PSGR

Physicians & Scientists for Global Responsibility

Address: PO Box 16164 Bethlehem
Tauranga 3147 New Zealand

Email:

Submission by PSGR relating to Application A1186 Soy Leghemoglobin

Physicians and Scientists for Global Responsibility New Zealand Charitable Trust - make the following recommendations:

Plant-based meat analogue products (PBM) containing the LegH Prep preparation that includes soy leghemoglobin - referred to as LegH Prep - present an altered nutritional and toxicological profile from naturally produced meat and should not be considered a dietary meat substitute.

(1) FSANZ should suspend any approval pending the receipt and review of data needed for a genuine safety assessment. 90-day rodent feeding studies of LegH Prep are required to be supplied.

(2) Approval should be delayed to take account of the European Food Safety Authority (EFSA) conclusion on the risk assessment of SLH as LegH Prep (the genetically modified product undergoing risk assessment), we recommend that any additional requirements following by the EFSA conclusion and implemented as policy by the European Commission - to (i) (ii) and (iii) are correspondingly implemented in New Zealand as policy and/or regulation relating to SLH.

(3) If the European Commission do not recommend that LegH Prep is authorised, that New Zealand observe the rationale given and follow the precedent set by the European Commission

(4) In addition and not withstanding the European decision, PSGR recommends that all commercial products containing genetically modified soy leghemoglobin (SLH) produced from genetically modified yeast Pichia pastoris, and referred to as LegH Prep - include the following labelling:

i. **Not a dietary substitute for meat protein**

In addition to including the following legally required statements:

ii. **Genetically Modified**[1]
iii. **Contains soy**[1]

(5) It is critical that the population does not interpret that this soy-based ultra-processed product is equivalent to naturally produced meat protein. The finished imitation meat products contain a mixture of ingredients that place the products in an uncertain as well as distinctly different food product category than naturally grown animal meat. The processed food product that is sold to consumers should not be regarded as a meat substitute and must be identified as such. We stress that long-term dietary studies, equivalent to the human lifetime, are required of the formulated product intended for consumption and that in particular, the estrogenic potential of soy should be evaluated at all life-stages.

(6) Lacking long term dietary studies this product cannot be generally regarded as safe (GRAS).

(A) A commercially produced ultra-processed product should not be interpreted as being equivalent

1. LegH Prep is an innovative compound which includes soy leghemoglobin derived from genetically modified yeast Pichia pastoris, residual P. pastoris (yeast) proteins, and suitable stabilizers (e.g., sodium ascorbate and sodium chloride).[1]

2. LegH Prep will form a minor ingredient in the commercial 'meat analogue products (including the Impossible™ Burger, meatballs, sausages, and as fillings in buns and dumplings)'. These products will be imported into New Zealand and consumed by civil society. The LegH Prep contains not only the publicly known novel soy leghemoglobin, but additionally contains incompletely identified proteins and genetic material from the Pichia host. It is intended that the finalised commercial products will be marketed as plant-based meat.

3. The risk assessment of this single mixture (LegH Prep) will result in the release onto the New Zealand market of the Impossible Foods product line including the Impossible™ Burger, meatballs, sausages, and as fillings in buns and dumplings. The risk assessment summary and conclusion makes no mention of the consequence of this authorisation – that the approval of LegH Prep will result in the release of an ultra-processed product onto the New Zealand market that is heavily marketed and promoted as a plant based meat.

4. Ultra-processed soy-based industry titled plant-based meat analogue products (PBM) cannot be represented as substantially equivalent to naturally grown meat products. Industry papers and data routinely promote the end-product as 'plant-based meat'. We interpret this as an industry claim that infers and promotes scientifically unfounded health benefits. We are concerned, in the absence of epidemiological studies, that this may be misleading to the public.

5. There is a paucity of data supporting the health claims of this ultra-processed food product, but also the disease risk. Independent research external to that produced by Impossible Foods or Monsanto (the patent owner of the genetically-modified soybeans used in production of the Impossible Burger and other soy-based products) that might independently and transparently, in the public interest, verify this claim, is absent. The scientific literature has documented that cascading health problems frequently accumulate from long-term processed food consumption.

6. It is likely that the finished product will be consumed by pregnant mothers, infants and children and that consumption of the product will be interpreted as safe for lifetime exposure.

