Leghemoglobin

A Submission by Friends of the Earth NZ

To the Food Standards Authority of Australia and New Zealand

11th February 2020

Introduction

Friends of the Earth New Zealand is an environmental research and campaigning organization founded in this country in 1975. It has been involved in a wide range of issues, including questions surrounding the integrity of our food supply. Two food issues have particularly concerned us long term.

i) the use of genetic engineering in the production of food, and the sale, consumption and labelling of such food in Aotearoa New Zealand.

ii) The use of food irradiation as a sterilizing agent of food entering New Zealand, and the labelling of such food in this country.

We also have general concerns around food, insofar as we advocate for regenerative farming practices that maximize ecological effectiveness and the protection of land and water. In 2001 we appeared before the New Zealand Royal Commission on Genetic Modification. There we presented international witnesses including the specialist in digestive physiology, Dr Arpad Puzstai. Our position in regard to work done by Pusztai's research team in an experiment whose design was peer-reviewed by Britain's Biotechnology and Bioscience Research Council and funded by the Scottish government - work concerning the effects on rats being fed potatoes that had undergone transgenesis - is that it was sound. In this we were supported by data published in the medical journal, *Lancet.* This data indicated the presence of significant alteration in the gut morphology of the rats after a short feeding trial. We do not wish to revisit the political controversy and the systematic slander of the Pusztai team by officials and scientists who were advocates for genetic engineering. But we mention the case because only a ten day trial was completed. A longer one was underway, but not able to be completed in the furore that surrounded the

publication of the short trial results. Puzstai and his team wished for the entire set of trials to be repeated so it could be seen more clearly whether initial concerns about serious changes to gut structure in the trial rats were fully justified. This was never allowed, for political reasons, and he was dismissed from his position at the Rowett Institute. The editor of *Lancet*, who published Puzstai's data for the short and completed trial on the basis of a favourable peer review of them, did not resile and withdraw them from the journal, despite considerable pressure being put on him to do so. (1)

We mention this case because it is relevant to the issue of the length of feeding trials, and the political dynamics surrounding them. In the case now under review, the applicant has not been forbidden to conduct longer feeding trials, or to repeat the trial already done, but appears to not to wish to do so, though initial results suggest this should be done. One anomaly in the test rat females was re-tested, to see if it appeared on a second run through. This was the issue of decreased uterus weight and pre-oestrus phase fluid content in the uterus. It did not, but more exhaustive testing would still be needed to see which of the two results was an aberration. Unlike the Pusztai team, the applicant is not threatened with calumny, dismissal or other sanctions by the US food authorities, but is acting by choice in the matter of not conducting more or longer tests.

Since 2001 we have maintained a watch on developments in the GE story, have submitted on a variety of genetic engineering applications, and on the framing of New Zealand's Hazardous Substances and New Organisms Act - a piece of legislation that establishes a precautionary approach to the presence of GE activities, particularly in the open environment. We also try to keep abreast of the latest developments in genetic theory and molecular biology.

We were active in preventing the establishment of a food irradiation plant at Mangere, Auckland, in 1989, and sucessfully advocated also against the building of such a plant in Mangakino, Bay of Plenty, in 1995. We continue also to campaign for proper labelling of imported irradiated foodstuffs that are being sold in to the New Zealand foods system.

Our Position on Leghemoglobin Based on Data We Have So Far Seen

We oppose the introduction of soy leghemoglobin into the New Zealand and Australian food system, by the US based food company, "Impossible Foods Inc".

They are currently applying (Application 1186) to FSANZ to sell this genetically engineered protein supplement in both countries. Our opposition is:

i) That it is produced by what is basically a transgenic placement of soybean plant genes in the genome of an industrial yeast, *Pichsia pastoris;* a placement causing the expression of the novel leghemoglobin. Transgenesis is liable to produce unanticipated effects in the host organism and in organisms that ingest proteins expressed by the host.

ii) That its sale here would set a precedent for further sales of genetically engineered food substances in Australia and New Zealand. New Zealand, particularly has a considerable stake in not having GE material and organisms out in the open environment, or in its food production chains.

iii) That, on the basis of three decades experience with the labelling of imported irradiated produce, we can say with regretful, but near certainty that leghemoglobin labelling would be wholly inadequate and virtually invisible - that is even in the optimum situation, where there is a legal requirement for labelling. The labelling system as we have observed it, is broke, and regulatory officers are uninterested in fixing it, or in enforcing the regulations. Unreadable or no labelling is the norm.

iv) That the leghemoglobin arising from the transgenesis in *Pischia pastoris* by genes from the root nodules of the *Glycine max* soybean plant is unsafe for human consumption.

Unsafe For Human Consumption

We reach this conclusion on reading the the current FSANZ assessment - "Risk and Assessment Report Application A1186. Soy Leghemoglobin in Meat Analogue Products, (20/12/19)". We are also influenced by reviewing the history of "Impossible Foods " applications within the USA, and by documents that give an account of those applications.

