FINAL RISK ANALYSIS REPORT

APPLICATION A363

Food produced from glyphosate-tolerant canola line GT73

Note:

This report is the "Inquiry" as referred to in Section 17 of the *Australia New Zealand Food Authority Act (1991)* and sets out the reasons for making a recommendation to the Australia New Zealand Food Standards Council under Section 18 of the Act.

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EXECUTIVE SUMMARY

Background

An application was received from Monsanto Australia Ltd on 10 September 1998 for the approval of food from genetically modified canola seed. The canola has been genetically modified to confer tolerance to the herbicide glyphosate. Glyphosate-tolerant canola is known commercially as Roundup Ready canola. This report describes the scientific assessment of the application and the safety of the final food fraction.

Issues addressed during safety assessment

(i) Safety evaluation

Glyphosate-tolerant canola has been assessed by ANZFA according to the safety assessment guidelines for foods produced using gene technology. This involves an extensive analysis of the nature of the genetic modification together with a consideration of general safety issues, toxicological issues and nutritional issues associated with the new GM food. This approach can establish whether the foods produced from the glyphosate-tolerant canola are as safe and nutritious as foods produced from non-GM varieties of canola.

Two genes were transferred to canola to confer tolerance to applications of the herbicide glyphosate. There were no issues of concern regarding the source of the novel genes or of their protein products and expression in the plant. Additionally, the evidence did not indicate that there are any unintended effects associated with the genetic modification of the canola plant. Both genes are transferred to the canola genome as a single insert and are stably inherited from one generation to the next over multiple generations.

Neither of the novel proteins expressed in glyphosate-tolerant canola were found to have physical or structural characteristics that are typical of known food allergens or toxins and are not considered to pose any safety concern to humans. Similarly, the breakdown products of glyphosate metabolism are also not considered to pose any safety concerns.

An evaluation of the major constituents, nutrients, anti–nutritional factors and natural toxicants of glyphosate tolerant canola line and conventional canola lines found no significant differences between the lines. An assessment of canola oil found it to be comparable to oil derived from conventionally produced canola in all respects.

Additionally, the only product derived from canola for human consumption is highly refined oil, which undergoes extensive processing such that all protein and DNA are removed. Consideration of all the above information has led to the conclusion that oil derived from glyphosate-tolerant canola does not pose any safety or public health concerns.

Canola meal is not considered to be a human food fraction due to the presence of the natural toxicants, erucic acid and glucosinolates and was evaluated to compare levels

of major components to determine any potentially unintended effects. Canola meal, whether genetically modified or not, is not regarded as a food fraction and the genetic modification does not change this pattern of consumption.

(ii) Labelling

Under the current Standard A18, oil derived from glyphosate-tolerant canola line GT73 would not require labelling as it can be regarded as substantially equivalent to oil from conventionally produced canola.

Under proposed amendments to Standard A18, it is possible that some genetically modified foods may require labelling once these amended provisions take effect. However, as no protein or DNA are likely to be present in canola oil, it may be exempt from labelling under the revised Standard A18.

(iii) Public submissions

The assessment of this application underwent two rounds of public comment. Fifty-eight submissions were received in the first round and 26 were received in the second round. The majority of submissions were not supportive of the application.

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 in the draft safety assessment report.

Conclusions

ANZFA considers that oil derived from glyphosate-tolerant canola GT73 is as safe for human consumption as oil from other commercial canola varieties, and therefore recommends that the Australian *Food Standards Code* be amended to give approval to the sale of such food in Australia and New Zealand. Canola meal is not considered a human food fraction, whether or not it is sourced from genetically modified canola.

ANZFA also considers that as oil derived from glyphosate-tolerant canola is substantially equivalent to oil derived from non-genetically modified canola, no mandatory labelling is required.

INTRODUCTION

The Australia New Zealand Food Authority (ANZFA) is a bi-national statutory body responsible for making recommendations on food standards which, when approved by the Australia New Zealand Food Standards Council (ANZFSC), are adopted by reference and without amendment into food law. ANZFA is currently working to establish a joint *Australia New Zealand Food Standards Code* that will apply in both countries. In the interim, a system of dual standards operates for the majority of the food standards. Standard A18 – Food Produced using Gene Technology has been accepted by New Zealand, and currently applies in both countries.

Standard A18 was adopted by ANZFSC as a joint Australia/New Zealand standard in July 1998 and came into force on 13 May 1999. Under this Standard, the sale of food produced using gene technology is prohibited unless the food is included in the Table to clause 2 of the Standard. The Standard requires that a pre-market safety assessment be conducted on all foods produced using gene technology. However, the Standard provides an exemption for those foods currently on the market provided that an application was accepted by ANZFA on or before 30 April 1999, that the food is lawfully permitted in a country other than Australia or New Zealand, and that ANZFSC has not become aware of evidence that the food poses a significant risk to public health and safety.

It is likely that the proposed amendments to Standard A18 will require labelling of genetically modified foods that previously did not require labelling.

BACKGROUND TO THE APPLICATION

ANZFA received an application from Monsanto Australia Ltd on 10 September 1998 to amend the Australian *Food Standards Code* to include food derived from glyphosate-tolerant canola line GT73 in the Table to clause 2 of Standard A18 – Foods Produced Using Gene Technology.

The single genetically modified canola line GT73, is able to survive applications of the herbicide glyphosate as a result of the transfer of two genes. These genes encode for enzymes that have distinct modes of action to confer glyphosate tolerance: the first is an enzyme whose activity is not inhibited by applications of glyphosate and the second is an enzyme that can degrade the herbicide. Both genes are bacterially-derived and were transferred to the parental canola variety Westar using an *Agrobacterium*-mediated transformation system.

