FOOD STANDARDS
Australia New Zealand
Te Mana Kounga Kai – Ahitereiria me Aotearoa

15 July 2009
[11-09]

FIRST REVIEW REPORT

APPLICATION A614

FOOD DERIVED FROM GLYPHOSATE-TOLERANT COTTON LINE GHB614

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 9 February 2009, the Australia and New Zealand Food Regulation Ministerial Council (Ministerial Council) requested a First Review of Application A614, which seeks approval of food derived from genetically modified (GM) cotton – namely, glyphosate tolerant cotton line GHB614. 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 granted an extension of time and was required to review the decision by 31 August 2009.

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 First Review

A First Review of FSANZ's decision to approve Application A614 was sought on the grounds that the proposed amendment to Standard 1.5.2, to permit the sale and use of food derived from glyphosate-tolerant cotton line GHB614, does not protect public health and safety.

3.1 Protection of public health and safety

A number of reasons has been put forward in asserting that the decision to approve food derived from glyphosate-tolerant cotton line GHB614 does not protect public health and safety.

Firstly, FSANZ is asked to clarify what is known about any potential health implications of work establishing proof of principle for persistence and uptake of foreign DNA in and across the gastrointestinal (GI) tract of mammals. The rationale for requesting a First Review of food derived from glyphosate-tolerant cotton line GHB614 on these grounds is identical to that used for the First Review of Applications A592 (glyphosate-tolerant soybean line MON89788), A595 (insect protected corn line MON 89034), A589 (glufosinate ammonium-tolerant rice line LLRICE62) and A1001 (insect-protected corn line MIR162). It has been suggested that the First Review Report for these Applications did not provide that clarity, although FSANZ has noted that the Ministerial Council did not request a Second Review of any of these applications.

Secondly, clarification is requested as to whether glyphosate-tolerant cotton line GHB614 and control samples used in the compositional analysis were pure, as contamination of non-GM control samples with GM material would mask differences and reduce the confidence that can be placed in a conclusion of no significant difference. The concern arises as a previous safety assessment, for glyphosate-tolerant soybean MON 89788 (A592) acknowledged contamination of one of the non-GM control samples with GM material ($\leq 3.05\%$).

It is contended that such contamination may not be unusual and the Final Assessment Report for Application A614 provides no information about sampling and testing protocols. On this basis, the Review request further states that a conclusion of compositional equivalence cannot be accepted.

In summary, the Review request states that FSANZ should determine whether purity was adequately assessed, the outcome of that assessment, and if contamination occurred, clarify the policy it applies when evaluating compositional analysis results and cross-contamination, including whether a contamination tolerance has been set. The First Review request for this Application claims that 'this matter was not addressed adequately in the First Review Report for A1001, and so is raised again'.

3.2 Previous reviews

The First Review request for this Application claims that the issue of trace levels of contamination in samples used in the compositional analysis of glyphosate-tolerant soybean line MON89788 (Application A592) was not adequately clarified. FSANZ cannot re-open issues that have been previously addressed to the satisfaction of the Ministerial Council, and where the matter has subsequently been finalised.

3.3 Use of animal feeding studies in GM food assessments

The safety assessment of Application A614 did not rely on the results of a 40-day study in broiler chickens, however the study was included in the assessment. The Ministerial Council states that it is debatable whether this study is useful and therefore questions whether it was appropriate regulatory conduct for FSANZ to include the data in the assessment report. Concerns were expressed about FSANZ considering this study when it has been acknowledged that such studies are of limited scientific value for assessment purposes. It was asserted that FSANZ was using a 'technical assessment process' to 'influence public perceptions of the risks of GM food' and the use of animal feeding studies.

4. Background

FSANZ received an Application from Bayer CropScience Pty Ltd on 27 September 2007 seeking approval in the Code for food derived from GM cotton, line GHB614 (known commercially as GlyTol^{TM}), under Standard 1.5.2 – Food produced using Gene Technology. Cotton line GHB614 is tolerant to the broad leaf herbicide glyphosate. 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.

