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Te Mana Kounga Kai – Ahitereiria me Aotearoa

6 August 2008
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FIRST REVIEW REPORT

APPLICATION A589

FOOD DERIVED FROM GLUFOSINATE AMMONIUM-TOLERANT RICE LINE LLRICE62

For information on matters relating to this Assessment Report or the assessment process generally, please refer to http://www.foodstandards.gov.au/standardsdevelopment/

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1. Introduction

On 12 May 2008, the Australia and New Zealand Food Regulation Ministerial Council (Ministerial Council) requested a First Review of Application A589, which seeks approval of food derived from a genetically modified (GM) rice – namely, glufosinate ammonium-tolerant rice line LLRICE62. Approval of this Application involves a variation to Standard 1.5.2 – Food produced using Gene Technology, of the *Australia New Zealand Food Standards Code* (the Code).

Following a request for a formal review, FSANZ has three months to complete a response. In this instance, FSANZ was required to review the decision by 12 August 2008.

2. Objectives of Review

The objective of this Review is to reconsider the draft variation to Standard 1.5.2 in light of the Ministerial Council's grounds for review as outlined in Section 3 below.

3. Grounds for the Review requested by the Ministerial Council

A First Review of FSANZ's decision to approve Application A589 was sought on the grounds that the proposed amendment to Standard 1.5.2, to permit the sale and use of food derived from GM rice line LLRICE62:

(i) does not protect public health and safety;
(ii) is difficult to enforce or comply with, in both practical or resource terms; and
(iii) places an unreasonable cost burden on industry or consumers.

3.1 Protection of public health and safety

A number of reasons have been put forward in asserting that the decision to approve food derived from LLRICE62 does not protect public health and safety. Firstly, a report on the safety of LLRICE62 released by the European Food Safety Authority (EFSA) in October 2007, considered compositional studies on LLRICE62 conducted in 2005 and 2006, whereas the Final Assessment Report for Application A589 produced by FSANZ, refers to compositional data from trials conducted in 1998 and 1999. FSANZ is asked to explain why it did not request and use the additional compositional studies, particularly as they appear to be directly relevant to the assessment.

The First Review request states that the Final Assessment Report for A589 does not address the issue of the persistence and uptake of foreign DNA in and across the gastrointestinal (GI) tract of mammals. The rationale for requesting a review of LLRICE62 on these grounds is identical to that used for the First Review of Application A592 (glyphosate-tolerant soybean line MON89788). In not addressing this issue in the respective Final Assessment Reports, it is suggested that FSANZ has assumed one of the following:

1. that recombinant plant DNA is so completely degraded during digestion as to be effectively unavailable to facilitate perturbations along the GI tract or tissues and organs beyond it that could be of human health significance; or

2. that transfer of recombinant plant DNA to gut micro-organisms, gut epithelial and other cells, the blood stream and internal tissues and organs is so infrequent as to be unlikely to be of human health significance; or

3. that potential consequences of persistency and uptake of recombinant plant DNA in and across the GI tract are not likely to occur or not likely to be sufficiently different from persistence and uptake of naturally occurring DNA to warrant evaluation from a food safety perspective.

A list of scientific publications are cited as evidence that, following ingestion of GM foods, foreign (recombinant) DNA can survive, to some degree, digestion in the GI tract where it can remain available for uptake by gut micro-organisms/gut cells or cross the intestinal mucosa into the bloodstream. Once there, it is claimed the DNA may then be taken up by various tissues and cells where it may persist for some time. Scientific articles are also cited as evidence that foreign DNA will not always be rendered non-functional, and it is further claimed that the state of scientific knowledge is such that it is not yet possible to determine the consequences of this for human health. FSANZ is therefore requested to confirm or articulate clearly the rationale it uses for excluding such issues from consideration in the safety assessment.

Thirdly, it is claimed that independent animal studies should be undertaken by FSANZ. It is believed that independent safety testing is currently lacking and is necessary to demonstrate that the assessment is an objective, transparent process that can provide consumers with confidence in the safety of foods.

Finally, it is argued that the risk of accidental presence in the Australian and New Zealand food supply is not a good reason to approve a GM food, because currently LLRICE62 is not permitted in food.

3.2 Enforcement and compliance

FSANZ is requested to provide details of how the costs associated with enforcement by jurisdictions were determined for the cost/benefit analysis presented in the Final Assessment Report. It is claimed that current monitoring and enforcement of GM food laws is not being adequately undertaken due to the costs associated with enforcement and the lack of resources at both the Commonwealth and State level. It is believed that the apparent level of concern in the community and the lack of enforcement activity therefore warrant a cautious approach to approving any new GM applications.

3.3 Cost burden on industry and consumers

FSANZ is required to substantiate a statement in the Final Assessment Report to the effect that approval of LLRICE62 would provide consumers with access to a wider range of imported rice products *at lower prices*.

In considering the impact of approval of Application A589 on the Australian rice industry, it is claimed that Australian rice competes in world markets because of its quality and ‘clean, green, non-GM’ image. It is felt that a new compliance regime may be imposed on rice exports from Australia by certain importing countries, particularly those that are intolerant of GM foods.

It is therefore claimed that industry would be burdened by additional certification costs, generated by the approval for LLRICE62, and these would be likely to have an adverse impact on the economic viability of the industry.

4. Background

An Application was received from Bayer CropScience Pty Ltd on 6 September 2006 seeking approval in the Code for food derived from glufosinate ammonium-tolerant rice line LLRICE 62, under Standard 1.5.2. To be approved for food use in Australia and New Zealand under this standard, GM foods undergo a pre-market safety assessment, which is conducted by FSANZ.

LLRICE62 is a GM variety of rice that is tolerant to the herbicide glufosinate ammonium by the addition of a bacterial gene, known as *bar*, to the rice genome. This gene encodes the enzyme phosphinothricin acetyltransferase (PAT), which inactivates the herbicide. The purpose of the modification is to provide growers with a line of rice that more effectively allows for weed control without affecting the crop.

LLRICE62 has been developed primarily for cultivation in overseas countries where the herbicide will be registered for use on tolerant crops. It has already been approved for food use in the USA (2000), Canada (2006), Argentina (2006) and the Russian Federation (2003). The Scientific Panel on Genetically Modified Organisms of the European Food Safety Authority (EFSA) adopted a favourable opinion on LLRICE62 on 30 October 2007. The Panel concluded that *LLRICE 62 is as safe as its non-GM comparator with respect to potential effects on human and animal health or the environment*.

FSANZ undertook a pre-market safety assessment of food derived from glufosinate ammonium-tolerant rice line LLRICE 62 according to the safety assessment guidelines applied to all GM foods. The safety assessment included a full molecular characterisation of the genetic modification in the rice, an evaluation of the safety of the expressed gene product, the PAT enzyme, and a comprehensive compositional analysis of the food. The conclusion of the safety assessment was that, on the basis of all the available evidence, food derived from rice line LLRICE62 is as safe for human consumption as food derived from other rice varieties.

