



GRAS - Generally Recognized as Safe

Any substance that is reasonably expected to become a component of human or animal food must be an approved food additive or a substance that is Generally Recognized as Safe (GRAS) among experts qualified by scientific training and experience to evaluate the safety of the substance for the intended use. Food additives are subject to premarket approval by the US Food and Drug Administration (FDA or Agency). A GRAS substance, however, does not require premarket approval; it relies on the safety of the substance to be adequately shown through scientific procedures, or through experience based on common use in food prior to 1958, under the conditions of its intended use. A conclusion that a substance is GRAS requires both technical evidence of safety and a basis to conclude that the technical evidence of safety is generally known and accepted. The data and information relied on to establish safety must be generally available and there must be consensus among qualified experts about the safety of the substance for the intended use. A substance that is GRAS for an intended use may be marketed for that use without the Agency's review and approval that is normally required for a new food additive as defined in definition (s) of 21 U.S.C. § 321(s).

In 1958, FDA published a list of GRAS ingredients (codified in 21 CFR Part 182), and in 1972 created a GRAS affirmation process for industry to petition the agency to make a GRAS determination. The GRAS affirmation process became overly burdensome, and in 1997 FDA published a Proposed GRAS Notice Rule for voluntary notification of a substance's GRAS status to FDA, with FDA publicly listing its response. The proposed GRAS Notice Rule was finalized in August 2016. FDA's Center for Food Safety and Applied Nutrition (CFSAN) has posted on its website the full list of GRAS Notices (the GRAS Notice Inventory) that have been filed since 1998. Once FDA responds to a GRAS Notice, the text of FDA's response letter is also available as part of the record for that notice. FDA updates this information periodically throughout the year. Over 819 GRAS Notices have been filed with CFSAN at the time of preparing this brief (Dec. 2018), of which approximately 15% are related to food enzymes. Food enzyme GRAS Notices meet the GRAS criteria consistently and result in very few findings that the notifier's GRAS conclusions were unsubstantiated by FDA or withdrawn by the notifier.

The review of GRAS Notices was not implemented by FDA's Center for Veterinary Medicine (CVM) as accepted practice for animal food until 2010. The CVM GRAS Notification Program is not identical to that of CFSAN and leaves much more room for discretionary requirements by CVM. To date, only 11 of 29 CVM-reviewed GRAS Notices appear on CVM's publicly available GRAS Notice Inventory list with a "No Questions" response letter, three of which are for enzymes.

When making a GRAS conclusion for an enzyme preparation, members of the Enzyme Technical Association follow publicly available guidelines and methodology for evaluating the safety of microbial enzyme preparations used in food and feed. There are five main elements that must be considered when conducting a safety evaluation of microbially-derived food enzymes: 1) the enzyme; 2) the production strain; 3) the manufacturing process; 4) safety studies; 5) estimation of dietary exposure and calculation of resulting safety margin.

The published safety evaluation methodology addresses the safety of the genetic transformation materials and methods, the safety of the newly introduced enzyme for its intended use, as well as the safety of the production host as supported by published information. The manufacturing process for enzyme preparations is quite standardized in the enzyme industry and usually consists of submerged fermentation of pure cultures followed by inactivation of the production organism, enzyme recovery steps, and final formulation. Consideration of dietary exposure is also an essential piece of the assessment. As enzymes may be used in multiple food manufacturing processes or in multiple animal feed sources, the highest consumption by humans/animals is used in the safety calculations. Generally, a 90-day oral toxicity study in rats is used to support the safety in humans, pigs or poultry,



with the requirement that the margin of safety be at least 100. Alternatively, animal feed safety can be supported with target animal safety studies.

The GRAS process is well suited for enzymes, given the long history of safe use, general availability of scientific data supporting enzyme safety, the generally recognized (peer-reviewed) methodology and decision trees for evaluating the safety of microbial enzymes used in food processing and in animal feed, respectively, including the frequent use of production organism belonging to well-documented Safe Strain Lineages.

Supporting materials:

- ETA GRAS PowerPoint presentation: http://www.enzymeassociation.org/wp-content/uploads/2016/10/Yes_We_GRAS_June_22.pdf
- Publications: Sewalt et al. (2016): <http://www.enzymeassociation.org/?p=534>
- FDA GRAS web page, including GRAS Notice lists, SCOGS database, GRAS Enzymes page: <https://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/default.htm>
- FDA guidance document for food enzyme dossiers: <https://www.fda.gov/food/guidanceregulation/guidancedocumentsregulatoryinformation/ucm217685.htm>
- Sewalt, V., Shanahan, D., Gregg, L., La Marta, J., Carrillo, R., 2017. Letter to the editor regarding “GRAS from the ground up: Review of the Interim Pilot Program for GRAS notification” by Hanlon et al., 2017, *Food and Chemical Toxicology*, <http://www.enzymeassociation.org/wp-content/uploads/2017/08/ETA-Response-GRAS-from-the-ground-up-final.pdf>.