 Other Decisional Criteria

In addition to the Public Health criteria discussed above, the Post-market Assessment Prioritization Tool also considers Other Decisional criteria. These criteria include the degree of concern about the chemical by the public generally and whether any regulatory partners have taken action to restrict or expand uses of the chemical in food. Taken together, high scores in these criteria would indicate significant public interest in an assessment and/or regulatory partners who have restricted or eliminated use of the chemical in food. This type of scoring would increase the priority of the food chemical for a post-market assessment.

3.2.1 External stakeholder activity/attention:

Description	Scoring
Is there specific activity by/from external groups/organizations?	9 = High attention raising concerns (e.g., Congress, GAO, HHS Secretary, FDA Commissioner call for action; national news/social media coverage); there are multiple organizations watching this; stakeholder groups are active in setting standards and establishing best practices; 5 = Moderate attention raising concerns (e.g., consumer organizations, public interest groups, major trade groups are calling for action; some concerted news/social media); there are one or two active groups or efforts active in looking at the problem (e.g., collecting data) or setting standards; individual industry members are raising the concern; 3 = Uncertain due to conflicting attention with some groups calling for attention and others indicating no concerns; 1 = Low or no attention (e.g., silence; discussion with no organized efforts to raise concerns; single news/social media reports); no one is exerting pressure on FDA or industry to specifically address this topic

3.2.2 Other government decisions:

Description	Scoring
Has there been action (e.g., issuing regulations, revoking regulations, publishing risk assessments, initiating risk assessments, revising ADIs, etc.) by other governmental agencies (e.g., international, state-level, locality-level, or other federal agencies)?	9 = Restrictive action by multiple other governmental agencies; 5 = Restrictive action by another governmental agency; 3 = No action by other governmental agencies or pending activity with unknown outcomes (e.g., monitoring or data calls); 1 = Recent permissive action by one or more governmental agencies (e.g., permitted for use in food in most other nations with little controversy; governmental agencies affirm safe use)

3.2.3 Building public confidence:

Description	Scoring
If post-market assessment is not conducted, what potential impact may that have on public confidence in the safety of the U.S. food supply?	9 = High risk of losing public confidence; 5 = Medium risk of losing public confidence; 1 = Low to no risk of losing public confidence

3.3 Description of Calculation of the Total Public Health Criteria Score, Total Other Decisional Criteria Score, and Post-market Assessment Prioritization Score for Each Chemical

The Total Public Health Criteria Score and Total Other Decisional Criteria Score are each calculated and then used to determine the overall Post-market Assessment Prioritization Score, as described below.

3.3.1 Calculating the Total Public Health Criteria Score

The Total Public Health Criteria Score is calculated by summing the weighted criterion scores across the four Public Health criteria (i.e., toxicity; change in exposure; susceptible subpopulation; new scientific information and potential impact):

$$score_{publicHealth_i} = \sum_{j=1}^{4} w_j \times score_{publicHealthCriteria_{j,i}}$$

Where:

w_j = weight assigned to Public Health criterion *j*

$score_{publicHealthCriteria_{j,i}}$= criterion score for the j[th] Public Health criterion associated with i[th] chemical

Equal weighting among the Public Health criteria is used to determine the Total Public Health Criteria Score. The selection of equally weighting is consistent with previously peer-reviewed MCDA methodology developed for food safety public health prioritization (e.g., FDA Risk-Ranking Model). While equal weighting among the Public Health criteria and (separately), among the Other Decisional criteria (see below) was selected for our draft prioritization tool, the methodology can accommodate non-equal weights.

Using 'Chemical Y' as an example, with Public Health sub-criterion scores of [9, 3, 9, 3] for the four criterions (i.e., toxicity; change in exposure; susceptible subpopulation; new scientific information and potential impact), respectively, and each given a public health sub-criterion weight of $\frac{1}{4}$, the Public Health score = $9 \times \frac{1}{4} + 3 \times \frac{1}{4} + 9 \times \frac{1}{4} + 3 \times \frac{1}{4} = 6$.

