7 March 2001
13/01

DRAFT RISK ANALYSIS REPORT

APPLICATION A375

Food derived from glufosinate ammonium tolerant corn line T25

Note:

This report is the "Full Assessment" as referred to in Section 15 of the *Australia New Zealand Food Authority Act (1991)*.

Public comments are now sought before completion of a Final Risk Analysis Report (referred to as the "Inquiry" in Section 16 of the Act). See under 'Invitation for Public Submissions' for details.

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EXECUTIVE SUMMARY

BACKGROUND

ANZFA received an application from Aventis on 27 April 1999 to amend the Australian *Food Standards Code* to include food produced from glufosinate ammonium tolerant corn line T25 in the Table to clause 2 of Standard A18 – Food Produced using Gene Technology. The modified corn under consideration is known commercially as Liberty Link® corn and is tolerant to applications of the herbicide glufosinate ammonium. This report describes the scientific assessment of the application.

ISSUES ADDRESSED DURING ASSESSMENT

(i) Safety Evaluation

Nature of the genetic modification

Glufosinate ammonium tolerant corn line T25 was generated by the transfer of two new genes: the *pat* gene and a truncated *bla* gene. The *pat* gene is derived from the microorganism *Streptomyces viridochromogenes* strain Tu494, and codes for the enzyme phosphinothricin acetyl transferase (PAT). This modifies and inactivates the herbicide glufosinate ammonium, and its presence thus confers to the plant tolerance to this herbicide. The *pat* gene was modified at the DNA sequence level to increase its level of expression in the plant. The modification to the DNA sequence of the gene did not result in any changes to the amino acid sequence of the PAT protein.

The *bla* gene is derived from *Escherichia coli* and encodes β-lactamase, which confers resistance to ampicillin. This gene was used to confer resistance to these antibiotics to bacterial cells and was used as a selectable marker when the plasmid was being generated in *Escherichia coli*. The antibiotic resistance gene was intentionally disrupted by the removal of the 3'end of the gene sequence and has been shown to be non-functional in the plant. Corn cells were transformed by direct gene uptake by protoplast cultures with additional DNA.

Single copies of the *pat* gene and the truncated *bla* gene were found to be stably integrated at one insertion site in corn plants over multiple generations. They were also found to be inherited in a Mendelian manner, and always segregated together.

General safety issues

Corn represents a staple food for a significant proportion of the world's population. Corn-based products are routinely used in a wide range of foods, and have a long history of safe use. Sweet corn varieties are grown largely for human consumption, although corn grain is also widely used as an animal feedstuff.

Phosphinothricin acetyl transferase (PAT) is an enzyme which acts specifically on the herbicide phosphinothricin (as well as the natural substrate produced by *S. viridochromogenes*), neither of which are found in the human body. The highest level of expression of the enzyme in kernels of corn line T25 was less than 0.0005% of the total

protein. The level of the PAT protein in highly processed corn food fractions is expected to be even lower and therefore the exposure to the novel protein is likely to be extremely low.

No stable transcript or any ß–lactamase activity was detected from the truncated *bla* gene. The impact on human health from its potential transfer to gut micro-organisms was therefore not considered any further. The transfer of novel genetic material from corn line T25 to human cells via the digestive tract was assessed, but was considered to be extremely unlikely to occur, and unlikely to pose any special additional risks compared with the large amount of DNA naturally present in all foods.

Toxicological issues

The presence of naturally-occurring toxins and allergens in glufosinate ammonium tolerant corn line T25 was investigated, as well as the potential toxicity and allergenicity of the PAT protein.

Corn contains no naturally-occurring toxins or allergens, and as noted above has a long history of safe use.

The toxicity of PAT protein was assessed using biochemical and acute toxicity studies. The PAT protein did not share any significant amino acid similarity with any known toxins. Results from acute oral toxicity testing in mice did not indicate any toxic effects. In addition, the substrate for the enzyme is not found in humans.

The potential for the novel proteins to be allergenic was investigated using a number of criteria, including amino acid sequence homology with known allergens, history of use and common physicochemical properties of allergens, including the sensitivity to digestion by digestive enzymes. The PAT protein was found to be rapidly digested in conditions that mimic human digestion. Additionally, it shows no amino acid similarity to known allergens and it is present at very low levels, if at all, in corn kernels.

Nutritional issues

Detailed compositional analyses were carried out to establish the nutritional adequacy of glufosinate ammonium tolerant corn line T25, and to look for any unintended effects by comparing it to non-modified control lines. The effect of glufosinate ammonium use on the composition of corn kernels was also examined. Samples were taken from trials in the USA and Canada. Composition in terms of key chemical components (protein, ash, fat, moisture, carbohydrate and fibre), including amino acids, fatty acids, calcium and phosphorous were investigated.

Although small but significant differences were seen in each of the USA and Canadian field trials, no differences were consistent across locations (or years) that would indicate a change in the composition due to the genetic modification. Additionally, the differences were minor and were within the normal range for that component cited in literature. It is also noteworthy that these minor differences are not considered biologically significant and do not raise any health and safety concerns. Glufosinate ammonium treated samples were also examined and there were no significant differences between the treated and untreated genetically modified lines. The differences observed in the compositional studies are also not considered to raise safety or nutritional concerns and are likely to reflect normal variation in corn hybrids.

Corn does not contain natural toxins or anti-nutrients at a level that are considered biologically significant.

Animal feeding studies were not considered essential in this case because sufficient information had been provided about the genetic modification and the composition of the food. It can be concluded from the data provided that glufosinate ammonium tolerant corn line T25 corn is nutritionally adequate.

Conclusion

On the basis of the data submitted in the present application, glufosinate ammonium tolerant corn line T25 is equivalent to other commercially available corn in terms of its safety and nutritional adequacy.

(ii) Labelling

Under the current Standard A18, which remains in effect until 7 December 2001, food derived from glufosinate ammonium tolerant corn line T25 does not require labelling as it is regarded as substantially equivalent to food derived from non-genetically modified corn varieties.

When the amended Standard (A18 in the Australian *Food Standards Code*, 1.5.2 in the *Australia New Zealand Food Standards Code*) comes into effect on 7 December 2001, food products made from glufosinate ammonium tolerant corn line T25 will require labelling if it can be shown that novel DNA and/or protein is present in the final food.

(iii) Public Submissions

Forty-five public submissions were received in relation to this application, of which only four were supportive. Those opposing the application did so primarily on the basis that they perceive GM food to be unsafe. The food safety concerns raised in submissions have been addressed by the safety assessment carried out by ANZFA, the details of which are in Attachment 2.

CONCLUSIONS

On the basis of the data submitted with the application and evidence obtained from the scientific literature, it is concluded that:

- the introduced gene in glufosinate ammonium tolerant corn line T25 is not considered to produce any increased public health and safety risk;
- food derived from glufosinate ammonium tolerant corn line T25 is equivalent to food derived from other commercial varieties of corn in terms of its safety and nutritional adequacy.

RECOMMENDATION

Based on the data submitted in the application, ANZFA concludes that food derived from glufosinate ammonium tolerant corn line T25 is as safe for human consumption as food from other commercial corn varieties, and therefore recommends that the Australian *Food*

Standards Code (Volume 1) and the recently adopted joint *Australia New Zealand Food Standards Code* (Volume 2) be amended to give approval to the sale of such food in Australia and New Zealand. The proposed amendment to Standard A18 and Standard 1.5.2 is provided in Attachment 1.

ANZFA now seeks public comment on the proposed amendment in accordance with the procedures described in Section 16 of the *Australia New Zealand Food Authority Act 1991*.

INVITATION FOR PUBLIC SUBMISSIONS

The Authority has completed a Draft Risk Analysis Report on this application, (referred to as the 'Full Assessment' in section 15 of the Act), which includes a draft Safety Assessment report and a draft variation to the Australian *Food Standards Code* (Volume 1) and the recently adopted *Australia New Zealand Food Standards Code* (Volume 2) which comes into effect on 7 December 2001. The Authority now seeks public comment on the draft Safety Assessment Report, the draft variation to the Food Standard *Codes,* and the Regulatory Impact Assessment before preparing a Final Risk Analysis Report (referred to as the 'Inquiry' in section 16 of the Act).

Written submissions containing technical or other relevant information, which will assist the Authority in preparing the Final Risk Analysis Report for this application, are invited from interested individuals and organisations. Technical information presented should be in sufficient detail to allow independent scientific assessment.

Submissions providing more general comment and opinion are also invited. The Authority's policy on the management of submissions is available from the Standards Liaison Officer upon request.

The processes of the Authority are open to public scrutiny, and any submissions received will ordinarily be placed on the public register of the Authority and made available for inspection. If you wish any information contained in a submission to remain confidential to the Authority, you should clearly identify the sensitive information and provide justification for treating it as commercial-in-confidence. The *Australia New Zealand Food Authority Act 1991* requires the Authority to treat in confidence trade secrets relating to food and any other information relating to food, the commercial value of which would be, or could reasonably be expected to be, destroyed or diminished by disclosure.

All correspondence and submissions on this matter should be addressed to the **Project Manager - Application A375** at one of the following addresses:

Australia New Zealand Food Authority

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Submissions should be received by the Authority by **20 April 2001**.

General queries on this matter and other Authority business can be directed to the Standards Liaison Officer at the above address or by Email on slo@anzfa.gov.au. Submissions should not be sent by Email as the Authority cannot guarantee receipt. Requests for more general information on the Authority can be directed to the Information Officer at the above addresses.

BACKGROUND TO THE APPLICATION

Liberty Link® corn is tolerant to applications of the herbicide glufosinate ammonium through the transfer of the *pat* gene which encodes an enzyme that permits detoxification of the broad-spectrum herbicide phosphinothricin, the active ingredient of glufosinate ammonium. A second non-functional gene is also transferred to corn line T25. A truncated form of the *bla* gene is present in corn line T25 and has had the 3' end of the gene intentionally removed thereby rendering it non-functional in the plant.

Glufosinate ammonium-tolerant corn line T25 is not currently grown in either New Zealand or Australia. However, domestic production of corn-derived food products in both countries is supplemented by a small amount of imported corn-based products, including high-fructose corn syrup, which is not currently manufactured in either Australia or New Zealand. Corn ingredients include flour, syrup, oil, starch, meal or whole kernels and cobs. Corn-based processed products include snap frozen vegetable packs, corn chips, corn oil, breads, flours, popcorn, pastries, crackers, meat substitutes, milk substitutes and confectionary. There are also many industrial uses of corn products.

The main benefits of glufosinate ammonium tolerant corn line T25 are agronomic in nature, and are therefore likely to accrue mainly to the primary producer. It is envisaged that production of these crops reduce reliance on agricultural chemicals for weed control with potentially higher overall crop yields. More general benefits may flow to the community as a result of reduced primary production costs.

PUBLIC CONSULTATION

ANZFA completed a Notice of Application (formally referred to as the Preliminary Assessment Report) upon receipt of the application and called for public comment on 3 November 1999. A total of 45 submissions were subsequently received. Attachment 5 contains a summary of the submissions.

NOTIFICATION OF THE WORLD TRADE ORGANIZATION

During the ANZFA assessment process, comments are also sought internationally from other Members of the World Trade Organization (WTO). As Members of the WTO, Australia and New Zealand are signatories to the agreements on the Application of Sanitary and Phytosanitary Measures (SPS Agreement) and on Technical Barriers to Trade (TBT Agreements) (for further details on WTO, see Attachment 4). In some circumstances, Australia and New Zealand have an obligation to notify the WTO of changes to food standards to enable other member countries of the WTO to make comment.

As there is significant international interest in the safety of these foods, the proposed changes to Standard A18 are considered to raise potential Technical Barrier to Trade or Sanitary/Phytosanitary matters and will therefore be notified to the WTO.

ISSUES ADDRESSED DURING ASSESSMENT

1. Safety assessment (Attachment 2)

Glufosinate ammonium tolerant corn line T25 has been evaluated according to safety

assessment guidelines prepared by ANZFA[1]. The assessment involved an extensive analysis of the following issues: (1) the nature of the genetic modification; (2) general safety issues such as novel protein expression and the potential for transfer of novel genetic material to cells in the human digestive tract; (3) toxicological issues; and (4) nutritional issues. On the basis of the data submitted in the present application, ANZFA concludes from the assessment of this data, that glufosinate ammonium tolerant corn line T25 does not raise any public health and safety concerns and is equivalent to other commercially available corn in terms of its nutritional adequacy. The safety assessment report can be found at Attachment 2 including a summary of findings at the beginning of the document.

2. Labelling of food produced from glufosinate ammonium tolerant corn line T25

On 28 July 2000 the Australia New Zealand Food Standards Council agreed to a revised standard which requires labelling of food where novel DNA and/or protein is present in the final food and also where the food has altered characteristics. The revised standard (A18 in the Australian *Food Standards Code*, 1.5.2 in the Australia New Zealand Food Standards Code) was gazetted on 7 December 2000 and will come into effect 12 months from the date of gazettal.

Until the new labelling requirements take effect, the provisions in the original Standard A18 apply. Under these provisions, food derived from glufosinate ammonium-tolerant corn line T25 does not require labelling as it is regarded as substantially equivalent to food derived from non-genetically modified corn varieties.

3. Issues arising from public submissions

3.1 General issues

Of the 45 submissions received, only a small number addressed issues specific to this application. Rather, the majority of submissions raised issues of a general nature relating to gene technology or issues that had already been addressed in the safety assessment report (see Attachment 2). A discussion of some of the general issues in relation to gene technology that were raised in public submissions can be found in Attachment 6.

3.2 Specific issues

This section of the report will only address those issues raised in public submissions that are specific to an assessment of this application.

(i) Toxicity of glufosinate ammonium breakdown products

The South Australia Public and Environmental Health Service raised the point that the ANZFA safety assessment should address the issue of whether residues of the herbicide degradation process are present, toxic and/or subject to an MRL. The Consumers' Association of South Australia Inc. & National Council of Women of Australia raised similar concerns.

Response

There is currently no MRL for either glufosinate ammonium or its metabolites in corn in Australia. Therefore, no glufosinate ammonium residues (or metabolites) are permitted on

[1] ANZFA (1999) Guidelines for the safety assessment of foods to be included in Standard A18 – Food Produced Using Gene Technology.

any foods in Australia. New Zealand also does not have an MRL for glufosinate ammonium , however a level of 0.1 ppm is allowed under default clause 6b of the regulation 257 (2A). A Codex MRL of 0.1 ppm also exists. There is no evidence to suggest that the metabolites MPP and MPA are any more toxic than glufosinate, and sub-chronic and developmental studies in the US concluded that they were of similar or lower toxicity compared to the parent compound.[2] The chemical is permitted for use on glufosinate ammonium tolerant corn line T25 corn in the USA and the US regulatory assessment concluded that a single tolerance limit of 0.2 ppm was suitable for field corn. The consumption of food produced from corn line T25 is therefore not considered to pose a risk to human health.

4. Risk management

Under Standard A18 (and Standard 1.5.2 in the Australia New Zealand Food Standards Code), a GM food must undergo a pre-market safety assessment in accordance with ANZFA's safety assessment guidelines. The requirement for the food to be labelled must also be assessed in accordance with the labelling criteria specified in clause 4 of the amended Standard. Labelling according to the original standard A18 must be in accordance with the criteria specified in clause 2 and will be permitted until 7 December 2001. After this date, labelling will be required to comply with Standard 1.5.2 of the Australia New Zealand Food Standards Code.

On the basis of the conclusions from the safety assessment report, together with a consideration of the public submissions, it is proposed that the Table to clause 2 of Standard A18 be amended to include food from glufosinate ammonium tolerant corn line T25. The proposed amendment is provided in Attachment 1.

