# WORKFLOW FOR EVALUATING SAFETY OF FOOD INGREDIENTS

**Petitions for food ingredient safety evaluation to the US Food and Drug Administration (FDA) Center for Food Safety and Applied Nutrition (CFSAN) do not require animal testing. A general workflow for food ingredient safety testing is provided below.**

## 1. REVIEW EXISTING SAFETY INFORMATION.

Similar ingredients may have similar toxicity profiles, and existing data can be used as follows to support read-across to similar ingredients:

- Identify and provide the case for ingredient similarity with other generally recognized as safe (GRAS) ingredients based on physicochemical properties.
- Available human studies provide the strongest evidence for safe consumption, but animal and *in vitro* data can also be used. Search for a history of safe consumption of similar ingredients in the following sources:
  - Published literature (existing human, animal, or *in vitro* studies)
  - Other GRAS notices[1] and toxicology studies therein
  - Decisions from other regulatory agencies (e.g. the European Food Safety Authority[2] and the Joint FAO/WHO Expert Committee on Food Additives[3])

## 2. DEVELOP A NON-ANIMAL TESTING STRATEGY.

Prior to conducting any new testing, develop a non-animal testing strategy following guidelines established by the Organisation for Economic Co-operation and Development (OECD),[4] the International Organization for Standardization (ISO),[5] and the International Life Sciences Institute.[6,7,8]

- *In silico* approaches can be used for the following:
  - Digestibility and allergenicity: BLAST[9] and AllergenOnline[10] searches
  - Absorption, distribution, metabolism, and excretion (ADME): GastroPlus[11]
  - Genotoxicity, carcinogenicity, and developmental and reproductive toxicity: quantitative structure-activity relationship (QSAR) models[12,13]
- *In vitro* methods can be used for the following:
  - Digestibility: dynamic gastrointestinal model[14,15]
  - Genotoxicity: bacterial reverse mutation test (OECD 471),[16] chromosomal aberration test (OECD 473),[17] mammalian cell gene mutation tests using the Hprt and xprt genes (OECD 476),[18] mammalian cell gene mutation tests using the thymidine kinase gene (OECD 490),[19] and micronucleus test (OECD 487)[20]

## 3. SCHEDULE A PRE-SUBMISSION MEETING WITH THE FDA.

The FDA recommends arranging a pre-submission consultation prior to conducting any new testing to discuss alternative testing plans.[21] This meeting is your opportunity to show the agency the value of your scientifically sound, non-animal testing approach to self-affirming ingredient safety. Be sure to include your team's scientific experts in this meeting so they can support and explain the scientific rationale.

## 4. PERFORM NON-ANIMAL TESTING BASED ON THE OUTCOME OF THE FDA PRE-SUBMISSION MEETING.

Ensure the FDA specifies all testing requirements in writing. If no product-related health claims are made, animal testing is not required.

**If you have any questions or require additional information, contact PETA Science Consortium International e.V. at AndrewN@thepsci.eu.**

+49 (0) 711-860-591-0
ThePSCI.eu • Info@thepsci.eu
PETA SCIENCE CONSORTIUM INTERNATIONAL e.V.

[1]FDA. GRAS notices. https://www.accessdata.fda.gov/scripts/fdcc/?set=GRASNotices. Updated 16 September 2019.
[2]European Food Safety Authority. Food ingredients and packaging. https://www.efsa.europa.eu/en/topics/topic/food-ingredients-and-packaging.
[3]Food and Agriculture Organization of the United Nations. Chemical risks and JECFA. http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/en/.
[4]OECD. Chemical safety and animal welfare. http://www.oecd.org/chemicalsafety/testing/46725331.pdf.
[5]ISO. Standards. https://www.iso.org/standards.html.
[6]Delaney B, Astwood JD, Cunny H, *et al*. Evaluation of protein safety in the context of agricultural biotechnology. *Food Chem Toxicol*. 2008;46(Suppl 2):S71-S97.
[7]Hammond B, Kough J, Herouet-Guicheney C, Jez JM. Toxicological evaluation of proteins introduced into food crops. *Crit Rev Toxicol*. 2013;43(Suppl 2):25-42.
[8]Hampton Creek, Inc. GRAS notice no 684, page 37. https://www.fda.gov/media/103224/download.
[9]US National Library of Medicine. Basic Local Alignment Search Tool (BLAST). https://blast.ncbi.nlm.nih.gov/Blast.cgi.
[10]AllergenOnline. http://www.allergenonline.org/.
[11]SimulationsPlus. GastroPlus®. https://www.simulations-plus.com/software/gastroplus/.
[12]Arvidson KB, Chanderbhan R, Muldoon-Jacobs K, Mayer J, Ogungbesan A. Regulatory use of computational toxicology tools and databases at the United States Food and Drug Administration's Office of Food Additive Safety. *Expert Opin Drug Metab Toxicol*. 2010;6(7):793-796.
[13]Lo Piparo E, Worth A, Manibusan M, *et al*. Use of computational tools in the field of food safety. *Regul Toxicol Pharmacol*. 2011;60(3):354-362.
[14]Triskelion. Determination of the digestible indispensable amino acid score (DIAAS) using a dynamic *in vitro* gastrointestinal model. 8 June 2016. https://www.triskelion.nl/determination-digestible-indispensable-amino-acid-score-diaas-using-dynamic-vitro-gastrointestinal-model/.
[15]Havenaar R, Maathuis A, de Jong A, Mancinelli D, Berger A, Bellmann S. Herring roe protein has a high digestible indispensable amino acid score (DIAAS) using a dynamic in vitro gastrointestinal model. *Nutr Res*. 2016;36(8):798-807.
[16]OECD. Test No 471: Bacterial Reverse Mutation Test. https://www.oecd-ilibrary.org/environment/test-no-471-bacterial-reverse-mutation-test_9789264071247-en.
[17]OECD. Test No 473: In Vitro Mammalian Chromosomal Aberration Test. https://www.oecd-ilibrary.org/environment/test-no-473-in-vitro-mammalian-chromosomal-aberration-test_9789264264649-en.
[18]OECD. Test No 476: In Vitro Mammalian Cell Gene Mutation Tests Using the Hprt and xprt Genes. https://www.oecd-ilibrary.org/environment/test-no-476-in-vitro-mammalian-cell-gene-mutation-tests-using-the-hprt-and-xprt-genes_9789264264809-en.
[19]OECD. Test No 490: In Vitro Mammalian Cell Gene Mutation Tests Using the Thymidine Kinase Gene. https://www.oecd-ilibrary.org/environment/test-no-490-in-vitro-mammalian-cell-gene-mutation-tests-using-the-thymidine-kinase-gene_9789264264908-en.
[20]OECD. Test No 487: In Vitro Mammalian Cell Micronucleus Test. https://www.oecd-ilibrary.org/environment/test-no-487-in-vitro-mammalian-cell-micronucleus-test_9789264264861-en.
[21]FDA. Guidance for industry and other stakeholders: Toxicological principles for the safety assessment of food ingredients (Redbook 2000). Revised 2007. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-and-other-stakeholders-toxicological-principles-safety-assessment-food-ingredients-0.

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