



September 17, 2020

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Submission: Application A1186: Soy leghemoglobin in meat analogue products

Many thanks for the opportunity to comment on FSANZ's proposal to amend the Australia New Zealand Food Standards Code (the Code) to permit the use of soy leghemoglobin (SLH) in the form of LegH Prep in meat analogue products (including the Impossible™ Burger, meatballs, sausages, and as fillings in buns and dumplings).

We share the view of the Victorian Department of Health and Human Services, the Victorian Department of Jobs, Precincts and Regions, PrimeSafe and others that the “quality of the risk assessment information provided in order to ensure the protection of public health and safety is inadequate” and that FSANZ has not “adequately assessed the safety of this product for Australian and New Zealand consumers”.¹

SLH does not have a history of safe use in food

SLH in its natural state exists in the roots of soybeans and has thus far never been an integral part of the human diet. Consequently, GMO-derived SLH has no history of safe use as a foodstuff. Therefore, consumer safety following consumption of GMO-derived SLH cannot be assured. Given the potential for harm, FSANZ must enforce stronger safety standards for this product.

The lack of independent safety assessments leaves the government and public without critical scientific data about the direct and indirect health consequences from the GMO-derived SLH.

***Pichia pastoris* does not have a history of safe use in food**

Impossible Foods' SLH is derived from a strain of genetically modified (GM) *Pichia pastoris* yeast. FSANZ states that:

*“While there is limited evidence that *P. pastoris* has been consumed by humans, this organism does have a long history of safe use for the production of pharmaceuticals and industrial chemicals.”²*

These uses obviously pose completely different potential risks when compared to intentionally adding an extract of a genetically modified version of this yeast to food. The safety of this substance should not be inferred on this basis, without robust supporting evidence. While FSANZ asserts that “no reports of adverse effects from products produced from *P. pastoris* strains were identified” this is clearly not the same as demonstrating the safety of deliberately adding an extract of GM *P. pastoris* to food.³

FSANZ has not assessed all the proteins potentially found in the product for safety

All products derived from genetic engineering techniques require regulation and assessment for their potential health and environmental impacts.

FSANZ notes that not all batches of the LegH Prep “contained the same proteins, nor proteins at the same levels.”⁴ FSANZ states that “The most common *Pichia* proteins present in the LegH Prep have been identified and characterised”.⁵ Given that even trace amounts of protein have the potential to cause anaphylaxis, we consider it important that all the proteins produced be identified, characterised and compared with known allergens.

Furthermore, contrary to FSANZ’s assertion that none of the 17 proteins that it assessed are significantly similar to known toxins or allergens, Impossible Foods’ supporting documents (which for some reason have now been removed from FSANZ’s website) state that a number of the proteins produced show similarities to known toxins and allergens (Appendix 8 – pp. 8-11). Such a finding should prompt further investigation to ensure public health and safety are protected, but they are recklessly dismissed as insignificant.

FSANZ assessed data from a different strain of GM yeast

FSANZ acknowledges in its Risk Assessment that

“Some of the data provided to FSANZ for the risk assessment analyses was obtained from a predecessor of MXY0541, designated MXY0291. The major differences between these two strains is the copy number of the leghemoglobin gene (MXY0291 contains fewer copies) and MXY0541 contains extra DNA sequences associated with one of the haem-synthesis enzyme genes.”⁶

This is completely unacceptable - the risk assessment analyses need to be based on data from the actual production strain that is to be used commercially. Despite the Victorian Government seeking clarification in February “as to whether the supporting safety data relates to strain MXY0541 or strain MXY0291”⁷ it is not clear what strain FSANZ is referring to in its biochemical analysis, and assessment of allergenicity and potential toxicity in its risk assessment document.⁸

However, it is clear from FSANZ’s risk assessment document that the dietary toxicity studies in rats and in vitro genotoxicity tests were conducted using MXY0291 rather than MXY0541 which is proposed for commercial use. Similarly, the evidence Impossible Foods provided to demonstrate the bioavailability of iron from haem was based on extracts of soy leghemoglobin, rather than the preparation itself.⁹

FSANZ also misleadingly states that “Impossible Foods obtained self-affirmed USFDA GRAS [Generally Recognised as Safe] status (GRN 737) in July 2018 to use its soy leghemoglobin at levels up to 0.8% in its raw ground (minced) beef analogue products as a flavour optimiser.”¹⁰ However, in its Risk Assessment document FSANZ admits that this was for

strain MXY0291 not MXY0541.¹¹

FSANZ's conflation of these two strains is more disturbing when FSANZ reveals that:

*"The data provided by the applicant demonstrated that for every gene introduced, there is at least one full copy of the insert that has been integrated into the host. In some situations, more than one copy of a gene has been inserted. In one situation, a truncated version of a single gene has been inserted multiple times."*¹²

According to FSANZ, it:

*"also identified base pair differences in some of the leghemoglobin gene inserts, where the sequence data was of high quality. These differences could result in amino acid changes and expression of truncated proteins."*¹³

FSANZ argues that:

*"it is unlikely these proteins would be translated because of the non-functional polyadenylation sequence. These changes would therefore not impact safety."*¹⁴

Truncated proteins can have different biological and toxicological properties. FSANZ should have demanded further information from the applicant to demonstrate that these proteins aren't in fact produced by strain MXY0541, rather than making assumptions in the absence of evidence.