5. Conclusions from the Final Assessment Report

The Executive Summary and the reasons for the decision, which were approved by the FSANZ Board in March 2008, are provided in this Report at **Attachment 2**.

The Board agreed to the recommendation at Final Assessment to approve food from glufosinate ammonium-tolerant rice line LLRICE62 in view of the findings of the safety assessment that food derived from line LLRICE62 is as safe as food derived from other rice varieties.

6. Issues addressed in First Review

6.1 Additional compositional studies were available

Six of the thirty-two appendices submitted to FSANZ in September 2006 with Application A589 consisted of studies on the compositional analysis of LLRICE62. For the analyses, LLRICE62 grain samples were generated from fourteen different trial sites in the USA over a two year period (1998 and 1999) to compensate for environmental effects such as soil fertility, temperature, light and water variability at each single site. In every trial, the non-transgenic parental rice variety (Bengal) was planted as the comparator line, grown under the same field conditions as LLRICE62, except for the application of glufosinate ammonium herbicide which was only used on LLRICE62. The composition of grain samples (rough rice/paddy rice) from the GM and non-GM lines harvested from the 1998 and 1999 field trials were analysed at two independent laboratories (Woodson-Tenent Laboratories, Des Moines, IA and Ralston Analytical Laboratories, St Louis, MO).

Compositional studies were also conducted on processed rice fractions: brown rice, polished rice, hulls, bran, rice flour, bran oil (crude) and parboiled brown rice. Processing of the grain to generate these various fractions was carried out under GLP at the Food Protein Research and Development Center, Texas A&M University (Bryan, Texas). The processed commodities were subsequently shipped to Woodson-Tenent Laboratories (as above) for compositional analyses, to Ralston Analytical Laboratories (as above) for analyses of antinutrients, to Riceland Foods (Stuttgart, AR, USA) for analysis of the rice bran oil, and to the University of Arkansas for the determination of rice storage proteins. The methods used for the compositional analyses were either published AOAC (Association of Official Analytical Chemists) International methods, AOCS (Official Methods and Recommended Practices of the American Oil Chemists' Society, or AACC (American Association of Cereal Chemists) official methods.

These compositional data comprehensively meet the requirements of the FSANZ safety assessment guidelines. FSANZ is aware that identical compositional data pertaining to LLRICE62 were submitted to all countries where food approval was required (Argentina, Australia/New Zealand, Canada, Colombia, European Union, Mexico, Philippines, Russia, South Africa, Uruguay and USA), however only the European Union requested the applicant to repeat certain studies.

6.1.1 Additional field trials

The field trials were repeated by the Applicant in 2005 and 2006 as a direct result of factors that are unique to the European system of assessment. One of the primary reasons was due to a sequence of changes introduced into the guidance document by EFSA, at various times after the original field trials had been conducted and the application being submitted to the United Kingdom Food Standards Agency (UKFSA) in August 2004. The process of revising the guidance document introduced minor changes to the data requirements, which meant that the original submission from the company did not meet every detail in the new requirements.

The GMO Panel of EFSA requested that the field trials conform to a randomised complete block design for three study lines: the non-GM comparator, LLRICE62 with conventional herbicide and with glufosinate ammonium herbicide, over two seasons at the same location.

The company claims that only EFSA insisted on this field design, which is not a normal design for rice trials, while numerous other regulatory authorities considered the original design and field data to be valid. The more common field design for rice research, used by the company in the original studies submitted to FSANZ, was a split plot design to allow the application of the two herbicide regimes whilst minimising the potential drift between the small plots. Nevertheless, Bayer conducted new trials designed strictly to comply with EFSA's general requirements.

In October 2007, EFSA released a report on its evaluation of LLRICE62, concluding that LLRICE62 is compositionally equivalent to the conventional counterpart. FSANZ has now obtained the additional studies[1] generated specifically for assessment in the European system. The results obtained from the additional field trials, as noted by EFSA and confirmed recently by FSANZ, merely duplicate those from the original studies.

6.1.2 Commercial reference range

EFSA also requested the company to provide new data reflecting the composition of other conventional rice varieties. In response to this request, the field trial from 2006 included lines such as Cocodrie, Francis and Cherniere, *to allow a wider comparison of any compositional differences in LLRICE62*[2], compared to its conventional counterpart, Bengal.

As often observed in compositional studies in which a GM and non-GM line are directly compared, small differences in some of the analytes measured in LLRICE62 and the non-GM comparator were detected. In this case, there were small differences observed in fibre components, two amino acids (tyrosine and tryptophan), two fatty acids (palmitoleic acid and behenic acid), and in vitamin E levels. The results for the nutrient iron suggested higher levels in the transgenic rice (unsprayed) compared to the non-transgenic control, and both the control and transgenic line were outside of the range of values reported in the literature. In addition, for all treatment groups (i.e. non-transgenic control, sprayed and unsprayed LLRICE62), the vitamin B1 levels in rough rice exceeded the reported literature range by a significant margin.

In the assessment of this Application, FSANZ reported that the values used for the non-transgenic literature range were compiled from references with incomplete information on the variety of rice tested and methodology used to measure particular analytes, and thus could not be considered necessarily to reflect a range from current conventionally-produced rice[3]. Although this was noted, after careful consideration of the results from the compositional analyses, FSANZ considered that the observed differences between LLRICE62 and its non-GM counterpart could not in any comparison be associated with the new trait.

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[1] **Studies submitted:**
1. Amendment to the Nutritional Impact Assessment Report on LibertyLink® Rice Transformation Event LLRICE62 (NI 01 EUR 01), completed February 2007, Bayer CropScience GmbH, Frankfurt, Germany.
2. Amendment to the Nutritional Impact Assessment Report on LibertyLink® Rice Transformation Event LLRICE62 (07 B 002), completed May 2007, Bayer CropScience GmbH, Frankfurt, Germany.

[2] Opinion of the Scientific Panel on Genetically Modified Organisms on an application (reference EFSA-GMO-UK-2004-04) for the placing on the market of glufosinate ammonium tolerant genetically modified rice LLRICE62 for food and feed uses, import and processing, under Regulation (EC) No 1829/2003 from Bayer CropScience GmbH. *The EFSA Journal* (2007) 588, 1-25.

[3] Section 5.1 Levels of key nutrients and other constituents, Attachment 2, Final Assessment Report for Application A589 – Food derived from glufosinate ammonium-tolerant rice LLRICE62.

The difference in each case occurred randomly (that is, no pattern of change was evident) and was much more likely to reflect normal biological variation due to environmental factors at different test sites and years of growth. As the number of analytes in question, and the magnitude of the differences apparent in LLRICE62 were generally small, no valid food safety issues could be identified.

In 2005, the Applicant published the original compositional data in a peer reviewed journal – the Journal of Agricultural and Food Chemistry[4] – where a comprehensive discussion of the differences in LLRICE62 compared with the parental line was presented. This publication also outlined the limitations of the reference range used in the analyses, however the compositional data were sufficiently detailed to allow a valid statistical comparison and conclusion that LLRICE62 is nutritionally equivalent to its conventional counterpart.

