

Lay summary

This contribution from the New Zealand Institute of Gene Ecology (NZIGE) is meant to support Food Standards Australia/New Zealand's preparation of a Draft Assessment on application A549. Our comments and wording are direct, but our spirit is constructive. The NZIGE is dedicated to the development for the public good of all responsible biotechnologies. We are an assemblage of serious researchers with independent credentials in the area of biotechnology and its social impact.

A549 is an application to amend the Australia New Zealand Food Standards Code to allow foods derived from corn line LY038 to be sold in Australia and New Zealand. "Corn line LY038 has been genetically modified to have higher than usual levels of the amino acid lysine," particularly in the corn grain.^{1[1]} LY038 was modified by the gene *cordapA*, sourced from the bacterium *Corynebacterium glutamicum*, inserted into the corn genome using genetic engineering techniques. The gene "encodes the enzyme dihydrodipicolinate synthase (DHDPS). This enzyme is involved in lysine biosynthesis. The bacterial DHDPS enzyme, unlike the plant DHDPS enzyme, is not sensitive to lysine feedback inhibition, so lysine biosynthesis will continue in the presence of high levels of free lysine."^{2[2]}

Our submission begins with introductory material describing who we are and why we are involved. We then provide a summary of the major recommendations gathered from the detailed sections of our submission. These sections are organized into three main parts. In Part One, we undertake risk *forecasting*, an exercise at the leading edge of the research literature that serves to forewarn of risk where the science is not certain. Novel potential hazards of *C. glutamicum* Dihydrodipicolinate Synthase (cDHDPS) protein, its metabolic products expressed in maize, and other side-effects of inserting DNA into the maize genome were identified to the best of our ability on the very tight timeframe available to us for this phase of consultation. Some of these properties, moreover, will be particularly influenced by the protein's environment and thus are even more important for assessments of food safety.

In Part Two, we review the scientific documents submitted by the Applicant in support of A549. We judged this material by two criteria: 1. Was the science at the best possible standard? and 2. Does the science add up to a package that is sufficient to assure the citizens of Australia and New Zealand that they may safely consume food derived from corn line LY038? In most cases we recommend how, why and when the Applicant should supplement their findings with additional data.

In Part Three, we comment upon the Impact Analysis contained in the Initial Assessment Report (IAR). We assess the costs and benefits listed and propose further costs and benefits of the options under consideration.

^{1[1]}FSANZ (2004). Initial Assessment Report: Application A549 Food Derived from High Lysine Corn LY038, p. 6.

^{2[2]}Ibid, p. 9.

The Authority (FSANZ) has made plain “the need for standards to be based on risk analysis using the best available scientific evidence”^{3[3]}. Above this need is the objective of the “protection of public health and safety” and “the provision of adequate information relating to food to enable consumers to make informed choices”^{4[4]}, which requires the Authority to determine if the best scientific evidence available is good enough. Our contribution has therefore been to help the Authority identify areas of scientific uncertainty in the application so that these uncertainties can be addressed during the Authority’s development of a complete assessment.

We provide compelling new scientific evidence of risk and hazard. We also cannot exclude certain hazards from the information in the studies submitted by the Applicant and not made available to the public by FSANZ.

- *The transgenic protein cDHDPS may have a different risk spectrum when a component of food.*
- *cDHDPS and its catabolic products could create novel risks in processed or cooked food.*
- *The creation of novel RNA molecules by insertion of DNA into the maize genome could create species of RNA that are harmful to humans, possibly through food.*
- *The molecular characterization of the DNA inserted into the maize genome, the LY038 event, and DNA donated from the transgenic Cre-recombinase line used to create the LY038 maize line, is incomplete. The present data does not exclude, with a high level of confidence, the possibility that corn line LY038 contains additional novel genes, be they derived from the expression of fragments of inserted DNA or novel fusion proteins created at the junctions of inserted DNA and the maize genome.*
- *The molecular characterization of the transgenic protein cDHDPS produced by the genetically modified plant is flawed because the Applicant has not demonstrated that all novel proteins were included in this analysis.*
- *The digestibility study of cDHDPS, required as part of an assessment of allergenicity, does not meet FAO/WHO standards for concentration of pepsin or standard comparisons to known allergens. Moreover, the digestibility study was fundamentally flawed by not using material from the actual genetically modified organism that the people of Australia and New Zealand would be eating.*
- *An adequate molecular characterization of all novel RNA molecules, that may pose a risk to consumers, is missing along with microarray analysis of the transcriptome of the LY038 line. There is published evidence that genetic components of the LY038 event produce novel RNA molecules. There is also evidence in animal studies that some small RNA molecules can be transmitted through food, causing lasting, sometimes heritable, effects on consumers and their children.*