7. There is no food safety assessment of the imported ultra-processed retail food product, of which LegH Prep will constitute a minor ingredient (0.8%). The burger is predominantly soy based, combining LegH Prep, soy protein concentrate and soy protein isolate. Commercial soy-based food products are commonly derived from genetically modified organisms. In New Zealand, food-based modified organisms are legally required to be labelled as such[2]. Further, due to lack of transparency it is difficult to assess the provenance of many of the ingredients in the ultra-

[1] Impossible Foods. APPLICATION TO AMEND THE AUSTRALIA AND NEW ZEALAND FOODSTANDARDS CODE TO ALLOW FOR THE USE OF SOY LEGHEMOGLOBIN. A1186. Redwood City, USA.
https://www.foodstandards.gov.au/code/applications/Documents/A1186%20Executive%20Summary.pdf
[2] FSANZ Standard 1.5.2 Food produced using gene technology.
https://www.foodstandards.gov.au/code/Documents/1.5.2%20GM%20foods%20v157.pdf

processed product, including the vitamins. Many vitamins in food products are chemically synthesised and genetically engineered.[3] [4]

8. The ingredients listed above place the products in an uncertain as well as distinctly different food product category than naturally grown animal meat.

9. The applicant intends to 'import these products into Australia and New Zealand as raw, frozen, packaged products. These products will be marketed to retailers (such as grocery stores) and caterers (such as fast food restaurants) for final sale to the general population'[5].

10. A significant proportion of sales are intended to be a commonly available catering, fast food and restaurant product. Sales through these outlets, the Impossible Burger, and related meatballs, sausages, and fillings evade labelling and transparency requirements to the New Zealand public.

11. Civil society includes pregnant women, infants, children and individuals with vulnerable health profiles who may be more at risk from the exposures at hormonally relevant levels to uptra-processed soy products that claim equivalence to naturally produced meat protein.

(B) Data Gaps – Political choices by regulators leave known areas of risk outside consideration, in favour of the industry applicant.

12. FSANZ food safety risk assessment contains 'siloed' procedures which compartmentalise individual risk concerns of ingredients in the commercial product and ignore the potential toxicity or risk profile of the commercial product that deviate significantly from a naturally produced meat product. Regulatory authorisation of LegH Prep effectively will act, in Trojan horse style, to facilitate the release of a novel ultra-processed dietary product onto the New Zealand market that has never had long term tests, but that industry marketing hype promotes as a meat replacement product.

13. There are several elements that have the result of Impossible Foods products, (containing LegH Prep and genetically modified soy), differing markedly from naturally produced meat products and constitute an unknown and uncertain health risk. These are due to the:

    a. Increased levels of toxic herbicides applied on the genetically modified food crop that remain in the commercially sold ultra-processed soy product at residue levels which significantly exceed herbicide residues levels commonly detected in naturally produced meat products;
    b. Increased sodium content that significantly exceeds naturally occurring levels detected in meat;

[3] Survase SA, Bajaj IB, Singhal RS. Biotechnological production of vitamins. Food Technol Biotechnol. 2006;44(3):381–396. http://www.ftb.com.hr/archives/76-volume-44-issue-no-3/388-biotechnological-production-of-vitamins. Accessed April 26, 2018.
[4] zu Berstenhorst SM, Hohmann H-P, Stahmann K-P. Vitamins and vitamin-like compounds: microbial production. In: Schaechter M, ed. Encyclopedia of Microbiology. 3rd ed. New York, NY: Elsevier Inc.; 2009:549-561.
[5] FSANZ 20 December 2019 [106-19] Call for submissions – Application A1186 Soy leghemoglobin in meat analogue products https://www.foodstandards.govt.nz/code/applications/Documents/A1186%201st%20CFS%20report.pdf

c. The greater estrogenic potential from the ultra-processed soy which may encourage adverse hormone responses at particular life-stages and impact male and female sex hormones differently.
d. The classification of these products as ultra-processed foods. Ultra-processed foods are increasingly demonstrated to confer adverse health outcomes.

14. The soy ingredients in Impossible Foods are derived from genetically modified soybeans, which are commonly herbicide tolerant. Genetically engineered crops that are herbicide tolerant are produced with the intention of applying the herbicide formulation on the growing food crop. Pesticide residue levels for these food crops have been increased to reflect the higher exposure levels that result from spraying on the food crop. These chemicals are not commonly found in naturally produced meat products at similar residue levels.

15. Only the probable carcinogen glyphosate (and its metabolite aminomethylphosphonic acid, AMPA) have been residue tested for in the Impossible Burger. The herbicide glyphosate and its formulation ingredients (including petroleum compounds and heavy metals[6] which are not considered in risk assessment, despite being more toxic[7]) are applied on genetically modified soy (GMS) and permitted residue levels have been increased to reflect the increased dietary load.