A public discussion paper on the safety assessment process for GM food[3] is widely available and may assist in addressing some of the concerns raised by the public. Other government and industry bodies are also addressing the broader concerns in relation to gene technology.

5. Regulatory Impact Assessment

The benefits and costs associated with the proposed amendment to Standard A18 to approve food from glufosinate ammonium tolerant corn line T25 have been analysed in a draft Regulatory Impact Statement (Attachment 3). The benefits of the proposed Standard A18 amendment primarily accrue to the food industry and government, with potentially a small benefit to the consumer.

CONCLUSIONS

ANZFA has conducted a comprehensive assessment of the application according to its *Guidelines for the safety assessment of foods to be included in Standard A18 – food produced using gene technology*. These guidelines are based on internationally accepted principles for establishing the safety of foods derived from genetically modified organisms.

It is concluded that:

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[2] US Federal Register, Volume 65 (98), May 19 2000.

[3] ANZFA (2000) GM foods and the consumer: ANZFA's safety assessment process for genetically modified foods. ANZFA Occasional Paper Series No. 1.

- the introduced gene in glufosinate ammonium tolerant corn line T25 is not considered to produce any increased public health and safety risk;
- on the basis of the data provided in the application, food derived from glufosinate ammonium tolerant corn line T25 is equivalent to food derived from other commercial varieties of corn in terms of its safety and nutritional adequacy.

RECOMMENDATION

Based on the data submitted in the application, ANZFA concludes that food derived from glufosinate ammonium tolerant corn line T25 is as safe for human consumption as food from other commercial corn varieties, and therefore recommends that the Australian *Food Standards Code* (Volume 1) and the recently adopted joint *Australia New Zealand Food Standards Code* (Volume 2) be amended to give approval to the sale of such food in Australia and New Zealand. The proposed amendment to Standard A18 and Standard 1.5.2 is provided in Attachment 1.

ATTACHMENTS

1. Draft variation to the Australian *Food Standards Code*
2. Draft safety assessment report
3. Draft regulatory impact assessment
4. World Trade Organization Agreements
5. Summary of public comments
6. General issues raised in public comments

ATTACHMENT 1

DRAFT VARIATION TO THE FOOD STANDARDS CODE

A375 — FOOD DERIVED FROM GLUFOSINATE AMMONIUM TOLERANT CORN LINE T25

To commence : On gazettal

The Food Standards Code is varied by

(1) *inserting into Column 1 of the Table to clause 2 in Standard A18 in Volume 1 –*

Food derived from glufosinate ammonium tolerant corn line T25.

(2) *inserting into Column 1 of the Table to clause 2 in Standard 1.5.2 in Volume 2–*

Food derived from glufosinate ammonium tolerant corn line T25.

ATTACHMENT 2

DRAFT SAFETY ASSESSMENT REPORT

A375 — FOOD DERIVED FROM GLUFOSINATE AMMONIUM TOLERANT CORN LINE T25

SUMMARY AND CONCLUSIONS

Nature of the genetic modification

Tolerance to the herbicide glufosinate ammonium was conferred on a proprietary inbred corn line, B73, by the transfer of the *pat* gene. Herbicide-tolerant corn line T25 was developed and is known commercially as Liberty Link corn. The *pat* gene is derived from the bacterium *Streptomyces viridochromogenes* strain Tu494. This gene is responsible for the production of the enzyme phosphinothricin acetyl transferase (PAT), which confers resistance to glufosinate ammonium herbicides by acetylating phosphinothricin, the active moiety of the herbicide.

A truncated ampicillin resistance gene (*bla*) was also transferred to the corn in the transformation process. This gene is non-functional in corn.

The transferred novel genetic material is stably integrated at a single site and maintained in the corn over multiple generations.

General safety issues

Corn is a staple food for a significant proportion of the world's population. Corn-based products are routinely used in a wide range of foods and have a long history of safe use. Products derived from corn line T25 may include highly processed corn products such as flour, breakfast cereals, high fructose corn syrup and other starch products.

Glufosinate ammonium resistant corn line T25 produces one new protein — PAT. Expression of the PAT enzyme in corn kernels is low, with the highest level detected being in inbred T25 corn lines. In kernels of hybrid T25 corn lines, PAT could not be detected. Thus exposure to the novel protein is expected to be extremely low. Higher levels of the PAT protein were detected in other plant tissues that are not a normal part of the human diet such as leaves, whole plant and silage.

One of the important issues to consider in relation to genetically modified foods is the impact on human health from potential transfer of novel genetic material to cells in the human digestive tract. Much of the concern in this regard is with the presence of antibiotic resistance genes in genetically modified foods. Corn line T25 however, only contains a non-functional truncated copy of the ampicillin resistance (*bla*) gene, therefore the issue of transfer of an antibiotic resistance gene does not need to be addressed in this application. Transfer of the *pat* gene from corn line T25 to human cells via the digestive tract was considered to be unlikely. The amount of novel genetic material in corn line T25 is minute compared to the total amount of DNA present and is therefore unlikely to pose any special additional risks compared with the large amount of DNA naturally present in all foods.

Toxicological issues

Corn contains no naturally-occurring toxins or allergens and has a long history of safe use.

The potential toxicity and allergenicity of the PAT protein has already been assessed by ANZFA in other genetically modified food applications and is not considered likely to cause an allergic or toxic reaction. In summary, in acute toxicity studies of the PAT protein in mice, there were no signs of toxicity at a dose of approximately 2.6 g/kg bodyweight. The newly

expressed protein is also readily degradable in conditions that mimic human digestion and has no similarity with any known allergens. Thus, the evidence does not indicate that there is any potential for the novel protein to be toxic or allergenic. Additionally, the PAT protein is present at very low levels in kernels, therefore dietary exposure to PAT would be extremely low.

Nutritional issues

Detailed compositional analyses were undertaken to establish the nutritional adequacy of corn line T25, and to compare it to non-modified control lines. No consistent differences in corn components or nutrients were observed in genetically modified corn line T25 compared to controls, or in glufosinate ammonium -treated plants compared to untreated controls. Although some statistically significant differences were observed, these were small and did not have any biological significance or raise any safety concerns. All reported values fell within the range cited in the published literature.

An animal feeding study using chickens was provided as additional supporting data to the application. The results of this study confirm the results of the compositional studies and demonstrate that corn line T25 is able to support typical growth and well-being.

Overall, these results demonstrate that corn line T25 is compositionally similar to non-modified corn hybrids, and support the conclusion that unintended secondary effects are unlikely to have occurred as a result of the genetic modification.

Conclusion

No potential public health and safety concerns have been identified in the assessment of glufosinate ammonium tolerant corn line T25. On the basis of the data provided in the present application, herbicide-tolerant corn line T25 is equivalent to other commercially available corn in terms of its safety and nutritional adequacy.

1. BACKGROUND

Aventis Pty. Ltd. have made an application to ANZFA to amend the Australian *Food Standards Code*, to include food derived from corn which has been genetically modified to be tolerant to the herbicide glufosinate ammonium. The corn is marketed as Liberty Link® corn.

Tolerance in T25 corn to the herbicide glufosinate ammonium is achieved through the expression of the *pat* gene which produces the phosphinothricin acetyl transferase (PAT) enzyme that chemically modifies the herbicide, thus rendering it inactive. Glufosinate ammonium tolerant corn line T25 can be grown under application of this herbicide.

Maize varieties are generally classified into flint, pop, dent and flour lines based on the hardness of the kernel. Flint varieties are preferred by dry millers for flour, grits and meal based products such as cereals and dent varieties are preferred by wet millers for starch and starch based products such as high fructose corn syrup. Corn oil may be produced from the germ of all varieties. Fermentation of cereal grains is also used for beverage and alcohol production.

A wide variety of food products are derived from the genetically modified corn including highly processed corn-based food ingredients such as high-fructose corn syrup, which is not currently manufactured in either Australia or New Zealand. Corn ingredients include flour, syrup, oil, starch, meal or whole kernels and cobs. Corn-based processed products include snap frozen vegetable packs, corn chips, corn oil, breads, flours, popcorn, pastries, crackers, meat substitutes, milk substitutes, breakfast cereals, and confectionary. There are also many industrial uses of corn products.

Food derived from glufosinate ammonium tolerant corn line T25 are most likely to be imported as processed food products, containing whole, part or constituents of corn and as corn derivatives.

2. DESCRIPTION OF THE GENETIC MODIFICATION

2.1 Methods used in the genetic modification

Corn line T25 was developed from a proprietary inbred corn line, B73, which was transformed with a plasmid containing the *pat* gene and the *bla* gene. The *pat* gene confers glufosinate ammonium tolerance and the *bla* gene confers resistance to the antibiotic ampicillin. The *bla* gene has been truncated and is non-functional in the plant. The transformed plant cells were produced by direct DNA uptake by protoplast cultures with additional DNA. The full details of the method of transformation and the proprietary plasmid used in the transformation have been provided to ANZFA for assessment, however, at the request of the applicant, this information has been accepted as confidential commercial information under the ANZFA Act 1991.

2.2 Function and regulation of the novel genes

The pat *gene*

The *pat* gene is derived from the soil microorganism *Streptomyces viridochromogenes* strain Tu494. It codes for the enzyme phosphinothricin acetyl transferase (PAT) which modifies

and inactivates the herbicide glufosinate ammonium. (Strauch *et al*, 1988)

The *pat* gene is often used as a selectable marker to distinguish genetically modified plant cells from unmodified cells. In this application, the *pat* gene has been transferred to corn to confer tolerance to glufosinate ammonium herbicides. The *pat* gene is under the control of the cauliflower mosaic virus (35S CaMV) promoter (Odell *et al*, 1985) and termination signal (Pietrzak *et al*, 1986). The CaMV 35S promoter drives constitutive expression of the *pat* gene throughout the plant. The bacterial *pat* gene contains a high G:C content that is not typical of plant genes. To optimise expression in plants, a synthetic gene that has a lower G:C content has been transferred to corn and has approximately 70% DNA sequence similarity with the native gene. However, the amino acid sequence of the PAT protein has not been altered (Wohlleben *et al*, 1988; Strauch *et al*, 1988).

The bla *gene*

The *bla* gene is derived from *Eschericia coli* and encodes β-lactamase which confers resistance to some β-lactam antibiotics, including the moderate-spectrum penicillin, ampicillin. The *bla* gene is under the control of bacterial and was used as a selectable marker to distinguish transformed bacterial cells from non-transformed cells. The plasmid was cut with restriction enzymes to generate a DNA fragment containing a truncated and thus non-functional copy of the *bla* gene. The *bla* gene was disrupted by the removal of 25% of its 5' sequence. This fragment was then used to transform corn embryos. Thus there is no functional *bla* gene present in the modified corn.

2.3 Characterisation of the novel genes in the plant

Aventis submitted the following study regarding characterisation of the novel genes in corn line T25.

Klonus D (1998). Genomic characterization of maize transformant T25. Performing laboratory: Hoescht Schering Aventis GmbH, Department D-65926, Frankfurt am Main, Federal Republic of Germany. Report No. PSR98/029.

Southern blot experiments of the original T25 transformant and a third generation of back-crossing with line B73, confirmed the presence of the *pat* and *bla* genes in the genetically modified corn line. The transformation process resulted in a single copy of the *pat* and *bla* genes being integrated into T25 corn. Prior to the transformation of the corn cells, the *bla* gene was disrupted (25% of the gene sequence was truncated) and is consequently not functional in the plant. This is supported by polymerase chain reaction (PCR) analysis and also that β–lactamase activity was not detected by HPLC-radio-monitoring as discussed in Section 3.3.

2.4 Stability of genetic changes

Aventis submitted the following study regarding the stability of genetic changes in T25 corn.

Klonus D (1998). Genomic characterization of maize transformant T25. Performing laboratory: Hoescht Schering Aventis GmbH, Department D-65926, Frankfurt am Main, Federal Republic of Germany. Report No. PSR98/029.

To determine the stability of the transgenic locus over multiple generations, T25 corn backcrossed with the parental line B73 was analysed by Southern blotting. Two generations of corn were tested; the original transformant and the third generation of back-crossing with B73. The inbred line B73 and non-transgenic regenerate plants of line HE89 were used as controls. The DNA fragments hybridising with a *pat* probe on Southern blots were identical in the original transformant and subsequent back-crossed generations, indicating stability of the DNA introduced into the corn.

Plants screened for phenotypic stability, i.e. tolerance to the herbicide glufosinate ammonium, demonstrated inheritance patterns consistent with a single insertion site that was stable over multiple generations.

2.5 Conclusions regarding the nature of the genetic modification

A single copy of the *pat* and truncated *bla* genes are transferred to corn resulting in the development of herbicide tolerant (glufosinate ammonium) corn line T25. Segregation analyses indicate that the transferred DNA is integrated into the corn genome as a single and stable insert.

3. GENERAL SAFETY ISSUES

3.1 History of use

Corn has been cultivated for centuries and is used as a basic food item by people throughout the world. A large part of corn production is used for human food products, and a wide variety of food products are derived from corn kernels. Sweet corn varieties are grown for human consumption. Grain and by-products from processing of corn are also used as animal feedstuffs.

Dry milling is a mechanical process in which the endosperm is separated from the other components of the kernels and fractionated into coarse particles (grits). The process is used to produce meal and flour for use in cereals, snack foods and bakery products, or for use in brewing (Alexander 1987). Food products derived from dry milling include flakes and grits. Corn flakes are produced by a process that involves high temperatures and pressures, grits are prepared by boiling.

The wet-milling process is designed to physically separate the major component parts of the kernel: starch, protein, oil and fibre. Wet milling produces primarily starch (typically 99.5% pure) (May 1987). In this process grain is steeped in slightly acidic water for 24–48 hours before being milled. Oil is produced from wet-milled corn by solvent extraction and heat (Rogers 1990).

Food derived from glufosinate ammonium tolerant corn line T25 will most likely be imported as processed food products, containing whole, part or constituents of corn and as corn derivatives.

3.2 Nature of novel protein

Only one new protein is expressed in corn line T25: phosphinothricin acetyltransferase (PAT). This protein, encoded by the *pat* gene, allows plants to detoxify the broad-spectrum herbicide

phosphinothricin (the active moiety of glufosinate ammonium herbicide). The PAT protein has a very narrow substrate specificity for phosphinothricin and demethyl-phosphinothricin, both of which are not found in humans. Acetyl transferases are a class of enzymes common to all bacterial, plant and animal cells and play a major role in both the synthesis and oxidation of fats. Although the PAT protein may not normally be consumed, *Streptomyces* is a common soil bacterium which may be found on and around plant produce.

In plants, the enzyme glutamine synthetase, plays a central role in the uptake of nitrogen by catalysing the incorporation of ammonia into glutamine. The herbicide glufosinate ammonium inhibits this enzyme in plants, leading to an accumulation of ammonia in the tissues, which kills the plant. The PAT protein catalyses the acetylation of phosphinothricin, thus eliminating its herbicidal activity (Strauch *et al*, 1988). Acetylation of phosphinothricin produces N-acetyl-glufosinate (NAG) and two further metabolites, 3-methylphosphinico-propionic acid (MPP) and 3-methylphosphinicoacetic acid (MPA).

The level of expression of the PAT protein in corn line T25 is sufficiently high for the corn to be marketed as herbicide tolerant. Biapholos, an antibiotic produced by *S. viridochromogenes* is the natural substrate for the PAT protein. No additional substrates, apart from phosphinothricin, have been reported.

3.3 Expression of novel protein in the plant

PAT protein

The level of expression and activity of the PAT protein has been determined, in order to establish potential dietary exposure to this protein. Studies to confirm that the *bla* gene is non-functional were also done. Aventis submitted the following studies on this topic:

Van Wert S and Forster V (1996). Composition, nutrition and/or amount of phosphinothricin acetyltransferase in whole and processed fractions of glufosinate resistant corn: transformation events T14 and T25 and nontransgenic counterparts. Performing laboratory: Aventis USA Company, Wilmington DE, United States. Report No. BK-95B-01.