The 5-enolpyruvylshikimate-3-phosphate synthase (CP4 EPSPS) gene confers glyphosate tolerance to canola because this enzyme can function under applications of glyphosate unlike plant-derived forms, which are sensitive to glyphosate.

The glyphosate oxidoreductase (*gox*) gene encodes the GOX protein, which confers additional glyphosate tolerance to canola because it degrades glyphosate to aminomethylphosphonic acid (AMPA) and glyoxylate.

No antibiotic resistance genes were transferred to canola.

The principle food product from canola is refined, bleached and deodorised oil (RBDO). Processing of canola seed to oil involves the removal of all DNA and protein which effectively results in the removal of the CP4 EPSPS and GOX proteins from the food fraction.

Currently, glyphosate-tolerant canola is not grown commercially in Australia or New Zealand but is undergoing assessment with the Office of the Gene Technology Regulator (OGTR) for commercial growing in Australia. The principle food product is oil and can be used in a variety of other manufactured foods such as salad and cooking oil, margarine, shortening, mayonnaise, sandwich spreads, creamers and coffee whiteners.

This genetic modification aims primarily to assist in agricultural production only, with no intention to alter any characteristic or property of the oil derived from the canola. The applicant claims that cultivation of glyphosate-tolerant canola will allow efficacious and environmentally compatible control of weeds. It is suggested that the improved control of weeds through the use of glyphosate will reduce production costs for growers and these savings may have a flow on effect in the rest of the industry.

PUBLIC CONSULTATION

The Authority received the first six applications for foods produced using gene technology from Monsanto Australia Ltd. Due to commonalities in these applications, a combined Notice of Application (formally referred to as the Preliminary Assessment Report) was advertised on 28 October 1998, which called for public comment on the applications. A total of 58 submissions were received in response to the combined Notice of Application, of which 53 relate to this application. The submissions were primarily from individuals, consumer organisations and special interest groups from both New Zealand and Australia. The submissions are summarised in Attachment 5.

ANZFA then conducted an assessment of the application, including a safety evaluation of the food, taking into account the comments received. A draft risk analysis report was released for public comment on 19 June 2000. A total of 26 submissions were subsequently received in response to the release of this report. Attachment 6 contains a summary of the second round public comment.

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 Technological 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 were therefore notified to the WTO.

ISSUES ADDRESSED DURING ASSESSMENT

1. Safety assessment

The food safety of glyphosate-tolerant canola has been assessed according to the safety assessment guidelines prepared by ANZFA[1]. The safety assessment considers: the nature of the genetic modification; (2) general safety issues such as novel protein expression and the potential for transfer of antibiotic resistance genes to gut microorganisms; (3) toxicological issues; and (4) nutritional issues.

Nature of the genetic modification

Two genes were transferred to the glyphosate-tolerant canola line GT73 using an *Agrobacterium*-mediated transformation system. The transferred genes - the CP4 EPSPS and *gox* genes confer tolerance to the herbicide glyphosate. Both genes are bacterially-derived and have distinct modes of action. The CP4 EPSPS gene encodes a 5–enolpyruvyl shikimate–3–phosphate synthase enzyme that is not sensitive to applications of glyphosate and the *gox* gene encodes the glyphosate oxidoreductase enzyme that can degrade the herbicide.

There were no issues of concern raised about the origin of the genes and their protein products. Additionally, there was no evidence to indicate that there were any unintended effects associated with the modification.

The molecular and genetic analyses indicated that the introduced genes for the CP4 EPSPS and *gox* genes have been stably transferred into the plant genome and are stably inherited from parent to offspring over several generations.

General safety issues

The introduced proteins are present in very low levels in the canola seed and therefore their potential consumption prior to any processing is likely to be very small. Given that oil is highly processed and protein is removed from the final food fraction, oil is not considered to contain any protein (or DNA).

It is important to note that only canola oil from glyphosate-tolerant canola has been assessed for human consumption and that canola meal, whether genetically modified or not, is not considered fit for human consumption due to naturally occurring toxicants. The genetic modification of canola line GT73 will not change this pattern of consumption and therefore the dietary exposure to genetically modified canola oil is expected to be as for other commercially available canola lines.

This glyphosate tolerant canola line GT73 presents no risk of the transfer of antibiotic resistance genes to gut microorganisms as there are no antibiotic resistance genes present in the genetically modified canola line.

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[1] ANZFA (1999) Guidelines for the safety assessment of foods to be included in Standard A18 – food produced using gene technology.

Toxicological Issues

The toxicity and allergenicity of the novel proteins, CP4 EPSPS and GOX, as well as the levels of naturally occurring toxins in canola were evaluated in this assessment.

The novel proteins expressed in glyphosate-tolerant canola do not possess any characteristics of known allergens or toxins as determined by amino acid sequence comparisons and lack of other physical or chemical features. No signs of toxicity were observed in mice exposed to high doses of these proteins. In addition, the proteins were rapidly digested upon exposure to model mammalian digestive systems. It is concluded that there is no evidence for any potential toxicity or allergenicity for either of the novel proteins in humans.

The levels of naturally occurring toxicants, erucic acid and glucosinolates, were assessed against the levels found in conventional canola lines. The erucic acid levels in the glyphosate-tolerant canola line were found to be consistently lower than that found in the control line. Glucosinolate levels in canola meal were found to be higher than the canola meal from the control line but were well below the industry standard. This difference is not attributed to the genetic modification and is considered to reflect the natural variation that occurs in canola.

