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Comment on Food Additive Petition FDA-2024-N-3609

We appreciate the opportunity to comment on *the Development of an Enhanced Systematic Process for the FDA's Post-Market Assessment of Chemicals in Food*.

The Food Packaging Forum (FPF) is a charitable, independent, and science-based organization at the science policy interface. FPF is dedicated to raising awareness for hazardous chemicals in and environmental impacts caused by all types of food contact materials (FCMs) and articles, including food packaging. Our work enables science-based decision-making in the interest of protecting public health and the environment.

We would like to focus our comments on supporting the development of a **robust process** to ensure the safety of food contact substances, **using modern science**. Importantly, we strongly encourage any assessments to be conducted in a **transparent way that ensures participation of all stakeholders during all stages**.

General Comments

The **assessment of safety** needs to be founded on modern scientific knowledge and principles. These include but are not limited to low-dose effects/non-monotonic dose responses (e.g. EDCs) and the fact that some population groups are more vulnerable than others (e.g., infants). Also to be considered is the complexity of chemical exposures, e.g. mixture and cumulative effects (Maffini & Vandenberg, 2024). Chemicals which migrate from food contact materials, but which have not been tested for their hazard properties should not be considered safe. Equally, chemicals that have not been tested for all relevant hazard properties should not be considered safe (see next point).

To ensure consumer safety, **toxicity testing must expand beyond genotoxicity** to multiple endpoints associated with non-communicable diseases relevant to human health, such as cardiovascular diseases, brain-related disorders, metabolic and endocrine diseases, as well as immunological and reproductive disorders, and cancers not related to genotoxicity. Modern frameworks that allow assessing how chemicals affect these chronic diseases have been described and allow for selecting or developing suitable *in vitro* assays (Muncke et al. 2023). Novel testing approaches can utilize adverse outcome pathways (AOPs) and the Key Characteristics concept (Smith et al. 2016).

Defining a set of relevant and robust ***in-vitro assays*** allows screening for functional effects associated with chronic diseases in a standardized approach. Results of sensitive assays can be transferred to vulnerable populations (like pregnant women, infants, and elderly people) to ensure increased consumer safety.

Importantly, besides toxicity, **persistence and bioaccumulation** properties also affectchemical hazard and warrant inclusion in the hazard assessment. For instance, per- and polyfluoroalkyl substances (PFAS) are of high environmental and human health concerns due to their extreme persistence (Cousins et al., 2020).

One way to streamline efforts is to address **groups of chemicals, i.e. chemicals** with similar structures

(as structure is related to intrinsic hazard properties, also known as “read across”) instead of assessing individual chemicals which is extremely time consuming. Accordingly, data from a few chemicals can be used to regulate others in the same group even before they reach the market and in the absence of dedicated safety assessments. FDA has already used the chemical class approach for long- and short-chain PFAS.

One approach to considerably reduce the time and resources of post-market assessments while improving consumer protection, is to move to a **hazard-based approach** for food contact chemicals management (Zimmermann et al. 2020). It is commonly acknowledged that exposure data are missing for many chemicals. At the same time, a hazard-based approach is favorable for chemicals for which no safe levels exist (e.g., carcinogens, mutagens, endocrine disruptors), as well as for chemicals that migrate into foodstuffs in mixtures and renders future assessment unnecessary in case new data demonstrate hazards at lower exposure levels than previously known.

To keep up with the ever-evolving scientific findings and ensure consumer protection, **reassessments** must be **proactive and periodic** instead of reactive. Importantly, action is to be taken if there are doubts concerning safety and not only when proven that harm has already occurred.

Given the large number of chemicals of concern used in food and food packaging (more than 1600), and the vast data gaps associated with most known food contact chemicals, **their prioritization based on existing information is key.** We would like to draw your attention to our open-access resources that integrate state-of-the-art scientific information enabling prioritizing.

(1) The **PlastChem** report and database identify plastic chemicals of concern, including chemicals used in FCMs, and provide six lists for prioritization of plastic chemicals for regulatory action. E.g., the Red List contains chemicals identified as hazardous according to well-established criteria. Prioritization is based on hazard, including toxicity and persistence, bioaccumulation, and mobility. The PlastChem report also provides data on use, detection, production volume, and details on the number of studies providing evidence. It further identifies priority groups of chemicals of concern (Wagner et al. 2024).

