Food and Chemical Toxicology 107 (2017) 520–521

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Letter to the editor

Letter to the editor regarding "GRAS from the ground up: Review of the Interim Pilot Program for GRAS notification" by Hanlon et al., 2017

Keywords:
GRAS
Enzymes
History of safe use
Decision tree
Safe strain lineage

A B S T R A C T

Present letter is aimed at clarifying some critical points highlighted by Hanlon et al. regarding the common knowledge element of the safety of food enzymes in support of their GRAS designation. Particularly, we outline the development of peer-reviewed, generally recognized safety evaluation methodology for microbial enzymes and its adoption by the enzyme industry, which provides the US FDA with a review framework for enzyme GRAS Notices. This approach may serve as a model to other food ingredient categories for a scientifically sound, rigorous, and transparent application of the GRAS concept.

The review article "GRAS from the ground up: Review of the Interim Pilot Program for GRAS notification" authored by Hanlon et al. appearing in the July edition of FCT is a positive contribution to our collective understanding of the GRAS Notification Program (https://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/default.htm) as it outlines changes over time in utilization of the program, review timelines and success rates, and begins to look at industry practices in support of the GRAS designation by defined ingredient categories.

In the process of their review, the authors noted that the success rate for enzymes in the GRAS Notification process has been higher (almost 100%) than for other ingredients (approximately 80%) and that enzyme GRAS Notice reviews tend to be completed faster than for most other ingredient types. In addition, based on the first 600 GRAS Notifications, the enzyme industry tends to rely less on GRAS expert panels to support the common knowledge element essential to gain GRAS designation. Hanlon et al. provide interesting discussion around some underlying reasons why submitters of GRAS Notices use a GRAS panel or not, e.g., the complexity of the determination and/or the function of the ingredient.

The authors wondered whether, in the case of enzymes, "the requirement to 'provide a basis for your conclusion that the notified substance is generally recognized, among qualified experts, to be safe under the conditions of its intended use' could be fulfilled through means other than the inclusion of a conclusion from a GRAS Expert Panel, such as through the review of the experts within the FDA, or through reference to other previously approved enzyme preparations."

We felt compelled to address the issue of how the enzyme industry supports the common knowledge element of food enzyme GRAS designations. We agree with the authors of the article that enzymes merit a separate category within the scope of GRAS Notification. Indeed, most GRAS determinations for enzymes used as processing aids represent relatively low complexity based on many factors we will discuss here. In agreement with that observation, the FDA Guidance for Industry: "Enzyme Preparations: Recommendations for Submission of Chemical and Technological Data for Food Additive Petitions and GRAS Notices." (https://www.fda.gov/downloads/Food/GuidanceRegulation/UCM217735.pdf) does not stipulate the use of a GRAS panel for GRAS Notices.

Part of the answer to the authors' question restated above is embedded in the article itself. The authors state that speed of review is aided for those categories that have clear standards previously established in performing safety assessments (such as the FDA guidance for enzyme submissions). The issuance of such agency guidance for enzyme preparations was facilitated by the availability of international guidance, published use information on enzymes and on the safety of microbial species used as production strains, and peer-reviewed decision trees, which, collectively, represents a body of generally recognized safety evaluation methodology on which the enzyme industry can rely for its GRAS determinations.

The enzyme industry is relatively small and the visibility of its main industry association (the Enzyme Technical Association or ETA) is relatively low and largely technical in nature. Some food safety scientists are not aware of the efforts by the ETA to inform national and international regulatory agencies and the scientific community of advances made in enzyme technology and safety evaluation in scientific presentations (e.g., Pavel et al., 2016) and publications (e.g., Sewalt et al., 2016), aiding

DOI of original article: http://dx.doi.org/10.1016/j.fct.2017.06.045.

http://dx.doi.org/10.1016/j.fct.2017.06.042
0278-6915/

those agencies in developing guidance for the evaluation of enzymes.

It is of further note that, in developing a standard enzyme evaluation approach, the ETA has incorporated landmark peer-reviewed safety evaluation publications by Dr. Michael Pariza and international guidance documents regarding food safety and biotechnology from, amongst others, WHO/FAO, Codex Alimentarius, IFBC and OECD, as summarized in ETA's recent publication (Sewalt et al., 2016). This latter article discusses each of the five main elements of an enzyme safety evaluation:

- Enzyme identity, history of safe use, and sequence analysis
- Safe production organisms, based on selection of safe, non-pathogenic, non-toxigenic hosts, safe host improvement techniques, and thorough characterization of the resulting production organism
- Manufacture process conducted under controlled conditions against standard specifications defined specifically for enzymes in the Food Chemical Codex and by the FOA/WHO Joint Evaluation Committee for Food Additives (JECFA, 2006)
- Selection of toxicological data; and
- Exposure in the intended use.