Nutritional Issues

The comprehensive compositional analyses indicate that there are no significant differences in the levels of major constituents, nutrients or anti-nutritional factors between the glyphosate-tolerant canola line and the control canola line. The major constituents examined were protein, fat, moisture, fibre, ash, carbohydrates, calories, amino acid and fatty acid profile. Analyses of sinapines, mineral and phytic acids were also evaluated.

Analysis of the refined bleached and deodorised oil, which is the only product for human consumption derived from glyphosate tolerant canola, indicated the composition to be comparable, in all respects, to the control line.

Feeding studies using canola meal were carried out in rat, trout and quail. No differences were detected between trout and quail fed glyphosate-tolerant canola diets and control diets.

Differences in liver weight were observed in rats fed the genetically modified canola line compared to the parental line but these differences were not considered to arise as a result of the genetic modification of canola. This difference has been attributed to a higher level of glucosinolates in the glyphosate-tolerant canola than in control line. There were no other differences noted between control and test animals. It is important to note that canola meal is not eaten by humans because of the naturally occurring toxicants, erucic acid and glucosinolates.

Conclusion

No potential public health and safety concerns have been identified in the assessment of glyphosate-tolerant canola line GT73. Oil derived from glyphosate-tolerant canola line GT73, can be regarded as equivalent to oil derived from conventional canola in respect of its composition, safety and end use.

2. Labelling of food derived from glyphosate-tolerant canola

Clause 3 of Standard A18 prescribes mandatory labelling of a food produced using gene technology when it contains new or altered genetic material and where it is not substantially equivalent in any characteristic or property of the food. As the oil derived from glyphosate-tolerant canola has been found to be equivalent in terms of its nutritional value and safety compared to the oil from the parental variety of canola, there is no requirement for mandatory labelling under the current standard.

It should be noted, however, that the labelling provisions in Standard A18 are in the process of being amended and will require labelling of genetically modified foods that contain novel DNA and/or protein (with some exemptions). These proposed amendments may result in some products derived from foods produced using gene technology being labelled in the future.

3. Issues arising from public submissions

3.1 General issues

Six applications, including this application, were combined in the Notice of Application and most of the comments received by ANZFA did not specifically address an individual application. Many of the submissions received in both the first and second rounds of public comment 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

Issues raised in first round of public comment (see Attachment 5 for summary)

(i) Outcrossing potential for Brassica *species*

Bridget Thrussell (NZ) is concerned about gene transfer between glyphosate-tolerant canola and other *Brassica* species.

Response

ANZFA is responsible for developing food safety and public health standards. The Genetic Manipulation Advisory Committee and OGTR assess the environmental impact of genetically modified organisms. The potential for genetically modified crops to outcross with related species is considered in detail by GMAC in their environmental assessment of genetically modified organisms.

(ii) The consumption of unprocessed seeds that are normally processed into oils

Australian GeneEthics Network (Aus) raised the issue that not all glyphosate-tolerant canola oils are extensively processed to remove DNA and protein before human consumption. They indicated that the assessment does not take into account the use of whole seeds for sprouting, the inclusion of whole seeds in uncooked foods, and the cold pressing of oils.

Response

Canola contains natural toxicants that are not removed without processing. Whole or raw canola seed or canola meal are not considered human food fractions due to the presence of the naturally occurring anti-nutritional and toxic compounds erucic acid and glucosinolates.

Only oil derived from glyphosate-tolerant canola is being assessed in this application. Canola meal is not a human food fraction and canola seeds are not normally consumed whole or raw. The genetic modification of canola line GT73 does not change the pattern of consumption. Thus the dietary exposure to genetically modified canola oil is expected to be as for other commercially available canola lines.

Furthermore, the novel proteins have been assessed for their toxicity and allergenic potential and they are not considered to pose any significant risk to human health and safety, even if present in the oil. The consumption of whole or raw canola seed, whether genetically modified or not, would be of great concern given the presence of the toxicants and would not be recommended for human consumption.

(iii) Increase in anti-nutrient levels over time

The Consumers' Federation of Australia Incorporated is concerned that anti–nutrient levels in canola are safe and that they will not rise over time

Response

The assessment of the introduction of novel genetic material into glyphosate-tolerant canola found that the DNA is stably inserted into the canola genome. The anti-nutrient levels in the genetically modified canola have not increased over the three years of field trials conducted. There is no reason to expect that nutrient, anti-nutrient or toxicant levels are likely to change over time, apart from natural variation that may occur particularly under different environmental conditions.

Additionally, erucic acid in canola oil must not exceed the maximum permitted level as specified in the Australian Food Standards Code.

(iv) Trade issues

Elaine Attwood (Aus) believes that canola oil free of genetic modification would be [more] marketable overseas.

Response

ANZFA's role is in evaluating the safety of food and ensuring the consumer's right to make an informed decision. ANZFA cannot influence issues that are outside the scope of food safety.

Issues raised in second round of public comment (see Attachment 5 for summary)

(i) The significance and metabolism of AMPA

The New Zealand Ministry of Health, the (New Zealand) Environment and Scientific Research Institute raised the issue of the fate of the glyphosate breakdown product aminomethylphosphonic acid (AMPA). The Australian GeneEthics Network was also concerned about glyphosate residues in canola.

Response

The applicant provided studies that demonstrated that AMPA has minimal toxicity in acute and subchronic toxicity studies. Animal metabolism and feeding studies demonstrated that AMPA is rapidly eliminated and does not bio-accumulate in edible tissues, milk or eggs. Furthermore, no AMPA (or glyphosate) was present in the oil derived from canola seed. This data is detailed in the Safety Assessment Report (Attachment 2), Section 6 Other Issues.