The genetic modification in cotton line GHB614 consists of a single herbicide tolerance trait introduced by the transfer of a modified 5-enol-pyruvylshikimate-3-phosphate synthase gene, *2mepsps*, derived from corn. The EPSPS protein is a key enzyme involved in the shikimate pathway for biosynthesis of aromatic amino acids in plants, and is normally inhibited by glyphosate, ultimately leading to the death of the plant. Two simple mutations were introduced into the wild type e*psps* gene from corn, using site-directed mutagenesis. The mutations introduced into the 2mEPSPS enzyme significantly reduce its sensitivity to glyphosate, allowing the enzyme to continue to function in the presence of the herbicide.

Plants expressing 2mEPSPS are therefore able to tolerate treatment with herbicides containing glyphosate as the active ingredient.

The Applicant has developed glyphosate-tolerant cotton line GHB614 for cultivation in major cotton producing countries worldwide, including eventually in Australia. While cottonseed oil is used in a large number of food products consumed by humans, the main source in the Australian domestic market is from cotton cropped locally. It is expected therefore that if approved, oil derived from GHB614 cotton would be found mainly in imported foods and would be unlikely to be present in significant amounts in the Australian or New Zealand markets.

Prior to Final Assessment, FSANZ completed a comprehensive safety assessment of food derived from glyphosate-tolerant cotton line GHB614, which included consideration of (i) the genetic modification introduced into the plant; (ii) the potential toxicity and allergenicity of the novel protein; and (iii) the composition of GHB614 cottonseed, compared with that from conventional cotton varieties. This included a comprehensive scientific evaluation of the food (oil and linters) derived from cotton line GHB614 according to FSANZ guidelines[1], and consideration of issues raised in two rounds of public consultation.

No public health and safety concerns were identified in the safety assessment. On the basis of the available evidence, including detailed studies provided by the Applicant, food derived from glyphosate-tolerant cotton line GHB614 is considered as safe and wholesome as food derived from other commercial cotton 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 December 2008, are provided in this Report at **Attachment 2**. The decision to approve food from glyphosate-tolerant cotton line GHB614 was made on the basis of the findings of the safety assessment which identified no public health and safety concern.

6. Issues addressed in First Review

6.1 Ingestion of recombinant DNA in food

The persistence and uptake of ingested recombinant DNA in the GI tract is a general issue that has been the subject of extensive consideration and publication for more than 15 years. Based on prolonged scientific discourse, the consensus view is 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 (WHO 1991, WHO 1993, Karenlampi 1996, Jonas *et al* 2001, Gaye & Gillespie 2005, Flachowsky et al 2007, EFSA 2007)[2]. Similar conclusions have been reached by expert consultations and intergovernmental bodies which have been convened specifically to address the safety of the presence of antibiotic resistance marker genes in foods (WHO 1993, Karenlampi 1996).

FSANZ continues to monitor the scientific literature for studies relevant to the safety assessment of GM foods and is fully cognisant of the literature dealing with this topic.

[1] FSANZ (2007) Guidance Document – Safety Assessment of Genetically Modified Foods
[2]Full citations are listed in **Attachment 3**.

FSANZ does not regard this as an issue that requires specific and explicit consideration for each GM food assessment. A response on this issue prepared for other reviews is available on FSANZ's website at: http://www.foodstandards.gov.au/newsroom/factsheets/factsheets2008/gmfoodssafetyofinges4072.cfm.

6.2 Purity of samples used for compositional analyses

Clarification was requested as to whether glyphosate-tolerant cotton line GHB614 and control samples used in the compositional analysis were sufficiently pure, as contamination of non-GM control samples with GM material could mask any differences, and reduce the confidence that can be placed in a conclusion of no significant difference.

Information provided by the Applicant states that in relation to control cotton Coker 312, the 'seed lot was found to be free of adventitious presence' of genetically modified cottonseed, including glyphosate tolerant cotton line 1445 (RoundUp Ready) and cotton line 15985 (Bollgard II) 'at the 0.1% limit of detection with a 95% confidence interval'. This analysis was undertaken with lateral flow strip detection following the guidelines and protocols established by the product manufacturer.