16. Glyphosate is a commonly detected contaminant of genetically modified soy and processed foods. It was detected at eleven times the levels contained in the non-genetically modified competitor product Beyond Burger (sold in New Zealand by Beyond Meat), and considerably higher than levels detected in naturally grown meat or demonstrated to be harmful in scientific studies. The testing laboratory, Health Research Institute Laboratories, detected glyphosate at 11.3ppb.

17. Trials have never been undertaken to understand the cumulative effect of environmentally relevant levels of glyphosate-based herbicides *and* genetically modified soy. The published scientific literature increasingly indicates glyphosate and its formulations act in multiple, non-exclusive ways. Studies demonstrate glyphosate and glyphosate-based formulations probably causes cancer[8]; glyphosate is a likely endocrine disruptor[9]; is neurotoxic[10]; causes toxic health affects in subsequent generations[11]; and that microbiome dysbiosis may be involved in neurotoxic responses.[12]

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[6] Defarge, N., de Vendômois, J., & Séralini, G. (2018). Toxicity of formulants and heavy metals in glyphosate-based herbicides. Toxicology Reports, 156-163
[7] Mesnage, R., & Antoniou, M. (2018). Ignoring Adjuvant Toxicity Falsifies the Safety Profile of Commercial Pesticides. Frontiers in Public Health, 361.
[8]IARC (2017) IARC Monographs on the evaluation of carcinogenic risks to humans—volume 112: some organophosphate insecticides and herbicides. https://monographs.iarc.fr/wp-content/uploads/2018/06/mono112-10.pdf
[9] Vandenberg LN, et al. Is it time to reassess current safety standards for glyphosate-based herbicides? *J Epidemiol Community Health* 2017;71:613–618. doi:10.1136/jech-2016-208463
[10] Martínez et al. Neurotransmitter changes in rat brain regions following glyphosate exposure. *Environmental Research.* 2018;212-219
Cattani et al. Mechanisms underlying the neurotoxicity induced by glyphosate-based herbicide in immature rat hippocampus: Involvement of glutamate excitotoxicity. *Toxicology.*2014;320:34-45
[11] Milesi et al. Perinatal exposure to a glyphosate-based herbicide impairs female reproductive outcomes and induces second-generation adverse effects in Wistar rats. *Archives of Toxicology.* 2018 Aug;92(8):2629-2643
Kubsad et al. Assessment of Glyphosate Induced Epigenetic Transgenerational Inheritance of Pathologies and Sperm Epimutations: Generational Toxicology. Scientific Reports, 2019; 9 (1) DOI: 10.1038/s41598-019-42860-0
[12] Rueda-Ruzafa, L., et al. Gut microbiota and neurological effects of glyphosate. Neurotoxicology. 2019 Aug 20. pii: S0161-813X(19)30081-6. doi: 10.1016/j.neuro.2019.08.006.

18. It is noteworthy that glyphosate is a patented antibiotic, yet the potential for glyphosate as a food contaminant to promote antimicrobial resistance in what the applicant appears to intend to be a common dietary component, appears to have remained outside regulatory scrutiny.[13]

19. Due to resistance to glyphosate-based herbicides and increasing weed problems, genetically modified soy is now 'stacked' to tolerate multiple formulations of herbicides. Many genetically modified soybean lines are approved for sale in New Zealand[14]. Traits of approved soybeans include traits for glyphosate (Roundup) tolerance; glufosinate tolerance; dicamba tolerance; imidazolinone tolerance; double stacked 2,4-D and glufosinate tolerance; glyphosate and isoxaflutole tolerance; glufosinate and mesotrione tolerance; triple stacked 2,4-D, glufosinate and glyphosate tolerance.

20. Food safety regulators are yet to commission independent studies to understand combined contaminant levels of the other herbicides permitted as 'stacked events' which will alter the toxicity profile of the processed food product; nor are they yet to consider the combined toxicity of the commercially developed formulation, outside of company developed, privately supplied studies. This toxicity profile casts further doubt over the claims that soy-based products, developed for the New Zealand market, may be equivalent in its health effect to naturally produced meat.

21. The potential for altered estrogen levels (either from naturally occurring dietary estrogen, but also from chemicals that mimic or block estrogen) to induce hormonally related diseases including cancer is recognised. While supplementation is recognised to be beneficial at later stages in life, exposure to altered estrogen levels in earlier life stages may encourage disease. Different risk profiles exist for male and female hormone systems.