The History

The history of testing the leghemoglobin food supplement is characterized by contradictory claims about its safety and contradictory actions by the FDA (Food and Drug Administration) in the USA. It is to them that "Impossible Foods" had to apply for permission to market its meat analogue soy/leghemoglobin. In 2015 "Impossible Foods" applied to the FDA for endorsement that this was safe to eat as an element in the makeup of vegetarian and vegan burgers and buns.

Endorsement was withheld. "The 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." (2)

"Impossible Foods" made a second application in 2017. With this they submitted results of a short feeding study in which rats ingested leghemoglobin over 28 days. In normal practice 28 days would be deemed rather short, unless there were also much longer additional trials. The sample size of the rats tested was also small. The study was commissioned by the company. We are unaware of the extent to which "Impossible Foods" natural desire that test results would not indicate problems was at play in what we can only assume was a reviewing organization of their choice and entirely funded by them for doing the work. Nonetheless,, the study yielded data unfavourable to any notion that soy leghemoglobin was safe. The dosed rats, as compared with control animals showed:

- 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 anaemia and/or damage to bone marrow (production site) of these cells
- decreased blood-clotting ability
- decreased blood levels of alkaline phosphotase (which can indicate acute malnutrition and or coeliac disease)
- increased blood albumin (can indicate acute infection or damage to tissues)
- increased potassium values
- decreased blood glucose
- decreased chloride (can indicate kidney problems)
- increased blood globulin values (commonly indicates inflammatory disease and cancer)

These effects and others, relating to dysfunction in the female reproductive system and alterations in the structure thereof, were airily dismissed by "Impossible Foods" as being probably transitory and not seriously problematic. (3)

We believe the impermanence and/or seriousness of the changes away from the homeostatic 'normal' of any living system cannot be known on the basis of short-time tests on very small test populations. If the rats were being tested for the effects of a pharmaceutical that was ultimately be taken by humans, a testing regime as brief and slight as the "Impossible Foods " test would not be tolerated. It is hard to see why it should be

tolerated in regard to a foodstuff that is potentially to be ingested by at least as many humans as would be the case with a major pharmaceutical. Homeostasis in a vertebrate species is the outcome of many millions of years of evolutionary consolidation in numberless individuals. Any changes away from the homeostatic 'average' in the structure, biochemistry and physiology of a test organism, ranging from the molecular and genotypic level, to the level of the phenotype, would have to be considered as serious and, potentially at least, long term.

We do not know whether the FDA agree with this. We do know that again, they did not endorse the release of the GE leghemoglobin into the human food supply. Nor did they forbid it. Instead they took the curious step of issuing a "no questions letter" which was, in effect, washing their hands of the problem. Leghemoglobin is now in the food systems of the USA, South Korea, Singapore and Macau, with results unknown. (4)

"Impossible Foods had achieved a GRAS notification, which stands for " Generally Recognized As Safe". But this , it appears , is a rhetorical sleight of hand. A GRAS notification is not clearance of a product as being safe. It is a statement by which the FDA clears itself of any legal responsibility for mishaps or disasters that might arise from the human consumption of leghemoglobin. The applicant gains the right to market the product, but also carries responsibility to assert its safety, plus the legal consequence for any negative outcomes, The FDA has withheld real endorsement, but has freed itself from legal responsibility. This is a highly undesirable outcome and undermines the duty of care, the protective function by which such an agency should operate.

We wonder whether the issuance of a "No questions" letter in October 2017 is the result of the anti-regulatory policies of the (by then) entrenched Trump administration, which has resulted in a general weakening of protective functions by agencies concerned with environmental oversight.

The warning case that has relevance to the present application 1186, for acceptance of Leghemoglobin is the Showa Denka KK - Tryptophan case in 1989 . Showa Denka KK, a Japanese company, were manufacturers of a genetically engineered food supplement, L - Tryptophan . It was released for human consumption and implicated in a health catastrophe where, in the USA, 37 people died, 1500 were disabled and 5000 were 'affected'. It was argued that it was specifically the genetic engineering involved in the manufacture of an L-tryptophan batch that had caused the disaster. It was also argued that a failure in the filtration of the L - tryptophan had been at fault. In the event, the Court decided that the technical failure was in the batch filtration, not the genetic engineering process. The question was still unresolved, though discussed, at New Zealand's Royal commission of

Genetic Modification in 2001. In ensuing litigation Showa Denka KK had to accept guilt, to the extent of paying massive compensation to surviving victims and families of victims. (5)

The case reveals an inherent reluctance to accept that there may be flaws in the theory and practice of genetic engineering. We note in the response of "Impossible Foods" to reported irregularities in test animals ingesting leghemoglobin a tendency to understate risk with genetic engineering processes. As an emerging "high" technology, genetic engineering is subject to a naïve faith in its infallibility.

