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Submission on the DAR for **APPLICATION A549 FOOD DERIVED FROM HIGH-LYSINE CORN LY038: to permit the use in food of high-lysine corn**

Submitted to Food Standards Australia/New Zealand (FSANZ)

by

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Non-technical summary of key points in this submission

According to the Authority's Draft Assessment Report (section 5.4.2.1), "LY038 corn must be shown to be as safe as other varieties of corn currently available if it is to be approved by FSANZ". Only if the people of New Zealand and Australia can completely substitute LY038, or its descendant hybrids, for conventional corn, and only if they can prepare and eat it the same way and with exactly the same possible consequences as consuming conventional corn, has the Authority met its burden to responsibly recommend that the Food Code be amended.

FSANZ does not have the evidence to declare that LY038 is as safe as other corn when consumed in the same manner. There is strong evidence to suggest that LY038 will produce a spectrum of food hazards significantly different from cooked or processed conventional corn because LY038 has extremely high concentrations of the amino acid lysine and its derivatives saccharopine, α-aminoadipic acid, pipecolic acid and cadaverine. The precise nature of these hazards cannot be adequately predicted from analysis of raw or cooked conventional corn, or raw LY038 corn.

1. Scientific studies on LY038 do not prove it to be as safe as conventional corn

FSANZ spokesperson Lydia Buchtmann was reported as saying to the *West Australian* on 10 April 2006 that "FSANZ used product data from GM companies and compared it with data about conventionally grown food of the same type in deciding to approve products", a process that would be consistent with international standards of review. That standard was not demonstrated in the Draft Assessment Report on A549. In particular, the control did not meet this test in the following respects:

a. The molecular and compositional studies seeking to establish equivalence between LY038 and conventional counterparts remains outside of Codex Alimentarius guidelines[1] and FSANZ policy. LY038 was compared to LY038(-), a sibling of the modified corn line and itself a product of gene technology. In the Authority's own words, "[t]he Applicant has provided information comparing LY038 corn to a closely related control corn crop, LY038(-), both grown in the same location" (DAR p. 11). *LY038(-) is not a conventional food*.

b. The high level of lysine in LY038 corn is dismissed as a dietary risk to humans by saying that "when compared to lysine from other dietary sources this is not a large amount of lysine" (DAR, p. 31 and p. 65). The comparison in this case was to eggs, red meat, chicken, fish, lentils, rolled oats and broccoli, none of which are conventional foods *of the same type as corn*.

c. High levels of the lysine catabolite saccharopine were dismissed as a food hazard by

[1] When referring to the Codex Alimentarius Commission (CAC), we make specific reference to the standards CAC/GL 44-2003 and CAC/GL 45-2003 found at http://www.codexalimentarius.net/web/standard_list.do?lang=en. Access date 26 April 2006.

saying that "[t]he levels of saccharopine found in LY038 corn grain (499 – 818 μg/g dwt, mean 650 μg/g) are substantially higher than those found in broccoli or cauliflower, but similar to the level in button mushrooms" (DAR, p. 48). Button mushrooms are not a conventional food *of the same type as corn*.

d. High levels of the lysine catabolite α-aminoadipic acid, which has a known neurotoxic activity (Rozan et al., 2001), were dismissed as a human food hazard because '[c]ompared to the levels found in other common plant foods, [e.g. lentils, mushrooms, cauliflower, green beans and broccoli] this level is not a cause for concern" (DAR, p. 48). These plants are not a conventional food *of the same type as corn*.

The foods used as a comparison to LY038 differ from corn in the varieties of ways they are prepared, the types of processed foods in which they are found, and in the quantities in which they are consumed. Kiwis and Aussies eat corn chips, but probably do not eat mushroom chips.

2. LY038 has a substantially different potential to create food hazards during cooking

LY038 has high concentrations of compounds that are known to produce food hazards when heated with the sugars found in corn. The modification results in highly elevated concentrations of lysine (total), free lysine (not in protein), saccharopine, α-aminoadipic acid, cadaverine and pipecolic acid, all of which may be converted into advanced glycoxidation endproducts (AGEs) during cooking and processing.