Klonus D. 1999. Expression of the phosphinothricin acetyltransferase in glufosinate tolerant T25 corn. Hoechst Schering Aventis GmbH, Germany. Report PSR99/005

Schulz 1993. Beta-lactamase activity in Ignite (Glufosinate ammonium based herbicide) resistant corn.

Klonus D. 1999. Polymerase chain reaction analysis (PCR) of the glufosinate tolerant maize line T25.

Field trials of glufosinate ammonium tolerant corn line T25 were conducted in 1994 at two locations in the USA (Indiana and Puerto Rico). Genetically modified hybrid and isogenic or near isogenic control corn lines (i.e. same genetic makeup except for the novel gene) were grown at the Indiana site using a randomised block design. A genetically modified inbred and their respective near isogenic control lines were grown in Puerto Rico. An independent laboratory, Woodson-Tenent Laboratories, Illinois, undertook duplicate analyses of at least three representative samples per site for each genetic background. PAT protein levels were analysed in several plant tissues including the mature kernel, forage (tasseling to silking), silage (late milk to early dough) and fodder (dry plant at harvest).

A double-antibody enzyme-linked immunosorbent assay (ELISA) was used to quantify the PAT protein from T25 hybrids and their isogenic controls. The ELISA detects both intact and denatured PAT, therefore the results are likely to overestimate the level of active protein. The limit of detection of the assay is approximately 1 ng PAT/mg protein.

No PAT protein was detected in any control plants or in kernels of T25 hybrid plants grown in Indiana (Table 1). Grain from inbred T25 corn grown in Puerto Rico contained 4.02 ng PAT/mg protein (± 0.62 ng/mg protein), representing a maximum of 0.00046% of the crude protein in the kernel. The highest level of protein was found in the silage, containing 119.24 ng PAT/mg protein representing a maximum of 0.00132% total protein. It is significant that most commercial corn lines are hybrids rather than inbred lines and these results indicate that PAT protein levels are virtually non-detectable in hybrid lines.

Table 1: Level of PAT protein in corn tissues from hybrid and inbred T25 corn[1]

		Mean levels ± standard deviation (ng/mg protein)[2]			
Indiana		**kernel**	**silage**	**forage**	**fodder**
Hybrid T25	T25-1	nd	14.82 ± 0.86	-	-
	T25-2	nd	12.51 ± 1.38	-	-
	T25-2[3]	nd	14.81 ± 1.30	-	-
Control	*T25*	nd	nd	-	-
Puerto Rico					
Inbred T25	T25-3	4.02 ± 0.62	119.24 ± 13.36	62.70 ± 40.07	79.91 ± 5.23
Control	*T25*	nd	nd	nd	nd

[1]Values are expressed as ng PAT/mg protein. At least three samples were analysed in duplicate.
[2]nd = not detected; '-' = analysis not done. Limit of detection is approximately 1 ng PAT/mg protein.
[3]Plants were treated with glufosinate ammonium at the V8 stage (ie 69 days prior to harvest of silage, 115 days prior to harvest of fodder and grain).

PAT activity

The level of PAT activity was measured in kernels, leaves, roots, stem and pollen of greenhouse grown flowering T25 corn plants. The enzyme was detectable in kernels, leaves, roots and stems but not in pollen. The highest activity was found in stems (62.54 µMol N-acetyl-glufosinate produced/minute/mg protein extract). The activity in kernels was significantly lower (less than 60 times lower), ranging from 0.192 - 1.29 µMol N-acetyl-glufosinate produced/ minute/ mg protein extract.

In most processed corn products, i.e. those produced from dry- and wet-milling corn fractions (including flakes and grits), it is unlikely that the enzyme is active, given that the corn is processed using temperatures up to 105°C (220°F) and this is sufficiently high to denature proteins and thus inactivate the enzyme.

β-lactamase

The glufosinate ammonium tolerant corn line T25 contains a single copy of the bacterial *bla* gene that has been intentionally disrupted by the removal of the 3' end of the gene. Northern analyses were used to verify that the *bla* gene is neither transcribed to produce a stable transcript nor translated into an active protein with a β-lactamase function. β-lactamase activity in the genetically modified corn was assessed by HPLC-radio-monitoring. The standard assay contained 4.25 pmol of radio-labelled penicillin and β-lactamase activity could

be detected in 1:500 dilutions of a bacterial culture fluid with a protein concentration as low as 6.6 μg/ml. No β-lactamase activity was detected in protein extracts of young growing leaves from wildtype and transgenic corn plants, at protein concentrations of 500–1000 fold higher than and incubation times of up to 12 times longer than the bacterial system. It can be concluded that the partial *bla* gene from the plasmid vector does not produce an active β-lactamase in the herbicide-tolerant corn line T25.

3.4 Impact on human health from the potential transfer of novel genetic material to cells of the human digestive tract

The potential human health impact of transfer of novel genetic material to cells of the human digestive tract depends on the nature of the novel genes and must be assessed on a case-by-case basis.

In 1991, the World Health Organization (WHO) issued a report of a Joint FAO[4]/WHO Consultation , which looked at strategies for assessing the safety of foods produced by biotechnology (WHO 1991). The consultation concluded that as DNA from all living organisms is structurally similar, the presence of transferred DNA in food products, in itself, poses no health risk to consumers.

The major concern in relation to the transfer of novel genetic material to gut microorganisms is with antibiotic resistance genes. Antibiotic resistance genes can be present in some transgenic plants as a result of their use as marker genes to select transformed cells. It is generally accepted that there are no safety concerns with regard to the presence in the food of antibiotic resistance gene DNA *per se* (WHO 1993). However, concerns have been expressed that there could be horizontal gene transfer of antibiotic resistance genes from ingested food to microorganisms present in the human digestive tract and that this could compromise the therapeutic use of antibiotics. However, no functional antibiotic resistance gene was transferred to corn line T25, as indicated by a range of analyses including PCR, enzyme assay and northern analysis. Therefore, as the disrupted *bla* gene is not functional and there is no functional gene product, it is not considered to pose any safety risk.

It is equally unlikely that novel genetic material from genetically modified food would transfer to human cells via the digestive tract. In considering the potential impact on human health, it is important to note that humans have always consumed large amounts of DNA as a normal component of food and there is no evidence that this consumption has had any adverse effect on human health. Furthermore, current scientific knowledge has not revealed any DNA sequences from ingested foods that have been incorporated into human DNA. Novel DNA sequences in genetically modified foods comprise only a minute fraction of the total DNA in the food (generally less than 0.01%) and are therefore unlikely to pose any special additional risks compared with the large amount of DNA naturally present in all foods.

DNA digestibility study

Schneider, R., 1993. Fate of introduced DNA in gut: Degradation of phosphinotrhicin acetyl transferase gene from transgenic rape HCN 92 (Brassica napus) in stomach fluids from pig, chicken and cow. Hoechst AG Agricultural Division, Frankfurt am Main, Germany. Study No. BR 93/06

[4] Food and Agriculture Organization.

A study was conducted to determine whether the introduced *pat* gene is sensitive to degradation by mammalian and avian digestive processes. Although the study was conducted on canola that was genetically modified for tolerance to glufosinate ammonium, the outcomes are also relevant to the fate of the *pat* gene inserted into corn. The study used plant leaf material from transgenic rape line (*B. napus*) incubated in the digestive stomach fluids extracted from pig, chicken and cow. This genetically modified canola is also under assessment by ANZFA (Application A372 - Liberty Link canola). Samples were tested in pH step gradients of the digestive fluids over a range of time points up to 1 hour.

The study also aimed to determine whether the novel gene in the plant material could transfer to competent *E. coli* bacteria in a laboratory situation, using the kanamycin resistance gene (*npt*II) as a marker for transformation. By extrapolation, this experiment attempts to determine whether novel DNA in plant material that has been subjected to degradative conditions can transfer to *E. coli* present in the gut. The *E. coli* strain was converted from a disabled laboratory strain to a competent living strain for the purpose. A PCR assay system was used to detect the presence of the *pat* gene in the various phases of the experiments.

The PCR analysis of DNA fragments remaining after digestion indicated that the *pat* gene was readily degraded in any of the digestive fluids tested. Detection was pH dependent, being most efficient at low pH which mimics physiological conditions. The degradation was less complete at higher pH, which is well above the normal acidic environment of the human stomach.

Some antibiotic resistant bacteria were recovered at the beginning of the experiment using the proprietary plasmid as the DNA source. However, no colonies were recovered after the plasmid was incubated for 60 minutes in the various stomach fluid preparations. More significantly, when the transgenic plant material was used as the DNA source, no transformed colonies could be recovered either initially or after 1 hour incubation in the stomach fluids from any of the test animal species.

This experiment demonstrates that DNA consumed in plant (canola) material is efficiently degraded by normal digestive fluids from a number of different animal species, in conditions which closely resemble the physiological environment in humans. These results confirm that it is highly unlikely that introduced DNA present in the canola plants, including the antibiotic resistance gene, *nptII,* could transfer to intestinal bacteria.

3.5 Conclusions regarding general safety issues

Although the PAT protein would not normally be present in the food supply, it is sourced from a common soil bacterium and is not considered to pose a health and safety risk. Additionally, the class of enzymes PAT belongs to is very commonly found in all bacterial, plant and animal cells and has a major metabolic role.

The *pat* gene is expressed at low levels in corn line T25. It is expressed at the highest levels in the plant silage tissue and is much lower in the kernel where it represents less than 0.0005% total protein. The level of DNA and protein in highly processed corn based products are expected to be very low and in some cases, negligible. It is also likely that the proteins will be degraded and/or removed during processing steps.

No functional antibiotic resistance genes were transferred to corn line T25. The novel genetic material in corn line T25comprises only a minute fraction of the total DNA present in the corn and is therefore unlikely to pose any additional risks. Additionally, DNA digestibility studies in genetically modified canola (containing the *pat* gene), demonstrated that novel DNA was readily digested in conditions that mimic the human digestive system.

4. TOXICOLOGICAL ISSUES

4.1 Levels of naturally occurring toxins

There are no naturally occurring toxins known to occur at biologically significant levels in corn (Wright, 1987).

4.2 Potential toxicity of novel protein

Phosphinothricin, the substrate for PAT, is not present in humans. The acute oral toxicity of the PAT protein has been evaluated previously as part of applications A385 – Insect protected herbicide-tolerant Bt-176 corn, A386 – Insect-protected herbicide-tolerant Bt-11 corn and A380 DBT-418 corn. The following studies on the acute toxicity and physical and chemical characteristics of the PAT protein have been previously assessed.

An exemption from requirement to establish a maximum permissible level for residues of PAT and the genetic material necessary for its production was granted by the United States Environmental Protection Agency in April 1997 (US EPA 1997).

Reports submitted by Novartis:

Kuhn JO (1995). Phosphinothricin acetyltransferase (Sample PAT-0195) Acute oral toxicity study in mice. Performing Laboratory: Stillmeadow Inc, Sugar Land, Texas. Sponsor: Ciba-Geigy Corporation, Research Triangle Park, NC

Kuhn JO (1995). Phosphinothricin acetyltransferase (Sample PAT-0195) Acute oral toxicity study in mice. Performing Laboratory: Stillmeadow Inc, Sugar Land, Texas. Sponsor: Ciba-Geigy Corporation, Research Triangle Park, NC

(i) Similarity with known toxins

The PAT protein has been evaluated in Applications A385 Bt-176 corn and A386 Bt-11 corn. A comparison of the amino acid sequence of the PAT protein to the sequences of known toxins present in public databases (EMBL, Swissprot), demonstrated that it does not share any significant similarity with any known protein toxins. Additionally, no reports were found of toxicity associated with acetyl transferases as a class and the donor organism has no known pathogenic potential.

(ii) Equivalence of the plant PAT protein to the bacterially produced protein

The PAT protein was purified from plants by a combination of precipitation with ammonium sulphate and size-exclusion/ion-exchange chromatography. After purification, the protein extracted from the glufosinate ammonium tolerant canola migrated as a single band on a sodium dodecyl sulfate (SDS)-polyacrylamide gel, with a molecular mass of around 22 kDa. The kinetics and substrate specificity of the protein were characterised and PAT was found to

be highly specific for the substrate L-phosphinothricin, with a very low affinity for related compounds and amino acids. High temperatures and extremes of pH were found to inactivate PAT. These properties of the PAT protein extracted from T35 corn were found to be indistinguishable from the protein extracted from *E. coli.*

(iii) Acute oral toxicity in mice – bacterially produced PAT

The scientific basis for using an acute test is that known protein toxins generally act via acute mechanisms (Jones and Maryanski 1991). Hsd:S-D ICR albino mice (source: Harlan Sprague Dawley Inc, Texas) were housed individually in controlled conditions with free access to food and water, except for the 16 hours before dosing when food was withheld. Groups (5/sex) of mice were given a single oral dose (gavage) of PAT protein (PAT-0195, purity 51% phosphinothricin acetyltransferase, expressed by the *bar* gene in *E. coli*) in carboxymethyl cellulose; heat inactivated PAT (PAT-0195C, 52% purity) in carboxymethyl cellulose; or carboxymethyl cellulose to a total dose of PAT protein of approximately 2600 mg/kg bw (ie 51-52% of 5050 mg/kg bw, given that this was the purity of the protein).

Mice were observed for clinical signs at least 3 times on the day of dosing and once daily after this for a 14-day observation period. Bodyweight was determined predosing (day 0) and on days 7 and 14. At the end of the study, mice were killed for postmortem examination of gross pathology.

One male receiving the test substance died during the study. The only notable clinical signs were decreased activity, piloerection and ptosis (drooping eyelid) on days 6–8 in the male that died. One male receiving the reference substance showed slight piloerection on the day of dosing. However, as no other clinical signs were observed in animals of any group, these signs are not considered to be treatment related. Bodyweight gain was unaffected by treatment, except in the male that died. There were no abnormal findings on postmortem of animals surviving until the end of the study. The results do not indicate any potential toxicity from the PAT protein.

4.3 Levels of naturally occurring allergenic proteins

Corn does not contain any known naturally occurring allergenic proteins (Wright, 1987).

4.4 Potential allergenicity of novel protein

Although there are no simple predictive assays available to assess the allergic potential of proteins, a number of characteristics are common among many of the allergens that have been characterised. For instance, amino acid sequence similarity with known allergens may be a useful gauge of allergenic potential. A string of 8-12 consecutive amino acid residues in common with known allergens could be an indicator for allergenicity given that many T-cell epitopes of allergenic proteins are that length (Taylor and Lehrer, 1996). In terms of the chemical and physical nature of proteins, known allergens tend to be glycosylated proteins with a molecular weight of 10–70 KDa (Lehrer *et al*, 1996). Allergens also tend to be heat stable as well as resistant to peptic and tryptic digestion and the acidic conditions of the stomach. Consequently, many allergenic factors tend to be resistant to proteolytic digestion (Taylor and Lehrer, 1996). The PAT protein is evaluated for potential allergenicity against these criteria: molecular size, amino acid sequence similarity to known allergens, and how

easily the protein is degraded by heat, acid and gastric enzymes (Lehrer and Reese 1998, Jones and Maryanski 1991).

The applicant submitted one study relevant to the possible immunological effects of the transformed corn, showing the effect of simulated gastric conditions on enzyme activity. Since potential allergenicity is often related to the presence of large, undigested protein molecules, it is also important to look at the digestibility of a novel protein. The *in vitro* digestibility of the PAT protein has previously been evaluated by ANZFA in applications A385 – Insect protected herbicide-tolerant Bt-176 corn and A386 – Insect-protected herbicide-tolerant Bt-11 corn. As the PAT protein in Bt-176 and Bt-11 and T25 corn are identical, this study is also relevant to this application.