22. Increasingly, glyphosate is demonstrated to be harmful or toxic at lower levels than 11.3ppb, the levels detected in the Impossible Burger.
    i. Stur et al 2019. Glyphosate-based herbicides at low doses affect canonical pathways in estrogen positive and negative breast cancer cell lines.PLoS One. 2019 Jul 11;14(7):e0219610.
    ii. Mesnage et al 2017. Multiomics reveal non-alcoholic fatty liver disease in rats following chronic exposure to an ultra-low dose of Roundup herbicide. *Scientific Reports.* 7:39328
    iii. Mesnage R., Arno M., Costanzo M., Séralini G.-E., Antoniou M.N. Transcriptome profile analysis reflects rat liver and kidney damage following chronic ultra-low dose Roundup exposure. Environ. Health. 2015;14:70. doi: 10.1186/s12940-015-0056-1.

Aitbali, Y., et al. Glyphosate based- herbicide exposure affects gut microbiota, anxiety and depression-like behaviors in mice. Neurotoxicol Teratol. 2018 May – Jun;67:44-49

[13] Kurenbach, B., Gibson, P., Hill, A., Bitzer, A., Silby, M., Godsoe, W., & Heinemann, J. (2017). Herbicide ingredients change Salmonella enterica sv. Typhimurium and Escherichia coli antibiotic responses.. Microbiology, 1-11. doi:10.1099/mic.0.000573

Kurenbach, B., Hill, A., Godsoe, W., van Hamelsveld, S., & Heinemann, J. (2018). Agrichemicals and antibiotics in combination increase antibiotic resistance evolution. 2018. PeerJ, 6, e5801.

Kurenbach, B., Marjoshi, D., Amabile-Cuevas, C., Ferguson, G., Godsoe, W., Gibson, P., & Heinemann, J. (2015). Sublethal exposure to commercial formulations of the herbicides dicamba, 2,4-dichlorophenoxyacetic acid, and glyphosate cause changes in antibiotic susceptibility. mBio, 6.

[14] FSANZ Current GM applications and approvals August 2019. https://www.foodstandards.govt.nz/consumer/gmfood/applications/Pages/default.aspx

iv. Thongprakaisang S, Thiantanawat A, Rangkadilok N, Suriyo T, Satayavivad J (2013) Glyphosate induces human breast cancer cells growth via estrogen receptors. Food Chem Toxicol 59: 129–136. pmid:23756170

23. The toxicity studies of LegH Prep released by FSANZ to support the approval contain data gaps:

    i. 28-day tests are far too short to identify long term health effects.
    ii. The potential for hormonal alterations that can increase chronic disease risk are ignored.
    iii. Only one short term study discusses the liver – GM soy has been known to harm liver over the longer term.[15] Pancreas weights have not been discussed.
    iv. Toxicity studies are not for the commercial preparation intended for retail sale.
    v. Female reproductive problems were observed but neither intergenerational studies, nor developmental studies have been supplied.

24. Without evidence of safety from 90-day dietary studies for LegH Prep, FSANZ should not authorise LegH Prep as safe. European law requires that 90-day studies are supplied, they will exist. Reluctance of Impossible Foods to supply 90-day studies is a likely signal that scientific studies to date may have produced unsatisfactory results. 90-day rodent studies, but also lifetime 2-year studies, are a common component of risk assessment and deviation from 90-day studies as a minimum requirement is surprising, and unsupportive of the public interest. Weaker regulatory regimes are acceptive of the data gap.

25. The products that are manufactured by Impossible Foods and intended for sale in New Zealand contain ingredients that result in the commercial product categorisation of 'ultra-processed food'[16]. Ultra-processed foods are associated with adverse health outcomes[17]. Ingredients can be altered to change the nutritional and health profile to make a product more attractive. The salt (sodium) level of the Impossible Burger appears to be five times the level of ground beef[18].

26. If Impossible Foods gain approval for the Impossible Burger via the approval of LegH Prep, there will be no consideration of salt levels, which reflect problems associated with ultra-processed food and which deviate markedly from naturally produced meat products.