AGEs are strongly implicated in causing a variety of dietary-related diseases including diabetes and Alzheimer's and their sequela (Goldberg et al., 2004, Peppa et al., 2003a, Peppa et al., 2003b, Vlassara et al., 2002), as well as cancer (Heijst et al., 2005). AGE content in food increases with cooking and food processing temperatures and pressures (Elliott, in press, Goldberg et al., 2004).

Compound	Concentration in LY038	Potential Hazard
Lysine	50% higher	AGEs
Free Lysine	50 times higher	AGEs
Saccharopine	110 times higher	AGEs
α-aminoadipic acid	at least 10 times higher	AGEs, neurotoxic
Cadaverine	unknown but expected to be higher	AGEs, accentuates reactions to histamine, evidence of further toxic properties
Pipecolic acid	≥100% higher*	AGEs, chronic hepatic encephalopathy

*Applicant only reports L-pipecolic acid levels. Because D-pipecolic acid can be created from L-pipecolic acid by conversion of either pipecolic acid or lysine to the D-isoform during cooking or in the gut by bacteria, the Authority has likely underestimated pipecolic acid exposure levels derived from high lysine corn or produced by gut bacteria receiving higher levels of dietary lysine.

In their reply to our original submission, the Authority has confirmed that it believes a higher than normal standard of review may be warranted for high-lysine corn. "In cases where the

composition of food has been significantly changed, *as is the case with high-lysine corn,* feeding studies with suitable livestock species may be useful to confirm the wholesomeness of the food" [emphasis ours]. Only feeding studies, using whole plant material in food that has been cooked and processed in ways that humans would consume it, can provide the proper basis for a safety review. No such studies were provided for public review in A549, and from the DAR we have no reason to suspect that such studies were ever provided to the Authority. *We are particularly concerned that the Authority sight, or provide the people of Australia and New Zealand with, reliable data demonstrating that processing and cooking temperatures normal to products that could contain this corn are as safe as products that do contain conventional corn*.

3. Hybrids with LY038 could create significant additional food hazards

The Applicant has assured the Authority that corn derived from LY038 and hybrids will have total lysine in the range of 3500 to 5300 ppm, and free lysine in the range of 1000 to 2500 ppm. However, it is known that research hybrids with parents similar or identical to LY038 could have much higher levels of lysine and free lysine. Free lysine and lysine catabolites were higher in crosses with other GM varieties of corn (Monsanto study published under Huang et al., 2005). The Applicant already possesses hybrid lines of corn with total lysine levels reaching 6160 ppm and free lysine levels reaching 2908 ppm, but apparently did not include that fact in the application.

The Authority has argued that it also cannot restrict its amendment of the Food Code such that future hybrids of LY038 are not automatically approved. This is of concern because LY038 could be bred, on purpose or by accident, with other varieties developed by conventional breeding that might generate substantially increased lysine, free lysine and lysine catabolite levels. If the Authority's recommendation is approved, then it will be authorizing these uncharacterized hybrid varieties to enter the human food supply without further safety review. As we have repeatedly argued in this and a previous submission, the Authority would be making an extrapolation of safety that goes well beyond the scope of the existing scientific data.

Automatic approval of hybrids formed between an approved GM event and a conventional variety, or between two separately approved GM events, leaves the Authority in the potential position of mechanically approving a hybrid high lysine variety with significantly higher levels of lysine. The Applicant has already reported the existence of additional high lysine varieties produced using gene technology. Those varieties achieve high lysine levels through a different biochemical mechanism that works synergistically with the modification reported in LY038 (Huang et al., 2005). The synergistic effect reveals that, in "stacked" varieties (hybrids with both modifications) the levels of free lysine and lysine derivatives are higher than would be expected from an analysis of the modifications kept separate in different varieties. The Authority should indicate what levels of lysine and lysine catabolites it would consider to be potentially dangerous. If the Authority cannot restrict approval to the line described in A549, or provide reason to believe that future hybrids used in human food will not achieve dangerous levels of lysine and lysine catabolities, then it should not approve the LY038 event.

Should the Authority recommend a change in the Australia New Zealand Food Code to allow LY038 and its derivatives, it does so in the knowledge that total free lysine and lysine catabolite levels could reach significantly higher levels in LY038 hybrid corn varieties that do not require a safety assessment.