3.3.2 Calculating the Total Other Decisional Criteria Score

In parallel to the Total Public Health Criteria Score calculation, the Total Other Decisional Criteria Score is calculated by summing the weighted criteria scores across the three Other Decisional criteria (i.e., external stakeholder activity/attention; other government decisions; building public confidence):

$$score_{otherDecisional_i} = \sum_{k=1}^{3} w_k \times score_{otherDecisionalCriteria_{k,i}}$$

Where:
w_k = weight assigned to Other Decisional criterion k
$score_{otherDecisionalCriteria_{k,i}}$= criterion score for the k[th] other decisional criterion associated with i[th] chemical

As mentioned above, equal weighting among the Other Decisional criteria is used to determine the Total Other Decisional Criteria Score.

Using 'Chemical Y' as an example, with Other Decisional criteria scores of [9, 5, 5] for the three criteria (i.e., external stakeholder activity/attention; other government decisions; building public confidence) and each criterion score given a weight of $\frac{1}{3}$, the Other Decisional score = $9 \times \frac{1}{3} + 5 \times \frac{1}{3} + 5 \times \frac{1}{3} = 6.3$.

3.3.3 Calculating the Post-market Assessment Prioritization Score

The overall Post-market Assessment Prioritization Score is calculated by summing the weighted Total Public Health Criteria Score and the weighted Total Other Decisional Criteria Score, as follows:

$$score_{overall_i} = w_{publicHealth} \times score_{publicHealth_i} + w_{otherDecisional} \times score_{otherDecisional_i}$$

Where:
$score_{publicHealth_i}$= Total Public Health Criteria Score associated with i[th] chemical

$score_{otherDecisional_i}$= Total Other Decisional Criteria Score associated with i[th] chemical
$w_{publicHealth}$ = weight assigned to the Total Public Health Criteria Score
$w_{otherDecisional}$ = weight assigned to the Total Other Decisional Criteria Score
$score_{overall_i}$= Prioritization Score associated with i[th] chemical

Equal weighting among the Total Public Health Criteria Score and the Total Other Decisional Criteria Score is used to determine the overall Post-market Assessment Prioritization Score. We explored both equal and non-equal weighting during the prioritization tool development. While the draft tool currently uses equal weighting, the methodology can accommodate non-equal weights.

Given the above example for 'Chemical Y' with a Total Public Health Criteria Score = 6 and Total Other Decisional Criteria Score of 6.3, and each given a weight of $\frac{1}{2}$, the Prioritization Score for 'Chemical Y' = $6 \times \frac{1}{2} + 6.3 \times \frac{1}{2} = 6.2$.

4. QUESTIONS FOR PUBLIC COMMENT

FDA seeks to develop a science-based, data-driven, systematic, and reproducible process for the prioritization of chemicals in food that are candidates for post-market assessments, including food additives; color additives; generally recognized as safe (GRAS) substances (including GRAS substances that have not been notified to FDA); food contact substances; and chemicals that are present as unintentional contaminants. The draft Post-market Assessment Prioritization Tool focuses on potential risk to public health (risk ranking) and also includes other decisional considerations, using a Multi-Criteria Decision Analysis (MCDA) method.

The focus of this review is the draft Post-market Assessment Prioritization Tool, which is a critical part of FDA's overall systematic post-market assessment process. Considering the information in Sections 1-3 and the appendix of this document, please provide feedback on the following questions:

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.
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.
    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.
    c. Are there additional criteria that should be considered? If so, please describe additional criteria that might be considered and why.
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.

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.
    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?

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.
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?

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?

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

5. APPENDIX

Appendix A. Toxicity rubric and scoring for the Post-market Assessment Prioritization Tool

Table A1. Toxicity rubric[4]

Data Type[5]	Species and/or Study Type	High[6] - 9	Moderate – 5	Low - 1
Acute toxicity	Animal oral LD50 or similar (mg/kg bw)	<300, ***OR…***	300 to <2000, or insufficient data to evaluate in animals ***OR…***	≥2000, ***OR…***
	Human	Evidence/reports of poisonings or adverse events in humans	Insufficient data to evaluate adverse events in humans	Sufficient human data available to evaluate but no apparent adverse effects (history of safe consumption)
Carcinogenicity/ mutagenicity/ genotoxicity	Various	Substance is classified as GHS[7] 1A, 1B, GHS2, or by an authoritative entity as probable or likely	Weight of evidence across data streams (*in vitro,* animal, or human) is equivocal, or there is insufficient data	Weight of evidence (*in vitro*, animal, or human) that substance is not genotoxic, mutagenic, carcinogenic