Study submitted by Aventis:

Schulz A (1993) L-phosphinothricin N-acetyltransferase, biochemical chacterization. Performing laboratory: Biologische Forschung C, Biochemie der Pflanzen, Hoechst Aktiengessellschaft, Frankfurt. Report No. 93.01.

Van Wert S and V Forster. 1996. Composition, nutrition and/or amount of phosphinothricin acetyl transferase in whole and processed fractions of glufosinate resistant corn: Transformation events T14 and T25 and non-transgenic counterparts. Performing Laboratory: Xenos, Woodson-Tenent, Texas A&M, Agrevo.

Study by Novartis (A386):

Privalle L (1994). *In vitro* digestibility and inactivation of the *bar* marker gene product phosphinothricin acetyltransferase (PAT) under simulated mammalian gastric conditions. Ciba Seeds. Agricultural Biotechnology Research Unit, Ciba-Geigy Corporation, Research Triangle Park, NC, USA.

(i) Effect of simulated gastric conditions on activity of the PAT protein

The digestive lability of the PAT protein was assessed for stability in simulated gastric juices. Enzyme samples were incubated at 37°C in stomach fluid from beagle dogs, for up to 15 minutes. Over the course of the incubation samples were removed, diluted in buffer, adjusted to pH 8 and assayed immediately for enzyme activity. The original pH of the stomach fluid was 1.1, experiments were repeated with stomach fluid adjusted to pH 4, to determine the effect that pH modulating medications (taken for stomach disorders) might have on digestion of the protein.

Purified PAT in stomach fluid of pH 1.1 was rapidly inactivated, losing all activity within one minute. At pH 4, inactivation was slower, taking up to 10 minutes. Crude PAT was again inactivated rapidly by gastric juice at pH 1.1, at the higher pH inactivation of the crude protein was slower than that of the purified enzyme. This study supports the conclusion that any PAT protein consumed in foods derived from corn line T25 will be readily denatured upon entering an acidic environment, such as the human gut.

(ii) Digestibility of PAT protein

The PAT protein used in this trial was obtained from an *E. coli* expression system and was purified following fermentation. Simulated gastric fluid (SGF) contained NaCl (2 mg/mL), HCl and pepsin (3.2 mg/mL), the pH was 1.0 to 1.2, and the activity of the fluid was determined before use. Samples were taken at zero and two minutes. The presence of PAT in the fluid following incubation was determined by SDS-PAGE analysis. PAT enzymic

activity was also determined at the pH optimum for the enzyme, at gastric pH and following serial incubation with a gastric solution containing 0.0032 mg/mL pepsin.

In the presence of SGF containing a standard concentration of pepsin, the PAT protein was completely degraded at time zero. After 2 minutes of incubation with 0.1 or 0.01 times the standard pepsin concentration, PAT degradation appeared complete. When 0.001 times the standard pepsin concentration was used, a significant amount of PAT remained after a 2-minute incubation period. This concentration was thus selected for the enzyme inactivation studies.

The enzyme activity of PAT decreased to 56% of initial values after a 10-minute incubation at 37^{o}C. This reflects the thermal sensitivity of the enzyme above 35^{o}C, and would represent the maximum activity were gastric pH or pepsin to have no effect on PAT activity. Immediately after addition to SGF without pepsin, PAT activity decreased to 2.6% of the initial activity, and reached zero by 1 minute. When pepsin was included in the SGF, the initial activity was even lower. Activity was not restored by neutralisation, indicating that inactivation of the PAT enzyme was irreversible. The half-life of the PAT protein in SGF containing 0.0032 mg/mL was between 1 and 2 minutes.

This study demonstrates that the PAT protein is readily digested in the gastric environments and is not likely to be allergenic.

(iii) Comparison of PAT with known allergens

No similarity was found between the sequence of the PAT protein and sequences of known allergens in a search of public databases. Additionally, acetyltransferases in general have no similarity to any reported mammalian allergens.

4.5 Conclusion regarding toxicological issues

These studies indicate that the PAT protein loses enzymatic activity immediately upon exposure to gastric pH, and that the protein is readily digested in the stomach. The PAT protein is present at very low levels in the kernel, is readily digested and does not show any similarity with known allergens. Therefore it is highly unlikely that the PAT protein would be toxic or allergenic to humans.

5. NUTRITIONAL ISSUES

5.1 Nutrient analysis

The overall nutritional composition of corn line T25, including any changes resulting from the genetic modification, has been assessed. The composition of the food derived from corn line T25 has been compared with other commercial varieties of the crop. The major components examined were protein, moisture, ash, fibre, fat, carbohydrates, calcium, phosphorous, fatty acids and amino acid composition. Where there are statistically significant differences between the genetically modified and the conventionally bred crop, further comparisons can be made with values available in the literature to determine whether the parameter is within the normal range for non-transformed lines. As T25 is marketed as a herbicide-tolerant variety, the impact of glufosinate ammonium application on the biochemical composition of kernels has been assessed.

Studies submitted by Aventis:

Van Wert S (1999). Composition and nutrition of corn grain: a comparison of transgenic hybrids T25-2 and T25-5 in Canada and in the USA. Performing laboratory: Woodson-Tenent Laboratories Inc, Technical Assessment Systems Inc. Report No. C003219.

Van Wert S (1996). Composition of whole fractions of glufosinate resistant corn untreated and treated with glufosinate: Transformation event T25. Performing laboratory: AgrEvo USA Company, Willmington DE, United States. Report No. A55781.

Analysis of corn grown in the USA and Canada

The composition of two hybrids derived from transformation event T25 (T25-2 and T25-5) was assessed. Plants were grown in two sets of field trials: the first field trial was conducted over two consecutive years in 1994–95 in the USA (hybrid T25-2) and the second field trial was conducted at two sites (Breslau and Ridgetown, Ontario) in Canada in 1995 (hybrid T25-5). The genetically modified hybrid T25-2 was developed by backcrossing the original transformant to another inbred. T25-2 was backcrossed to this inbred three times in 1994 and four times in 1995. These hybrids are considered to have 87.5% and 93.25% genetic homology, respectively.

The genetically modified hybrid T25-5 was developed by backcrossing the original transformant four times to another inbred and has approximately 93.25% genetic homology. The genetically modified lines and their non-genetically modified counterparts are not true isolines but are considered genetic counterparts.

At each location, genetically modified plants and their respective non-genetically modified counterparts were planted in a randomised block design. Plants were harvested at maturity and at least three representative samples from each site, for each genetic background, were analysed. Analysis included moisture, fat, protein, fibre, ash, carbohydrate (by calculation), fatty acid composition, amino acid composition and minerals.

The samples of genetically modified and non-genetically modified corn were collected and nutrient analyses data was analysed statistically using SYSTAT software. The data was analysed using multiple comparisons (i.e. between sites or years, within country and combined countries) to determine any significant differences between the genetically modified and non-genetically modified counterparts.

In separate analyses of the data from each of the USA and the Canadian field trials, there were some significant differences between genetically modified and control corn lines. The values for all components are listed in Tables 3 (USA data) and Table 4 (Canadian data). The United States Department of Agriculture's Handbook 8 values for these components have also been listed as a reference.

USA

Significant differences in the proximate parameters protein and carbohydrate, in the fatty acids C18:3 and C20:0, in the minerals calcium and phosphorus and in seven amino acids (Table 3) were observed between the genetically modified T25-2 and control corn line. Additional statistical analyses of the data, separating data according to year, determined that there was an effect of season on many of these nutrient parameters. The data was collected

over two years, with different environmental conditions each year (temperature, rainfall, soil moisture and type). Additionally, these differences between the genetically modified and non-genetically modified corn were not consistent between years. Although these differences were identified as statistically significant, they are all within the range given in the United States Department of Agriculture's Handbook 8.

Table 3: Proximate, fatty and amino acid and mineral values for T25-2 and control grain grown in USA

Parameter[1]	Control	Transgenic	USDA HB-8[2]	Range[3]
Protein*	8.3 ± 0.6	10 ± 1.0	9.42 ± 0.89	9.0-11.2
Carbohydrate*	86.0 ± 0.8	84 ± 1.0	74.26	73.5
Fat	4.4 ± 0.1	4.6 ± 0.3	4.74 ± 0.91	4.1-4.8
Crude Fibre	2.6 ± 0.5	2.7 ± 0.6	2.90 ± 0.28	2.1-2.6
Ash	1.3 ± 0.2	1.5 ± 0.1	1.20 ± 0.14	1.4-2.0
C16:0	9.2 ± 0.2	9.3 ± 0.2	na	10.7-11.5
C18:0	2.5 ± 0.2	2.4 ± 0.2	na	2.2-4.1
C18:1	31.7 ± 0.8	31.8 ± 0.9	na	14-64; 24.5-27.
C18:2	54.3 ± 1.0	54.2 ± 1.3	na	19-71; 51.8-58.
C18:3*	1.0 ± 0.05	0.92 ± 0.04	na	0.5-2.0; 0.8-1.1
C20:0*	0.54 ± 0.01	0.51 ± 0.03	na	0.2
Calcium*	0.0051 ± 0.007	0.0141 ± 0.0007	0.007 ± 0.002	0.007- 0.05
Phosphorus*	0.286 ± 0.007	0.331 ± 0.001	0.210 ± 0.076	0.20-0.32
Alanine	0.53 ± 0.06	0.63 ± 0.1	0.61	na
Arginine*	0.28 ± 0.02	0.37 ± 0.05	0.41	na
Aspartic acid*	0.45 ± 0.04	0.55 ± 0.09	0.57	na
Cysteine	0.16 ± 0.02	0.18 ± 0.01	0.15	na
Glutamic acid	1.2 ± 0.1	1.3 ± 0.6	1.53	na
Glycine*	0.28 ± 0.02	0.32 ± 0.02	0.33	na
Histidine*	0.23 ± 0.02	0.27 ± 0.03	0.25	na
Isoleucine	0.20 ± 0.02	0.26 ± 0.06	0.29	na
Leucine	0.78 ± 0.09	0.98 ± 0.25	1.00	na
Lysine*	0.21 ± 0.01	0.25 ± 0.02	0.23	na
Methionine	0.17 ± 0.02	0.18 ± 0.03	0.17	na
Phenylalanine	0.30 ± 0.04	0.37 ± 0.09	0.40	na
Proline	0.56 ± 0.05	0.65 ± 0.2	0.71	na
Serine	0.35 ± 0.03	0.42 ± 0.07	0.39	na
Threonine*	0.26 ± 0.02	0.30 ± 0.04	0.31	na
Tryptophan	0.042 ± 0.008	0.050 ± 0.006	0.057	na
Tyrosine	0.12 ± 0.03	0.16 ± 0.05	0.33	na
Valine*	0.30 ± 0.02	0.37 ± 0.05	0.41	na

[1] Proximates and minerals expressed on a dry weight basis; fatty acids as percent of total lipids and adjusted for moisture. Amino acids reported as a % total protein.

[2] Values reported in Handbook 8, the United States Department of Agriculture (USDA), 1989. SD not available for fatty and amino acid values in the USDA HB-8.

[3] Wright, 1987 in Corn chemistry and technology, 1987, Watson SA and Ramstad PE (eds), American Association of Cereal Chemists, St. Paul, Minesota, USA; Ensminger *et al*, 1990; Macgregor, 1989; Perry 1988

[4] HB-8 lists values for fatty acid values adjusted for moisture.

*Significantly different from non-genetically modified counterpart.

Canada

T25-5 corn grown in Canada showed significant differences in the fatty acids C18:1, C18:2 and C20:0, and in the amino acid cystine (Table 4). C18:2 was at a higher level in the

transgenic than in the isogenic corn, whereas C18:1 and C20:0 were lower in the transgenic samples. Additional statistical analyses of the data, separating data according to sites, determined that there was an effect of location on some of these nutrient parameters. The samples were collected from two sites, with different environmental conditions at each site (temperature, rainfall, soil moisture and type).

Table 4: Proximate, fatty and amino acid and mineral values for T25-5 grain and control corn grown in Canada

Parameter[1]	Control	Transgenic	USDA HB-8[2]	Range[3]
Protein*	10.3 ± 0.5	10.1 ± 0.5	9.42 ± 0.89	9.0-11.2
Carbohydrate*	83. ± 0.5	83.7 ± 0.7	74.26	73.5
Fat	4.4 ± 0.2	4.7 ± 0.2	4.74 ± 0.91	4.1-4.8
Crude Fibre	2.6 ± 0.3	2.5 ± 0.3	2.90 ± 0.28	2.1-2.6
Ash	1.35 ± 0.05	1.41 ± 0.04	1.20 ± 0.14	1.4-2.0
C16:0	11.2 ± 0.4	11.8 ± 0.9	na	10.7-11.5
C18:0	1.9 ± 0.1	2.0 ± 0.1	na	2.2-4.1
C18:1*	29.0 ± 3.0	23.8 ± 0.7	na	14-64; 24.5-27.
C18:2	55.0 ± 3.0	60.0 ± 2.0	na	19-71; 51.8-58.
C18:3	1.2 ± 0.2	1.2 ± 0.1	na	0.5-2.0; 0.8-1.1
C20:0*	0.50 ± 0.03	0.46 ± 0.02	na	0.2
Calcium	0.0042 ± 0.0006	0.005 0.001	0.007 ± 0.002	0.007- 0.05
Phosphorus	0.29 ± 0.03	0.30 ± 0.03	0.210 ± 0.076	0.20-0.32
Alanine	0.60 0.05	0.60 0.06	0.61	na
Arginine	0.32 0.04	0.32 0.03	0.41	na
Aspartic acid	0.54 0.06	0.50 0.05	0.57	na
Cysteine*	0.15 ± 0.01	0.16 ± 0.01	0.15	na
Glutamic acid	1.5 ± 0.1	1.4 ± 0.2	1.53	na
Glycine	0.29 ± 0.02	0.28 ± 0.03	0.33	na
Histidine	0.25 ± 0.02	0.23 ± 0.02	0.25	na
Isoleucine	0.27 ± 0.02	0.26 ± 0.03	0.29	na
Leucine	1.02 ± 0.07	1.00 ± 0.11	1.00	na
Lysine	0.23 ± 0.02	0.22 ± 0.02	0.23	na
Methionine	0.15 ± 0.02	0.16 ± 0.02	0.17	na
Phenylalanine	0.40 ± 0.03	0.38 ± 0.03	0.40	na
Proline	0.69 ± 0.07	0.65 ± 0.08	0.71	na
Serine	0.40 ± 0.04	0.39 ± 0.04	0.39	na
Threonine	0.30 ± 0.03	0.28 ± 0.03	0.31	na
Tryptophan	0.052 ± 0.006	0.0049 ± 0.003	0.057	na
Tyrosine	0.16 ± 0.01	0.16 ± 0.01	0.33	na
Valine	0.35 ± 0.03	0.34 ± 0.03	0.41	na

[1] Proximates and minerals expressed on a dry weight basis; fatty acids as percent of total lipids and adjusted for moisture. Amino acids reported as a % total protein.
[2] Values reported in Handbook 8, the United States Department of Agriculture (USDA), 1989. SD not available for fatty and amino acid values in the USDA HB-8.
[3] Wright, 1987 in Corn chemistry and technology, 1987, Watson SA and Ramstad PE (eds), American Association of Cereal Chemists, St. Paul, Minesota, USA. Ensminger *et al*, 1990; Macgregor, 1989; Perry 1988;
[4] HB-8 lists values for fatty acid values adjusted for moisture
*Significantly different from non-genetically modified counterpart.

