Institute for the Advancement of Food and Nutrition Sciences

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IAFNS Food and Chemical Safety Committee

Request for Proposals

Title: Review of EU Novel Food submissions and US GRAS Petitions to identify opportunities for use of New Approach Methodologies for safety determinations of food substances

The Institute for the Advancement of Food and Nutrition Sciences (IAFNS) is a non-profit, 501(c)(3) scientific organization that pools funding from industry collaborators and advances science through the in-kind and financial contributions from public and private sector participants. IAFNS adheres to strict procedures to maintain scientific integrity in all work we support. These requirements are described further in the attached TOP Guidelines and Guiding Principles for Scientific Integrity addendums.

Issue to be addressed:

The risk assessment of some food substances have been slowly but steadily shifting to adoption of a high-throughput, non-animal method strategy for demonstrating safety. These methods, along with new *in vitro, in silico* and powerful computer modeling tools are collectively referred to as New Approach Methodologies, or NAMs. For example, many food enzymes now rely on non-animal methods, including such approaches as the Safe Strain Lineage approach and evaluation of allergenicity using protein sequences, to assume safety. The adoption of these non-animal methods for a specific subset of food substances was supported by a review of historical data (Ladics and Sewalt, 2018). The use of these “class safety” methods has also expanded to other food substances, such as proteins manufactured using fermentation (e.g., beta-lactoglobulin produced by *Trichoderma reesei* GRAS Notice No. 863). These examples demonstrate that risk assessors have accepted NAMs to demonstrate the safety of food substances in some cases, but gaining broader acceptance of these approaches will benefit from a greater understanding of the cases where non-animal data has been accepted as well as other situations where NAMs could be used in the future.

This proposal seeks to review available safety assessments of food substances to identify classes of food substances that have leveraged NAMs data to support a regulatory approval. This would include a review of safety determinations by the United States Food and Drug Administration (FDA) in their publicly available GRAS database, as well as those from the European Food Safety Authority (EFSA). Review of these safety determinations should identify a list of food substances that relied on NAMs data to support safety and should also elucidate class commonalities identifying when NAMs data were used and subsequently resulted in an approval of these ingredients. This could include whether NAMs were used to address specific endpoints or whether they were more commonly used for particular classes of substances (as described above for enzymes or proteins). The proposal can also seek to identify substances that utilized a NAM approach and were unsuccessful, along with an understanding of the

underlying justifications. Examples and learnings from applications of NAMs in the risk assessment of cosmetics can also be considered.

The review can also include determinations where two suppliers of the same chemical entity leverage the same source data along with read across and notifications that provide evidence of chemical equivalence to previously notified substances based on studies conducted by other companies.

Objectives:

- Review FDA and EFSA safety determinations for the use of NAMs data
    - Categorize the findings by the type of NAMs used, and the specific food substances in which their use was most (and least) common
    - Summarize the food substance/classes, or safety endpoints, where NAMs were used rather than (or in addition to) traditional toxicological studies for the safety assessment (e.g., a post-hoc view), and propose situations where a similar approach could be successful
- Review official determinations or commitments made on NAM use (reduction in animal use / streamlining of registrations, etc.)

Deliverables:

- The primary deliverable is a high-impact **publication in a peer reviewed journal**. additional deliverables:
    - Periodic updates to the IAFNS Food and Chemical Safety Committee
    - One to two presentations at appropriate scientific conferences

References:

- Ladics, GS, Sewalt, V (2018) Industrial microbial enzyme safety: What does the weight-of-evidence indicate? *Regul Toxicol Pharmacol* 98:151-154
- GRAS Notice for Non-Animal Whey Protein from Fermentation by *Trichoderma reesei*. (GRN) No.863. https://www.fda.gov/media/136754/download
- GRAS Notice for Proposed Use of 2'-O-Fucosyllactose in Term Infant Formulas, Toddler Formulas, and Foods Targeted to Toddlers. (GRN) No. 749. https://www.fda.gov/media/124475/download
- Vijay U, Gupta S, Mathur P, Suravajhala P, Bhatnagar P (2018) Microbial Mutagenicity Assay: Ames Test. *Bio Protoc*. Mar 20;8(6):2763
- Sommer S, Buraczewska I, Kruszewski M (2020) Micronucleus Assay: The State of Art, and Future Directions. *Int J Mol Sci.* Feb 24;21(4):15
- Dent, M et al. (2018) Principles underpinning the use of new methodologies in the risk assessment of cosmetic ingredients *Computational Toxicology* 7:20-26
- Middleton AM et al. (2022) Are Non-Animal Systemic Safety Assessments Protective? A Toolbox and Workflow. *Tox Sci* 189:124–147

Proposal Content:

1. **Approach:** Please provide your approach to the research design elements as described above. Identify key research questions, primary and secondary outcomes, methodology, and analysis plan. Where appropriate, please reference the validation of proposed methods.
2. **Anticipated Challenges**
3. **Research Team:** Please indicate the primary (and secondary) investigators, plus any additional contributors or collaborators.
4. **Investigator Credentials and CV of the principal investigator(s).**
5. **Potential Conflicts of Interest:** List any potential conflicts of interest for all investigators, co-investigators, collaborators. We suggest using the Conflict of Interest Guidelines as set forth by the American Society for Nutrition: https://nutrition.org/publications/guidelines-and-policies/conflict-of-interest/
6. **Budget:** Please provide a budget summary. IAFNS will directly pay publication fees for open access.
7. **Timeline and Key Deliverables:** This is intended as a narrow-focused short term project. The manuscript should be submitted for publication no more than 6 months after initiation.

Page Limit: No more than 3 pages excluding references and investigator CVs.

Proposal Deadline: Oct 10, 2023

Submission Instructions: Please submit completed proposals to:

Neal Saab, PhD

Senior Science Program Manager

nsaab@IAFNS.org

Proposal Review Process:

a) Proposals will be reviewed promptly by the Food and Chemical Safety Committee.

b) Applicants will be notified in writing if additional information is needed.

c) Once the review process is over, all applicants will be notified of the disposition of their proposals in a timely manner.

d) Upon project initiation, the project summary, principal investigator, and budget will be published on our funded projects portal: https://iafns.org/funded-projects/