27. Food safety regulators are yet to commission independent studies to understand the accuracy of the protein claims made by Impossible Foods. The protein in the Impossible Burger is not biologically equivalent to meat.

    i. Soy protein is considered an 'imbalanced protein source' and dietary soy protein has been found to trigger reduced feed intake and bodyweight gain[19]. Many of the

[15] Malatesta M, Boraldi F, Annovi G, et al. A long-term study on female mice fed on a genetically modified soybean: effects on liver ageing. Histochem Cell Biol. 2008;130:967–977
[16] Gibney, Michael J. "Ultra-Processed Foods: Definitions and Policy Issues." Current developments in nutrition vol. 3,2 nzy077. 14 Sep. 2018, doi:10.1093/cdn/nzy077
[17] Baker, PI. Ultra-processed food and adverse health outcomes. *BMJ.* 2019;365:i2289
[18] Gelsomin E. Impossible and Beyond: How healthy are these meatless burgers? August 15, 2019. https://www.health.harvard.edu/blog/impossible-and-beyond-how-healthy-are-these-meatless-burgers-2019081517448
[19] Song S. et al. Dietary soy and meat proteins induce distinct physiological and gene expression changes in rats. *Nature Scientific Reports*. 2016;6:20036. https://www.nature.com/articles/srep20036

responses are associated with the fact that the soy protein contains the amino acid methionine at a lower level than a naturally produced meat.[20]

ii. Phytoestrogens are present at levels significantly higher than is naturally available in a naturally produced meat burger. A diet with increased phytoestrogen content may alter hormone function and there is no scientific consensus as to the benefit or otherwise of increased phytoestrogen exposures.[21]

28. The compartmentalised nature of risk assessment, and the substantial data gaps addressed above (herbicide residues, mixture effects, short term studies, absence of consideration of hormonal effects) directly benefits the entity seeking the risk approval, Impossible Foods. Regulators have been unwilling to use science outside those supplied by the industry seeking the approval to address data gaps, and governments historically unlikely to fund the science that would fill this gap.

29. It is evident that the human population is witnessing an increase in chronic disease and dysfunction (of the reproductive system, nervous system and brain, and hormonally relevant cancers) directly related to hormone disruption.[22] Expert science knowledge on hormonal risk has not been integrated into risk assessment at a meaningful level where nuanced alterations would be extrapolated to demonstrate long term health risk. Risk assessment practices are profoundly outdated and have been culturally resistant to meaningful change in the field of endocrine disruption and health risk. There can be no claim risk assessment by regulatory agencies of environmental chemicals nor of results from exposure to genetically modified or edited food products, is safe at the hormonal (endocrine) level and protective of public health.

30. FSANZ can require long term dietary studies of the complete product to understand risks to the hormone system. Animal studies can effectively predict the effects of hormone disrupting effects from hormone mimicking substances. This has been known for several decades. This is because scientists have a 'good grasp of the mechanisms and actions of hormones'. [23]

31. Regulatory decision-makers should not conflate the greater difficulty of predicting cancer, for which the mechanisms can be more complex - with the knowledge that there is extensive scientific expertise in the field of endocrinology, and long term evidence that animal studies can help identify hormone risk to the reproductive system, nervous system and brain, and hormonally relevant cancers.

32. With consideration of the above it is legally and scientifically appropriate that industry titled PBM products are clearly labelled 'Not a substitute for meat protein'.

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[20] Friedman M. and Brandon, DL. Nutritional and Health Benefits of Soy Proteins. *Agricultural and Food Chemistry.* 2001;49:3:1069-1086

[21] Rietjens et al. Review Article: The potential health effects of dietary phytoestrogens. *British Journal of Pharmacology.* 2016;174:11

D'Adamo CR and Sahin A. Soy Foods and Supplementation: A Review of Commonly Perceived Health Benefits and Risks. *Alternative Therapies in Health & Medicine*. 2014;1:20:39-51

[22] Gore, A., Chappell, V., Fenton, S., Flaws, J., Nadal, A., Prins, G., . . . Zoeller, R. (2015). 2015. EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals. Endocr Rev, 36(6), E1-E150.

[23] Colborn T., Dumanoski D. and Myers P. Our Stolen Future: Are We Threatening Our Fertility, Intelligence, and Survival? A Scientific Detective Story. 1997. New York:Penguin Group. p.169

33. PSGR acknowledges that there is no legal obligation for FSANZ to consider the entirety of the product that the New Zealand population (including pregnant women and infants) will be exposed to, nor to favour precaution, a precautionary approach or to defer to the precautionary principle. These obligations are not required by the empowering legislation, the *Food Standards Australia New Zealand Act 1991*.

34. While the object of the Act is to 'ensure a high standard of public health protection', this is loosely interpreted as the many gaps in food safety assessment create loopholes that benefit the industry seeking the approval. Further, lower order guidelines that do not require long-term toxicity testing of commercially available food products; nor require that assessment incorporate publicly available literature nor nuanced endocrine effects. These eminently political choices have resulted in an industry friendly, weaker regulatory regime, similar to Canada and the United States.