(ii) Increased alkyl glucosinolate levels in GM canola meal and related increase in liver weight in rats fed GM canola meal

The National Council of Women of Australia, the Dietition's Association of Australia, the Australian GeneEthics Network, the Canberra Consumer, the New Zealand Ministry of Health, the (New Zealand) Environment and Scientific Research Institute and the South Australian Department of Human Services raised concerns about the increase in alkyl glucosinolates in GM canola and the related increased liver weight observed in rats fed genetically modified canola meal that wasn't observed in rats fed control line canola meal. Several submitters were concerned that consumption of canola meal could have adverse health effects and that the increase in liver weight was a health risk.

Response

Glucosinolate levels in canola can vary enormously and can be influenced by growth and environmental factors as well as the variety grown. The cultivar Westar is made up of a heterogeneous plant population which exhibits enormous variability. The genetically modified line GT73 was developed from a single plant that was selected from this heterogeneous population and the variation observed in glucosinolate content in the genetically modified plant can be expected for any line developed from a single plant selected from this population.

As outlined in the Safety Assessment report, breeders have been working to produce varieties that contain low levels of glucosinolates since they have been linked to enlargement of the thyroid, adrenal gland, kidney and liver in feeding studies using rapeseed (Verkerk et al, 1998). In the early stages of canola breeding, glucosinolate levels between 70-100 μmole/g meal and higher would have been observed. Modern

canola varieties that have achieved less than 30 µmoles glucosinolate content in the meal are considered to be low glucosinolate varieties and acceptable for animal feed.

Although liver weights were increased 12-16% in rats fed GT73 meal, livers appeared normal at gross necroscopy. The increase in liver weight has been attributed to a higher level of alkyl glucosinolate toxicants in the glyphosate-tolerant canola. Liver weights can vary and this can be an adaptive change that is indicative of a higher level of metabolic activity. Increased liver weight is commonly observed in toxicity studies, when it is often considered a physiological adaptation (if dose related), that reaches a steady state with continued dosing and is reversible after cessation of treatment. It is not necessarily harmless in itself (Glaister, 1986). Canola line GT73 contains glucosinolate levels well below the limit established for the safe use of meal derived from canola seed as animal feed. Although the value of alkyl glucosinolates in GT73 may be on the higher side of the range observed for Westar, it is well below the harvest survey value (17 umol/g in 1992 and 14 umole/g in 1993) for commercially produced No. 1 Canada canola.

Additionally, it is a significant point that canola meal is not a food fraction that is used for human consumption and approval for meal will not occur. Canola oil, from which glucosinolates are removed during processing, will be the only product approved for food use in Australia and New Zealand, as reflected in the drafting that refers to "oil derived from canola line GT73".

(iii) Approval should only be for canola oil

The Dietition's Association of Australia and the South Australian Department of Human Services have stated that only the oil should be given approval.

Response

Canola oil is the only food fraction that is considered fit for human consumption because of naturally occurring toxins such as erucic acid and glucosinolates, as indicated by the drafting. The genetic modification of canola does not change this view.

4. Risk management

Under Standard A18, a genetically modified food must undergo a 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 3 of the standard.

On the basis of the conclusions of the safety assessment report, together with a consideration of the public submissions, it is proposed that Table 1 to clause 2 of Standard A18 be amended to include food from glyphosate-tolerant canola line GT73. The proposed amendment is provided in Attachment 1.

In terms of the labelling of the food, the safety assessment report found that glyphosate-tolerant canola line GT73 is substantially equivalent to other

commercially available canola lines in terms of its safety and nutritional adequacy. Therefore, under the current standard, no mandatory labelling is required.

In relation to the concerns raised in the public submissions with regard to gene technology and GM food, ANZFA has prepared a public discussion paper on the safety assessment process for genetically modified food[2]. This 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 have been analysed in a draft Regulatory Impact Statement (Attachment 3). The benefits of the proposed Standard A18 amendment to approve food from glyphosate tolerant canola primarily accrue to the food industry and government, with potentially a small benefit to the consumer.

CONCLUSIONS

It is concluded that:

- the introduction of the novel genes in glyphosate-tolerant canola does not produce any additional public health and safety risk;
- based on the data submitted in the present application, the human food fraction, oil, is found to be substantially equivalent to oil derived from traditionally bred canola varieties;
- under the current Standard, labelling would not be required for oil from glyphosate-tolerant canola. Proposed amendments to the labelling provision of Standard A18 currently under consideration could result in some glyphosate-tolerant canola food products being labelled in the future; and
- the benefits of the proposed amendment are primarily to the grower, food industry and government with a small benefit to the consumer. Overall, the benefits of the proposed amendment outweigh the costs.

ATTACHMENTS

1. Variation to the Australian *Food Standards Code*
2. Final safety assessment report
3. Regulatory impact assessment
4. World Trade Organisation Agreements
5. Summary of public comments
6. General issues raised in public comments

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

ATTACHMENT 1

DRAFT VARIATION TO THE AUSTRALIAN FOOD STANDARDS CODE

A363 - OIL FROM GLYPHOSATE-TOLERANT CANOLA

Standard A18 *is varied by inserting into Column 1 of the Table to clause 2 -*

Oil derived from glyphosate-tolerant canola line GT73.

If Standard 1.5.2 has been adopted by the Ministerial Council at the time this recommendation is considered, the following applies -

To Commence: on gazettal

Standard 1.5.2 *is varied by inserting into Column 1 of the Table to clause 2 -*

Oil derived from glyphosate-tolerant canola line GT73.

ATTACHMENT 2

FINAL SAFETY ASSESSMENT REPORT

A363 – FOOD DERIVED FROM GLYPHOSATE-TOLERANT CANOLA LINE GT73

SUMMARY AND CONCLUSIONS

The glyphosate-tolerant canola line GT73 has been assessed by ANZFA to evaluate its safety in food. A number of criteria are used in this assessment including a characterisation of the genes, their origin and function, the changes at the DNA, protein and whole food levels, stability of the introduced genes in the canola genome, compositional analyses, evaluation of intended and unintended changes and the potential of the newly expressed proteins to be allergenic or toxic.