The lack of consistent differences between the wild-type hybrids and their modified counterparts suggests that these effects are likely to be due to normal variation, rather than an effect of the genetic modification. The genetic makeup and environmental conditions can

affect the composition and nutrient levels of corn. Furthermore, the differences observed are small and would not represent a difference that is nutritionally significant.

Combined USA and Canada

Data from all field trials were combined and analysed for significant differences between the genetically modified T25 corn line and its non-genetically modified counterpart. The results from this analysis are listed in Tables 5a-d. The ranges for each component as listed in the USDA Handbook-8 (HB-8) are given.

Table 5a: Proximate, amino and fatty acid and mineral values for kernels from T25 and control corn grown in USA and Canada

Parameter[1]	Control	Transgenic	USDA HB-8[2, 4]	Range[3]
Protein	10.18 ± 0.66	10.06 ± 1.09	9.42 ± 0.89	9.0-11.2
Carbohydrate	84.08 ± 0.66	84.09 ± 1.18	74.26	73.5
Fat*	4.39 ± 0.13	4.50 ± 0.12	4.74 ± 0.91	4.1-4.8
Crude Fibre	2.50 ± 0.36	2.37 ± 0.25	2.9 ± 0.28	2.1-2.6
Ash	1.34 ± 0.05	1.34 ± 0.05	1.20 ± 0.14	1.4-2.0
Moisture % H_2O	18.45 ± 3.29	20.77 ± 5.02	10.37 ± 3.28	7-23
C16:0*	11.13 ± 0.32	11.58 ± 0.51	na	10.7-11.5
C18:0*	2.00 ± 0.26	2.45 ± 0.15	na	2.2-4.1
C18:1*	29.22 ± 2.57	25.92 ± 0.69	na	14-64; 24.5-27.
C18:2*	55.05 ± 2.35	57.37 ± 1.37	na	19-71; 51.8-58.
C18:3	1.23 ± 0.16	1.20 ± 0.13	na	0.5-2.0; 0.8-1.1
C20:0	0.51 ± 0.03	0.51 ± 0.03	na	0.2
Calcium	0.0056 ± 0.0027	0.0072 ± 0.0026	0.007 ± 0.002	0.007- 0.05
Phosphorus*	0.3005 ± 0.0263	0.3200 ± 0.0221	0.210 ± 0.076	0.20-0.32
Alanine	0.61 ± 0.04	0.60 ± 0.06	0.61	na
Arginine	0.32 ± 0.04	0.30 ± 0.04	0.41	na
Aspartic acid	0.55 ± 0.05	0.50 ± 0.05	0.57	na
Cysteine	0.16 ± 0.02	0.16 ± 0.02	0.15	na
Glutamic acid	1.44 ± 0.13	1.38 ± 0.15	1.53	na
Glycine	0.30 ± 0.03	0.30 ± 0.05	0.33	na
Histidine	0.25 ± 0.01	0.24 ± 0.02	0.25	na
Isoleucine	0.26 ± 0.03	0.24 ± 0.04	0.29	na
Leucine	1.01 ± 0.09	0.95 ± 0.14	1.00	na
Lysine*	0.23 ± 0.02	0.21 ± 0.02	0.23	na
Methionine	0.17 ± 0.04	0.17 ± 0.02	0.17	na
Phenylalanine	0.40 ± 0.04	0.36 ± 0.04	0.40	na
Proline	0.70 ± 0.06	0.65 ± 0.07	0.71	na
Serine	0.41 ± 0.02	0.39 ± 0.03	0.39	na
Threonine	0.30 ± 0.02	0.28 ± 0.02	0.31	na
Tryptophan	0.05 ± 0.01	0.05 ± 0.00	0.057	na
Tyrosine	0.16± 0.01	0.15 ± 0.02	0.33	na
Valine	0.35 ± 0.04	0.32 ± 0.03	0.41	na

[1] Proximates and minerals expressed on a dry weight basis; fatty acids as percent of total lipids and adjusted for moisture. Amino acids reported as a % total protein.
[2] Values reported in Handbook 8, the United States Department of Agriculture (USDA), 1989
[3] Wright, 1987 in Corn chemistry and technology, 1987, Watson SA and Ramstad PE (eds), American Association of Cereal Chemists, St. Paul, Minesota, USA. Ensminger *et al*, 1990; Macgregor, 1989; Perry 1988;
[4] HB-8 lists fatty acid values adjusted for moisture only, no standard deviation available for amino acids
*Significantly different from non-genetically modified counterpart.

Overall there were no significant differences in the proximate variables or minerals between genetically modified corn line T25 and its non-genetically modified counterpart. A significant difference was noted in the crude fat value which was higher in the genetically modified corn. There were also differences between several fatty acids: values were higher in the genetically modified corn for C16:1, C18:0, C18:2 and lower for C18:1. The only amino acid showing a significant difference was lysine which was lower in the genetically modified corn than in the control line corn. The value for phosphorous was higher in genetically modified corn. Location was found to have a significant effect on some of these parameters. These differences are all small and are not considered to be biologically or nutritionally significant. Additionally, all nutrient values are similar to the values for USDA HB-8 or literature ranges for corn.

Analysis of GA treated corn

During the 1994 USA field trial of corn hybrid T25-2 at a site in Indiana, plants were also treated with glufosinate ammonium. The experimental design consisted of three treatments (T25-2 not treated with glufosinate ammonium, T25-2 treated with glufosinate ammonium and non-transgenic), with three or four replications. The treated T25-2 corn received one application of 400 gm glufosinate ammonium/hectare at growth stage V5. Grain was harvested at maturity. All compositional variables, with the exception of fatty acids, were adjusted for moisture prior to statistical analysis. Plants were harvested at maturity and at least three representative samples from each site, for each genetic background, were analysed.

There were no significant differences (P=0.05) between the treated and untreated transgenic corn (Table 6). Thus, the application of glufosinate ammonium on the genetically modified corn line does not appear to have an effect on the final composition of the corn kernel.

There were some significant differences between either the treated or untreated transgenic corn to the non-transgenic counterpart, which are indicated in Table 6. Although statistically significant differences were seen between the transgenic and the non-transgenic counterpart, all means observed fall within reported literature ranges and are not nutritionally significant.

5.2 Levels of anti-nutrients

Corn contains few anti-nutrients. The anti-nutrients trypsin and chymotrypsin inhibitors are present in corn at very low levels that are not considered nutritionally significant (Wright 1987).

5.3 Ability to support typical growth and well-being

In assessing the safety of food produced using gene technology, a key factor is the need to establish that the food is nutritionally adequate and will support typical growth and well-being. In most cases, this can be achieved through an understanding of the genetic modification and its consequences together with an extensive compositional analysis of the food.

Table 6: Proximate, amino and fatty acid and mineral values for kernels from treated and untreated T25 corn and control corn grown in the USA[1]

Parameter[1]	Control	T25-2 untreated	T25-2 GA-treated	USDA HB-8[2, 4]	Range[3]
Protein*	6.81 ± 0.50	7.87 ± 1.15	9.22 ± 0.39	9.42 ± 0.89	9.0-11.2
Carbohydrate*	74.64 ± 2.29	73.50 ± 1.53	71.43 ± 0.40	74.26	73.5
Fat	3.76 ± 0.09	3.93 ± 0.20	4.20 ± 0.13	4.74 ± 0.91	4.1-4.8
Crude Fibre	2.60 ± 0.29	2.70 ± 0.29	2.43 ± 0.21	2.9 ± 0.28	2.1-2.6
Ash*	1.02 ± 0.10	1.21 ± 0.12	1.15 ± 0.06	1.20 ± 0.14	1.4-2.0
Moisture % H_2O	13.77 ± 2.51	12.72 ± 1.77	14.00 ± 0.33	10.37 ± 3.28	7-23
C16:0	9.11 ± 0.24	9.16 ± 0.21	8.88 ± 0.06	na	10.7-11.5
C18:0*	2.63 ± 0.02	2.24 ± 0.17	2.15 ± 0.03	na	2.2-4.1
C18:1	32.27 ± 0.53	31.37 ± 1.10	32.28 ± 0.31	na	14-64; 24.5-27.
C18:2	53.50 ± 0.43	54.83 ± 1.45	54.32 ± 0.18	na	19-71; 51.8-58.
C18:3*	1.03 ± 0.04	0.94 ± 0.03	0.88 ± 0.01	na	0.5-2.0; 0.8-1.1
Alanine	0.49 ± 0.04	0.55 ± 0.08	0.66 ± 0.06	0.61	na
Arginine*	0.26 ± 0.01	0.36 ± 0.06	0.33 ± 0.03	0.41	na
Aspartic acid*	0.43 ± 0.03	0.50 ± 0.08	0.60 ± 0.06	0.57	na
Cysteine	0.15 ± 0.01	0.17 ± 0.02	0.16 ± 0.01	0.15	na
Glutamic acid	1.13 ± 0.10	0.24 ± 0.29	1.60 ± 0.15	1.53	na
Glycine*	0.27 ± 0.14	0.32 ± 0.03	0.32 ± 0.02	0.33	na
Histidine*	0.21 ± 0.01	0.26 ± 0.04	0.28 ± 0.02	0.25	na
Isoleucine	0.19 ± 0.03	0.21 ± 0.05	0.25 ± 0.01	0.29	na
Leucine	0.73 ± 0.09	0.81 ± 0.17	1.03 ± 0.05	1.00	na
Lysine*	0.20 ± 0.01	0.25 ± 0.02	0.26 ± 0.01	0.23	na
Methionine	0.15 0.005	0.15 ± 0.02	0.15 ± 0.01	0.17	na
Phenylalanine*	0.28 ± 0.03	0.33 ± 0.07	0.41 ± 0.01	0.40	na
Proline	0.53 ± 0.05	0.54 ± 0.16	0.69 ± 0.06	0.71	na
Serine	0.33 ± 0.03	0.37 ± 0.06	0.44 ± 0.04	0.39	na
Threonine*	0.24 ± 0.02	0.28 ± 0.04	0.30 ± 0.03	0.31	na
Tryptophan	0.040 ± 0.008	0.050 ± 0.008	0.047 ± 0.006	0.057	na
Tyrosine*	0.10 ± 0.01	0.14 ± 0.05	0.14 ± 0.00	0.33	na
Valine	0.30 ± 0.03	0.34 ± 0.05	0.35 0.03	0.41	na

[1] Proximates, amino acids and minerals expressed on a dry weight basis; fatty acids as percent of total lipids and adjusted for moisture. Amino acids reported as a % total protein.
[2] Values reported in Handbook 8, the United States Department of Agriculture (USDA), 1989
[3] Wright, 1987 in Corn chemistry and technology, 1987, Watson SA and Ramstad PE (eds), American Association of Cereal Chemists, St. Paul, Minesota, USA. Ensminger *et al*, 1990; Macgregor, 1989; Perry 1988;
[4] HB-8 lists fatty acid values adjusted for moisture only, no standard deviation available for amino acids
*Either the treated or non-treated genetically modified corn was significantly different from non-genetically modified counterpart – note: there were no significant differences between the treated and untreated genetically modified corns.

Where, on the basis of available data, there is still concern or doubt in this regard, carefully designed feeding studies in animals may provide further re-assurance that the food is nutritionally adequate. Such studies may be considered necessary where the compositional analysis indicates significant differences in a number of important components or nutrients or where there is concern that the bioavailability of key nutrients may be compromised by the nature of the genetic changes to the food.

In the case of corn line T25, the extent of the compositional and other data provided in the application is considered adequate to establish the safety of the food. Nonetheless, Aventis

also provided an animal feeding study to compare the wholesomeness of corn line T25 with conventional corn hybrids. Although not considered essential for establishing safety in this instance, this animal feeding study has been reviewed as additional supporting data.

Study submitted by Aventis:

Leeson D (1996). The effect of glufosinate resistant corn on the growth of male broiler chickens. Performing laboratory: Department of Animal and Poultry Sciences, University of Guelph, Ontario, Canada. Report No. C-5-96I.

Two hundred and eighty commercial strain Ross x Ross male broiler chickens were weighed and allocated at random to 1 of 2 treatment groups, replicated 4 times, 35 birds per replicate. Birds were reared on 1 of 2 diets, *ad libitum*; a commercial corn hybrid or genetically modified corn line T25. Each diet was a conventional corn-soybean type, prepared for starter, grower and finisher periods. The source of corn for the first diet (commercial corn hybrid) was the University of Guelph, for the second (glufosinate ammonium tolerant corn), the source was Aventis, USA. Birds were fed starter diets to 18 days, grower diets from 18–32 days, and finisher diets from 32–42 days of age. At 18, 32 and 42 days, feed intake was measured and all birds weighed individually. All occurrences of mortality were submitted for post mortem examination. On day 42, 8 birds were randomly selected from each group for processing.

Variables considered for analysis were initial body weight; 18, 32 and 42 day body weight; 0–18, 18–32 and 32–42 day body weight gain, feed intake; and feed intake:body weight gain. Carcass characteristics considered were chilled carcass weight; abdominal fat pad weight; total deboned breast meat yield and abdominal fat pad as a percent of carcass weight; and deboned breast meat yield as a percent of carcass weight. Percent mortality over the experimental period was calculated. Significance was accepted at $P<0.05$.

The source of corn in the starter, grower and finisher diets had no effect on body weight, feed intake, feed intake:body weight gain or percent mortality over the experimental period ($P>0.05$). The mortality rate of 7.14 ± 5.47% was normal for this fast-growing strain of bird, with normal values being 5 – 8%. Carcass characteristics measured and calculated were unaffected by source of corn in the experimental diets.

Herbicide-tolerant corn was comparable in feeding value for 0–42 day broilers, relative to commercially available corn. The results indicate that the nutritive value of the herbicide-tolerant corn hybrid is equivalent to a commercially available corn hybrid and also supports the conclusion of the compositional analyses that there are no biologically significant differences between corn line T25 and other commercial varieties of corn.

5.4 Conclusions regarding nutritional issues

The nutritional qualities of glufosinate ammonium tolerant corn line T25 were determined by compositional analyses of the major components of the kernels and these were found to be comparable in all respects to the conventional corn lines.

There is a long history of safe use of corn. Based on the data submitted in the present application, grain derived from corn line T25is nutritionally and compositionally comparable to that from conventional corn and is not considered to pose a risk to human health and safety.

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ATTACHMENT 3

DRAFT REGULATORY IMPACT ASSESSMENT

The Authority is required, in the course of developing regulations suitable for adoption in Australia and New Zealand, to consider the impact of various options (including non-regulatory options) on all sectors of the community, including consumers, the food industry and governments in both countries. The regulatory impact assessment will identify and evaluate, though not be limited to, the costs and benefits of the regulation, and its health, economic and social impacts.

Identification of affected parties

1. Governments in Australia and New Zealand

2. Consumers in Australia and New Zealand

3. Manufacturers, producers and importers of food products

Options

Option 1–To prohibit the sale of food produced using gene technology

GOVERNMENT Commonwealth, New Zealand Health Departments, State/Territory Health Departments	**Benefits** • no benefits were identified.	**Costs** • the governments of Australia and New Zealand may be challenged under the WTO to justify the need for more stringent restrictions than apply internationally. • a prohibition on food produced using gene technology in Australia and New Zealand could result in retaliatory trade measures from other countries. • there may be technical problems for AQIS in enforcing such a prohibition at the import barrier.
INDUSTRY Manufacturers, producers and importers of food products	**Benefits** • Some companies may benefit from being able to exploit niche markets for non-GM products overseas.	**Costs** • food manufacturers and producers will be unable to use the processed food fractions from foods produced using gene technology thus requiring the switch to non-GM ingredients and the reformulation of many processed food products. The cost to manufacturers of going non-GM has been estimated to be $A 207m in Australia and $NZ 37m in New Zealand[5]. This is equivalent to 0.51% of turnover in Australia and 0.19% in New Zealand.