35. By contrast, the European Commission and European Food Safety Authority are tasked with guaranteeing a 'high level of protection to human life and health' under the *General Food Law Regulation*[24]. The European Commission requires that the precautionary principle must be utilised where there are reasonable grounds of concern that an unacceptable level of risk to health exists, and that available supporting information and data are not sufficiently complete to enable a comprehensive risk assessment to be made. The Commission acknowledges that 'judging what is an "acceptable" level of risk for society is an eminently political responsibility. [25]

36. While weaker regulatory regimes (Canada and the USA) have approved LegH Prep, Europe is yet to produce a conclusion on the risk profile of the product. It is common for industry applicants to seek approval from weaker regulatory regimes to approve an innovative and controversial product with an uncertain risk profile, gaining a form of social licence to then pressure and seek approval from stricter regulatory regimes.

37. The precautionary principle requires action to protect human and environmental health in the case of uncertainty. There has been little public scrutiny of LegH Prep as there are no independently published risk studies, nor have the industry studies been broadly released to the public. This is common in approvals of genetically engineered products as independent scientists are rarely granted access to the newly patented product for laboratory testing.

38. A literature review to understand the scientific evidence on the safety of genetically modified Soy Leghemoglobin has identified only two published papers, both produced by Impossible Foods and/or scientists with professional connections to Monsanto (who own the patent on the soy used in the processed product):

    i. Evaluating Potential Risks of Food Allergy and Toxicity of Soy Leghemoglobin Expressed in Pichia pastoris. 2019. *Molecular Nutrition and Food Research.* Yuan Jin Xiaoyun He Kwame Andoh-Kumi Rachel Z. Fraser Mei Lu Richard E. Goodman
    ii. Safety Evaluation of Soy Leghemoglobin Protein Preparation Derived From Pichia pastoris, Intended for Use as a Flavor Catalyst in Plant-Based Meat. 2019.

[24] General Food Law Regulation. Articles 5-10. https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:32002R0178
[25] Communication from the Commission on the precautionary principle. https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:52000DC0001

International Journal of Toxicology. Rachel Z. Fraser1, Mithila Shitut, Puja Agrawal, Odete Mendes, and Sue Klapholz

39. Studies supplied by industry for the purposes of food safety assessment are frequently for short time periods, and the quality of an outcome can be weakened by small sample sizes. One of the studies of the supplied for food safety assessment contained these problems, however it also revealed statistically significant potentially adverse effects, compared with the control group (see Appendix for a detailed analysis). These effects, which included disruption to the rat's reproductive cycle (reproduction and fertility problems are a major health concern in New Zealand) were dismissed by the company.

40. It is common for the media to take an 'independent stance' on new technologies and optimistically regard new technologies as beneficial, and to trust risk assessment. We consider the issues raised above are unlikely to be deconstructed in the public environment. We are yet to see regulatory agencies discussing the deficits in current testing approaches, nor to see sceptical journalists pointing to the data-gaps. The result of this is that submissions pointing to the gaps that should raise uncertainties around risk to human health (particularly to pregnant women, infants and children) are unlikely to be debated in the public arena.

Conclusion

The authorisation of LegH Prep will have the result of release onto the market of a novel food. There have been no long term studies supplied for LegH Prep, without this data the substance that is not pure soy leghemoglobin (SLH), should not be released onto the New Zealand market.

In the pages above we have listed uncertainties and inconsistencies, which include nutritional discrepancies; endocrinological uncertainties; the potential for toxic effects from herbicides applied to genetically modified soy; the high sodium levels and the fact that the product is an ultra-processed food product that we make the recommendations listed on page 1.

We consider it scientifically unsound that the FSANZ does not require data to evaluate the risk (nutritional, toxicological and endocrinological) profile of products that will be released containing both genetically modified soy ingredients and the genetically modified soy leghemoglobin (SLH) produced from genetically modified yeast Pichia pastoris, and referred to as LegH Prep. We consider it deeply problematic that there is an absence of data that is produced separately from the industry applicant (Impossible Foods) with the vested interest in obtaining the approval from the FSANZ.

PSGR considers that New Zealand decisions should look to European guidance. Notwithstanding European decisions, appropriate and cautionary labelling should be required of all products containing LegH Prep to be identified. This is required in order to retain public trust in approvals for genetically modified or gene edited organisms and to ensure that the public are not misinformed and are lead to believe that the products that will contain LegH Prep are equivalent to naturally produced meat based products.