6.1.3 FSANZ approach

While additional evidence is always welcomed, the original studies provided with this Application fulfilled compulsory data requirements and adequately demonstrated that LLRICE62 is as safe as its conventional counterpart. In determining absolute data requirements, as distinct from those that FSANZ regards as non-essential, it is important to distinguish information that merely corroborates the primary, core scientific evidence. The costs to industry in generating further supporting data on soft grounds, and to government in assessing safety data of marginal additional value, should always be weighed accordingly.

It should be noted that FSANZ routinely reviews the type of data required to meet the demands of the safety assessment. This undertaking meets two primary objectives: to ensure that the approach used in the safety assessment (i) reflects the most recent advances in the relevant scientific disciplines, and (ii) is broadly consistent with assessment procedures for GM foods operating internationally.

The case-by-case approach also allows FSANZ to determine data requirements specific for any application, or request further information where data submitted with an application are insufficiently detailed or require clarification. In the case of LLRICE62, during the course of the assessment, FSANZ requested and received additional molecular characterisation data and sought clarifications on three occasions.

6.2 Ingestion of recombinant DNA in food

The issue of persistence and uptake of recombinant DNA, when ingested, is a general issue that has been the subject of extensive consideration and publication over more than 15 years. The issue was first addressed at the international level in 1991 by a joint FAO/WHO expert consultation which looked at strategies for assessing the safety of foods produced by biotechnology (WHO 1991). It was concluded that as DNA from all living organisms is structurally similar, the presence of recombinant DNA in food products, in itself, poses no additional health risk to consumers.

[4] Rice (*Oryza sativa* L.) Containing the *bar* Gene Is Compositionally Equivalent to the Nontransgenic Counterpart. J. Agric. Food Chem. **2005**, 53, 1457-1465.

Similar conclusions have been reached by other expert consultations and intergovernmental bodies which have been convened specifically to address the issue of the presence of antibiotic resistance genes in foods (WHO 1993, Karenlampi 1996). The safety of recombinant-DNA in foods has also been considered in a number of comprehensive literature reviews, where it has also been concluded that the scientific information available to date does not indicate any safety concerns (Jonas et al 2001, Gaye & Gillespie 2005, Flachowsky et al 2007, EFSA 2007).

FSANZ routinely monitors the scientific literature for studies relevant to the safety assessment of GM foods and is fully cognisant of the literature relating to the uptake and persistence of recombinant DNA when ingested as part of GM food. While the issue continues to be an active area of research and publication, FSANZ does not regard this as an issue that requires specific and explicit consideration for each and every application for GM food. A detailed response on this issue, recently prepared by FSANZ for the review of Application A592, is at **Attachment 3** to this Report.

6.3 Long-term animal feeding studies are lacking in the current assessment

FSANZ's safety assessment of food derived from rice line LLRICE62 included consideration of (i) the genetic modification to the plant; (ii) the potential toxicity and allergenicity of the gene expression product, in this case the PAT enzyme; and (iii) the composition of grain from LLRICE62 rice compared with that from the conventional parental variety. No public health and safety concerns were identified as a result of the safety assessment. The safety assessment did not rely on the results of two animal feeding studies submitted with the Application: one in growing-finishing swine, and the other in rapidly-growing broiler chickens. While FSANZ does not routinely require animal feeding studies to be undertaken, where such studies already exist, Applicants are expected to provide these to FSANZ to evaluate as additional supporting information.

From a toxicological perspective, there is no clear indication that the use of whole-food animal toxicity studies adds scientific value to the comparative assessment, particularly for GM foods that carry a single agronomic trait, and where there is no intended compositional change to the food. In these circumstances, the significant resource costs of conducting such a study, including the use of large numbers of laboratory animals, outweigh the very limited scientific benefits it could provide.

Factors that limit the apparent benefits of such studies include (i) the difficulty in accurately identifying a direct diet/response relationship; (ii) the challenges of selecting appropriate animal species as a model for the human diet, and (iii) natural limitations in the amounts of foods, designed for human consumption, that can be administered to animals without creating severe nutritional imbalances. Often cited experiments in animals conducted by Dr Arpad Pusztai[5] and Dr Irina Ermakova (unpublished data), which purport to demonstrate adverse effects, have failed to withstand independent scientific scrutiny; significant methodological flaws being identified in their experiments which compromise the integrity of their results.

[5] S.W.B. Ewen and A. Pusztai (1999). Effects of diets containing genetically modified potatoes expressing *Galanthus nivalis* lectin on rat small intestine. The Lancet, **354** (9187), 1353.

In the case of Pusztai's research using experimental GM potatoes, scientists who specialise in toxicity assessment noted that the rats became severely malnourished during the course of the study. Malnutrition can cause unpredictable immune responses and fluctuations in organ weights in animals, which meant that the Pusztai data were impossible to interpret. Six independent reviewers in the United Kingdom's Royal Society[6] concluded that the Pusztai study was flawed and *the data reviewed provide no reliable or convincing evidence of adverse (or beneficial) effects*. *The Lancet* was publicly criticised for publishing the work.

In 2007, the journal *Nature Biotechnology* approached Ermakova to ask for a detailed account of her study in animals using GM soy, as her results have never been published in the peer-reviewed scientific literature. Just one of the issues that was raised amongst the scientific community was the extraordinarily high mortality of the animals in the study, including in the control group, which pointed to problems concerning the entire study. In the same *Nature Biotechnology* article[7] , several respected scientists raised numerous other concerns on the study design and methodology used by Ermakova. Previously, the UK Food Safety Authority's Advisory Committee on Novel Foods and Processes[8] had raised similar concerns and noted the absence of verifiable information about the materials used in the study. It has also been noted that Ermakova's results are inconsistent with the results of a peer reviewed study that found no adverse effects in mice fed the same variety of GM soy.

6.3.1 The role of animal feeding studies in GM food assessments

FSANZ has considered the role of animal feeding studies in the safety assessment of GM foods over a number of years, and continues to monitor and participate in the international scientific debate. Approvals for numerous GM commodities in various countries over the past decade have provided a wealth of accumulated assessment experience on which to base further, better-informed, discussion on this topic.

In June 2007, FSANZ formally convened an expert group to examine this issue in detail. The expert panel noted that whole-food animal feeding studies may be informative in some limited circumstances only, but agreed with the current FSANZ approach: that any potential adverse health effects can generally be identified by a scientifically informed comparative assessment of the GM food against its conventional counterpart. The panel recommended that FSANZ should continue with its case-by-case assessment of GM foods on the basis of the best available science. The full report from the animal feeding studies workshop is available from the website at www.foodstandards.gov.au/srcfiles/Workshop%20Report%20FINAL.pdf

Despite continuing claims that animal studies with GM foods can be designed without inherent flaws, there has been no consensus of expert scientific opinion in relation to appropriate methodology. It is generally agreed that studies with whole foods are limited in terms of their capacity to reliably indicate any toxicological effects associated directly with the test diet, and this limited sensitivity is compounded with the duration of study time. As a consequence, FSANZ does not consider that animal feeding studies with whole GM foods should be undertaken on a routine basis, particularly where other components of the assessment have confirmed no significant compositional differences.