Nature of the genetic modification

One genetically modified canola line (GT73) was generated by the transfer of the CP4 EPSPS and gox genes which confer glyphosate tolerance to the plant. The protein products are both enzymes that have a distinct mode of action. The CP4 EPSPS enzyme is not sensitive to applications of glyphosate and the GOX protein can degrade the herbicide providing additional tolerance.

The molecular and genetic analyses indicated that the introduced genes have been stably integrated into the plant genome and were stably inherited for multiple generations.

General safety issues

The novel CP4 EPSPS and GOX proteins were detected in the seed at low levels (>0.02% fresh weight). Additionally, the only canola product considered to be a human food fraction is oil which has no DNA or protein present as they are removed during processing.

The glyphosate-tolerant canola line GT73 does not contain any antibiotic resistance genes and therefore poses no risk to the development of antibiotic resistant pathogenic bacteria.

Toxicological issues

The newly expressed CP4 EPSPS and GOX proteins in the glyphosate-tolerant canola lines have been evaluated for their potential toxicity. Neither protein possesses any characteristics of known toxins. No signs of toxicity were observed in mice exposed to doses of these proteins 1000 fold greater than likely human exposure.

In addition, exposure of the proteins to simulated mammalian digestive systems resulted in rapid digestion of the proteins. The proteins do not have chemical or physical characteristics that are typical of known food allergens and do not share significant amino acid sequence similarity with known allergens. Therefore, there is no evidence for any potential toxicity or allergenicity for either protein in humans.

Nutritional issues

The compositional analyses were comprehensive and demonstrate that there are no

significant differences in the levels of major constituents, nutrients, anti-nutritional factors or natural toxicants between glyphosate-tolerant canola line GT73 and the control canola line Westar. The components measured were proximate (protein, fat, moisture, fibre, ash, carbohydrates and calories), fatty acids and amino acids.

The major toxicants and anti-nutrient factors in canola were also assessed. Erucic acid levels in the canola oil were lower than in parental canola lines and glucosinolate levels in canola meal were higher than the control line but within an accepted industry standard.

Analysis of the refined, bleached and deodorised oil, which is the only product for human consumption, demonstrated that the composition is comparable, in all respects, to the control Westar line.

These analyses confirm that glyphosate-tolerant canola line GT73 is nutritionally and compositionally comparable to other canola lines and that no health or safety risks are posed by consuming food derived from the genetically modified canola.

Conclusion

No potential public health and safety concerns have been identified in the assessment of glyphosate-tolerant canola GT73 which will be marketed as Roundup Ready canola. Based on the data submitted in the present application, food derived from glyphosate-tolerant canola line GT73, refined oil, can be regarded as equivalent in terms of its safety and nutritional adequacy to food derived from conventional canola.

1. BACKGROUND

Monsanto Australia Ltd have made an application to ANZFA to vary Standard A18 of the *Food Standards Code* to include food derived from canola which has been genetically modified to be tolerant to the herbicide glyphosate. The genetically modified canola plants are known commercially as Roundup Ready canola.

The glyphosate-tolerant phenotype has been developed in canola through two distinct mechanisms: firstly, the introduction of an enzyme that is not sensitive to applications of glyphosate and secondly, the introduction of an enzyme that can degrade the herbicide. Monsanto Ltd developed the genetically modified canola for cultivation in the United States, Canada and potentially Australia. Canola based products produced from these plants may have been imported into Australia and New Zealand for several years.

Canola seeds are processed into two major products, oil and meal. The oil is the only product for human consumption and the only product assessed for approval in this application. Toasted meal is used as an animal feed. Canola seed oil is a premium quality oil that is used in a variety of manufactured food products including salad and cooking oil, margarine, shortening, mayonnaise, sandwich spreads, creamers and coffee whiteners. As a result of the processing steps, canola oil contains negligible protein. Canola oil may be present as an ingredient in some imported processed foods.

Canola (Brassica napus) is a leading oilseed crop because it has a good ratio of fatty acids comprising a very low level of saturated fatty acids, a moderate level of polyunsaturated fatty acids and a high level of the monounsaturated fatty acid, oleic acid (McDonald, 1999). It is also considered an important export crop in Australia. Over 550 000 tonnes of canola were produced in 1995-1996 with over 60% being exported. All new canola oil varieties including canola from glyphosate-tolerant canola line GT73 must meet CODEX specifications for oil quality. All canola varieties that meet CODEX specifications also meet specifications for canola as outlined in the Australian *Food Standards Code.*

2. DESCRIPTION OF THE MODIFICATION

2.1 Methods used in the genetic modification

Monsanto have submitted the following report:

Kolacz, K.H. et al. 1994. Glyphosate-tolerant canola: plant transformation vectors and transformation procedure. Monsanto Company, USA 63198.

Using *Agrobacterium*-mediated transformation, the parental canola line (Westar) was transformed with the plasmid, PV-BMNGT04 which carries the *gox* and CP4 EPSPS genes. Both genes allow the selection of transformed plants under application of glyphosate.

Glyphosate-tolerant canola line GT73 was produced by the above transformation event as a result of the transfer of the following genes:

. The 5-enolpyruvylshikimate-3-phosphate synthase (CP4-EPSPS) gene from *Agrobacterium sp*. strain CP4 EPSPS under the control of the modified figwort mosaic virus 35S promoter.