Overall, the article provides ample rationale for why enzyme GRAS Notification has followed its path of relying on publicly available/peer-reviewed evaluation methodology and published supporting information. GRAS panels are used mostly for validation of comprehensive new safety determinations where one or more of the above elements would include less familiar features, such as an enzyme with a novel activity or protein sequence; a new production organism; and/or an application that is less well-described in public information sources.

The many available publications used to support GRAS status of individual enzyme preparations have discussed such features as the safety of the specific microbial species for production of that specific enzyme; the long history of safe use of and published support for the safety of commonly used enzymes. The peer-reviewed safety evaluation decision trees address the safety requirements for genetically engineered production strains and trigger points for new toxicological studies, and the ability to establish well-documented Safe Strain Lineages for routine production of many enzymes, with the safety of any new member of the lineage building on the documented safety of earlier members of the lineage.

It is the judicious application and formalization of this type of knowledge building that will allow safety experts in industry and the FDA to continue to rely, with confidence, on the pivotal information to support safety of food ingredients, and on GRAS conclusions as an exemption to formal food additive review, thus enabling the FDA to focus its scarce resources on other food safety concerns.

As microbial enzyme technology evolves, so does the safety evaluation methodology employed by the enzyme industry to support the safety of its products. In fact, the Pariza and Johnson (2001) decision tree is an update to an earlier version originally published by Pariza and Foster (1983). While we can expect that such decision trees continue to evolve, members of the Enzyme Technical Association submit GRAS Notices to FDA to support transparency to the agency, the food industry, consumers, and other national and international entities. We hope that enzyme industry GRAS practices may serve as an example to manufacturers of other food ingredients of the successful application of the GRAS process, and invite GRAS experts from other food industry segments to interact with the ETA to model the development of their standard GRAS methodology after that developed for microbial enzymes.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.06.042.

References

Hanlon, P.R., Frestedt, J., Magurany, K., 2017. GRAS from the ground up: review of the Interim Pilot Program for GRAS notification. Food Chem. Toxicol. 105, 140–150. http://dx.doi.org/10.1016/j.fct.2017.03.064.

JECFA, 2006. General specifications and considerations for enzyme preparations used in food processing. Available at: http://www.fao.org/docrep/009/a0691e/A0691E03.htm.

Pariza, M.W., Foster, E.M., 1983. Determining the safety of enzymes used in food processing. J. Food Prot. 46, 453–468.

Pariza, M.W., Johnson, E.A., 2001. Evaluating the safety of microbial enzyme preparations used in food processing: update for a new century. Regul. Toxicol. Pharmacol. 33, 173–186.

Pavel, T., Gregg, L., Shanahan, D., Sewalt, V., LaMarta, J., 2016. Yes We GRAS! Enzymes as Catalysts for Successful Application of the GRAS Process. Session 109 at IFT16 Food Safety and Quality Forum, July 19, 2016, Chicago, Illinois. Presentation materials. http://www.enzymeassociation.org/?p=527.

Sewalt, V., Shanahan, D., Gregg, L., La Marta, J., Carrillo, R., 2016. Ind. Biotechnol. 12, 295–302. http://dx.doi.org/10.1089/ind.2016.0011.

Vincent Sewalt[*,1]
Enzyme Technical Association, Washington, DC, United States

DuPont Industrial Biosciences, 925 Page Mill Road, Palo Alto, CA 94304, United States

James LaMarta[1]
Enzyme Technical Association, Washington, DC, United States

DSM Nutritional Products, 45 Waterview Blvd, Parsippany, NJ 07054, United States
E-mail address: james.lamarta@dsm.com.

Diane Shanahan[1]
Enzyme Technical Association, Washington, DC, United States

BASF Corp., 3550 John Hopkins Court, San Diego, CA 92121, United States
E-mail address: diane.shanahan@basf.com.

Lori Gregg[1]
Enzyme Technical Association, Washington, DC, United States

Novozymes North America, Inc., 77 Perrys Chapel Church Road, Franklinton, NC 27525, United States
E-mail address: lobg@novozymes.com.

Roberto Carrillo[1]
Enzyme Technical Association, Washington, DC, United States

Enmex, Río Lerma 228, Tlalnepantla 54030, Mexico
E-mail address: rcarrillo@enmex.com.mx.

[*] Corresponding author.
E-mail address: vincent.sewalt@dupont.com (V. Sewalt).

23 June 2017
Available online 27 June 2017

[1] (http://www.enzymeassociation.org/).