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Utility of Weight-of-Evidence Components in Risk Assessment: Example of Digestion Results in the Allergenicity Assessment of Newly Expressed Proteins in Genetically Engineered Crops

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Abstract

Various weight-of-evidence risk-assessment frameworks have been used for regulatory decision making. In this policy commentary, we critically assess the value of including gastric and/or intestinal digestion results in the weight of evidence designed to inform the allergenicity assessment of newly expressed proteins in genetically engineered crops. This example highlights a general concept: specifically, that there is negligible value in considering a factor as a component of the risk assessment when differing outcomes for this factor do not result in different risk decisions under any reasonable hypothetical scenario regarding results from the other components of the risk assessment. We conclude that equitable and science-based regulatory guidance should include examples of weight-of-evidence scenarios illustrating how differing outcomes for each individual component within the weight of evidence would result in a different conclusion on the acceptability of the potential risk under consideration. Critically assessing each component of the weight of evidence in this manner helps avoid inclusion of components that can only distract risk assessors from the critical decision-making process, possibly resulting in inconsistent risk assessment outcomes for the same datasets.

Keywords: risk assessment, weight of evidence, genetically engineered crops, allergenicity, regulatory oversight

1. Introduction

A number of different weight-of-evidence frameworks have been used in regulatory decision making in the context of risk assessment [15]. These vary from subjective qualitative assessments to decision trees with specific criteria and/or thresholds. While the simplicity of decision trees with prescriptive thresholds are often preferred in the context of regulatory decision making, more subjective weight-of-evidence approaches are sometimes required due to the complexity of potential weight-of-evidence scenarios and the varying strength of each piece of evidence in predicting risk. By way of example, a decision-tree framework for evaluating the allergenic risk of newly expressed proteins in genetically engineered (GE) crops was initially adopted [4] but was later replaced by a more subjective weight-of-evidence framework as the variable predictive ability of the components of the weight of evidence became evident [12, 11]. The use of a weight-of-evidence approach likely precludes strict prescriptive decision making under such complexity. However, we propose that when weight-of evidence is invoked for decision making, illustrative examples of weight-of-evidence scenarios should be developed to show how differing results for each component would result in a different decision on the acceptability of risk. Including such examples in regulatory guidance would reduce the subjectivity of risk assessments and aid risk assessors in making consistent evidence-based decisions. Such analyses would also refine risk assessment by excluding components within the weight of evidence that do not impact decision making, thus simplifying and improving decisions on the acceptability of potential risk.

2. Current Weight-of-Evidence Components for the Allergenicity Assessment of Newly Expressed Proteins in Genetically Engineered Crops

By way of example, several components have historically been used in the weight-of-evidence allergenicity risk assessment of newly expressed proteins in GE crops. These components include: 1) bioinformatic analysis of the amino acid sequence identity or similarity to known allergens; 2) history of exposure and allergy to the protein or organism from which

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the protein was identified; 3) the concentration of the protein as expressed in the GE crop or food; 4) thermal and digestive stability of the protein; and when appropriate, 5) specific IgE binding studies [11]. The thermal stability of a protein has largely been dismissed as a useful component in the allergenicity risk assessment, most importantly because heat-induced alterations in protein structure can increase or decrease the allergenicity of a protein, and thus, results for a new food protein are not interpretable in the context of an allergenicity risk assessment [14]. Similarly, allergens have not been found to be generally more stable to gastric or intestinal digestion than non-allergens, and highly digestible allergens are known, thus making digestion results uninterpretable in the context of an allergenicity risk assessment [9, 17, 2]. However, some scientists continue to support the use of digestion results in the risk assessment based on its contribution to understanding exposure in the gut where allergenic sensitization and elicitation can occur [3, 1], and such results continue to be required globally by regulatory agencies [16].

3. Does Level of Exposure in the Gut Inform the Allergenicity Risk Assessment?

The proposed value of understanding the level of exposure in the gut on the allergenicity risk assessment was predicated on the initial belief that sensitization to food allergens occurred primarily in the gut, and that exposure to increased concentration in the gut increased sensitization rates. Both of these assumptions are increasingly inconsistent with developing scientific evidence. It is now understood that sensitization to food allergens can also occur both dermally and through inhalation (bypassing the digestive system), and that increased exposure to allergens in the gut at a young age actually reduces sensitization rates, likely through the tolerization process [9, 13, 8]. Interestingly, increasing the digestibility of a known allergen can actually decrease its ability to induce tolerization against allergy. A mutant digestively unstable form of the digestively stable carp parvalbumin Cyp c 1 was found to lack the normal tolerization properties observed for the native Cyp c 1 allergen in a mouse model system, suggesting that substituting this digestible version for the stable version could increase sensitization rates [5]. While elicitation of food allergy in already sensitized individuals increases with increasing exposure to the respective protein antigen in the gut, newly expressed proteins in GE crops that are suspected of being cross-reactive with known allergens, based on bioinformatic analyses or their sourcing from a known allergenic organism, are subjected to specific IgE binding studies that would reveal any cross reactivity. In such cases, digestive stability would not preempt or overturn the risk decisions based on IgE serum study results because some known allergens are readily digestible while others are very stable, and no clear correlation is present [10, 6]