In relation to cotton line GHB614, the 'seed lot was found to have a purity of 99.33% at the 95 % confidence interval' for glyphosate-tolerant cotton line GHB614 'with a trait homozygosity of 94.03% at the 95% confidence interval.' In addition, the 'seed lot was found to be free of adventitious presence' of:

- certain other genetically modified cottonseed, including glyphosate tolerant cotton line 1445 (RoundUp Ready) and cotton line 15985 (Bollgard II) at the 0.37% limit of detection with a 95 % confidence interval;
- events DGH066-2301[3] and DGH066-1802[4] at the 0.09% limit of detection with a 95% confidence interval.

The seed analysis used a polymerase chain reaction (PCR) protocol established by the testing laboratory. The quality control information provided by the Applicant indicates that the methods used to prepare and identify the materials used in the compositional analyses complied with Good Laboratory Practice (GLP). The Applicant has therefore demonstrated that the compositional studies, including the determination of the purity of samples used in the analyses, were conducted in compliance with GLP and that appropriate techniques with sufficient sensitivity for detecting any cross-contamination were used to verify the tested material. On this basis, FSANZ is satisfied that the conclusions drawn from the studies are scientifically valid. In future assessments, FSANZ will include relevant information on the integrity of the test materials used in the compositional analyses to ensure that there are no grounds for general concerns about sample purity.

[3] Another cotton variety with a different trait.
[4] Another cotton variety with a different trait.

6.3 The use of animal feeding studies in GM food safety assessments

It was asserted in the First Review request that FSANZ was using a 'technical assessment process' to 'influence public perceptions of the risks of GM food' and the use of animal feeding studies. A concern was expressed about FSANZ considering a 40-day study in broiler chickens when it has been acknowledged that such studies are of limited scientific value for assessment purposes.

In relation to animal feeding studies with whole GM foods, FSANZ agrees that studies measuring production quality parameters are only of limited value for assessing the safety of most GM foods. Where a GM food has been shown to be compositionally equivalent to the conventional variety, the evidence indicates that feeding studies using target livestock species do not contribute significant additional information[5]. For this reason, FSANZ does not regard such studies to be an essential part of the information dossier, and explicitly states this view in the safety assessment.

FSANZ includes animal feeding studies, where available, primarily in response to concerns raised in public submissions if such studies are specifically excluded. In fact, FSANZ is mindful that excluding such studies in the past on scientific grounds was perceived by some consumers as a lack of transparency in the assessment process. Therefore, FSANZ has adopted the practice of routinely including an evaluation of whole food animal studies, where they are provided in relation to a particular GM food, while bearing in mind the potential limitations of the studies for assessment purposes. Applicants are expected to provide to FSANZ any animal feeding studies already conducted for evaluation as additional supporting information.

The inherent technical limitations of whole food animal feeding studies are one of the reasons that FSANZ does not rely on these types of studies in its safety assessment of GM foods. FSANZ has addressed the issue of animal feeding studies previously and has posted further information on the website[6].

7. Review Options

Three options were considered within 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.

[5] OECD (2003) *Considerations for the safety assessment of animal feedstuffs derived from genetically modified plants*. Series on the Safety of Novel Foods and Feeds, No. 9. Organisation for Economic Cooperation and Development, Paris.

[6] http://www.foodstandards.gov.au/foodmatters/gmfoods/frequentlyaskedquest3862.cfm

8. Decision

FSANZ has considered the issues raised by the Ministerial Council in the First Review of Application A614 – Food derived from glyphosate-tolerant cotton line GHB614.
On the basis of the outcomes of the review, Option 1 is the preferred option. FSANZ has decided to re-affirm its approval of the draft variation to Standard 1.5.2 to permit the sale of food derived from glyphosate tolerant cotton line GHB614, as detailed in **Attachment 1**.

Decision

FSANZ re-affirms its approval of the draft variation to Standard 1.5.2 to permit the sale and use of food derived from glyphosate-tolerant cotton line GHB614.