[5] Report on the costs of labelling genetically modified foods (2000)

CONSUMERS	**Benefits** • no benefits were identified, however as some consumers perceive GM food to be unsafe, they may perceive prohibition of GM food to provide a public health and safety benefit.	**Costs** • could lead to decreased availability of certain food products. • increased costs to consumers because manufacturers and producers may have to source non-GM ingredients.

Option 2– to permit the sale of food produced using gene technology

GOVERNMENT Commonwealth, New Zealand Health Departments, State/Territory Health Departments	**Benefits** • increased innovation and competitiveness in the food industry will benefit the economy.	**Costs** • minor costs associated with amending the *Food Standards Code.*
INDUSTRY Manufacturers, producers and importers of food products	**Benefits** • food producers and manufacturers will be able to capitalise on the latest technology. • food importers will continue to be able to import manufactured products from overseas markets including the USA and Canada where there is no restriction on the use of food produced using gene technology.	**Costs** • there may be some discrimination against Australian and New Zealand food products in overseas markets that have a preference for non-GM foods (e.g., Japan and the European Union).
CONSUMERS	**Benefits** • consumers may have access to a greater range of food products.	**Costs** • those consumers who wish to avoid GM food may experience restricted choice in food products. • those consumers who wish to avoid GM food may have to pay more for non-GM food.

Conclusion of the regulatory impact assessment

Consideration of the regulatory impact for foods produced using gene technology concludes that the benefits of permitting foods produced using gene technology primarily accrue to the government and the food industry, with potentially a small benefit to consumers. These benefits are considered to outweigh the costs to government, consumers and industry, provided the safety assessment does not identify any public health and safety concerns.

ATTACHMENT 4

WORLD TRADE ORGANISATION AGREEMENTS

With the completion of the Uruguay Round of trade negotiations, the World Trade Organization (WTO) was created on 1 January 1995 to provide a forum for facilitating international trade.

The WTO does not engage in any standard-setting activities but is concerned with ensuring that standards and procedures for assessment of and conformity with standards do not create unnecessary obstacles to international trade.

Two agreements which comprise part of the WTO treaty are particularly important for trade in food. They are the;

- Agreement on the Application of Sanitary and Phytosanitary Measures (SPS); and
- Agreement on Technical Barriers to Trade (TBT).

These agreements strongly encourage the use, where appropriate, of international standards, guidelines and recommendations, such as those established by Codex (in relation to composition, labelling, food additives, veterinary drug and pesticide residues, contaminants, methods of analysis and sampling) and the code and guidelines on hygienic practice.

Both Australia and New Zealand are members of the World Trade Organization (WTO) and signatories to the agreements on the Application of Sanitary and Phytosanitary Measures (SPS agreement) and on Technical Barriers to Trade (TBT agreement). Within Australia, the Council of Australian Governments (COAG) has put in place a Memorandum of Understanding binding all States and Territories to the agreements.

The WTO agreements are predicated on a set of underlying principles that standards and other regulatory measures should be:

- based on sound scientific principles;
- developed using consistent risk assessment practices;
- transparent;
- no more trade-restrictive than necessary to achieve a legitimate objective;
- recognise the equivalence of similar measures in other countries; and
- not used as arbitrary barriers to trade.

As members of the WTO both Australia and New Zealand have an obligation to notify the WTO of changes to food standards to enable other member countries of the WTO to make comment. Notification is required in the case of any new or changed standards which may have a significant trade effect and which depart from the relevant international standard (or where no international standard exists). Matters raised in this proposal may be notified to the WTO as either SPS notifications or TBT notifications, or both.

SPS Notifications

These are primarily health related, and refer to any sanitary and phyto sanitary measure applied:

- to protect animal or plant life from risks arising from the entry, establishment or spread of pests, diseases or disease carrying organisms;

- to protect human or animal life or health from risks arising from additives, contaminants, toxins or disease-carrying organisms in foods, beverages or foodstuffs;

- to protect human life or health from risks arising from diseases carried by animals, plants or products thereof, or from the entry, establishment or spread of pests; and

- to prevent or limit other damage from the entry, establishment or spread of pests.

The Agreement on the Application of Sanitary or Phytosanitary Measures relates to any sanitary or phytosanitary measure applied to protect animal, plant or human life or health which may directly or indirectly affect international trade. Whether the SPS measure is in the form of a law or mandatory regulation, an advisory guideline, a code of practice or a requirement, it is the purpose of the measure that is important - not its regulatory status. Each WTO member country is entitled to apply SPS measures that are more stringent than the international standards in order to protect the health of its population. In the interests of transparency, each instance of such non-alignment which could result in an impediment to trade must be identified and justified and the documentation of that justification must be readily available

Each member country is also required to apply its methods of risk assessment and management consistently so arrangements under the SPS Agreement do not generate what may really be technical barriers to trade

Under the SPS Agreement, an exporting country can have resort to the WTO's dispute settlement procedures with respect to such a non-alignment. These arrangements mean there is potential for a code of practice to introduce an SPS measure that may bring about non-alignment with international requirements. Such non-alignment would need to be justified scientifically on the grounds that it is necessary to protect human, animal or plant life or health.

TBT Notifications

A technical barrier to trade arises when a mandatory requirement in a country's food regulatory system does not align with the international standard and it is more trade restrictive than is necessary to fulfil a legitimate objective. However, it can be acceptable for a country to have a more stringent requirement than that set internationally for reasons including:

- Maintaining national security;
- Preventing deceptive practices; and
- Protecting human health or safety.

Instances of non-alignment with international standards which could result in trade barriers must be identified and, if questioned, justified. Voluntary codes of practice are not expected to generate technical barriers to trade except where compliance with a code of practice or some aspect of a code of practice is expected. Consequently, it is possible for a voluntary code of practice to be viewed by the WTO as mandatory and subject to all the notification and other provisions applying to mandatory regulations.

The Agreement on Technical Barrier to Trade relates to requirements covering product characteristics or their related processes and production methods. TBT covers measures that are not SPS, such as requirements relating to terminology, symbols, packaging, marking, labelling, food composition and processing methods.

ATTACHMENT 5

SUMMARY OF PUBLIC COMMENTS

National Genetic Awareness Alliance (Aus)

- Believes that the patenting of life-forms and living processes represents a violation of human rights, threat to food security, impediment to medical research and a threat to animal welfare
- Believes that current GM techniques are inherently hazardous, and have been shown recently to offer no benefits
  - Lower yields with high pesticide input
  - Intensification of the corporate monopoly on food
  - Spread of antibiotic resistance marker genes and promoter sequences
  - Possible increase of allergenicity due to spread of transgenic pollen
- Urges governments to use precautionary principle and carry out research into sustainable agricultural methods
- Calls for suspension of trials and sale of GM products and public inquiry.

Pola Lekstan and Anna Clements (Aus)

- Are concerned that approval without long-term testing may pose a health threat, that more GM food means less choice for those wanting to avoid it, that Bt may affect non-target organisms, and that herbicide resistance may lead to overuse of chemicals.

Arnold Ward (Aus)

- Questions the system of MRL setting in light of the levels of high glyphosate residues in Roundup Ready soybeans and of other chemicals (including the Bt toxin) in GM crops
- Is concerned about detrimental effect of Bt on non-target (beneficial) organisms and on humans, and believes that genetic engineering is imprecise with uncertainties in outcomes
- Believes that the concept of substantial equivalence is inadequate and should not be used to avoid more rigorous testing, and that commercial factors are overriding need for basic research. Also believes that ANZFA's arguments defend the needs of biotechnology companies and food processing industry, and that since ANZFA does no testing itself, the results can't be trusted.

Australian GeneEthics Network

- Believes that the data provided is insufficient to make an assessment, and clock should be stopped on the applications. Concerns include:
  - Direct health effects of pesticide residues
  - Possibility of transfer of antibiotic resistance marker genes leading to resistant bacteria

  - The possibility that transfer of other traits e.g. herbicide tolerance to bacteria, could lead to horizontal spread of unfavourable traits
  - Insertion of viral DNA could create new and virulent viruses
  - The possibility that approval could lead to the growing of GMOs in Australia – ecological concerns including effects of, and increases in resistance to, Bt-toxins and the encouragement of increased herbicide use resulting from herbicide-tolerant crops
  - The threat to GE-free status export markets
- Believes that the term 'substantial equivalence' is not useful– compositional data alone does not establish equivalence

Public and Environmental Health Service (Aus)

- Believes that the data provided should cover both the intentional and unintentional effects of the genetic modification. The unintended consequences of random insertion of new genetic material into the host genome could include loss or change of function of gene or controlling element, disregulation or amended regulation of the gene or controlling element, or production of a novel hybrid protein which could occur in an unregulated manner. They should also cover any compositional changes e.g. nutrients, antinutritional factors, natural toxicants, and define when a change would be considered 'significant'
- Potential effect of introduced proteins on metabolic pathways should be addressed e.g. over-expression or inhibition of enzymes
- Data should include details of whether introduced proteins are detectable in whole commodities, processed products and highly processed derivatives
- Data should include details of toxicity and allergenicity tests to prove that food is safe, as well as address issues of specificity and potency of proteins. It should also address the ability to support typical growth and well-being
- Data for herbicide-tolerant plants should be derived from studies performed on plants treated with herbicide. They should address the human toxicity of the herbicide and whether residues of the herbicide degradation process are present, toxic and/or subject to an MRL.

David Grundy (Aus)

- Considers that the expression of Bt toxins and other chemicals in plant tissues removes the choice of washing chemicals off fruit and vegetables. Believes that Roundup Ready crops have glyphosate or glufosinate molecules genetically attached
- Believes that GM crops should not be used for feed given to animals bound for human consumption, that products encouraging antibiotic resistance should not be used, and that labelling should be mandatory for all products containing GM ingredients

Leesa Daniels (Aus) Member of the Genetic Engineering Action Group

- Believes that:
  - Scientific research although limited, has brought concerns to light
  - Substantial equivalence is a subjective principal

- Comprehensive and mandatory labelling must be urgently implemented
- The Cauliflower Mosaic Virus (CaMV) promoter could enhance the capability to transfer genes horizontally and has the potential for activating dormant or new viruses
- Antibiotic marker genes could lead to increase in antibiotic resistance
- Several of the transformations encourage the use of pesticides, all of which have shown to be harmful.

Australian Food and Grocery Council

- Fully endorses the policy of minimum affective regulation, supports these applications, and considers that food manufacturers should make their own choice with regard to use of GM crops or products derived from them
- Believes that since the growth of GM crops has been approved overseas, they would support their growth in Australia if approved through the GTAC/GMAC/OGTR process
- Considers it unfortunate that ANZFA has not negotiated "equivalence" agreements for products already approved overseas to enable approval without having to carry out its own safety assessment. In the absence of such an agreement it supports the ANZFA safety assessment process.
- Believes that an appropriate information and labelling scheme would enable consumers to make an informed choice.

New Zealand Ministry of Health

- Referred preliminary report to New Zealand Health Research Council, who stated concern that all safety aspects should be carefully considered in the ANZFA process.

Nestle Australia Ltd.

- Supports the continued approval of glufosinate ammonium-tolerant canola, and believes that manufacturers would be disadvantaged were approval not to be granted.

Consumers' Association of South Australia Inc. & National Council of Women of Australia (CASA supports submission of NCWA)

- Believe that current testing procedure is inadequate and that human trials are the only adequate method, as with testing of new drugs. Also that physiological and neurological effects as well as the toxicological and allergenic effects should be looked at, and that an independent body should be responsible for testing.
- Do not support the use of antibiotic markers, since they believe they may pose a threat to efficacy of antibiotics in humans.
- State that new research has shown that GM soybeans may be a less potent source of phytoestrogens than conventional soybeans confirming the inadequacy of the term 'substantial equivalence'.
- Raise the point that although these crops have been approved elsewhere, this situation may change with consumer pressure.

- Do not accept that it is impossible to source food to ascertain whether or not it contains GM ingredients. Believe that if McCain and Sanitarium can do it, then others should also be able to.
- State general concern about the risk that MRLs will be raised as a result of herbicide-tolerant crops being developed, and feel that the calculations used are flawed and are not based on safety criteria.
- Believe that the use of GM crops in animal feed should also be regulated. A378
- State concern over possible increase in glyphosate use (it is apparently confirmed in one reference that herbicide use increases with herbicide resistant crops), referring to studies that link the chemical to Hodgkin's lymphoma, and the possibility that Europe may ban it due to adverse effects on beneficial insects**.** They are particularly concerned that glyphosate is not looked at by the same regulatory body as that looking at GM foods.

A379, A38

- State concern over the persistence and toxicity of bromoxynil, and consider that these have not been adequately assessed by the US FDA. They understand that the breakdown product of bromoxynil (DBHA) may be more potent than bromoxynil itself, and believe that a safety assessment needs to be done on this too. This is apparently the main residue, and they believe that this may appear in cotton oil and linters.

A372, A375, A380, A381, A386

- With respect to glufosinate ammonium, state concern about toxicity, neurotoxicity, teratogenicity and residues in food, soil and water. They believe that Monsanto is likely to apply for an increase in the MRL, and that such increases are likely to constitute a health hazard.

A380, A382, A383, A384, A385, A386

- Raise issues of adverse effects of Bt toxins on non-target insects and think that it needs more study.

A387

- Believe that raising the amount of a nutrient in a food may have unknown drawbacks e.g. affecting the efficacy of other nutrients.

Health Department of Western Australia

- Highlights various health and environmental concerns:
  - the use of antibiotic resistance genes as markers may transfer resistance to animals via gut bacteria
  - the possibility that microbial gene sequences may contain fragments of other virulent genes, and also that ingesting Bt toxins may be harmful to humans
  - the possibility that insects may be more prone to developing resistance to Bt, since Bt toxins have been found to be released into the soil
- Believes that both safety data and gene sequences should be available for public scrutiny

Meat New Zealand

A379

- Concerned at how labelling regulations will apply to sausage casings that may contain cotton linters even if they are not to be eaten, i.e. are effectively a processing aid. Think that labelling should only be used to advise the sausage manufacturer not consumers.

BRI Australia

- Supports the approval of all 13 applications provided ANZFA is satisfied with their safety.

Food Technology Association of Victoria Inc.

- Supports the approval of all 13 applications provided ANZFA is satisfied with their safety.

Diane Davie (Aus)

- Believes all 13 applications should be rejected, since they have not undergone human safety testing here or overseas, and have not been assessed on their ethical merits
- Believes that risks include:
  - Bacterial and viral vectors which could affect human physiology
  - Herbicide and insect-resistance genes, which could increase allergies and antibiotic resistance
  - Environmental risks
- Also believes that ANZFA must heed the concerns of consumers opposed to GM foods.

Martin Hurley, David Hook, Ian Smillie, Margaret Dawson, Tee Rodgers-Hayden, David Lovell-Smith (Natural Law Party), Barbara Brown, Ngaire Mason, Robert Anderson (member, Physicians and Scientists for Responsible Genetics), Louise Carroll, Gilbert Urquart, Caroline Allinson-Dunn, Megan Lewis, Peter Barnes, James Harlow, Gabrielle Dewan, Scott Young, Virginia Murray, Stephanie Chambers, Kay Dyson, Peter Fenwick, Joanne Xerri, Paul True, Josh Gill, James & Peysha Charlwood, Mitta Hirsch, Alan Florence, Nicole Paul, Lawrence Clarke, David Snowman, Reg Paling, Mark and Johanna Blows, David and Bev Semour, Richard and Sharon Moreham (see also below), Stuart Drury and Helen Murphy (All Aus), Brennan Henderson (NZ) – Generic e-mail objection.

- Believe that most Australians and New Zealanders do not want GM foods, there are no benefits, and deferral would not be disadvantageous. Approval should be delayed until they are proven safe.