4. Example of Weight-of-Evidence Scenarios Should be Included in Regulatory Guidance

We propose that it should be possible to formulate hypothetical examples for useful weight-of-evidence components that illustrate how differing outcomes for each individual component would change the assessment of acceptable risk. In the example of digestion results as a component of the allergenicity risk assessment for newly expressed proteins in GE crops, we are unable to formulate a realistic scenario where results would affect risk assessment conclusions. Indeed, digestion results inform gut exposure, but gut exposure does not predictably inform the allergenicity risk assessment. However, inclusion in regulatory guidance of plausible illustrative scenarios (even if hypothetical), where digestion results would be the deciding factor in a risk decision, would promote consistency of evidence-based decision-making for transgenic proteins in food. Alternatively, if available evidence does not indicate a plausible scenario where digestion results would affect the risk decision, digestion results should not be considered in the weight-of-evidence used to evaluate allergenic potential.

5. Removing a Faulty Weight-of-Evidence Component Has Value Without Replacement

It is noteworthy that some favor maintaining the current simulated gastric digestion assay in the allergenicity assessment of newly expressed proteins in GE crops until a better weight-of-evidence component is identified to replace it [3]. However, removing a component that is not useful in making a risk decision under any reasonable scenario is an improvement in itself because maintaining such a component implies it is useful in decision making when it is not. As such, removing digestion results from the weight-of-evidence allergenicity assessment improves risk decision making even in the absence of identifying a replacement weight-of-evidence component (Figure 1).

6. Conclusion

Evaluating each component within a weight-of-evidence risk assessment framework in a manner similar to the allergen risk example discussed here should be applicable to other weight-of-evidence risk assessments, thus improving decision making. Development of plausible illustrative (hypothetical) scenarios enables risk assessors to understand the weight of each component and consistently and objectively reach evidence-based conclusions. Components that are found to not provide useful evidence in support of the risk assessment, as appears to be the case for digestive stability in the assessment of food protein allergenicity, should be dropped from the weight-of-evidence approach.

7. Declaration of Interest Statement:

The authors are employed by Corteva Agriscience which develops and markets transgenic seed.

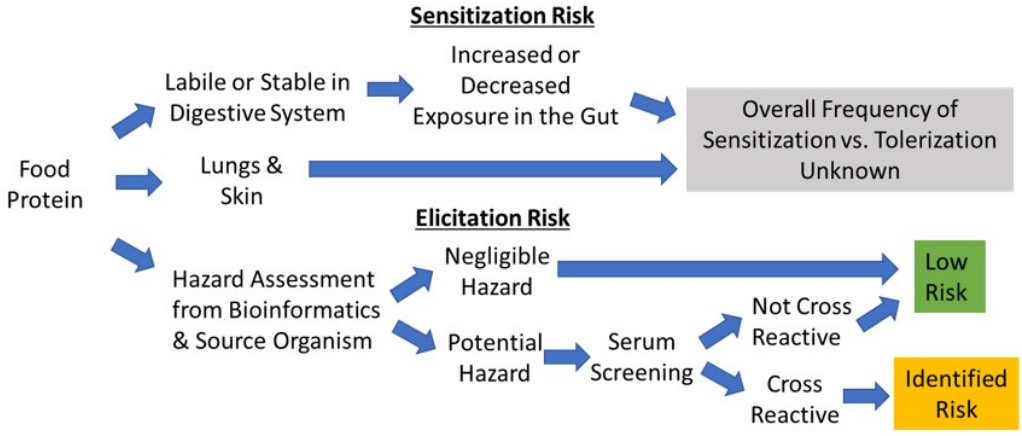

Figure 1: Allergenicity Risk assessment decision flow [7].

8. Article Information

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9. References

[1] Akkerdaas, J., Totis, M., Barnett, B., Bell, E., Davis, T., Edrington, T., Glenn, K., Graser, G., Herman, R., Knulst, A., Ladics, G., McClain, S., Poulsen, L., Ranjan, R., Rascle, J. B., Serrano, H., Spejjer, D., Wang, R., Mouriès, L. P., Capt, A., & Ree, R. V. (2018). Protease resistance of food proteins: a mixed picture for predicting allergenicity but a useful tool for assessing exposure. *Clinical and Translational Allergy, 8*(30), 1. https://doi.org/10.1186/s13601-018-0216-9

[2] Bøgh, K. L., & Madsen, C. B. (2016). Food allergens: is there a correlation between stability to digestion and allergenicity? *Critical Reviews in Food Science and Nutrition, 56*(9), 1545-1567. https://doi.org/10.1080/10408398.2013.779569

[3] EFSA Panel on Genetically Modified Organisms, Naegeli, H., Bresson, J. L., Dalmay, T., Dewhurst, I. C., Epstein, M. M., Firbank, L. G., Guerche, P., Hejatko, J., Moreno, F. J., Mullins, E., Nogué, F., Rostoks, N., Serrano, J. J. S., Savoini, G., Veromann, E., Veronesi, F., & Dumont, A. F., (2021). Statement on in vitro protein digestibility tests in allergenicity and protein safety assessment of genetically modified plants. *EFSA Journal, 19*(1), e06350. https://doi.org/10.2903/j.efsa.2021.6350

[4] Food and Argiculture Organization of the United States & World Health Organization. (2001). *Evaluation of allergenicity of genetically modified foods. Report of a Joint FAO/WHO Expert Consultation on Allergenicity of Foods Dervived from Biotechnology. Rome* Retrieved May, 2021 from http://www.fao.org/fileadmin/templates/agns/pdf/topics/ec_jan2001.pdf.