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[6] http://www.royalsoc.ac.uk/st_pol56.htm

[7] Marshall, A (2007) GM soybeans and health safety – a controversy re-examined. Nature Biotechnology 25: 981-987, http:/www.nature.com/nbt/journal/v25/n9/full/nbt0907-981.html

[8] ACNFP (2005) Statement on the effect of GM soya on Newborn Rats. http://www.acnfp.gov.uk/acnfppapers/gmissues/acnfpgmsoya

FSANZ recognises that there may be particular GM foods with nutritional modifications or intentional changes in composition, where the results of animal toxicity studies may be informative and therefore necessary to complete a safety assessment. In these cases, as a normal part of the assessment process, the nature of the genetic modification and the results of the comparative assessment would be taken into account.

6.4 Risk of accidental presence in foods is no reason to seek regulatory approval for LLRICE62 in Australia and New Zealand

Bayer CropScience states its intention to seek regulatory approval in a number of countries prior to any decision to commercialise LLRICE62. Where there is a genuine intention to proceed to commercialisation, pre-existing food approvals would of course be necessary before LLRICE62 or its derivatives may be present in imported foods. This is a reasonable course of action and one that government should consider appropriate to protect the health and safety of consumers. There is no validity to the claim that the Applicant is merely seeking approval for LLRICE62 in the Code to mitigate risks associated with the possibility of accidental presence of LLRICE62 in foods that enter the Australian and New Zealand market.

This view appears to be based on an incident that occurred in 2006, when an unapproved variety of GM rice, LLRice601, was detected in commercial rice exports in the USA, causing significant disruption to international trade. At the time of its detection, LLRice601 was regarded as an experimental variety and did not have regulatory approval anywhere in the world. The trade restrictions and compliance testing imposed at the time on rice consignments were a normal market reaction to trade involving an unapproved GM commodity.

6.5 Approvals for GM foods are associated with increasing costs of monitoring and enforcement activities

FSANZ is aware of concerns raised by various jurisdictions in relation to the costs of monitoring and enforcement activities associated with GM foods and agrees that, over time, the successive approval of new GM foods may impact on finite resources. This is a general issue affecting all GM applications and is not specific to food derived from LLRICE62, or any particular GM application.

FSANZ considers it is important to recognize that, because GM foods are continually entering international trade, such costs are largely unavoidable and will arise irrespective of whether or not GM foods are approved in Australia and New Zealand. In the case of approved GM foods, monitoring is required to ensure compliance with the labelling requirements, and in the case of GM foods that have not been approved, monitoring is required to ensure they are not illegally entering the food supply. The costs of monitoring and enforcement are thus expected to be comparable, whether a GM food is approved or not. Any regulatory decision taken by FSANZ is therefore unlikely to significantly affect the cost impact on jurisdictions, in terms of their responsibilities to enforce the Code.

Recently, FSANZ contacted a number of jurisdictions to seek quantitative information regarding the associated costs, in order to better reflect this in the benefit-cost analysis. The jurisdictions that were contacted indicated they undertake a range of testing and monitoring activities in relation to GM foods, as well as other types of foods.

Testing for GM foods is significantly more expensive than the cost of other testing, although the absolute cost depends on the level of detail required. Event-specific testing that relies on PCR analyses to detect independent GM lines is the most costly of the available test types. The National Measurement Institute (NMI) advises however that protein kits, designed to detect the presence of a novel protein, and general screening tests, designed to detect a number of GM events, are significantly cheaper than event-specific PCR analysis.

FSANZ understands that the current cost of testing (per sample) has reduced only slightly since 2003, when a review of GM labelling was undertaken[9]. At this stage however it is not possible to ascertain the total cost of monitoring activities for GM foods, and obviously this will vary between jurisdictions, depending on the amount of monitoring that is being undertaken. In the absence of detailed quantitative information, it is therefore only possible for the benefit-cost analysis to be qualitative in nature.

The increased monitoring and enforcement burden being placed on jurisdictions was discussed by the Implementation Subcommittee (ISC) at its meeting in April 2008, where it was agreed that a national compliance and monitoring strategy for GM foods is required to assist consistent implementation of Standard 1.5.2. It was also agreed to hold a workshop to develop a draft strategy for consideration by ISC. FSANZ welcomes the development of a national strategy to address this issue.

6.6 Approval of LLRICE62 would place an unreasonable cost burden on industry or consumers

FSANZ has considered the potential implications of an approval for LLRICE62 on the food industry, particularly companies involved in marketing rice products in Australia, and has been unable to find any compelling evidence that additional costs would be avoided if LLRICE62 is prohibited from entering the market. Moreover, if GM rice is intentionally introduced into the global food market, any additional costs would be spread over the entire industry and thus would not apply exclusively to the Australian environment. FSANZ therefore considers that claims of reduced competitiveness in the business sector may be exaggerated.

The rice industry in Australia is represented largely by Ricegrowers Limited, who trade commercially as SunRice. According to submissions from SunRice, this company is the fourth largest rice food company in the world and is one of Australia's largest exporters of branded food products. The company claims extensive expertise in marketing and trading rice to international markets such as Japan, the Middle East, South Korea and Papua New Guinea. It also targets the retail domestic consumer market as well as food service, food manufacturing and other channels for its products. In addition to milling operations in Australia, PNG and Jordan, the company manufactures value added products including retort meals, rice cakes, vitamin enriched rice, quick cooking rice and crisp rice.

SunRice is strongly opposed to the commercialisation of any GM rice varieties anywhere in the world, and believes that approval of LLRICE62 in Australia and New Zealand will facilitate the path towards the commercial planting of this line in the Northern hemisphere.

[9] In 2003, a review of labelling of GM foods was undertaken by FSANZ which included an assessment of compliance and enforcement activities and information from GM food surveys including a previous ISC Coordinated Survey. The ISC Coordinated Survey included a business record audit and product testing. A total of 51 samples were tested under the survey, costing a total of $AUD33,660 or $AUD660 per sample.

The company claims that approval of GM rice offers no benefits in the marketplace according to the following:

- the introduction of GM rice is strongly opposed by the US rice industry and rice growers;
- GM rice will not find a commercially viable and significant market in Australia;
- Australia is not a major market for long grain rice from the US;
- enforcement agencies [in Australia] will have to implement specific procedures to test for GM rice in imports;
- SunRice will face compliance costs is some key export markets;
- Australia's rice products will lose their 'clean, green' image, reducing price premiums for a niche, high value export crop; and
- approval of GM rice could affect the perception of consumers in Australia about rice products, adversely impacting on consumption and price.