Plant-based meat analogue products (PBM) present an altered nutritional and toxicological profile from naturally produced meat and should not be considered a dietary meat substitute and this must be clearly stated on all product ingredient labels.

Our recommendations are listed on page 1.

Appendix

Rat Feeding Study Suggests the Impossible Burger May Not Be Safe to Eat

Claire Robinson and Michael Antoniou, PhD

GMOScience, 25 Jun 2019

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

At-a-glance

- The Impossible Burger is a plant-based burger, the key ingredient of which is a protein called soy leghemoglobin (SLH), derived from genetically modified (GM) yeast
- A rat feeding study commissioned by the manufacturer Impossible Foods found that rats fed 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
- Impossible Foods dismissed these statistically significant effects as "non-adverse" or as having "no toxicological relevance"
- The company's conclusion of safety is unsound, due to the short duration of the feeding study and the small number of animals used. Only a longer-term study with a larger number of animals can clarify the significance of the worrying effects seen
- A nonprofit group is collecting data from people who believe they have had an adverse reaction to the burger.

The Impossible Burger is a plant-based burger, the key ingredient of which is a protein called soy leghemoglobin, derived from genetically modified (GM) yeast. The burger arrived in New York City's restaurants with much fanfare – but now it is almost impossible to find, according to an article in the New York Post.1

Possible reasons put forward by the Post's reporter include that the burger is expensive and can't compete with cheaper options; that the company that makes it, Impossible Foods, is having manufacturing problems that mean it can't keep up with demand; and that people don't see any reason to buy it when plant-based veggie burgers with more everyday ingredients are commonly available.

But it's also possible that NYC restaurant owners and their customers are becoming aware – and wary – of the GMO (genetically modified organism) status of the product and are choosing to avoid it. The results of a rat feeding study commissioned by Impossible Foods and carried out with soy leghemoglobin (SLH) suggest that they may have good reason.

SLH is the substance that gives the burger its meaty taste and makes it appear to bleed like meat when cut. The US Food and Drug Administration (FDA) initially refused to sign off on the safety of SLH when first approached by the company. The rat feeding study results suggest that the agency's concerns were justified. 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.

2015: FDA says SLH safety not proven

The company maintains that SLH is safe to eat.2 It wanted the US Food and Drug Administration to agree with its self-declared conclusion that SLH is "GRAS" (Generally Recognized As Safe), providing reassurance for consumers. But in 2015, in response to Impossible Foods' first application, the FDA refused to agree that the substance was safe. It responded with tough questions for the company, as revealed in documents obtained under a Freedom of Information request.3

The FDA was concerned that SLH has never been consumed by humans and may be an allergen. The agency pointed out that the safety information submitted by Impossible Foods was not specific enough: "Although proteins are a part of the human food supply, not all proteins are safe. Information addressing the safe use of modified soy protein does not adequately address safe use of soybean leghemoglobin protein from the roots of the soybean plant in food."3

The FDA concluded, "FDA believes that the arguments presented, individually and collectively, do not establish the safety of SLH for consumption, nor do they point to a general recognition of safety."3

2017: Impossible Foods tries again

In 2017 Impossible Foods tried again with a new application for GRAS status. It submitted data from a study that the company had commissioned in which rats were fed SLH.4 Although Impossible Foods had in its 2015 submission told the FDA it intended to conduct a 90-day feeding study (the standard length for subchronic toxicity in rats), the company said that following "feedback" from the agency, it had decided on a shorter study of 28 days.3

While this change would cut costs for Impossible Foods, it is not in the public health interest. That's because 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.

The number of animals and duration of a feeding study are two key design elements in an investigation of the safety of a new GM food substance.

It was always unlikely that SLH would have strong and obvious toxic effects in the short term; any adverse effects from a novel food substance would likely be subtle. Long-term studies with relatively large numbers of animals are required in order to reveal the significance of such effects. Given these requirements, it seems clear that Impossible Foods' study was statistically weak. There were too few animals in each test group (10 per sex per group) and again, the study was too short in duration (28 days in a rat is equivalent to just 2-3 years in a human) to clarify any health concerns from long-term consumption of this product.