[5] Freidl, R., Gstöttner, A., Baranyi, U., Swoboda, I., Stolz, F., Focke-Tejkl, M., Wekerle, T., Ree, R. V., & Linhart, B. (2020). Resistance of parvalbumin to gastrointestinal digestion is required for profound and long-lasting prophylactic oral tolerance. *Allergy, 75*(2), 326-335. https://doi.org/10.1111/all.13994

[6] Fu, T. T., Abbott, U. R., & Hatzos, C. (2002). Digestibility of food allergens and nonallergenic proteins in simulated gastric fluid and simulated intestinal fluid—a comparative study. *Journal of Agricultural and Food Chemistry, 24*(50), 7154-7160. https://doi.org/10.1021/jf020599h

[7] Herman, R. A., Bauman, P. A., Goodwin, L., Islamovic, E., Ma, E. H., Serrano, H., Silvanovich, A., Simmons, A. R., Song, P., & Wang, R. (2021). Mass spectrometric analysis of digesta does not improve the allergenicity assessment of GM crops. *Transgenic Research, 30* 283-288. https://doi.org/10.1007/s11248-021-00254-x

[8] Herman, R. A., & Ladics, G. S. (2018). Allergenic sensitization versus elicitation risk criteria for novel food proteins - short communication. *Regulatory Toxicology and Pharmacology, 94* 283-285. https://doi.org/10.1016/j.yrtph.2018.02.016

[9] Herman, R. A., Roper, J. M., & Zhang, J. X. (2020). Evidence runs contrary to digestive stability predicting protein allergenicity. *Transgenic Research, 29*(1), 105-107.

[10] Herman, R. A., Woolhiser, M. M., Ladics, G. S., Korjagin, V. A., Schafer, B. W., Storer, N. P., Green, S. B., & Kan, L. (2007). Stability of a set of allergens and non-allergens in simulated gastric fluid. *International Journal of Food Sciences and Nutrition, 58*(2), 125-141. https://doi.org/10.1080/09637480601149640

[11] Ladics, G. S. (2008). Current codex guidelines for assessment of potential protein allergenicity. *Food and Chemical Toxicology, 46*(10), S20-S23. https://doi.org/10.1016/j.fct.2008.07.021

[12] Ladics, G. S., & Selgrade, M. K. (2009). Identifying food proteins with allergenic potential: Evolution of approaches to safety assessment and research to provide additional tools. *Regulatory Toxicology and Pharmacology, 54*(3, Supplement), S2-S6. https://doi.org/10.1016/j.yrtph.2008.10.010

[13] Logan, K., Du Toit, G., Giovannini, M., Turcanu, V., & Lack, G. (2020). Pediatric Allergic Diseases, Food Allergy, and Oral Tolerance. *Annual Review of Cell and Developmental Biology, 36*, 511-528. https://doi.org/10.1146/annurev-cellbio-100818-125346

[14] Privalle, L., Bannon, G., Herman, R., Ladics, G., McClain, S., Stagg, N., Ward, J., & Herouet-Guicheney, C. (2011). Heat stability, its measurement, and its lack of utility in the assessment of the potential allergenicity of novel proteins. *Regulatory Toxicology and Pharmacology, 61*(3), 292-295. https://doi.org/10.1016/j.yrtph.2011.08.009

[15] Rhomberg, L. R., Goodman, J. E., Bailey, L. A., Prueitt, R. L., Beck, N. B., Bevan, C., Honeycutt, M., Kaminski, N. E., Paoli, G., Pottenger, L. H., Scherer, R. W., Wise, K. C., & Becker, R. A. (2013). A survey of frameworks for best practices in weight-of-evidence analyses. *Critical Reviews in Toxicology, 43*(9), 753-784. https://doi.org/10.3109/10408444.2013.832727

[16] Su, S., Ezhuthachan, I. D., & Ponda, P. (2020). Genetically modified foods and food allergy. *Journal of Food Allergy, 2*(1), 111-114. https://doi.org/10.2500/jfa.2020.2.200012

[17] Verhoeckx, K., Bøgh, K. L., Dupont, D., Egger, L., Gadermaier, G., Larré, C., Mackie, A., Menard, O., Adel-Patient, K., Picariello, G., Portmann, R., Smit, J., Turner, P., Untersmayr, E., & Epstein, M. M. (2019). The relevance of a digestibility evaluation in the allergenicity risk assessment of novel proteins. Opinion of a joint initiative of COST action ImpARAS and COST action INFOGEST. *Food and Chemical Toxicology, 129*, 405-423. https://doi.org/10.1016/j.fct.2019.04.052