

# WORKFLOW FOR EVALUATING FOOD INGREDIENT SAFETY

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<sup>1</sup> and toxicology studies therein
  - Decisions from other regulatory agencies (e.g. the European Food Safety Authority<sup>2</sup> and the Joint FAO/WHO Expert Committee on Food Additives<sup>3</sup>)

## 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<sup>4</sup>), the International Organization for Standardization (ISO<sup>5</sup>), and the International Life Sciences Institute.<sup>6,7,8</sup>

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

## 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.<sup>21</sup> 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 that 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 the PETA International Science Consortium Ltd. at [AndrewN@piscLtd.org.uk](mailto:AndrewN@piscLtd.org.uk).

+44 (0) 20 7837 6327  
[PISC@piscLtd.org.uk](mailto:PISC@piscLtd.org.uk) • [PISCLtd.org.uk](http://PISCLtd.org.uk)

PETA INTERNATIONAL   
SCIENCE CONSORTIUM LTD.

- <sup>1</sup>FDA. GRAS notices. <https://www.accessdata.fda.gov/scripts/fdcc/?set=GRASNotices>. Updated 16 September 2019.
- <sup>2</sup>European Food Safety Authority. Food ingredients and packaging. <https://www.efsa.europa.eu/en/topics/topic/food-ingredients-and-packaging>.
- <sup>3</sup>Food and Agriculture Organization of the United Nations. Chemical risks and JECFA. <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/en/>.
- <sup>4</sup>OECD. Chemical safety and animal welfare. <http://www.oecd.org/chemicalsafety/testing/46725331.pdf>.
- <sup>5</sup>ISO. Standards. <https://www.iso.org/standards.html>.
- <sup>6</sup>Delaney B, Astwood JD, Cunney H, *et al.* Evaluation of protein safety in the context of agricultural biotechnology. *Food Chem Toxicol.* 2008;46(Suppl 2):S71-S97.
- <sup>7</sup>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.
- <sup>8</sup>Hampton Creek, Inc. GRAS notice no 684, page 37. <https://www.fda.gov/media/103224/download>.
- <sup>9</sup>US National Library of Medicine. Basic Local Alignment Search Tool (BLAST). <https://blast.ncbi.nlm.nih.gov/Blast.cgi>.
- <sup>10</sup>AllergenOnline. <http://www.allergenonline.org/>.
- <sup>11</sup>SimulationsPlus. GastroPlus®. <https://www.simulations-plus.com/software/gastroplus/>.
- <sup>12</sup>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.
- <sup>13</sup>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.
- <sup>14</sup>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/>.
- <sup>15</sup>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.
- <sup>16</sup>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](https://www.oecd-ilibrary.org/environment/test-no-473-in-vitro-mammalian-chromosomal-aberration-test_9789264264649-en).
- <sup>17</sup>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](https://www.oecd-ilibrary.org/environment/test-no-487-in-vitro-mammalian-cell-micronucleus-test_9789264264861-en).
- <sup>18</sup>OECD. Test No 471: Bacterial Reverse Mutation Test. [https://www.oecd-ilibrary.org/environment/test-no-471-bacterial-reverse-mutation-test\\_9789264071247-en](https://www.oecd-ilibrary.org/environment/test-no-471-bacterial-reverse-mutation-test_9789264071247-en).
- <sup>19</sup>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](https://www.oecd-ilibrary.org/environment/test-no-490-in-vitro-mammalian-cell-gene-mutation-tests-using-the-thymidine-kinase-gene_9789264264908-en).
- <sup>20</sup>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](https://www.oecd-ilibrary.org/environment/test-no-476-in-vitro-mammalian-cell-gene-mutation-tests-using-the-hprt-and-xprt-genes_9789264264809-en).
- <sup>21</sup>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>.