In support of its position, SunRice provided to FSANZ a large dossier of information on international market perspectives on rice and documented recent trade issues, claiming that this provided evidence that the company would be likely to be burdened with additional compliance costs relating to the GM status of their products. As no other relevant information is available, the company focussed attention on the adverse effects to international trade in rice products following the detection of minute traces of LLRice601, an experimental GM rice line, found in consignments of long grain rice in the US in 2006. The United States exports long grain rice to a number of major trading partners, including Japan and the European Union.

At the time of its discovery in commercial grain, LLRice601 was not a commercialised variety of rice and was not approved as a food commodity anywhere in the world. As would be expected, it became necessary for USA rice exports to be tested for the presence of unapproved GM rice before importing countries, such as those in the European Union, would accept them. Compliance testing and documentation was extended to all US rice varieties, creating significant disruptions to trade. In order to avoid major restrictions in rice products, and to protect consumer confidence, the USA authorities sought safety data on LLRice601 from the developer, Bayer CropScience. EFSA also received data on LLRice601, but claimed that the data submitted were insufficient to provide a full risk assessment[10]. It is clear from these events that the market reactions were primarily due to responsibilities within importing countries to observe food laws and maintain the integrity of their food supply.

6.6.1 Possible effects from commercialising GM rice

In considering potential impacts on the food industry from the GM rice issue, FSANZ takes a broader perspective. In terms of the impact of commercialisation on international trade in rice products, FSANZ acknowledges that the trading environment would be likely to change once GM rice enters the marketplace. However, a decision to commercialise LLRICE62 ultimately will be based on key market forces at the time, and is not a matter for speculation by FSANZ or other areas of government, provided that all necessary regulatory approvals have been issued prior to the commencement of commercial-scale plantings.

[10] At the same time, EFSA was also conducting a risk assessment on LLRICE62, which has now been completed. EFSA has concluded that LLRICE62 is as safe for human consumption as conventionally produced rice.

An alternative view is that the rice industry, having decided to accept GM rice into global markets, may respond by devising an identity preservation system or equivalent protocol, which could consist of documentation relating to the source of the grain, to assist with maintaining separate supplies of non-GM and GM consignments. Such schemes are already in existence to separate the many other different varieties of conventional rice produced for different applications in the consumer market, so this may not present an insurmountable problem for the industry as a whole. Documentation on GM status based on the geographical or agricultural source would also be the most appropriate means of complying with mandatory labelling requirements in Australia and New Zealand.

6.6.2 GM rice should not be permitted because rice is a major food for humans

The argument that rice is an especially important food source for humans is also not sufficient to justify a prohibition on food derived from LLRICE62. International trade in staple commodities such as soybean and maize have not been adversely affected by the introduction of numerous GM varieties. In general, trade in major commodities has only been adversely affected where adventitious presence, albeit at very low levels, of unapproved GM lines detected in conventionally produced consignments has occurred.

As there is currently no trade in GM rice, whether viable markets for LLRICE62 emerge in the future is, again, a matter for speculation by the industry itself. FSANZ recognises however that regulatory procedures for approving GM commodities already exist in a number of the countries likely to be considered as markets for GM rice. However, it is also recognised that certain countries may be unwilling to accept GM rice, for a complex range of reasons, and therefore could be considered as markets specifically for non-GM rice. Given this scenario, it is possible that a premium might apply to non-GM rice products for particular export markets, which arguably could off-set the cost of compliance testing. SunRice advises that in a normal year, a large number of certificates are provided to Australian rice export customers to satisfy demand for proof of compliance with pesticides, heavy metals and other contaminants or residues, so it can be argued that the industry already has well-established mechanisms for satisfying the demands of individual markets.

SunRice also cited statistics taken from the US Department of Agriculture (USDA) Rice Situation Yearbook (November, 2006) as evidence that long grain rice is only a minor import to Australia as it is not competitively priced against regional imports from Thailand, Vietnam, India and Pakistan. FSANZ notes from this information that only a small percentage of the market may be affected by approval of food derived from LLRICE62, particularly in terms of the need for GM labelling.

6.6.3 Consumer confidence in rice products could be affected if LLRICE62 is approved

Recent survey information from Biotechnology Australia indicates that small numbers of consumers maintain polarised views concerning GM foods. At one end of the spectrum, a small population of consumers continues to express strong opposition to all GM foods, irrespective of the trait or commodity, for a range of reasons including philosophical, social and political reasons.

At the opposite end, a small population of consumers actively supports the use of biotechnology in the production of food. The survey information appears to indicate that the bulk of consumers hold views somewhere in between these two positions.

This is supported by recent consumer survey work. FSANZ commissioned the benchmark Consumer Attitudes Survey to establish the current views of Australian and New Zealand consumers with regard to overall confidence in the food supply. Similar research has been previously conducted by FSANZ in relation to specific issues, such as nutrition information and food safety. However, the findings from this study provide a broader interpretation of consumers' attitudes that support and inform FSANZ's consumer related communications and activities.

The research was conducted in April 2007 via an online survey of 1200 Australians and 800 New Zealanders aged 14 years and older and investigated consumers' attitudes to a number of food issues. The full results of this survey are available on the FSANZ website. In relation to GM foods, in this study only 2.9% of those Australian consumers with a food safety concern participating in the survey, nominated foods with GM ingredients as being of greatest concern. When asked to rank a number of concerns according to severity, respondents listed other concerns well above GM foods, including the amount of saturated fat in food and food safety/hygiene concerns.

FSANZ continues to address the ongoing need for openness and transparency in the processing of GM applications, as a means of reassuring the public that the risk assessment conducted by FSANZ is scientifically robust. For this reason, safety data remain substantially in the public domain and assessment reports are made available to the public on the website. FSANZ also recognises that there is a need to supply general information on the regulatory oversight of GM foods to the public on an ongoing basis. To this end, FSANZ continues to explore new avenues for improving communication with consumers to ensure that there is sufficient information available to allow informed choice.

The mandatory labelling requirements under Standard 1.5.2, mean that foods derived from LLRICE62 will be required to be labelled as GM, where products contain detectable levels of novel DNA or novel protein. FSANZ considers therefore that consumers who wish to avoid GM foods will be able to exercise their choice. FSANZ acknowledges that small numbers of consumers oppose the technology absolutely, and call for process-labelling of GM foods. In general, the number of public submissions expressing concerns relating to GM applications and calling for more extensive labelling has decreased significantly over time. Based on the number of submissions received for this Application, the approval of food derived from glufosinate ammonium-tolerant rice line LLRICE62 has not attracted widespread consumer concern or attention.

The public should also be aware of research into other varieties of GM rice that are currently under development. The International Rice Research Institute (IRRI) recently outlined future goals and directions for rice in its strategic plan. Research into transgenic rice lines with improved nutritional profiles is continuing, in particular lines with significantly increased levels of beta-carotene, zinc or iron content. Although these lines are a number of years away, biotechnology in rice production extends beyond the use of agronomic traits which may also have an impact on consumer perceptions.

7. Review Options

There are three options proposed for consideration under this Review:

1. re-affirm approval of the draft variation to Standard 1.5.2 as notified to the Ministerial Council; or

2. re-affirm approval of the draft variation to Standard 1.5.2, subject to any amendments FSANZ considers necessary; or

3. withdraw approval of the draft variation to Standard 1.5.2 as notified to the Ministerial Council.