That is a socio-cultural, not a scientific problem, just as liability is a legal problem, though it might be decided on the basis of scientific evidence. But we suggest these questions be seriously considered by FSANZ before clearing Leghemoglobin for consumption in Australasia. FSANZ should not be feeling the pressures that possibly caused the FDA to rule so indecisively. Nor should they rule according to the assumption, strengthened by the high kudos of genetic technology, that such a technology cannot be wrong, and should be subject to very much less rigorous testing processes than is the case with pharmaceuticals.

We say this because a reading of the FSANZ Assessment Document raises questions about the organisation's willingness to raise the bar very high in allowing a product already associated with significant changes in test animals to be commercially released.

Comment on the FSANZ Assessment Document

The report is detailed and competent. There is an anomaly however. The questions raised about the effects of ingesting leghemoglobin on rats do not influence the report's conclusions - namely that

> "FSANZ has concluded a comprehensive assessment following the internationally recognized risk analysis framework" and that "the assessment of soy leghemoglobin and the LegH Prep concluded that there are no public health and safety concerns associated with its use in meat analogue products at the proposed level of up to 0.8% soy leghemoglobin. (6)

In the assessments Executive Summary it is also stated that

"the novel soy leghemoglobin was shown to be equivalent to that expressed in soybean and was shown to be expressed as a holoprotein [A holoprotein is a protein bound to a prosthetic group. In this case the prosthetic group is haem and is conjugated in leghemoglobin] Analyses of the potential allergenicity or toxicity of the soy leghemoglobin and the *Pischia* proteins did not identify any significant similarities to known allergens or toxins. The proteins were shown to be susceptible to pepsin digestion and were denatured at standard cooking temperature and in acidic conditions that mimic the stomach environment. The shelf-life and specifications of the LegH Prep are also appropriate for addition to meat analogue products." (7)

This portrays a substance ready to launched into commercial life. But there is a significant disconnect between the language of the Executive Summary and the data of the main body of the report. This is so because where SFANZ found evidence of change and difference in the dosed rats, as compared with the control rats, they, like "Impossible Foods" took the view that these were of little importance. For instance, with the factor of differences of blood coagulation in the test rats in comparison with control animals FSANZ notes:

"a slight increase in activated partial thromboplastin time in males" but goes on to say this "was not considered as adverse as the increase did not show a dose response, the magnitude was slight and there were no correlated pathological or clinical changes". (8) Whether more extensive testing would show this to be too complacent an assessment in judging the crucial process of blood clotting, we cannot say. Nor can the FDA, FSANZ and "Impossible Foods", because the additional testing has not been done.

The only change observable in the (female) test rats that was more fully stated by FSANZ concerned changes in the(female) reproductive system . Here they noted "decreased absolute and relative uterus weights in treated females which were statistically significant in the low and high dose groups." (9) But it was deemed to be of too little significance to affect the Report's conclusions. This alone is troubling.

This and the "increase in partial thromboplastin time" should have been in themselves sufficient to close down the application process until such time as these had been proven to be temporary aberrations with no long term or serious effects on test populations. The danger of either of them to species survival were they to become regular, heritable specific characteristics would be considerable.

Despite the detailed and clear discussion of changes in the main body of the FSANZ assessment, its behavior in drawing the conclusions it does is similar to the gung-ho behavior of the applicant, "Impossible Foods" It suggests no further animal testing or

analysis of data, and is prepared to go further than the FDA. The Assessment report is a much stronger endorsement of the substance's safety than the wary "no questions " letter of an FDA, possibly under considerable political pressure to weaken its regulatory stance. We are concerned that "Impossible Foods" is still failing to show what the FDA called "a general recognition of safety" (10) and that FSANZ have in this assessment given them any incentive to do so.

In these circumstances we conclude by reiterating that transgenic Leghemoglobin should not be allowed into the Australasian food supply;. and that a *prima facie* case has been made that this novel foodstuff is unsafe for human consumption.

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References

1. See Stanley, W.B. Ewen and Pusztai, Arpad, "Effect of diets containing genetically modified potatoes expressing *Galanthus nivalis* lectin on rat small intestine " *The Lancet* 16/10//1999, Vol 354 No 9187, pp 1353-1354.

2. Morgan, Lewis and Bockius, L.L.P, "Response to FDA questions - GRAS Noticee 540, Soybean Leghemoglobin - "Impossible Foods" Inc, May 2015. https://wwwgoogle.com/URL

3. This account on the applicant, the FDA and testing results is based on that of GMO Science. See https://wwwgmoscience.org/rat-feeding-studies-suggest-the-impossible-burger-may-not-be-safe-to-eat

4. ibid

5. See *Report of The Royal Commission on Genetic Modification*', Report And Recommendation, Wellington, 2001, pp 43-44

6. FSANZ Risk and Technical Assessment Report - Application A1186 Soy Leghemoglobin Analogue Meat Products, pp 32-33

7 ibid p. 33

8. ibid p 11

9. ibid p 11

10. See Morgan, Lewis et al as recorded in Reference 2 above.