4. Recombinant protein has no history of safe use

The Authority should have undertaken work aimed at establishing that cDHDPS has a history of safe use by humans as food. However, the Authority has not reviewed data using whole plant derived material (grains) in feeding studies that demonstrate that the primary recombinant protein in LY038, cDHDPS, and its *in planta* produced derivatives, can be consumed safely by humans after normal cooking. Moreover, structural comparisons between cDHDPS (recombinant protein) with the natural corn DHDPS (mDHDPS) demonstrate non-equivalence (Blickling et al., 1997). Therefore, the safety of cDHDPS in cooked human food cannot be extrapolated from the historical presence of mDHDPS in cooked human food. In addition, there is no evidence that humans have been exposed to cDHDPS from natural sources at anywhere near the concentrations that they will be exposed to cDHDPS through eating LY038 corn. We estimate daily human exposure to cDHDPS from natural sources to be between 30 billion-4 trillion *times* less than exposure through LY038 corn (Table 6).

5. LY038 has been tested as an animal feed, not a human food

LY038 is the first genetically modified crop plant substantially different in its nutritional profile to be considered for approval as a human food. In this way, A549 is an application that differs from all previous applications for amendment of the Food Code. The novelty of this product requires, in our opinion, adherence without exception to the highest standard of review and international consensus standards for review, such as described by the international bodies the Codex Alimentarius Commission (CAC), the UN Food and Agriculture Organisation (UN FAO), and the World Health Organisation (WHO).

Despite its statement to the contrary (DAR section 5.4.2.1, p. 13), we believe that the evidence reviewed by FSANZ falls short of the evidence necessary to assure it is as safe as conventional corn. This is no surprise because the evidence provided was produced to assess LY038 only for use as animal feed. The key difference between the use of corn as an animal feed and a human food is cooking and processing, and the Authority has made no attempt to assess food hazards resulting from cooking or processing of LY038.

Frequent reference by FSANZ to the Applicant's "intent", and to future market forces, to limit incorporation of LY038 into human food implies an added safety margin that is both inappropriate (because amendment to the Food Code does not bind the Applicant to keep LY038 out of the human food supply, restrict the foods that LY038 is used in, or to minimize co-mingling with varieties that are used in human food) and is no reason for allowing its tests as an animal product to substitute for proper human food safety tests. Examples of such references in the DAR are reproduced in the table below.

"Furthermore, little LY038 will be entering the food supply, mostly in the form of processed products (e.g. corn syrup) that contain negligible amounts of protein"	DAR p. 11

"Although LY038 will be grown as a high value animal feed, a small percentage of this corn may enter the food supply"	DAR p. 20
"because LY038 corn is not intended for food, human consumption is expected to be extremely low"	DAR p. 23
"Further, it is expected that the amount of LY038 grain entering the food supply will be small"	DAR p. 31
"It is less likely that food industry would pay premium price for high-lysine corn and therefore likely that the levels of high-lysine corn entering the food supply would be small"	DAR p. 72

6. The Authority has accepted a standard of evidence of safety that is below what it could request under international guidelines

International bodies have set higher standards for the description and testing of genetically modified food organisms, such as LY038, that are significantly different from their conventional counterparts. According to CAC, the Authority could ask for:

a. feeding studies using LY038 grains cooked and processed in ways that humans prepare corn for food to identify food hazards that derive from, for example, unusually high concentrations of AGEs. "The potential effects of food processing, including home preparation, on foods derived from recombinant-DNA plants should also be considered."

b. feeding studies using cooked and processed LY038 grains to determine the potential for cDHDPS to form toxic aggregates or sugar-protein derived allergens (another AGE product). "The absolute exposure to the newly expressed protein [cDHDPS] and the effects of relevant food processing will contribute toward an overall conclusion about the potential for human health risk."

c. a compositional analysis using a comparator that was "the near isogenic parental line", and only if this were not feasible should the Authority consider another line that was "as close as possible". In this particular case, the Authority does not have to accept the use of LY038(-) as a control because the non-GM parental line, H99, is 65.6% identical to LY038. We have seen no evidence to prove that LY038(-), the GM sibling line, is above 50% related, the average relatedness of siblings.