8. Decision

FSANZ has considered the issues raised by the Ministerial Council in relation to Application A589 – Food derived from glufosinate ammonium-tolerant rice line LLRICE62.

The First Review concludes that the preferred review option is Option 1. FSANZ has decided to re-affirm the variation to Standard 1.5.2 to permit the sale of food derived from glufosinate ammonium-tolerant rice line LLRICE62, as detailed in **Attachment 1**.

The recommended option is Option 1.

Decision

FSANZ re-affirms the variation to Standard 1.5.2 to permit the sale of food derived from glufosinate ammonium-tolerant rice line LLRICE62.

9. Implementation and review

The draft variation to Standard 1.5.2 will come into effect on the date of gazettal.

Attachments

1. Draft variation to the *Australia New Zealand Food Standards Code.*
2. Executive Summary and Statement of Reasons from the Final Assessment Report
3. Safety of recombinant DNA in foods

Attachment 1

Draft variation to the *Australia New Zealand Food Standards Code*

Standards or variations to standards are considered to be legislative instruments for the purposes of the Legislative Instruments Act (2003) and are not subject to disallowance or sunsetting.

To commence: on gazettal

[1] ***Standard 1.5.2*** *of the Australia New Zealand Food Standards Code is varied by inserting in the* Table to clause 2 –

Food derived from glufosinate ammonium-tolerant rice line LLRICE62	

Attachment 2

Executive Summary and Reasons for Decision from the Final Assessment Report

An Application has been received from Bayer CropScience Pty Ltd seeking to amend the *Australia New Zealand Food Standards Code* (the Code) to approve food derived from a genetically modified (GM) variety of rice, LLRICE 62, under Standard 1.5.2 – Food produced using Gene Technology. This Standard requires that GM foods undergo a pre-market safety assessment before they may be sold in Australia and New Zealand.

LLRICE 62 is tolerant to the herbicide glufosinate ammonium through the addition of a bacterial gene (*bar*). Expression of the *bar* gene produces an enzyme, phosphinothricin acetyltransferase (PAT) which inactivates phosphinothricin (PPT), the active constituent of glufosinate ammonium herbicides, allowing the crop to grow in the presence of the herbicide. No marker genes are present in LLRICE62.

Rice line LLRICE 62 is intended to be grown overseas, principally in rice growing regions of the United States. Once the grain is commercialised however, rice products imported to Australia and New Zealand could contain derivatives of LLRICE 62. Approval is therefore necessary before these products could enter the Australian and New Zealand markets. LLRICE62 is not intended for cultivation in either Australia or New Zealand and, to date, no environmental approvals have been sought.

Safety assessment

FSANZ has completed a comprehensive safety assessment of food derived from glufosinate ammonium-tolerant rice LLRICE62, as required under Standard 1.5.2 in the Code. The assessment included consideration of (i) the genetic modification to the plant; (ii) the potential toxicity and allergenicity of the novel protein; and (iii) the composition of LLRICE62 compared with that of conventional rice varieties.

The assessment of this Application identified no public health and safety concerns. On the basis of the available evidence, including detailed studies provided by the Applicant, food derived from glufosinate ammonium-tolerant rice LLRICE62 is considered as safe and wholesome as food derived from other commercial rice varieties.

Labelling

Food derived from glufosinate ammonium-tolerant rice LLRICE62 will be required to be labelled as genetically modified if novel DNA and/or novel protein is present in the final food. Studies conducted by the Applicant show that the novel protein is present at low levels in the rice grain. Some processed derivatives such as rice bran oil would be unlikely to contain detectable plant DNA or proteins and would not require labelling.

Labelling addresses the requirement of section 18(1)(b) of the Food Standards Australia New Zealand Act: the provision of adequate information relating to food to enable consumers to make informed choices.

Impact of regulatory options

Two regulatory options were considered in the assessment: (1) no approval; or (2) approval of food derived from glufosinate ammonium-tolerant rice LLRICE62 based on the conclusions of the safety assessment.

Following analysis of the potential costs and benefits of each option on affected parties (consumers, the food industry and government), approval of this application is the preferred option as the potential benefits outweigh the costs associated with the approval, in comparison with not approving LLRICE62.

Purpose

The Applicant seeks amendment to Standard 1.5.2, to include food derived from glufosinate ammonium-tolerant rice LLRICE62 in the Table to clause 2.

Decision

Amend Standard 1.5.2 – Food produced using Gene Technology, to include food derived from glufosinate ammonium-tolerant rice LLRICE62 in the Table to clause 2.

Reasons for Decision

An amendment to the Code approving food derived from glufosinate ammonium-tolerant rice LLRICE62 in Australia and New Zealand is approved on the basis of the available scientific evidence, for the following reasons:

- the safety assessment did not identify any public health and safety concerns associated with the genetic modification used to produce glufosinate ammonium-tolerant rice LLRICE62;
- food derived from glufosinate ammonium-tolerant rice LLRICE62 is equivalent to food from the conventional counterpart and other commercially available rice varieties in terms of its safety for human consumption and nutritional adequacy;
- labelling of certain food commodities derived from glufosinate ammonium-tolerant rice LLRICE62 will be required if novel DNA and/or protein is present in the final food; and
- a regulation impact assessment process has been undertaken that also fulfils the requirement in New Zealand for an assessment of compliance costs. The assessment concluded that the preferred option is option 2, an amendment to the Code.

Consultation

The Initial and Draft Assessments were each open for public comment for a period of six weeks. Eight submissions were received during the first consultation period and nineteen submissions were received during the second round. A summary of all submissions is attached to this Report (Attachment 3).

FSANZ has taken the submitters' comments into account in preparing the final assessment of this Application. Specific issues relating to glufosinate ammonium-tolerant rice LLRICE62 have been addressed in the Report.

Attachment 3

The safety of recombinant DNA in food

1. Recombinant DNA is no different to DNA from non-GM sources

All DNA is made up of the same chemical elements; recombinant DNA and DNA from non-GM sources is therefore composed of the same four nucleotides. Genetic modification results in the re-assortment of sequences of nucleotides but leaves chemical structure unchanged. Recombinant DNA is therefore chemically identical to non-recombinant DNA. There is also very little that is unique about the sequences of recombinant DNA, as most gene constructs that are used for transformation are derived from naturally occurring gene sequences, the vast majority of which would have been encountered before in food, either because they are derived from plant genes, or from bacteria or plant viruses that are often found associated with food (e.g. *Bacillus subtilis*, a common soil bacterium from which *Bt* genes are derived, might often be found on the surface of fresh fruit and vegetables; the cauliflower mosaic virus from which promoter sequences are often derived is frequently present in fresh vegetables).