- Feel that there is insufficient time to assess these applications thoroughly, and there are so many products under development that there is a high overall risk of a major disaster
- Believe that GM foods encourage pesticide use, and applications have made for commercial purposes only, and also that here could be commercial benefit to Australia and New Zealand in remaining GM-free.

Richard and Sharon Moreham (see also above)

- In addition to the points above, also think that it is unfortunate that the NZ government agreed to joint approval of food, as the Australian public are less educated about the issues surrounding GM foods
- Think that approval would only prove that ANZFA serves the interests of large multinational companies rather than those of the public.

Vicky Solah (Aus)

- Is for GM foods if the safety evaluation is carry out using approved, validated methods by an independent body, if the results are made available to consumers, and if all GM food is labelled
- Is concerned that transformation may lead to disruption of another gene, and that more research is needed before it is clear whether the process is safe
- With regard to herbicide tolerant crops, is concerned that consumers may not be aware of the need to wash products that have been sprayed, and that this therefore impacts on food safety. Also concerned about environmental impact of these chemicals, and of the possibility of resistance necessitating higher pesticide use in the future.

Dr Rosemary Keighley (Aus)

- Will not purchase foods unless they are certified GM-free. Believes that Australian producers who do not actually use GM products, but who fail to label them as such, will suffer.

Nicola Roil (Aus)

- Believes that GM foods pose health threats and may contaminate non-modified crops.

Ian and Fran Fergusson (Aus) – also in generic email above

- Believe there has been inadequate testing, and are concerned about possible side-effects.

Lyndal Vincent (Aus)

- Urges delay of approval until proven safe by extensive testing. Considers that genetic material is being released without knowing what the effects are, and cannot be recalled.
- Believes that there is no benefit to the consumer, and that national economic interests are best served by maintaining a GM-free market.

Fay Andary (Aus)

- Does not want any of the 13 products covered by the applications to be approved for inclusion in the food supply.

John and Francesca Irving (Aus)

- Thinks that no GE foods should be approved for inclusion in the food chain.

Diana Killen (Aus)

- Believes that there is no proven benefit to consumers and in many instances nutritional value is actually lower in GM crops, and it is therefore irresponsible to push through approval without thorough assessment of their long-term safety for public health.
- Suggests that research has highlighted adverse allergic reactions and a lowered immune response in some individuals, and that there are health implications with crops designed to be grown with greater concentrations of pesticides.
- Thinks that labelling is essential for consumers to discriminate in purchasing, and that Australia has a unique opportunity in supply of organic and GM-free food.

Sheila Annesley (Aus)

- Does not want any of the 13 foods included in the food supply.

David and Edwina Ross (Aus)

- State concern for the future food supplies and well-being of their grandchildren.

Beth Schurr (Aus)

- Wishes to protest against the threat of GM foods, the possible future detrimental effects and the further endangering of the planet.

Beth Eager (Aus)

- As a parent is concerned that neither the long-term effects on health nor the environment are being considered.

Bruce Pont and Ljiljiana Kuzic-Pont (Aus)

- Believe that safety has not been, and cannot be satisfactorily determined, and that any party associated with GM foods could be legally liable should adverse health effects be seen. Thalidomide, smoking, 'Agent Orange' and asbestos all show that such things can affect subsequent generations
- Believe that an increase in use of pesticides will result from pesticide-tolerant crops, and that the emphasis should be on organic and/or safe agriculture
- Believe that GM-food is a retrograde step, contrary to nature and has the potential to destroy the human race.

Chitta Mylvaganum (Aus)

- Wishes to know what tests were done to assess negative effects on human and environmental health, how thorough they were, what the outcomes were, are the results publicly available, and what further avenues of inquiry are open to the public
- Requests the prevention of the import or release of any products until tests are carried out by unbiased scientists in order to prove the lack of health or environmental effects.

John Stevens (Aus)

- Would be concerned if approval were granted before sufficient research had been completed on potential impacts on human health and gene pools of nearby crops. Once grown, spread via pollen would be impossible to stop, and labelling would not prevent exposure by this route.
- Considers that utmost caution should be exercised and import approval denied indefinitely.

Tim Carr (Convenor of the Emergency Committee against GE Foods)

- Believes that GM-foods are produced using a radical and unpredictable new technology so should be subject to more rigorous testing.
- States that it is unknown how the introduced gene will interact with and influence genetic expression in the host genome, and could change the chemical nature of the food.
- Considers that health risks could result from the increased use of pesticides, and also that ANZFA should consider wider environmental, ethical and socio-economic issues.

Jan Kingsbury (Aus)

- Believes that GM-foods could result in loss of economic advantage for Australia and New Zealand since they are known internationally for pure and safe products.
- Believes that foods are being complicated and pushed by big internationals, and organic farmers are being contaminated by cross-pollination.

Teresa Sackett (Aus)

- Believes that:
  - The KPMG report on labelling was prepared in a ridiculously short time and provided limited analysis
  - The proposal of 'no label' for foods which 'may contain' or in which there is 'no evidence' of GM material is inadequate
  - Inadequate testing procedures should not be used to declare a product is GM-free just because material can't be detected. In fact testing methods have been developed that can be used to work out the GM content
  - Government and industry seem to be favouring the introduction of GM foods. This will result in:
  - Increased use of chemicals
  - Destruction of soil life
  - Organic farming pay high costs for producing healthy plants, while conventional farmers have little restriction on pollution of air, soil and water. Salinity problems, the death of the Great Barrier Reef, rivers and streams has resulted from ignorance in farming and broader community. Such problems will increase with GM foods.
  - The implication that the public will not understand the issues is wrong. Everyone needs to be fully informed.
- Asks the question of whether workers in the food industry are to be better informed, and also why no 'verification documents' are to be required by retailers? Believes that certification schemes should be on a par with those for Kosher foods and organics.

John and Sandy Price (Aus)

- Approval of GM foods and seeds should not be allowed, as it is an affront to the sovereignty of Australia and the dignity of the Australian people. The results of the experiment cannot be reversed.

John Scott (NZ)

- Encloses article from The Irish Times, which describes the restrictions that have been placed by the US EPA on the cultivation of GM corn. These appear to have resulted from fears that Bt crops may be harmful to Monarch butterflies and that resistance may develop to Bt.

R A Randell (NZ)

- Believes that all GM products should be placed under a moratorium until the Royal Commission of Inquiry has considered the issue, and until all scientific, philosophical, ethical and moral issues have been looked at.

National Council of Women of New Zealand

- Believes that:
  - approval of all 13 applications should be rejected, and that none should be approved for planting.
  - Independently-funded body should be responsible for safety assessments
  - If it is possible to segregate high-oleic soybeans, then RoundUp Ready soybeans should be segregated too
  - Consumers should be made aware of the extent of GM ingredients in their food
  - GM foods, additives or processing aids already on the market must be labelled comprehensively and without extra cost to the consumer – suggest 'GM unknown' rather than 'may contain'
- Appreciates that rejection may contravene the WHO agreement, but consider that the primary role of ANZFA is the assurance of health and safety.

Safe Food Campaign (NZ)

- Believes that approval should be rejected, and a moratorium be put in place until after the Royal Commission of Inquiry, for various reasons:
  - Possible effects on non-target insects
  - Spread of GM pollen may cause contamination of non-GM (especially organic) crops, and may result in the spread of herbicide-tolerance genes and an increase in resistance development. Cross-pollination is considered a particular risk for canola (A372 & A388). Bt resistance development is noted as being a particular risk for A382, A383 & A384
  - Lack of long-term testing means health risks are not known
  - Use of broad-spectrum pesticides affects wild flowers and non-target insects.

Jocelyn Logan, Caroline Phillips (NZ)

- Oppose all 13 applications for the following reasons:
  - Testing has not been long-term or independent, precautionary principle should apply. Approval can happen later if GM is proven safe.
  - No clear public benefit, and lack of opportunity for informed choice (immoral and undemocratic). Labelling regulations also unsatisfactory in this respect.
  - Environmental concerns (increase in pesticides, threat to organic farming, Bt resistance)

Robert Anderson (member of Physicians and Scientists for Responsible Genetics - NZ)

- Considers that the GM issue should be reconsidered in the light of the release of internal FDA documents made available for a recent lawsuit aimed at amending their policy. Attached document (presentation given by Steven Druker, Alliance for Bio-integrity) suggests that:
  - Scientist's warnings have been ignored

- FDA policy may be illegal, violating the Food, Drugs and Cosmetic Act – Mr Druker believes that the term generally-regarded-as-safe (GRAS) cannot apply to foreign DNA

Stephen Blackheath (NZ)

- Argues that ANZFA's approach to safety assessments is scientifically unsound:
  - Antibiotic resistance marker genes have been cited as being potentially dangerous by groups other than ANZFA e.g. the Royal Society
  - Unanticipated toxins and allergens are a concern, and it is suggested that the ANZFA process does not adequately consider these possibilities
  - Doesn't address the question of whether risks exist that are unique to the GM process
  - It relies on data from the manufacturers themselves, with little sway given to evidence from public submissions. Companies have vested interests the results and cannot be trusted (also gives evidence of Monsanto's past dishonesty)
- Believes that ANZFA is subject to undue influence through the directors, and is biased towards being pro-GM
- Suggests that RoundUp Ready soybeans are not substantially equivalent as the stems have been found to be more brittle than traditional lines, and may be lower in phytoestrogen content
- Also cites the lawsuit being brought by the Alliance for Bio-integrity, and the internal FDA documents that suggest concern from FDA scientists, as evidence of the FDA ignoring important evidence.

Claire Bleakley (NZ)

- Believes that approval should be rejected for various reasons:
  - They may be against Maori views
  - Further long-term trials are needed and should be carried out by ANZFA themselves - certain trials have apparently shown effects on immune system, allergies and rare syndromes
  - Health concerns of pesticide overuse
  - The possibility of horizontal gene transfer with respect to antibiotic resistance transfer
  - Lack of labelling and the use of the unsatisfactory 'substantial equivalence' concept, which makes hazard difficult to assess
  - There is no substantial gain to consumers.

ATTACHMENT 6

GENERAL ISSUES RAISED IN PUBLIC COMMENTS

The majority of submissions received in response to the Section 14 Gazette Notice, expressed general views against the use of gene technology, asserted that food produced using this technology is unsafe for human consumption and expressed opposition to the sale of the food, irrespective of the type of food concerned or the particular genetic modification. An evaluation of these general issues raised by the submissions appears below.

1. The safety of genetically modified foods for human consumption

A majority of submitters raised the issue of public health and safety in relation to food produced using gene technology. In particular, it was stated that there has been inadequate testing of genetically modified foods, that there is limited knowledge concerning the risks associated with the technology and that there may be potential long–term risks associated with the consumption of such foods.

Evaluation

It is a reasonable expectation of the community that foods offered for sale are safe and wholesome. In this context, 'safe' means that there is a reasonable certainty of no harm. As with other aspects of human activity, the absolute safety of food consumption cannot be guaranteed. Conventionally produced foods, while having a long history of safe use, are associated with human disease and carry a level of risk which must be balanced against the health benefits of a nutritious and varied diet.

Because the use of gene technology in food production is relatively new, and a long history of safe use of these foods has yet to be established, it is appropriate that a cautious approach is taken to the introduction of these foods onto the market. The purpose of the pre–market assessment of a food produced using gene technology under Standard A18 is to establish that the new food is at least as safe as existing foods. The comprehensive nature of the scientific safety assessment, undertaken on a case-by-case basis, for each new modification is reflective of this cautious approach.

The safety assessment focuses on the new gene product(s), including intentional and unintentional effects of the genetic modification, its properties including potential allergenicity, toxicity, compositional differences in the food and it's history of use as a food or food product.

Foods produced using gene technology are assessed in part by a comparison with commonly consumed foods that are already regarded as safe. This concept has been adopted by both the World Health Organisation (WHO)/Food and Agriculture Organisation (FAO) and the Organisation for Economic Cooperation and Development (OECD). The Authority has developed detailed procedures for the safety assessment of foods produced using gene technology that are consistent with international protocols developed by these bodies.

2. The need for long-term feeding studies

A number of submissions were concerned about the lack of long-term toxicity studies on genetically modified foods.

Evaluation

Animal studies are a major element in the safety assessment of many compounds, including pesticides, pharmaceuticals, industrial chemicals and food additives. In most cases, the test substance is well characterised, of known purity and of no nutritional value, and human exposure is generally low. It is therefore relatively straightforward to feed such compounds to animals at a range of doses (some several orders of magnitude above expected human exposure levels) in order to identify any potential adverse effects of importance to humans. Establishing a dose-response relationship is a pivotal step in toxicological testing. In this way it is possible, in most cases, to determine the levels of exposure at which adverse effects are not present and so establish safe upper limits through applying appropriate safety factors.

By contrast, foods are complex mixtures of compounds characterised by wide variations in composition and nutritional value. Due to their bulk, they can usually be fed to animals only at low multiples of the amounts that might be present in the human diet. Therefore, in most cases, it is not possible to conduct dose-response experiments for foods in the same way that these experiments are conducted for chemicals. In addition, a key factor to be considered in conducting animal studies on foods is the need to maintain the nutritional value and balance of the diet. A diet that is poorly balanced will compromise the interpretation of any feeding study, since the effects observed will confound and usually override any small adverse effect which may be related to a component or components of the food. Identifying any potentially adverse effects and relating these to an individual component or characteristic of a food can, therefore, be extremely difficult. Another consideration in determining the need for animal studies is whether it is appropriate from an ethical standpoint to subject experimental animals to such a study if it is unlikely to produce meaningful information.

If there is some reason to question the safety of a newly-expressed protein in a genetically-modified food, it is more appropriate to examine the safety of this protein alone in an animal study rather than when it is part of a whole food. For newly-expressed proteins in genetically-modified foods, the acute toxicity is normally examined in experimental animals. In some case, studies up to 14 days have also been performed. These can provide additional re-assurance that the proteins will have no adverse effects in humans. Such experiments can provide more meaningful information than similar experiments on the whole food. Additional re-assurance regarding the safety of newly-expressed protein can be obtained by considering the digestibility of the new protein in *in vitro* assays using conditions which simulate the human gastric system.

3. Substantial equivalence

A number of submitters expressed concern regarding the use of the concept of substantial equivalence. Some rejected the premise of substantial equivalence on the grounds that differences at the DNA level make foods substantially different.

Evaluation

Substantial equivalence embodies the concept that, as part of the safety assessment of a genetically modified food, a comparison can be made in relation to the characteristics and properties of the new and traditionally-produced food. This can include phenotypic[2] characteristics and compositional factors, as well as the levels of naturally occurring allergens, toxins and anti-nutrients.

This allows the safety assessment to focus on any significant differences between the genetically modified food and its conventionally produced counterpart. Genotypic differences (i.e. differences at the DNA level) are not normally considered in a determination of substantial equivalence, if that difference does not significantly change the composition of the new food relative to the conventional food.

The concept of substantial equivalence allows for an evaluation of the important constituents of a new food in a systematic manner while recognizing that there is a general acceptance that normally consumed food produced by conventional methods is regarded by the community as safe. It is important to note that, although a genetically modified food may be found to be different in composition to the traditional food, this in itself does not necessarily mean that the food is unsafe or nutritionally inadequate. Each food needs to be evaluated on an individual basis with regard to the significance of any changes in relation to its composition or to its properties.

The concept of substantial equivalence was first espoused by a 1991 Joint Consultation of the Food and Agricultural Organisation (FAO) and the World Health Organisation (WHO) where it was noted that the '*comparison of a final product with one having an acceptable standard of safety provides an important element of safety assessment*.'
The concept has been internationally recognised and embraced as a valuable tool in the safety assessment of foods produced using gene technology. The OECD also advocates an approach to safety assessment based on substantial equivalence as being '*the most practical to address the safety of foods and food components derived through modern biotechnology*.'

