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European Food Safety Authority
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Re: Draft Guidance on Allergenicity Assessment of Genetically Modified Plants (https://www.efsa.europa.eu/en/consultations/call/160726)

The European Food Safety Authority (EFSA) has opened a "Public consultation on the draft Guidance Document on allergenicity assessment of genetically modified plants" intended "to provide supplementary guidance on specific topics for the allergenicity risk assessment of GM plants to incorporate new developments in the area. The topics addressed are non-IgE-mediated immune adverse reactions to foods, *in vitro* protein digestibility tests and endogenous allergenicity."[1] This letter provides comments to the proposal from the Information Technology and Innovation Foundation (ITIF). ITIF is an independent, nonpartisan research and educational institute focusing on the intersection of technological innovation and public policy. Recognized as one of the world's leading science and technology think tanks, ITIF's mission is to formulate and promote policy solutions that accelerate innovation and boost productivity to spur growth, opportunity, and progress.

Food allergenicity is a significant issue for a substantial portion of the human population (approximately 2-6 percent). The majority of what we commonly refer to as food allergens are caused by IgE-mediated immune responses. But there is also a separate and distinct category of adverse reactions to foods caused by non-IgE-mediated adverse immune reactions. It is to this latter category that the present EFSA guidance refers.

In the draft under consideration, EFSA has departed from the pattern established in its previous guidance documents, which aimed to provide pragmatic advice to regulators. The material in the present draft, though interesting, is generally not pragmatic in focus, and its relevance to risk assessment and management in the real world is not clear. The kind of information provided in this document by EFSA with respect to non-IgE-mediated immune reactions appears to hold some potential value, and perhaps when more fully informed and

[1] European Food Safety Authority, Public consultation on the draft Guidance Document on allergenicity assessment of genetically modified plants, https://www.efsa.europa.eu/en/consultations/call/160726.

developed, advances in this area may enable researchers not only to predict the potential for new proteins and peptides to cause symptoms such as those seen in celiac disease (CD) patients, but also to allow for clinical and therapeutic interventions beyond avoidance. They may also allow for the manipulation of plant proteins so as to reduce or eliminate their immunogenicity. But the present state of the art is far from delivering against such potential.

To routinely conduct the full panoply of molecular analyses and characterizations described in the EFSA draft would be a lengthy and expensive proposition. It would do little or nothing to improve safeguards for human health, however, when compared to a much more truncated screening such as an amino acid homology screening with validated, risk-associated thresholds, or even more basic appraisals such as if a protein is derived from wheat, barley, or rye as there is no more clinically valuable and proven advice to CD sufferers than simply to avoid it. EFSA cites no research demonstrating any improved safety margins that might result from quantification of the presence of such proteins in order to justify the added costs. Such data would not commensurately reduce the level of uncertainty associated with the tests and assays described. In other words, most of what is laid out in the EFSA guidance describes information that may be "nice to know" but which regulators do not "need to know" in order to make cost-effective risk management decisions. Further specific comments follow.

p. 6, line 153: "Thus, allergenicity assessment of newly expressed proteins with regard to non-IgE mediated immune reactions should focus on CD." What is needed here is some discussion of the incidence and relative significance of CD vs. other non-IgE-mediated adverse immune reactions to food antigens. As it stands, the recommendation is akin to searching under a streetlight for lost keys because that's where the light is best, rather at the location where the keys were actually lost and might therefore be expected in fact to be found. In other words, that the pathology and mechanism of CD are better understand than for some other adverse immune responses is not, in itself, sufficient to emphasize CD at the expense of other conditions unless warranted by epidemiological data, which EFSA does not provide.

p. 8, line 238: "Thus, at least three factors contribute to the immunogenicity of gluten: (a) resistance to proteolytic degradation, (b) specific recognition by TG2, and (c) peptide binding properties of HLA-DQ2.5 and HLA-DQ8." EFSA here makes the case against the simplistic reliance of some regulatory regimes on resistance to proteolytic digestion as a presumed indicator of allergenicity, when the data clearly show, in fact, that there is no clear relationship. Each of the three criteria mentioned are relevant; none are predictive on their own. In short, the best available *in vitro* assays are only suggestive, none are dispositive.

Annex A-1, p. 30, line 1007: "[T]he necessary number of amino acids identical in a peptide to trigger a response is challenging to define, since the ability to bind to CD specific MHC molecules and the interaction with T cells is highly dependent on the nature and position of certain amino acids. Therefore, a definite size cut-off in respect to identity to a known epitope indicating potential hazardous peptides, for which further assessment would be needed, is demanding." This means that it is not now possible to identify a non-zero threshold for the presence of homologous sequences that allows unambiguous sorting of novel proteins into clearly demarcated categories of hazardous vs. safe.

p. 9, line 293: "These structures can be used to model a peptide of interest into HLA-DQ2 or HLA-DQ8." But per Annex A-3, such structures may be sufficient to predict CD response but are neither necessary nor limiting. The utility of this parameter for risk assessment and regulatory review is therefore imperfect.

p. 18, line 597: The EFSA draft singles out soybeans for special attention, inasmuch as it is the only food commonly recognized as allergenic for which genetically engineered varieties have been developed and submitted to EFSA for review (so far, for traits unrelated to allergenicity). EFSA notes that "the quantitative measurement of soybean allergens (as referred to in the relevant OECD consensus document) as part of the compositional analysis is now a mandatory requirement … ." But as there is no generally recognized safe threshold level of exposure to allergenic proteins for sensitive individuals, it is difficult to see any basis or justification for this requirement for quantification. Such information does not define any useful category of reduced or enhanced risk among sensitive individuals and would appear to qualify for an exemption from provision of such data based on EFSA's discretion to set aside such mandates "if they are demonstrated not to be scientifically necessary for food/feed safety assessment or technically not possible to perform."

General points that emerge from the draft EFSA guidance include the following.

- Adverse immune responses to food consumption can be sorted into two categories: IgE mediated and non-IgE mediated. The former make up most of what we refer to as food allergies, while the latter includes a number of different syndromes of which celiac disease is the best understood. The present guidance focuses on the latter.

- Neither type of adverse immune response is reliably predicted by *in vitro* simulated digestion assays. Resistance to peptidase digestion is, however, suggestive, especially if larger peptide fragments persist. Digestion products smaller than 9 amino acid residues are generally consistent with a lack of

immunogenicity. It would be useful to regulators if EFSA were explicitly to highlight this observation.

- The ability to which non-IgE-mediated immune responses can be elicited is understood with sufficient granularity that it can be traced to the presence of specific molecular moieties, but it is not clear that this understanding provides information of any added value to regulators beyond that provided by identifying the source as coming from wheat, barley, or rye. The lengthy explication of these factors in the EFSA draft is therefore of theoretical value, but, at this point, no clear practical significance. EFSA guidance here should stress that the only sure guidance of value to clinicians at present is that individuals should avoid exposure to immunogenic proteins to which they are or may be sensitive.

- The EFSA draft devotes considerable attention to evaluation of endogenous allergenicity and the potential of changes resulting from genetic manipulation. But if an immunogenic molecular moiety is present, it is by no means clear what might be a safe level of exposure for sensitive individuals. The relevance of any potential changes in endogenous allergenicity to risk assessment or risk management, as EFSA suggests, is therefore unclear.

Overall, the EFSA draft document summarizes our current understanding of some complicated and completely understood frontiers of human immune responses to some foods. The present level of understanding falls short of delivering a truly predictive or clinical response capability and is insufficient to support most of the EFSA policy recommendations.

Thank you for the opportunity to provide these comments.

Sincerely,

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