2. Human beings are exposed to large quantities of foreign DNA and other nucleic acids (e.g. RNA) from a wide variety of sources on a daily basis as part of the diet

Nucleic acids are a natural component of food. Their total amount varies according to the type of food. For example, edible offal and animal muscle tissue comprise a high content of both DNA and RNA (per gram of tissue), whereas plant storage tissues, such as grains or potatoes, contain less DNA and RNA because they contain less cell nuclei (Jonas et al 2001). Dietary intake of nucleic acid is therefore influenced heavily by the diet of individuals and varies widely, but has been estimated to be in the range 0.1-1.0 g/person/day (Doerfler & Schubbert 1997).

3. The presence of recombinant DNA in food does not increase the overall dietary intake of DNA

Genetic modification typically results in the introduction of one or two new genes into an organism's genome. Given the large size of plant genomes, the contribution made by recombinant DNA to the total DNA in the genome will be very small. For example, for corn, which has an average genome size of 2,292 Mb, transformed with an insert of approximately 5 kb, the inserted recombinant DNA will make up only 0.00022% of the total DNA in the genome (Jonas et al 2001).

4. Nucleic acids are broken down during food processing

Food processing may lead to partial or complete degradation or removal of DNA. Physical and chemical factors, such as shear forces, heat or pH, may cause random cleavage of DNA strands, thus reducing the average DNA length but not total DNA content (Jonas et al 2001). Some processes such as the purification of sugar and the production of refined oils will remove most, if not all, DNA.

A number of studies focussing on various thermal treatments applied to food during processing (e.g. canning, fermentation), indicate that most DNA (including recombinant DNA) will be reduced to lengths of approximately 300 base pairs or less (Ebbehoj & Thomsen 1991, Hupfer et al 1998, Straub et al 1999). DNA fragments of such size are unlikely to encode functional genes, since this would require not only the full coding region to be present but also the appropriate regulatory sequences (e.g. promoter, terminator).

5. Ingested nucleic acids are extensively broken down in the digestive tract

Irrespective of whether GM foods are subject to processing prior to consumption, nucleic acid will also be broken down during digestion. Ingested DNA is cleaved through acid hydrolysis and enzymatic digestion (especially by pancreatic and intestinal nucleases) into small DNA fragments and mixtures of mono-, di-, tri-, oligo- and polynucleotides, which are then further catabolised into sugar phosphates and purine and pyrimidine bases (Carver & Walker 1995).

The fate of ingested DNA has been extensively studied and is discussed in a number of reviews (e.g. Beever & Kemp 2000, Jonas et al 2001). Given the chemical and structural similarity of all DNA, there is no basis for considering that in vivo hydrolysis and absorption of recombinant DNA will be different from non-recombinant DNA.

While the vast majority of ingested DNA will be degraded in the GI tract, a number of studies, including one in humans, have demonstrated that this process may not completely degrade all ingested DNA, with some incompletely digested DNA fragments being absorbed and detected transiently in cells of the GI tract as well as blood, liver, spleen and other organs and tissues. The most quoted of these is the human study reported by Netherwood et al (2004) as well as the series of studies in mice reported by Schubbert et al (1994, 1997, and 1998).

In the Netherwood et al study, nineteen human volunteers (twelve with intact digestive tracts, seven with ileostomies[11]) were fed GM soy containing the *epsps* gene. The amount of recombinant DNA that survived passage through the small bowel varied between the seven ileostomists, with a maximum of 3.7% recovered from the stoma of one individual. This rate of recovery was similar to an endogenous soy gene, suggesting the recombinant DNA was digested similarly to other plant DNA. The *epsps* gene could not be detected in faeces from subjects with intact digestive tracts, suggesting that any DNA surviving digestion in the upper GI tract is readily degraded in the large intestine. The study also found evidence of pre-existing transfer of a fragment of the *epsps* gene between GM soy and a small number of micro-organisms in the small intestine of the ileostomists. The authors speculated this had occurred prior to commencement of the study. There was no evidence of the intact *epsps* gene being transferred. In subjects with intact digestive tracts, none of the endogenous bacteria in the faeces were found to contain any *epsps* gene fragments from GM soy.

In the studies reported by Schubbert et al, M13 bacteriophage DNA was fed to mice at high doses and transiently detected as fragments in various tissues including foetal tissue. The vast majority of cells identified as containing M13 DNA fragments appeared to be macrophages or other differentiated phagocytes of the immune system.

[11] An ileostomy involves resection of the terminal ileum and diversion of digesta via a stoma to a colostomy bag.

The purpose of such cells is to destroy foreign macromolecules. It has been suggested that the relatively high frequency of cells that contained M13 DNA is probably related to the occurrence of unmethylated CpG sequences, which would stimulate macrophages and other immune cells to phagocytose the fragments (Beever and Kemp, 2000). Unmethylated CpG sequences are characteristic of bacterial DNA but not DNA in either plants or animals, therefore M13 DNA is probably not a good model for plant-derived recombinant DNA.

Other studies undertaken with livestock species ingesting GM plants (e.g. Einspanier et al 2001, Aulrich et al 2002, Reuter & Aulrich 2003, Tony et al 2003, Flachowsky et al 2005, Broll et al 2005, Mazza et al 2005) have confirmed that plant DNA may be readily detected in the tissues of animals. In some of these studies, small fragments of recombinant DNA were also detected in the GI tract or specifically the stomach, and in one case in the blood, liver, spleen and kidney (Mazza et al 2005), but so far, intact genes of recombinant-DNA origin have not been detected.

These results clearly indicate that the systemic uptake of ingested foreign DNA is a normal physiological process, and the demonstration of fragments of DNA in phagocytic cells should be expected as a natural consequence of that uptake. These cells provide immune surveillance of the digestive tract and other tissues, and recirculate frequently to the liver as a normal mechanism of removing debris. The rare appearance of foreign DNA fragments in a few foetal or neonatal cells should likewise not be of concern as it indicates that a few macromolecules have crossed the placenta and been engulfed by phagocytes of the foetus.

It should also come as no surprise that, with the improved sensitivity of analytical techniques, small fragments of recombinant DNA will occasionally be detected. The less frequent detection of recombinant DNA fragments probably reflects that recombinant DNA makes up only a very small proportion of the total DNA ingested (see 6.3 above).

6. Uptake and expression of foreign DNA by micro-organisms inhabiting the digestive tract is likely to be an extremely rare event

The horizontal DNA transfer of recombinant DNA into gut micro-organisms has been the subject of intense scientific scrutiny and debate, particularly in relation to the use of antibiotic resistance genes, and the possibility that such transfer could compromise the therapeutic use of antibiotics. Some studies are available which demonstrate that, in certain circumstances, foreign DNA may be taken up and expressed by micro-organisms, at least in vitro (e.g. Mercer et al 1999). To date, there is no evidence of transfer to and expression of recombinant DNA in bacteria under natural conditions. Transfer and expression has only been observed under laboratory conditions and only if homologous recombination is possible (Nielsen et al 1998). While such studies provide evidence of the possibility of DNA uptake by bacteria, they do not provide evidence that recombinant DNA poses any greater risk. The overwhelming scientific consensus is that, while theoretically possible, the likelihood of transfer and functional integration of recombinant DNA in gut micro-organisms is extremely low.