4. The nutritional value of food produced using gene technology

A small number of submitters expressed concern that the genetic alteration of food decreases its nutritional value.

Evaluation

The assessment of food produced using gene technology by ANZFA entails an exhaustive evaluation of technical data on any intentional or unintentional compositional changes to the food. This assessment encompasses the major constituents of the food (fat, protein, carbohydrate, fibre, ash and moisture) as well as the key nutrients (amino acids, vitamins, fatty acids). There is no evidence to suggest that genetic modification *per se* reduces the nutritional value of food.

In the future, it is proposed that genetic modification be used intentionally to improve the nutritional value of food. In this regard, GM foods may be able to assist in addressing the

[2] characteristics that are visible

general nutritional issues of the community and also specific dietary problems of sub-populations.

5. Potential toxins and allergens

Some submitters expressed concerns about the risks of the introduction of new toxins or allergens.

Evaluation

This issue is considered in detail as part of the safety assessment conducted on each new genetic modification applied to a food or commodity crop. New toxins or allergens may be introduced into food by either gene technology or by traditional breeding techniques, or by altered production processes. It is also possible to use these techniques to develop foods specifically where such compounds are significantly reduced or eliminated. One advantage of gene technology, in comparison with these other methods, is that any transferred genes are well characterised and defined, thus the possibility of developing a food with a new toxic or allergenic compound is likely to be reduced.

6. Antibiotic resistance

Some submitters raised concerns about increased antibiotic resistance resulting from the use of gene technology. Some felt that it would be reassuring if independent biomedical advice were available to reassure the public that the use of antibiotic resistance markers does not pose a risk to the future use of antibiotics in the management of human disease.

Evaluation

The human health considerations in relation to the potential for the development of antibiotic resistance depend on the nature of the novel genes and must be assessed on a case-by case basis. This issue arises because of the use of antibiotic resistance marker genes in the generation of genetically modified plants. In some circumstances, antibiotic resistance genes are linked to the gene of interest, to enable the initial selection of the engineered cells in the laboratory. Those cells that contain the antibiotic resistance marker gene, and hence the gene of interest, will be able to grow in the presence of the antibiotic. Those cells that failed the transformation process are eliminated during the selection procedure.

Concern has arisen that ingestion of food containing copies of antibiotic resistance genes could facilitate the transfer of the gene to bacteria inhabiting the gut of animals and humans. It is argued that these genes may then be transferred to disease causing bacteria and that this would compromise the therapeutic use of these antibiotics.

In 1993, the World Health Organisation Food Safety Unit considered this issue at a Workshop on the health aspects of marker genes in genetically modified plants. It was concluded at that Workshop that the potential for such gene transfers is effectively zero, given the complexity of the steps required. Since this time, several separate expert panels (Report to the Nordic Council, Copenhagen 1996; Advisory Committee on Novel Foods and Processes, UK 1994, 1996; The Royal Society, UK 1998) and numerous scientific papers published in peer reviewed journals have also considered the available evidence on this issue. It is generally agreed that the presence and subsequent transfer of an intact functional gene from transgenic

food to micro-organisms in the human intestine is an extremely unlikely event. Furthermore, if this were to occur, bacteria would not normally retain the resistance genes unless there was an environment for positive selection. The majority of these genes provide for resistance to antibiotics whose use is confined to the laboratory and are not considered to be of major therapeutic use in humans.

Antibiotic resistant bacteria are naturally occurring, ubiquitous and normally inhabit the gut of animals and humans. There is a general consensus that the transfer of antibiotic resistance genes is much more likely to arise from this source and from associated medical practices, rather than from ingested genetically modified food. Even so, at the recent OECD Conference (GM Food Safety: Facts, Uncertainties, and Assessment) held in Edinburgh on 28 February – 1 March 2000, there was general consensus that the continued use of antibiotic marker genes in GM food crops is unnecessary given the existence of adequate alternatives, and should be phased out.

7. Transfer of novel genes

Some submitters have expressed concern that the transfer of any novel gene may be a health concern.

Evaluation

It is extremely unlikely that novel genetic material will transfer from GM foods to bacteria in the human digestive tract because of the number of complex and unlikely steps that would need to take place consecutively. It is equally unlikely that novel genetic material will transfer from GM foods to human cells via the digestive tract. In considering the potential impact on human health, it is important to note that humans have always consumed large amounts of DNA as a normal component of food and there is no evidence that this consumption has had any adverse effect on human health. Furthermore, current scientific knowledge has not revealed any DNA sequences from ingested foods that have been incorporated into human DNA. Novel DNA sequences in GM foods comprise only a minute fraction of the total DNA in the food (generally less than 0.01%) and are therefore unlikely to pose any special additional risks compared with the large amount of DNA naturally present in all foods.

8. Viral recombination

Some submitters expressed concern about the long term effects of transferring viral sequences to plants.

Evaluation

This is an issue that is commonly raised because some of the genes that are transferred to plants use a plant virus promoter. Promoters are controlling DNA sequences which act like a switch and enable the transferred genes to be expressed (i.e. to give rise to a protein product) in a plant cell. The routine use of these viral promoters is often confused with research which has shown that plant virus genes, which have been transferred into plants to render them virus–resistant, may recombine with related plant viruses that subsequently infect the plant, creating new viral variants. This research demonstrates that there may be a greater risk to the environment if viral genes are transferred to plants because it may lead to the generation of

new plant virus variants capable of infecting a broader range of plants. This is a matter that will be addressed by the Genetic Manipulation Advisory Committee (GMAC) on a case–by–case basis when it assesses such plants.

However, the presence of plant viruses, plant virus genes or plant virus segments in food is not considered to pose any greater risk to human health as plant viruses are ubiquitous in nature and are commonly found in food eaten by animals and humans. Plant viruses are also biologically incapable of naturally infecting human or animal cells.

9. Labelling of foods produced using gene technology

A majority of submissions focussed on this issue. Specifically, the submissions called for the labelling of all foods produced using gene technology, regardless of whether they are substantially equivalent to conventional foods. The submitters based their demands for full labelling on the presumption that all foods produced using gene technology are unsafe and on consumer "right to know" arguments. It was stated that full labelling was the only means of identification of foods produced using gene technology available to consumers.

Evaluation

The existing Standard A18 already makes provision for mandatory labelling of genetically modified foods that are substantially different from their conventional counterparts. However, ANZFA is committed to implementing the in-principle decision of ANZFSC Health Ministers of August 1999 to require labelling of all genetically modified foods, including those that are substantially equivalent in composition to the unmodified form. In conjunction with a task force of officials from State and Territory Health Departments and the New Zealand Ministry of Health, ANZFA developed draft revision to Standard A18 in October 1999 that requires labelling of other categories of genetically modified foods. At the Ministers request this draft was circulated for public review and a cost-benefit analysis of full labelling was commissioned. The task force considered both public comments and the cost-benefit analysis in finalising their recommendations to Ministers, which were delivered in May 2000. Ministers are to meet to resolve the issue in July 2000 following whole-of-government consideration of the issue. It is therefore expected that, following a decision and legal amendments to the standard, labelling requirements will be implemented that will apply to all current and subsequent applications.

10. The need for post marketing surveillance of genetically modified foods

A number of submitters have commented on the need for post-market surveillance of genetically modified food consumption.

Evaluation

Surveillance of potential adverse or beneficial effects of GM foods is seen by many as a logical follow-up to the initial scientific risk assessment. Nevertheless, it is recognised that there are limitations to the application of epidemiology studies, particularly in relation to food components. A key requirement for post-market surveillance systems is that a clear hypothesis be identified for testing. Establishing a system for the surveillance of potential health effects of exposure to novel foods requires monitoring of the consumption patterns of novel foods in the population, and health effects in both "exposed" and "non-exposed" individuals/populations,

so that risk estimates can be derived. For any such monitoring system to be useful, there needs to be a range of exposures, otherwise, any variation in health outcome would be unexplainable by that exposure. Variations in exposure could be apparent over time (temporal trends), space (geographical trends) or both.

Availability of robust data on consumption of the foods in question is vital in order to establish a surveillance system. The other side of the equation is the need for access to data on population health outcomes. Such a system could also be used to identify potential positive health outcomes, such as improved nutritional status or lower cholesterol levels. The availability of linked basic data (e.g. date of birth, sex, geographical location), and the ability to correlate with demographic data, could potentially offer the means of establishing links with food consumption.

The possibility of setting up a post-market health surveillance system for novel foods, including GM foods, has been examined by the UK's Advisory Committee on Novel Foods and Processes (ACNFP). Recognising the many difficulties involved in developing such a system, an initial feasibility study to look at the available data and its usefulness has been proposed. Work is currently being commissioned; when completed in 18 months, it will be subject to peer review. If such a feasibility study suggests that post-market surveillance is practical, methods and details concerning data collection will be determined in the UK, but common strategies might be able to be harmonised internationally in order to minimise the use of resources while maximising the reliability of the final results. This is an area that ANZFA will be monitoring closely, along with international regulatory bodies such as the OECD Taskforce for the Safety of Novel Foods and Feeds.

11. Public consultation and information about gene technology

A number of submitters were concerned that the public has not been properly consulted or informed by government or ANZFA on the introduction of foods produced using gene technology. Some submitters urged to undertake wider consultation with all affected parties including growers, the food industry and consumers before these food commodities are introduced, and to ensure that adequate consultation is undertaken as part of its assessment process.

Evaluation

The issue of gene technology and its use in food has been under consideration in Australia since 1992. The Agreement between the Governments of Australia and New Zealand for a joint food standard setting system, however, did not occur until 1995, and the New Zealand community therefore had not been consulted on this matter by the Authority until after that time. Consequently, the proposed standard (the current Standard A18) underwent only one round of public comment in New Zealand at which time significant objections were raised by the New Zealand community to the use of gene technology in food production. Many New Zealand consumers, both in these submissions, and in previous submissions to the Authority, have expressed the view that there has been insufficient consultation and a consistent lack of information about gene technology.

Although Standard A18 came into force in May 1999, the public have a continuous and ongoing opportunity to provide comment in relation to applications under the standard. ANZFA's statutory process for all applications to amend the *Food Standards Code* normally

involves two rounds of public comment. Furthermore, all the documentation (except for commercial in confidence information) relating to these applications is available in the public domain, including the safety assessment reports. There is ample evidence that the provision of such information by ANZFA has already significantly stimulated public debate on this matter.

In addition, other government departments including the Environmental Risk Management Authority (ERMA), are potential sources of information about gene technology available to consumers in New Zealand. ERMA is a statutory authority set up by the New Zealand Government to administer the *Hazardous Substances and New Organisms (HSNO) Act 1996*, and has responsibility for assessing the risks to the environment from genetically modified organisms. This body has been assessing applications for the approval of genetically modified organisms since July 1998 and this has involved a number of public meetings.

In response to the concerns raised in public submissions with regard to gene technology and GM foods, ANZFA has prepared a public discussion paper on the safety assessment process for GM foods called "GM Foods and the Consumer". This is available off the ANZFA website (www.anzfa.gov.au) or from the ANZFA Information Officer and may assist in addressing some of the concerns raised by the public. Other government and industry bodies are also addressing the broader concerns in relation to gene technology.

12. Maori beliefs and values

Some New Zealand submitters stated that Maori people find genetic engineering in conflict with their beliefs and values and that, out of respect to Maori, no genetically modified foods should be allowed into New Zealand until a wider discussion, both within Maori and non–Maori, is held.

Evaluation

This issue was also raised during consideration of the proposal for the establishment of Standard A18. At that time, it was stated that the likely implications for Maori regarding genetically modified organisms surround the issues of the rights of Maori to the genetic material from flora and fauna indigenous to New Zealand and the release into the environment of genetically modified organisms. The *HSNO Act 1996* requires that these matters be considered by ERMA.

13. Environmental concerns and the broader regulatory framework

A number of submitters have raised concerns that genetically modified crops may pose a risk to the environment.

Evaluation

These issues are considered in the assessment processes of GMAC in Australia and the Environmental Risk Management Authority (ERMA) in New Zealand. The Authority does not have the mandate to assess matters relating to environmental risks resulting from the release of food produced using gene technology into the environment. However, links exist between ANZFA and other regulatory agencies in both Australia and New Zealand, and a large degree of information sharing occurs. ANZFA would not recommend the approval of a food produced using gene technology if the genetically modified organism from which it was

derived did not have the appropriate clearance for general release from either GMAC (or its successor) or ERMA, as appropriate.

The regulatory system in Australia will comprise the existing regulators with a legal remit to cover some aspects of GM products (such as imports, food, agricultural and veterinary chemicals):

- the Australia New Zealand Food Authority (ANZFA)
- the Therapeutic Goods Administration (TGA)
- the National Registration Authority for Agricultural and Veterinary Chemicals (NRA)
- the National Industrial Chemicals Notification and Assessment Scheme (NICNAS)
- the Australian Quarantine and Inspection Service (AQIS).

Similarly, various other departments and agencies play their role in the regulatory process in New Zealand:

- the Ministry of Agriculture and Fisheries (MAF)
- the Ministry of Health (MoH)
- the Ministry of Research, Science and Technology (MoRST)

In Australia a new Office of the Gene Technology Regulator (OGTR) will complement the existing arrangements. OGTR will supersede the existing arrangements under the Genetic Manipulation Advisory Committee (GMAC), which advises on research and environmental release of GMOs. OGTR will regulate all GMOs and any 'gap' products (i.e. products for which no other regulator has responsibility).

All GM food is assessed and regulated by the Australia New Zealand Food Authority (ANZFA) under the direction of Commonwealth, State and Territories Health Ministers and the New Zealand Health Minister, sitting as Australia New Zealand Food Standards Council (ANZFSC).

There will be an interface between ANZFA and OGTR. Consequential amendments proposed to the ANZFA Act arising from the draft Gene Technology Bill 2000 will establish a statutory interface between OGTR and ANZFA. This will involve amendments to the ANZFA Act requiring the Authority to advise OGTR of recommendations to ANZFSC regarding the standard for foods produced using gene technology (currently Standard A 18).

14. Maximum residue levels

A number of submitters have raised concerns that residues of agricultural and veterinary chemicals in genetically modified (e.g. herbicide tolerant) crops may pose a health risk.

Evaluation

Residues of these chemicals can only legally be present if the chemical has been registered for use in Australia and/or New Zealand, and it has been demonstrated that the residue at specified levels does not lead to adverse health impacts. The concentration of a chemical residue that may be present in a food is regulated through maximum residue limits (MRLs). The MRL is the highest residue concentration that is legally permitted in the food. Food products have to meet the MRL, whether or not they are derived from genetically modified organisms. The

MRL does not indicate the chemical residue level that is always present in a food, but it does indicate the highest residue level that could result from the registered conditions of use.

It is important to note that MRLs are not direct public health and safety limits but rather, are primarily indicators of appropriate chemical usage. MRLs are always set at levels lower than, and normally very much lower than, the health and safety limits. The MRL is determined following a comprehensive evaluation of scientific studies on chemistry, metabolism, analytical methods and residue levels. In Australia, the National Registration Authority (NRA) applies to ANZFA to amend the MRLs in the Food Standards Code and the application is considered by ANZFA through its legislated decision making processes. In New Zealand MRLs are set by the Ministry of Health， generally following a request from, and in collaboration with, the Ministry of Agriculture and Forestry. Only following demonstration that the use of agricultural and veterinary chemicals will not result in unsafe residues will the MRL enter into food law through its inclusion in either the Food Standards Code in Australia, or the New Zealand (Maximum Residue Limits of Agricultural Compounds) Mandatory Food Standard 1999.