Adverse effects in SLH-fed rats

In light of these limitations, it is remarkable that the SLH-fed rats did show a large number of statistically significant potentially adverse effects, compared with the control group – for example:

- unexplained transient decrease in body weight gain
- increase in food consumption without weight gain
- changes in blood chemistry
- decreased reticulocyte (immature red blood cell) count (this can be a sign of anemia and/or damage to the bone marrow where red blood cells are produced)
- decreased blood clotting ability
- decreased blood levels of alkaline phosphatase (can indicate malnutrition and/or celiac disease)
- increased blood albumin (can indicate acute infection or damage to tissues) and potassium values (can indicate kidney disease)
- decreased blood glucose (low blood sugar) and chloride (can indicate kidney problems)
- increased blood globulin values (common in inflammatory disease and cancer).4
- The fact that these changes were seen in spite of the statistical weaknesses of the study gives particular reason for concern.

Reproductive changes in SLH-fed females?

In the study, apparent disruptions in the reproductive cycle were found in some groups of females fed SLH. In normal healthy rats, the uterus fills up with fluid during the proestrus phase of the cycle, in the run-up to the

fertile and sexually receptive phase (estrus). In the SLH-fed rats, significantly fewer "fluid filled" uteri were seen. This correlated with decreased uterus weight, as might be expected.4

In response to this finding, Impossible Foods commissioned a second rat feeding study,4 which found no effect on the SLH on the rats' estrus cycle. The company concluded that the findings of the first study had been a mere artifact of the experimental method used.4 For the sake of the women who eat the Impossible Burger on a regular basis, we hope that the company is correct.

All effects dismissed

All these effects were dismissed by Impossible Foods as "non-adverse", as having "no toxicological relevance", as "transient" on the grounds that they appeared to reverse themselves after some days, and as not dependent on the dose (i.e. the effect did not increase with increasing dose).

It is true that the adverse outcomes may appear somewhat haphazard. However, the fact that there were so many statistically significant changes in multiple organs and systems suggests that closer scrutiny of the safety of SLH is urgently required. The apparent randomness of the effects may be due to the fact that the study design was statistically weak. And it is well known that toxic effects do not always follow a linear dose-response pattern.5 Dismissing the findings as irrelevant appears irresponsible.

The only way of ascertaining if potentially adverse effects seen in short studies are truly adverse or have lasting consequences is to extend the study length to the rats' full lifetimes (2-3 years) and to do multigenerational testing. In this case, neither was done.

FDA capitulates

Impossible Foods' second attempt to obtain GRAS status for SLH succeeded and the FDA issued a "no questions" letter, indicating that it had no further questions.6

Contrary to what many people believe, such letters are not an assertion by the FDA that the food in question is safe. They state that the company asserts that the food is safe and remind the company that it, and not the FDA, is responsible for ensuring that it only puts safe foods on the market.

"No questions" letters may protect the FDA from liability in case something goes wrong. But they do not protect the consumer from unsafe novel foods.

Another GMO ingredient

Impossible Foods recently introduced a new recipe for its Impossible Burger. In addition to GMO-derived SLH, the burger now contains another GMO ingredient: protein from herbicide-tolerant soy.7 The company introduced soy protein to replace wheat protein in order to improve the texture and to avoid gluten, the protein in wheat that some people cannot tolerate.8 As a result, Impossible Burger Version 2.0 may contain residues of the "probable carcinogen" glyphosate,9 the main ingredient of the herbicide used on GM soy.

Knowing the concerns that the use of GMO soy protein and glyphosate residues may raise, Impossible Foods CEO Pat Brown has gone to some lengths to reassure the buying public.10 But the history of the Impossible Burger thus far suggests that people are unlikely to get meaningful answers to safety questions from the regulators or the manufacturer.

Now a nonprofit group has stepped in to try to fill some of the information gaps. GMO Free USA states that its mission is to educate people about the potential hazards of GMOs and synthetic pesticides. The group has launched a health survey to gather the experiences of people who believe they have had an adverse reaction to the burger. GMO Free USA says it took action because "We have been contacted by a few people who have experienced gastrointestinal problems after eating the Impossible Burger (IB). There is currently no simple mechanism for people to report these problems to the FDA."

The group plans to send its findings to the FDA and Impossible Foods. Whatever the results, based on what we already know about the potential health effects of the Impossible Burger, the company would be well advised to shelve SLH and the reformulate their product with natural – and if possible organic – ingredients.

Authors: Claire Robinson is editor at GMWatch.org. Michael Antoniou, PhD is a London-based molecular geneticist. Contrary to allegations received following the publication of a previous article about the Impossible Burger, they were not paid to write this article by the livestock industry. They are vegetarian, but respect all dietary choices based on minimally processed and organic foods.

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