. the glyphosate oxidoreductase (*gox*) gene from *Ochromobactrum anthropii* strain LBAA [previously *Achromobacter sp*] under the control of the modified figwort mosaic virus 35S promoter. The gene encodes the GOXv247 variant protein.

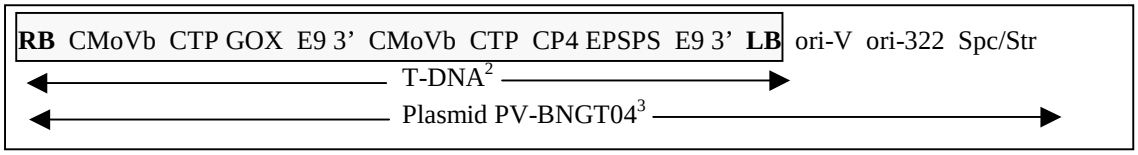
The *Agrobacterium* mediated DNA transformation system is well understood (Zambryski, 1992). The genes of interest were inserted into the plasmid between DNA sequences known as the Left and Right Borders (LB and RB). These sequences have been isolated from Ti plasmids from *Agrobacterium* and are 25 base pair repeat sequences. The Left and Right Borders delimit the DNA to be transferred (T-DNA), which includes the CP4 EPSPS and *gox* genes.

Genes outside the Left and Right Border segments are generally not transferred during the transformation. The genes in the plasmid outside the border sequences are:

. the vegetative origin of replication (ori-V) that permits plasmid replication in *Agrobacterium* (Rodgers *et al*, 1987).
. the bacterial origin of replication (ori-322) that permits plasmid replication in *Escherichia coli* (Sutcliffe, 1979)
. the spectinomycin (spc) and streptomycin (str) genes for antibiotic resistance (Fling *et al*, 1985).

The gene arrangement is shown in Figure 1.

Figure 1: Schematic diagram of PV-BNGT04[1]



[1]See text or Table 1 for an explanation of the abbreviations.
[2]The boxed region denotes the T-DNA – genes within the LB and RB which are transferred to canola.
[3]The genes in the entire plasmid. Genes outside the LB and RB are not transferred.

2.2 Function and regulation of the introduced gene(s)

Monsanto have submitted the following reports:

Barry, G.F. et al, 1994. Cloning and expression in *Escherichia coli* of the glyphosate-to-aminomethylphosphonic acid degrading activity from *Achromobacter sp*. strain LBAA. Monsanto Company, USA 63198.

Padgette, S.R. et al. 1994. Characterisation of glyphosate oxidoreductase. Monsanto Company, USA 63198.

Woodward, H.D. etal. 1994. Isolation and characterisation of a variant of the enzyme glyphosate oxidoreductase with improved kinetic properties. Monsanto Company, USA 63198.

Each gene transferred to canola requires regulatory sequences that allow it to be transcribed into RNA and then translated into a protein product. A promoter is the key control element that enables a gene to be transcribed into messenger RNA (mRNA) and a terminator is a DNA (polyadenylation) sequence which stops the transcription of mRNA. These sequences can be unique in each organism and thus regulatory elements that already exist in plants are often used in gene constructs to enable functioning in the plant. Regulatory regions for each of the transferred genes are summarised in the table below.

Table 1: Description of Genes transferred to Canola

Gene	Region	Name	Origin
CP4 EPSPS	Promoter Chloroplast Transit Peptide Terminator	P-CMoVb CTP 2 E9 3'	Modified figwort mosaic virus 35S promoter CTP sequence from *A. thaliana* EPSPS gene Pea rbcS E9 gene
gox	Promoter Chloroplast Transit Peptide Terminator	P-CMoVb CTP 1 E9 3'	Modified figwort mosaic virus 35S promoter CTP sequence from *A. thaliana* SSU1A gene Pea rbcS E9 gene

CP4 EPSPS

EPSPS is an essential enzyme involved in the biosynthesis of the aromatic amino acids by the shikimate metabolic pathway. This metabolic pathway is present in all plants, bacteria and fungi (Haslam, 1993). Thus plants naturally contain an EPSPS enzyme but they are inhibited by the herbicide glyphosate, whereas the bacterial EPSPS enzyme is not inhibited (Schültz *et al*, 1985). The *Agrobacterium*–derived CP4 EPSPS gene has a reduced affinity for glyphosate and has been transferred to canola to confer tolerance to glyphosate.

The CP4-EPSPS gene is fused to the following regulatory sequences: the 35S promoter from a modified figwort mosaic virus (P-CMoVb) and the 3' end of the pea rbcS E9 gene (E9 3'). The bacterial EPSPS enzyme is targeted to the plastid using a chloroplast transit peptide sequence derived from the *Arabidopsis thaliana* EPSPS (CTP 2) which has been shown to deliver bacterial EPSPSs to the chloroplasts of higher plants where the aromatic amino acid biosynthetic pathway and endogenous EPSPS activity is located (della Ciopa *et al*, 1986).

gox

The *gox* (glyphosate oxidoreductase) gene is derived from *Ochromobactrum anthropii* strain LBAA [formerly *Achromobacter sp*] which is a commonly found bacteria in the soil. As in other bacteria, it degrades glyphosate to aminomethylphosphonic acid (AMPA) and glyoxylate thus effectively inactivating the herbicide (Pipke and Amrhein, 1988; Barry *et al*, 1992). AMPA is the principal metabolite of glyphosate that is degraded by several microorganisms and glyoxylate is commonly found in plant cells and is broken down by the glyoxylic pathway for lipid metabolism.