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 Reasons for Decision from the Final Assessment Report
3. List of references on the safety of recombinant DNA in food

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 glyphosate-tolerant cotton line GHB614	

Attachment 2

Executive Summary and Reasons for Decision from the Final Assessment Report

Executive Summary

On 27 September 2007, Food Standards Australia New Zealand (FSANZ) received a paid Application from Bayer CropScience Pty Ltd (the Applicant) seeking approval for food derived from genetically modified (GM) cotton, line GHB614 under Standard 1.5.2 – Food produced using Gene Technology in the *Australia New Zealand Food Standards Code* (the Code). Standard 1.5.2 prohibits a food produced using gene technology from being sold or used as an ingredient or component of any food unless it is listed in the Table to clause 2 of that Standard. To be approved under Standard 1.5.2, FSANZ conducts a pre-market safety assessment on all GM foods before they may be sold in Australia and New Zealand.

The genetic modification in cotton line GHB614 consists of a single herbicide tolerance trait introduced by the transfer of a gene encoding a modified form of the enzyme 5-enol-pyruvylshikimate-3-phosphate synthase (EPSPS). This enzyme catalyses a key step in the shikimate pathway for biosynthesis of aromatic amino acids in plants, and is normally inhibited by glyphosate which ultimately leads to the death of the plant. Two simple mutations were introduced into the wild type e*psps* gene derived from corn, using site-directed mutagenesis. The mutations introduced into the 2mEPSPS enzyme significantly reduce its sensitivity to glyphosate, allowing continued function in the presence of the herbicide. Plants expressing 2mEPSPS are therefore able to tolerate treatment with glyphosate-containing herbicides.

Cotton line GHB614 has been developed for cultivation in major cotton producing countries worldwide, including eventually in Australia. Cotton derivatives, such as cottonseed oil and linters, are used in many food products and may enter the Australian and New Zealand food supply via locally produced and imported processed products. Currently, there is no approval to grow cotton line GHB614 in Australia or New Zealand.

Safety Assessment

FSANZ has completed a comprehensive safety assessment of food derived from glyphosate-tolerant cotton line GHB614, which included consideration of (i) the genetic modification introduced into the plant; (ii) the potential toxicity and allergenicity of the novel protein; and (iii) the composition of GHB614 cottonseed, compared with that from conventional cotton varieties.

No public health and safety concerns were identified in the safety assessment. On the basis of the available evidence, including detailed studies provided by the Applicant, food derived from glyphosate-tolerant cotton line GHB614 is considered as safe and wholesome as food derived from other commercial cotton varieties.

Labelling

If approved, food derived from glyphosate-tolerant cotton line GHB614 will be required to be labelled as genetically modified if there is novel DNA and/or novel protein present in the final food. Studies undertaken by the Applicant indicate detectable levels of the novel protein, 2mEPSPS, in cottonseed meal, but not in processed fractions including refined cottonseed oil and linters.

Labelling addresses the requirement of section 18(1)(b) of the FSANZ Act, namely 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) not approving; or (2) approving food derived from glyphosate-tolerant cotton line GHB614, 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 to all sectors outweigh the costs associated with the approval.

Purpose

The Applicant seeks amendment to Standard 1.5.2 to include food derived from glyphosate-tolerant cotton line GHB614 in the Table to clause 2.

Preferred Approach

To amend Standard 1.5.2 – Food produced using Gene Technology, to include food derived from glyphosate-tolerant cotton line GHB614 in the Table to clause 2.

Reasons for Preferred Approach

An amendment to the Code approving food derived from glyphosate-tolerant cotton line GHB614 in Australia and New Zealand is proposed 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 glyphosate-tolerant cotton line GHB614;
- food derived from glyphosate-tolerant cotton line GHB614 is equivalent to food from the conventional counterpart and other commercially available cotton varieties in terms of its safety for human consumption and nutritional adequacy;
- labelling of certain food commodities derived from glyphosate-tolerant cotton line GHB614 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 an amendment to the Code.

Consultation

The Initial Assessment was advertised for public comment between 12 December 2007 and 6 February 2008; thirteen submissions were received. The Draft Assessment Report was advertised for public comment between 6 August 2008 and 17 September 2008; eighty-two submissions were received. The majority of second round submissions were campaign notices calling for process-labelling of all GM foods.

FSANZ has taken submitters' comments into account in preparing the Final Assessment Report. Specific issues relating to glyphosate-tolerant cotton line GHB614 have been addressed in this Report.

Attachment 3

List of references on the safety of recombinant DNA in food

References considered in previous reviews

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