The gene transfer mechanisms by which bacteria may acquire new genes (conjugation, transduction and transformation) are well described and a number of comprehensive reviews on these processes are available (e.g. Levy & Miller 1989). In food, transfer by all three mechanisms is believed to be possible, at least from micro-organisms consumed in food, although studies on gene transfer in the human and animal gut are limited (Jonas et al 2001).

The gut and the colon in particular are considered to be a favourable environment for such transfer because of the high density of micro-organisms; direct cell to cell contact favours conjugation, and natural transformation is also favoured because of the relatively high DNA concentration at the recipient cell surface (Paul 1992).

For free DNA however there is only a very low probability per gene and per passage through the GI tract, of uptake and stable integration into the genome of a bacterial cell. There are several reasons for this, which are extensively elaborated in Jonas et al (2001), but briefly:

- degradation of DNA through the gastric and ileal passage makes it highly unlikely that linear DNA molecules of sufficient size will enter the colon;
- for transformation by linear DNA the bacterial cell must be competent:

    - a bacteria is said to be competent if it is able to naturally take up DNA from the environment. Competence usually occurs at a particular stage in the bacterial growth cycle when the bacterium produces a protein called a competence factor. Only between 1-2% of microbial species are thought to be naturally competent;

- DNA transferred through transduction or transformation may be susceptible to restriction by bacterial restriction endonucleases, which cleave double-stranded DNA;
- in the case of linear DNA, homology with sequences in the bacterial genome is necessary for integration to occur;
- to be expressed, the transferred DNA must contain an intact coding region and be associated with the appropriate bacterial expression signals:

    - most recombinant DNA derived from GM plants will be linked to plant-specific expression signals which are unlikely to function in bacterial cells;

- to be maintained by the bacterial population, acquired DNA must confer a competitive advantage to the transformed cell.

Therefore, although bacteria possess sophisticated systems for DNA uptake from their environment, horizontal transfer into and expression of free recombinant DNA present in food is predicted to be an extremely rare event.

Given the similarity between recombinant DNA and non-recombinant DNA, both in terms of chemical structure as well as sequence, the likelihood of transfer and functional integration of recombinant DNA by gut micro-organisms will be theoretically the same as for non-recombinant DNA present in food. It might also be argued that, as recombinant DNA would represent only a very small proportion of the total DNA ingested in food, successful transfer of recombinant DNA to gut micro-organisms would be far less likely to occur than transfer of non-recombinant DNA.

7. Should a small proportion of ingested DNA survive digestion in the GI tract, mammals possess effective mechanisms to avoid incorporation of foreign DNA into the genome

Mammalian cells have evolved with several mechanisms of defence against the uptake, integration and continued expression of foreign DNA (Doerfler 1991).

In addition to the initial degradation and/or excretion of foreign DNA that occurs following ingestion and the action of cells of the immune system e.g. phagocytes, to remove foreign macromolecules, most mammalian cells produce at least one DNase with exonuclease activity, and these would be expected to degrade most exogenous DNA, should it actually survive and be taken up by the cell (Jonas et al 2001).

The nuclear membrane is also a strong barrier against the penetration of nucleic acids. Entry is tightly regulated by nuclear pores, with nuclear targeting signals required for penetration, especially in the case of cells that have finished their division and the nuclear envelope is not disrupted (Gorlick & Mattaj 1996, Guralnick et al 1996, Collas & Aelstrom 1997, Palacios et al 1997, Popov et al 1998, Zeimienovicz et al 1999, Saphire et al 2000). Should DNA succeed in penetrating the nucleus, and become integrated in the genome, the evidence indicates that any integrated foreign DNA is likely to be rendered inactive through targeted methylation (Doerfler 1991, Doerfler et al 1995, Orend et al 1995).

8. The risk posed by the presence of recombinant DNA in food is no different to that posed by non-recombinant DNA

While the Review Request raises a number of interesting questions in relation to the potential impact on human health, should foreign DNA not be inactivated if taken up by cells, the studies cited (e.g. Palka-Santini et al 2003, Woodhams et al 2007, Rosenberg et al 2007) do not provide any compelling arguments that such health impacts, should they occur, are likely to be any greater with recombinant DNA compared to non-recombinant DNA.

The study by Malatesta et al (2002) on the ultrastructure of hepatocytes from mice fed GM soybean[12], is interesting in that the authors report that the GM soy-fed mice exhibited some slight but statistically significant ultrastructural differences in hepatocyte nuclei[13] relative to controls. Cells bearing slightly more irregularly shaped nuclei were postulated to be indicative of an increased metabolic rate and the slight increase in the number of nuclear pores was apparently suggestive of increased molecular trafficking between the nucleus and cytoplasm.

The study itself is quite unusual because it undertakes an investigation at the ultrastructural level in the absence of any clear evidence of effects in the liver at either the macroscopic or light microscopic level. Typically, ultrastructural investigations are only undertaken to identify an underlying mechanism if there is clear evidence of cellular change or clinical signs. In the Malatesta et al study only 100 cells/mouse were examined. Consequently the relevance of the subtle ultrastructural morphometrical changes observed are difficult to interpret, especially in the absence of any corroborating evidence of atypical liver activity (e.g. classical markers of liver cell damage). In addition, it is not clear that such effects, were they to be reproduced, would necessarily be attributable to the presence of recombinant DNA itself. The relevance of this study to the issue of persistence and uptake of recombinant DNA is therefore questionable.

The main objective of a GM food safety assessment is to identify whether new or altered hazards are present in the food as a result of the genetic modification, and if present to determine what risk, if any, they may pose to human health (Codex 2004, FSANZ 2007).

[12] The GM soy line used was glyphosate tolerant soybean line 40-3-2, not MON 89788.
[13] Irregularly shaped nuclei and increased numbers of nuclear pores.

Therefore, the key issue for FSANZ is whether the occurrence of recombinant-DNA in food poses any greater risk to human health, than that posed by the significantly larger amount of non-recombinant DNA already present in food.

In general, FSANZ considers the risk to be equivalent between recombinant and non-recombinant DNA and therefore does not regard this as an issue that requires explicit consideration for each and every GM food application. Rather, this issue need only be addressed if the molecular characterisation identifies an element or elements in the gene construct that may significantly increase the likelihood of recombinant DNA in GM food being taken up and stably incorporated in either gut micro-organisms or human cells. The constructs typically used to date contain coding and regulatory sequences that have been used many times before and are well known not to increase the likelihood of such events occurring.

9. Conclusion

The transferred DNA in rice line LLRICE62 does not contain any genetic elements which may significantly increase the likelihood of recombinant DNA in GM food being taken up and stably incorporated into the genome of either gut micro-organisms or human cells. Given this, FSANZ does not consider that the issue of persistence and uptake of recombinant DNA requires specific consideration in the safety assessment of food derived from glufosinate ammonium-tolerant rice LLRICE62; consideration of such issues is already implicit in the molecular characterisation component of the safety assessment.

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