Despite compelling scientific evidence that food hazards will form when corn derived from LY038 is cooked, and that the absolute exposure to cDHDPS will be astronomically higher than from natural sources, the Authority has not required studies that would be necessary to detect the presence of hazards specific to the use of LY038 as a human food. The Authority should explain why it believes that it is satisfactory to allow high lysine corn into the food supply following a safety review whose standards, in important respects, is frequently below what is allowed and recommended by international intergovernmental food safety agencies when this is acknowledged to be an important precedent.

7. A recommendation to amend the Food Code does not follow from a case-by-case assessment

The Authority has expressed its commitment to case-by-case assessment. "The safety of GM foods cannot be assessed as a single class because the safety concerns depend on the type of food and the nature of the genetic modification. For this reason, safety assessments are performed on the foods derived from *individual types of GM plants or animals*"[2]. The Draft Assessment does not, however, adhere to its case-by-case assessment policy because the Authority is drawing general safety conclusions from experience with different types of modified corn. For example, the Authority's statement that—

> "[t]o date, all approved GM plants with modified agronomic production traits have been shown to be compositionally equivalent to their conventional counterparts. Feeding studies with feeds derived from the approved GM plants have shown equivalent animal performance to that observed with the non-GM feed. Thus the evidence to date is that for GM varieties shown to be compositionally equivalent to conventional varieties, feeding studies with target livestock species will add little to a safety assessment and generally are not warranted" (DAR p. 49).

is not specific to LY038, *its use in human food*, or the potential hazards that have been identified for LY038. Such use of evidence is outside the case-by-case assessment framework.

In contrast, our submission is composed of an in depth examination of the scientific studies submitted to the Authority by the Applicant. This examination is supported by an analysis of up-to-date, peer-reviewed, scientific literature. This literature is specific to hazard identification or evaluation, consistent with CAC and OECD[3] recommendations.

The Authority (FSANZ) has committed itself to making assessments "based on risk analysis using the best available scientific evidence"[4]. *Our submission is based on the best available scientific evidence.* It has been updated with relevant references as recent as early 2006. Thus, we believe that to be consistent in the 'case-by-case' approach to assessment, and to be consistent with international recommendations for hazard identification, the Authority must refrain from substituting unsupported speculation—such as "expected to be", "not expected", "considered to be" or "not considered to be"—for hard scientific data, and either dismiss, or justify its use of, data that are not specifically relevant to High-Lysine Maize LY038, in reply to our specific analysis of LY038.

8. Conclusions

We believe that too much legitimate scientific uncertainty exists after consideration of the scientific studies submitted in support of A549 for the Authority to assert that LY038 and any hybrids derived from it are as safe as food derived from conventional corn. There is no case

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[2] ANZFA Occasional Paper Series No. 1 GM foods and the consumer (2000).

[3] When referring to the OECD, we make specific reference to the Consensus Document on Compositional Considerations for New Varieties of Maize (*Zea Mays*): Key Food and Feed Nutrients, Anti-Nutrients and Secondary Plant Metabolites (ENV/JM/MONO(2002)25) from OECD found at http://www.oecd.org/document/9/0,2340,en_2649_34385_1812041_1_1_1_1,00.html (access date 2 May 2006).

[4] FSANZ (2004). Initial Assessment Report: Application A549 Food Derived from High Lysine Corn LY038, p. 8-9.

made for a benefit to Australians or New Zealanders to have LY038 in their food. There is considerable evidence of probable harm in comparison to conventional corn.

In our view, the Authority is making a recommendation that is also inconsistent with Codex Alimentarius. At the very least, the Authority should commission the following:

- a compositional study using H99 as the control in five sites over at least two years because H99 is the closest relative of LY038 and is the non-GM parental;
- a compositional study describing the compounds formed during heating and processing of LY038 corn material as it would be in human foods—using the parental varieties as controls;
- an animal feeding study using whole food derived from LY038 corn heated and processed as per normal use in human food—using the parental varieties as controls; and
- human exposure studies (should the previous two studies not reveal clear hazards) that measure the effects of using whole food prepared from LY038 corn, pipecolic acid levels contributed from gut bacteria, and the potential for an allergic response to LY038 following inhalation of LY038 flour.

The Authority, if it ultimately recommends an amendment to the Food Code, should restrict that approval to the specific line evaluated in A549, and ensure that the approval cannot be extended to hybrids. The authority should also impose an actively managed post-marketing monitoring programme.

References for the non-technical summary

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