[4] For purposes of prioritization, toxicity studies will be considered for the chemical/substance under review only. Determining chemicals/substances that may serve as appropriate surrogates for data-poor chemicals/substances is out of scope for the prioritization process.
[5] Exposure may be by any route except for intravenous or intraperitoneal.
[6] For repeated dose animal studies, the upper-bound (1000 mg/kg bw/day) was informed by the limit dose from relevant guideline studies (e.g., OECD, EPA OPPTS 870 Series). The lower-bound (250 mg/kg bw/day) was informed by select criteria from TSCA's prioritization and verified using food chemicals.
[7] United Nations Globally Harmonized System of Classification and Labelling of Chemicals (GHS)

		carcinogen (any route) in animal or human, ***OR…*** Weight of evidence (*in vitro*, animal, or human) supports substance is genotoxic, mutagenic, or carcinogenic	to assess genotoxicity, mutagenicity, or carcinogenicity	
Developmental and reproductive toxicity (DART) or activity	Animal (mg/kg bw/day)	<250 ***OR…***	250 to <1000 or insufficient data to evaluate in animals ***OR…***	≥1000 ***OR…***
	Human	Evidence in humans of DART	Insufficient data to evaluate DART	Sufficient human data available to evaluate but no evidence of DART
Neurotoxicity or neurological activity	Animal (mg/kg bw/day) Acute, repeated dose or delayed neurotoxicity studies	<250 ***OR…***	250 to <1000 or insufficient data to evaluate neurotoxicity in animals ***OR…***	≥1000 ***OR…***

	Human	Evidence in humans of irreversible neurotoxicity	Evidence in humans of reversible neurotoxicity; or insufficient data in humans to evaluate neurotoxicity regardless of reversibility	Sufficient human data available to evaluate but no evidence of neurotoxicity
Other organ-specific toxicity (e.g., cardiovascular) or activity	Animal, repeated dose (mg/kg bw/day)	<250 ***OR…***	250 to <1000 or insufficient data in animals ***OR…***	≥1000 ***OR…***
	Human	Evidence in humans of organ-specific effects (e.g., exposure associated with greater odds of disease outcome; treatment-related lesions in animals)	Insufficient data in humans to evaluate organ-specific effects	Sufficient human data available to evaluate but no evidence of organ-specific effects in humans

Immunotoxicity or immune activity	Various	Evidence (animal or human) of immune effects	Insufficient data (animal or human) to evaluate immune effects	Sufficient animal or human data available to evaluate but no evidence (animal or human) of immune effects
Bioaccumulation/ biopersistence	Various	Evidence (animal or human) or *in silico* estimates of high bioaccumulation or long half-life (e.g., bioaccumulation factor, BCF, ≥1000, or half-life in mammals of approximately > 12-24h)	Insufficient data (animal or human) to evaluate bioaccumulative potential or inability to estimate *in silico*	Sufficient data available to evaluate bioaccumulative potential but evidence (animal, human or *in silico*) of low bioaccumulation or short half-life (e.g., BCF < 1000, or half-life in mammals of approximately <12-24h)

Table A2. Calculation of toxicity criterion score using “Chemical X” as an example.

	Toxicity data type scores for Chemical X
Acute toxicity	5
Carcinogenicity/ mutagenicity/ genotoxicity	9
Developmental and reproductive toxicity (DART) or activity	5
Neurotoxicity or neurological activity	5
Other organ-specific toxicity (e.g., cardiovascular) or activity	5
Immunotoxicity or immune activity	5
Bioaccumulation/ biopersistence	1

For the above example, Chemical X would be assigned a toxicity criterion score of 9 in the Post-market Assessment Prioritization Tool because the highest scoring toxicity data type in the rubric was a 9.