We support calls from the Victorian Department of Health and Human Services and the Victorian Department of Jobs, Precincts and Regions and PrimeSafe for "safety data on the specific production strain related to this application."¹⁵

Inadequate safety study: Strong third-party scientific studies must be required

The 28-day feeding study which Impossible Foods commissioned, where laboratory rats were fed a GMO-derived SLH from a different strain of the *P. pastoris*,¹⁶ was inadequate to address questions of safety even for that strain. It covered too short a study period and had too small a sample size to ensure adequate statistical power. After the US Food and Drug Administration told Impossible Foods that their 2014 submission did not "point to a general recognition of safety,"¹⁷ and after Impossible Foods withdrew their 2014 GRAS application,¹⁸ Impossible Foods proposed a 90-day feeding study,¹⁹ a standard length of time for sub-chronic testing for toxicity in rats.

As Michael Antoniou, PhD and Claire Robinson note in an article discussing the study, "the shorter the duration of a study, the less likely it is to find health effects such as organ damage, which take time to show up."²⁰ It is therefore unclear why Impossible Foods disregarded the 90-day feeding study proposal and standard scientific procedure and only conducted a 28-day feeding study. No claims of long-term safety from the consumption of its product can be made on the basis of this inadequate short-term study.

The small sample size of the study is a major limitation. There were only 20 rats in each of the 4 test groups (10 rats per sex per group).²¹ This impedes researchers' ability to draw statistically significant conclusions about the health consequences of small physiological

changes, which would require long-term studies with significantly larger numbers of animals.

Despite the shortcomings of the study design, a number of statistically significant physiological differences were observed between some of the controls, and test groups fed the GMO-derived SLH. “Rats fed the genetically modified (GM) yeast-derived SLH developed unexplained changes in weight gain, changes in the blood that can indicate the onset of inflammation or kidney disease, and possible signs of anemia.”²² Statistically significant findings such as these should signal that more thorough long-term studies are needed to fully evaluate the safety of GMO-derived SLH.

However, FSANZ has not required long-term safety assessments and data. And without presenting experimental evidence, Impossible Foods dismissed the statistically significant effects found in their study as “non-adverse,”²³ which ignores the norms of sound scientific practice.

Not only is the GMO-derived SLH a potential liability for FSANZ’s reputation, it may also be potentially hazardous and risky for consumers. Without clear long-term, independent data sets and safety assessments, FSANZ cannot know whether there could be adverse reactions to GMO-derived SLH in the intermediate to long-term in the human population.

The Impossible Burger is not a healthy food

The Impossible burger is an ultra-processed food that is high in sodium and contains added preservatives. A recent review found that ultra-processed foods in the diet are associated with higher risks of obesity, heart disease and stroke, type-2 diabetes, cancer, frailty, depression and death.²⁴

We believe that the health benefits claimed for this burger are overstated. High levels of heme iron intake from red and processed meat consumption have been associated with elevated risk for type 2 diabetes, cardiovascular disease, colorectal cancer, and lung cancer.²⁵ Impossible Foods has reported that the heme in its beef substitute is comparable in amount and, once cooked and digested, identical molecularly to that found in farmed beef²⁶, suggesting that consumption of this plant-based substitute could be associated with similar chronic disease risks as red and processed meat consumption.²⁷

FSANZ dismisses research that suggests that heme iron may contribute to an increased risk of colon cancer and other health problems on the basis of reviews by Kruger and Zhou (2018) and Turner and Lloyd (2017) – however both reviews were funded by the beef industry.²⁸ FSANZ also argues that “the available studies with soy leghemoglobin found that it was not genotoxic.” Importantly, these studies used strain MXY0291 not MXY0541. It remains unknown whether the haem iron from soy leghemoglobin may pose that same risk as that from meat.

We believe that by applying an overly narrow definition of food safety, FSANZ is failing in its key object of ensuring a “high degree of consumer confidence in the quality and safety of food produced, processed, sold or exported from Australia and New Zealand.”

Labelling

One of the key objectives of FSANZ as prescribed by its Act is “the provision of adequate

information relating to food to enable consumers to make informed choices.”²⁹ It is therefore vital that this ingredient be clearly labelled as genetically modified. FSANZ notes that “novel DNA and novel protein from genetically modified *P. pastoris* strain will be present in the meat analogue product from a liquid preparation.”³⁰ We therefore expect the ingredient to be clearly labelled as genetically modified in the event that it is approved.

Conclusion

FSANZ has full authority to require independent safety assessments for ingredients derived from genetic engineering, particularly those that are new to the human diet and have no established history of safe use such as the GMO-derived SLH. FSANZ must not deem Impossible Food’s GMO-derived SLH safe on the basis of the inadequate scientific evidence submitted.

Impossible Food’s application to use GMO-derived SLH in the Australian and New Zealand food chain should be declined and the substance should not be approved for sale in Australia and New Zealand.