^{3[3]}FSANZ (2004). Initial Assessment Report: Application A549 Food Derived from High Lysine Corn LY038, p. 9.

^{4[4]}Ibid, pp. 8-9.

- *The data comparing the composition of the transgenic lines to commercial reference lines of maize may be skewed by selective choice of commercial lines. The commercial reference lines chosen may inflate the 99% tolerance interval to more closely match the composition of LY038, thereby reducing the apparent number of significant compositional differences between the LY038 line and conventional corn.*
- *The compositional analysis does not appear to fully support the conclusion of equivalence between LY038 and its closest relative. The comparison found 103 (26% of total comparisons across 5 field studies) statistically significant differences between LY038 and the negative segregant.*
- *The acute toxicity study was fundamentally flawed by not using material from the actual genetically modified organism that the people of Australia and New Zealand would be eating.*
- *The broiler performance study may have falsely overestimated the positive effects of LY038 on chickens due to the choice of commercial reference controls.*
- *The broiler performance study indicates some unexplained negative effect on growth over the first 21 days when broilers were fed LY038.*
- *A549 lacks a subchronic toxicity study of adequate duration to conclude that the amino acid levels in LY038 are safe.*
- *A549 lacks a long-term toxicity and carcinogenicity study necessary to conclude that the amino acid levels in LY038 are safe.*

We also provide information and analysis indicating that the Impact Analysis is currently incomplete in some respects and mistaken in others. Addressing these deficiencies would significantly shift the balance of the analysis.

We encourage a precautionary approach when assessing LY038. The scientific community is not uniformly convinced about the adequacy of existing risk assessments (Pusztai, et al. 2003), comfortable with the evidence that genetically modified food organisms are generally safe (Pryme and Lembcke 2003), nor confident that if approval were revoked, a GMO could be removed from the food chain before it caused harm (Heinemann, et al. 2004).

FSANZ has stated that the primary data^{5[5]} received from Applicants in support of their claims “enables a more rigorous analysis of experimental outcomes than the summary data of the type submitted in support of publication of a scientific article in a peer reviewed journal.” On the contrary, the data we have seen in A549 is not so different from that included in papers we have reviewed for journals. Nevertheless, direct access to the primary data is certainly an important requirement. It is important to note that, just as when peer-reviewing papers for publication, the reviewer cannot ‘tweak’ the experiment or explore all the unwritten parameters. This can lead to mistakes in reviewing. And

^{5[5]}Not ‘raw’ data as indicated in the FSANZ document “FSANZ Response to Article Entitled ‘GE Foods and Human Health Safety Assessments’ By Dr Judy Carman, Spokesperson on GE Food, Public Health Association of Australia”, unless FSANZ receives machine print-outs and traces as well as photographs and tables.

while the publication of a paper with a flaw generally has very little influence on the daily lives of most citizens, the change in the New Zealand and Australia Food Code has implications for tens of millions of people directly and, because it may be connected to changes in global agriculture, it could have global ramifications. Therefore, the standard of review must both be better and more interrogating than for routine research results submitted for publication.

We have the view that truly good biotechnologies will be vindicated by not just the best available science, but science adequate to the task of making a sound decision on safety. Our *a priori* view is this: it is not a given that the science of the day is adequate for the task. It is possible for an applicant to do state-of-the-art analyses and not meet a standard of risk identification or resolution that may be necessary.

Should the best available science be ambiguous on A549, then New Zealand's precautionary stance (as defined by the Convention on Biodiversity and the Hazardous Substances and New Organisms Act 1996 and amendments) must take priority.

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