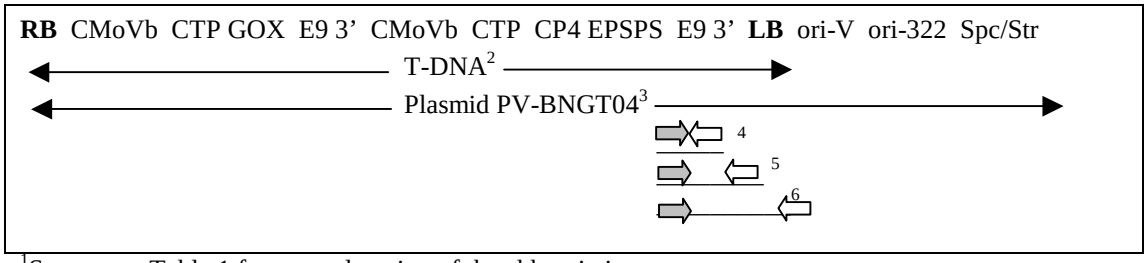
The *gox* gene is fused to the following regulatory sequences: the 35S promoter from a modified figwort mosaic virus and the 3' end of the pea rbcS E9 gene (E9 3'). The gene is targeted to the plastid by the action of the N-terminal of the small subunit 1A of the ribulose 1,5-bisphosphate carboxylase chloroplast transit peptide of *Arabidopsis thaliana* (CTP1) (Timko *et al*, 1988) which has been fused to the gene.

2.3 Characterisation of the genes in the plant

Southern blot analysis is used to detect the presence of specific DNA sequences and to determine the mode, number and stability of inserted DNA. It was used by the applicant to demonstrate that there is a single DNA insertion in line GT73 consisting of the T-DNA (ie. the DNA contained within the left and right border as shown in Figure 1). The T-DNA contains one complete copy of the CP4 EPSPS gene and a complete copy of the *gox* gene and their respective regulatory sequences.

PCR analyses using specifically designed primers for the T-DNA, the Left Border region and vector DNA also supported that only the T-DNA is inserted into the plant genome. A diagram of these primers is shown in Figure 2. PCR analysis supported that no other vector DNA including the antibiotic resistance genes was transferred to glyphosate tolerant canola line GT73.

Figure 2: Primer locations for PCR analysis of the transferred genes[1]



[1]See text or Table 1 for an explanation of the abbreviations.
[2]Denotes the T-DNA – genes within the LB and RB which are transferred to canola.
[3]The entire plasmid. Genes outside the LB and RB are not transferred.
[4]Both PCR primers are within the T-DNA (within the E9 3' element) and produce a 252 bp product in GT73
[5]One PCR primer is within the T-DNA (within the E9 3' element) and the other primer lies across the E9 3' and LB sequences and produces a 559 bp product in GT73.
[6]One PCR primer is within the T-DNA (within the E9 3' element) and the other primer is located in the vector sequence and produces a 661 bp product which was not produced using GT73 DNA.

2.4 Stability of the genetic changes

Monsanto have submitted the following:

Kolacz, K.H. et al. 1994. Determination of the stability of the GT genes in glyphosate-tolerant canola line GT73. Monsanto Company, USA 63198.

The stability of inserted DNA was demonstrated from R_3 generation and R_5 generation using Southern blot analysis. Segregation analysis for line GT73 is

consistent with a stable, single dominant gene segregating according to Mendelian genetics. The glyphosate-tolerant phenotype and inheritance pattern have been consistent for multiple generations.

Conclusions regarding the genetic modification

Glyphosate-tolerant canola line GT73 contains two new genes - CP4 EPSPS and *gox* – which were transferred using an *Agrobacterium* mediated transformation system. No other genes were transferred during transformation. The DNA has transferred into the canola genome as a single and stable insert.

3. GENERAL SAFETY ISSUES

Canola is grown in Australia largely as an export crop but some processed foods, including imported processed foods may contain genetically modified canola. These foods include salad and cooking oil, margarine, shortening, mayonnaise, sandwich spreads, creamers and coffee whiteners.

The glyphosate-tolerant canola has been evaluated against the safety assessment guidelines developed by ANZFA (ANZFA, 1999a). As the data presented is for canola seed and processed fractions, in particular, refined, bleached and deodorised canola oil (RBDO), the safety assessment issues relate to Group D foods – food ingredients.

3.1 History of the use of canola as a food source

Rapeseed (*Brassica napus* or *Brassica campestris*) was not widely grown as a commercial crop for consumption until the late 1940's and it was previously grown largely for the production of oil to be used as an industrial lubricant. Early rapeseed varieties were very high in erucic acid and glucosinolates, which made them unsuitable for consumption. Initial endeavours in breeding programs resulted in the development of varieties with lower amounts of these natural toxicants but were found to have poor yields and high susceptibility to disease.

In the 1970's, very intensive breeding programs in several countries including Australia produced high quality varieties that were significantly lower in erucic acid and glucosinolates. These varieties are largely *Brassica napus* species and were called canola, the term denoting an industry standard that these varieties contain an erucic acid level below 2% in oil and less than 30 micromoles of total glucosinolates in toasted meal. Canola oil is the only fraction considered to be fit for human consumption and toasted meal is used in animal feeds.

The demand for canola has risen sharply, particularly in canola oil, margarine and other canola based products. Canola is the leading oilseed crop in Australia and is a growing export industry. These canola-based products are routinely used in food and have a history of safe use.

3.2 Nature of the novel protein

CP4 EPSPS Protein

Monsanto have submitted the following reports:

Donovan, D.E. etal. 1993. Validation of the ELISA V3.0 excel macro and template. Monsanto Company, USA 63198.

Taylor, M. 1994. Validation of an indirect ELISA to quantitate of CP4 EPSPS in genetically improved canola. Monsanto Company, USA 63198.