¹ *Application A1186 – Soy leghemoglobin in meat analogue products: Comments from the Victorian Department of Health and Human Services and the Victorian Department of Jobs, Precincts and Regions and PrimeSafe.* available at: <https://www.foodstandards.gov.au/code/applications/Pages/A1186.aspx>

² FSANZ (2020) *Supporting document 1: Risk and technical assessment report – Application A1186: Soy leghemoglobin in meat analogue products*, p. 8, https://www.foodstandards.gov.au/code/applications/Documents/A1186_SD1%20at%202nd%20CFS.pdf?csf=1&e=AIDvJz

³ *Ibid.*

⁴ *Ibid.* p. 12.

⁵ *Ibid.*

⁶ *Ibid.*, p. 5

⁷ *Application A1186 – Soy leghemoglobin in meat analogue products: Comments from the Victorian Department of Health and Human Services and the Victorian Department of Jobs, Precincts and Regions and PrimeSafe.*

⁸ FSANZ (2020) *Supporting document 1: Risk and technical assessment report – Application A1186: Soy leghemoglobin in meat analogue products*

⁹ FSANZ (2020) *Supporting document 1: Risk and technical assessment report – Application A1186: Soy leghemoglobin in meat analogue products*, p. 19.

¹⁰ FSANZ (2020) *2nd Call for submissions – Application A1186: Soy leghemoglobin in meat analogue products*

¹¹ FSANZ (2020) *Supporting document 1: Risk and technical assessment report – Application A1186: Soy leghemoglobin in meat analogue products*, p. 31.

¹² *Ibid.*, p. 33.

¹³ *Ibid.*, p.31.

¹⁴ *Ibid.*

¹⁵ *Application A1186 – Soy leghemoglobin in meat analogue products: Comments from the Victorian Department of Health and Human Services and the Victorian Department of Jobs, Precincts and Regions and PrimeSafe.*

¹⁶ Impossible Foods, Inc. GRAS notification for soy leghemoglobin protein preparation derived from *Pichia pastoris*: GRAS Notice (GRN) No. 737. October 2017. <https://www.fda.gov/media/124351/download>

¹⁷ Impossible Foods FOIA documents. 2017. “FDA’s Evaluation of the Notifier’s Response to FDA’s Questions.” Page 26. Retrieved from https://1bps6437gg8c169i0y1drtgz-wpengine.netdna-ssl.com/wp-content/uploads/2017/08/072717_Impossible_Burger_FOIA_documents.pdf

¹⁸ Impossible Foods FOIA documents. 2017. Page 28. Retrieved from https://1bps6437gg8c169i0y1drtgz-wpengine.netdna-ssl.com/wp-content/uploads/2017/08/072717_Impossible_Burger_FOIA_documents.pdf

¹⁹ Impossible Foods FOIA documents. 2017. Page 30. Retrieved from https://1bps6437gg8c169i0y1drtgz-wpengine.netdna-ssl.com/wp-content/uploads/2017/08/072717_Impossible_Burger_FOIA_documents.pdf

²⁰ <https://www.gmoscience.org/rat-feeding-studies-suggest-the-impossible-burger-may-not-be-safe-to-eat/>

²¹ Impossible Foods, Inc. GRAS notification for soy leghemoglobin protein preparation derived from *Pichia pastoris*: GRAS Notice (GRN) No. 737. October 2017. <https://www.fda.gov/media/124351/download>

²² *Ibid.*

²³ *Ibid.*

²⁴ Elizabeth, L.; Machado, P.; Zinöcker, M.; Baker, P.; Lawrence, M. Ultra-Processed Foods and Health Outcomes: A Narrative Review. *Nutrients* **2020**, *12*, 1955.

²⁵ Santo, R. E., Kim, B. F., Goldman, S. E., Dutkiewicz, J., Biehl, E., Bloem, M. W., & Nachman, K. E. (2020). Considering plant-based meat substitutes and cell-based meats: A public health and food systems perspective. *Frontiers in Sustainable Food Systems*, *4*, 134

²⁶ Impossible Foods, Inc. GRAS notification for soy leghemoglobin protein preparation derived from *Pichia pastoris*: GRAS Notice (GRN) No. 737. October 2017. <https://www.fda.gov/media/124351/download>

²⁷ Santo, R. E., Kim, B. F., Goldman, S. E., Dutkiewicz, J., Biehl, E., Bloem, M. W., & Nachman, K. E. (2020). *op. cit.*

²⁸ Kruger C and Zhou Y. (2018) Red meat and colon cancer: a review of mechanistic evidence for heme in the context of risk assessment methodology. *Food Chem Tox.* 118:131-153. Transparency Document, available at: <https://www.sciencedirect.com/science/article/pii/S0278691518302655#!>; Turner ND and Lloyd SK. 2017.

Association between red meat consumption and colon cancer: A systematic review of experimental results. *Exp Biol Med.* 242:813-839.

²⁹ Food Standards Australia New Zealand

Act 1991

³⁰ FSANZ (2020) *2nd Call for submissions – Application A1186: Soy leghemoglobin in meat analogue products*, p. 22.