(2) Specific to FCM, the “database on migrating and extractable food contact chemicals” (FCCmigex) includes data systematically compiled from over 1200 scientific studies. The database includes more than 3000 food contact chemicals either detected to be present in FCMs (“extracted”) or transferred from FCMs into foods (“migration”) (Geueke et al. 2023).

(3) A recent systematic study identified 3601 **food contact chemicals present in humans**, of which 80 have hazard properties of high concern (Geueke et al. 2024). The data is freely available in an interactive dashboard and could support systematic prioritization.

(4) Another study lists 388 food contact chemicals with properties considered hazardous under the EU Chemicals Strategy for Sustainability (CSS) (carcinogenic, mutagenic, or toxic to reproduction (CMRs), or persistent and bioaccumulative, or endocrine-disrupting chemicals (EDCs)) and phased out. For 127 of the 388 hazardous chemicals, there is empirical evidence for their presence in FCMs (Zimmermann et al. 2022).

Based on the experience of other agencies (US EPA, European Food Safety Authority), a **clear separation between risk assessment and risk management** is prudent. The role of risk assessment is to objectively review all relevant evidence and to conclude whether there is a reasonable certainty that the actual use of a food contact chemical causes harm. Using this outcome of the risk assessment, risk management then bases its decisions on additional considerations, such as economic, societal and political will.

Responses to specific questions listed at the end of the discussion paper

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

To maximize transparency, all stakeholders should be engaged as early in the process as possible, so public input is integrated into every step of the post-market assessment.

2. **Is the frequency and mechanisms of the envisioned public engagement described in Section V of the 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.**

External engagement is insufficient if FDA engages the public only during a Comprehensive Assessment, and in only two parts. Instead, we suggest FDA engage stakeholders at every step of the reassessment, starting with the development of protocols, processes, criteria all the way to the peer review of the risk assessment. Similar engagement is encouraged for Focused Assessments and approaches related to Signal monitoring, triage and fit for purpose decisions.

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?**

To avoid any bias, other individuals than the ones involved in the pre-market approvals must be tasked with the reassessment. They may either be within the FDA and with relevant expertise to do such an assessment, e.g., familiar with the methods, data analysis, and integration of evidence from different data streams from human epidemiology to molecular pathways. Alternatively, an advisory committee seems an even better option assuming it consists of independent experts (that have provided a detailed conflict of interest declaration that is publicly available) and equipped with the required knowledge. . Such a committee should be consulted in the following steps: 1. Prioritization, and 3. Draft Scientific (Risk and Safety) Report.

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

Section III is not readily accessible, not meeting expectations for a decision tree. Questions lack answers as to how FDA would proceed if an answer is "yes" or "no" for a given question. Also, descriptions are lacking of what constitutes "significant resources", "scientific consensus", "strong weight of evidence", or "significant public health interest". Such definitions would be essential for following this approach. Therefore, we suggest that FDA develop procedures that can systematically be applied in a transparent manner. Both the US Environmental Protection Agency and the European Food Safety Authority have processes in place which may serve as inspiration.

5. **Is the Prioritization of Risks scheme the FDA outlines in this document 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 would you modify the Prioritization of Risks scheme? Please provide supporting rationale for the changes.**

The prioritization scheme lacks some fundamental information, such as a description of the criteria FDA will use in its approach. It is unclear how the EPA method for chemical prioritization and the FDA's risk-ranking model for pathogens traceability would be applied.
Additionally, the prioritization of risk should not only include toxicity as a hazardous characteristic of a chemical but also persistence and bioaccumulation, since such chemicals are less quickly eliminated from the body.

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).**

A Focused Assessment should not be used to assess public health risks. Based on the reassessment of the sweetener erythritol as an example, there are several concerns including the lack of transparency, inexistent external engagement, and absence of peer review. However, another major concern relates to the fact that FDA reaffirmed the safety of erythritol after reviewing merely one single publication without considering the entire weight of evidence in the scientific literature, and its mandate to assess cumulative effects. It is very concerning that FDA may use Focused Assessments to disregard chemicals by reviewing them in isolation and we strongly recommend revision of this approach.

Again, we thank you for the opportunity to provide input and look forward to contributing to future opportunities.

Sincerely,

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Justin Boucher, Operations Director
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