Harrison L.A., et al. 1993. Characterisation of microbially-expressed protein: CP4 EPSPS. Monsanto Company, USA 63198.

Harrison L.A., et al. 1994. Equivalence of plant- and microbially expressed proteins: CP4 EPSPS from glyphosate-tolerant canola and *E. coli*. Monsanto Company, USA 63198.

Heeren, R.A. et al. 1993. The purification of recombinant *Escherichia coli* CP4 5-enolpyruval-shikimate-3-phosphate synthase for equivalence studies. Monsanto Company, USA 63198.

The CP4 EPSPS gene is a 47.6 KDa protein consisting of a single polypeptide of 455 amino acids. In the genetically modified canola line, the CP4 EPSPS gene has been fused to the *A. thaliana* EPSPS CTP. *In vitro* chloroplast uptake assays have shown that the *A. thaliana* EPSPS CTP delivers CP4 EPSPS to the chloroplast and is subsequently cleaved from the pre–protein, yielding mature CP4 EPSPS with no CTP amino acids retained (della Ciopa *et al*, 1986). It has been shown that the chloroplast transit peptides are rapidly degraded after cleavage *in vivo* by cellular proteases. Thus, the only newly expressed protein present in the glyphosate-tolerant canola line would be mature CP4 EPSPS, without any additional CTP residues at the amino terminus.

GOX protein

Monsanto have submitted the following reports:

Harrison L.A., et al. 1994. Characterisation of microbially-expressed protein: GOX (M4-C1) and GOXv247 (M4-C1). Monsanto Company, USA 63198.

Harrison L.A., et al. 1994. Characterisation of GOX (canola) and GOXv247 (canola) and assessment of equivalence relative to E. coli GOX (M4-C1) and GOXv247 (M4-C1). Monsanto Company, USA 63198.

Nickson, T.E. 1994. Validation of an ELISA for the detection and quantification of glyphosate oxidoreductase (GOX). Monsanto Company, USA 63198.

The *gox* gene encodes a single polypeptide of 431 amino acids with a molecular mass of 46.1 KDa. The glyphosate oxidoreductase (GOX) protein breaks glyphosate down to aminomethylphosphonic acid (AMPA) and glyoxylate. The metabolism and toxicology of AMPA is discussed further in Section 6. As the gox gene is under the control of a constitutive promoter in glyphosate-tolerant canola, the GOX gene will be present but targeted to the chloroplast using the *A. thaliana* SSU1A gene chloroplast transit peptide (CTP).

The *gox* gene has been modified to improve the affinity of the enzyme for glyphosate and is referred to as the *gox* variant (GOXv247). Nucleotide sequencing has determined that there are three amino acid substitutions in the *gox* variant protein and that the two proteins are greater than 99% identical.

3.3 Expression of the novel protein in the plant

Expression levels of the introduced proteins were measured using enzyme linked immuno-sorbent assay (ELISA) which is a highly sensitive technique that can detect the presence of a protein generally to a sensitivity of 10-100 pg. ELISA analysis was used in the analysis of leaf tissue, seed and processed fractions (toasted meal) from the glyphosate-tolerant canola line. The level of total protein present in RBDO was also determined.

Three separate field trials of glyphosate-tolerant canola were done, two in Canada and a third in Europe. In the 1992 Canadian season, the seed analysed was not treated with herbicide. In the 1993 and 1994 seasons, plants were both untreated and treated with the herbicide Roundup (active ingredient is glyphosate).

ELISA analysis of glyphosate-tolerant canola and control Westar seed from all trials as well as leaf tissue from the 1992 trial demonstrated that the introduced proteins CP4 EPSPS and GOX are expressed at very low levels in these tissues (Table 2). The level of expression constitutes less than 0.02% of the seed on a fresh weight basis. No detectable CP4 EPSPS or GOX protein was measured in Westar seed or tissue from any year.

In line GT73, expression of both CP4 EPSPS and GOX proteins in the seed was comparable for all trials (Table 2). The expression of the novel proteins in the seed was also comparable for plants treated with the herbicide glyphosate.

Table 2: Protein expression levels in canola as determined by ELISA[1]

	Expression levels in seed (µg/mg fresh weight)			
	Mean	**Range**	**Mean**	**Range**
	1992 leaf[2]		**1992 seed[2]**	
GT73				
CP4 EPSPS	0.034	0.028-0.037	0.049	0.044-0.051
GOX	0.108	0.071-0.161	0.154	0.109-0.203
Westar[6]				
CP4 EPSPS	nd	-	nd	-
GOX	nd	-	nd	-
GT73	**1993 un-treated[3]**		**1993 treated[3,5]**	
CP4 EPSPS	0.028	0.018-0.047	0.030	0.014-0.042
GOX	0.193	0.108-0.334	0.206	0.125-0.379
Westar[6]				
CP4 EPSPS	nd	-	nd	-
GOX	nd	-	nd	-

Table 2 continued: Protein expression levels in canola as determined by ELISA[1]

	1994 un-treated[4]		1994 treated[4,5]	
GT73				
CP4 EPSPS	0.018	0.016-0.022	0.018	0.012-0.022
GOX	0.160	0.126-0.240	0.186	0.119-0.232
Westar[6]				
CP4 EPSPS	nd	-	nd	-
GOX	nd	-	nd	-

[1]Means of all samples taken from all locations except for 1992 where samples were taken from 3 of the 7 sites.
[2]CP4 EPSPS & GOX Leaf n=4: Seed CP4 EPSPS n=3, GOX n= 6; Westar n=7. No treated values for 1992
[3]Untreated and Treated CP4 EPSPS n=8, GOX n= 16; Westar n=4.
[4]Untreated CP4 EPSPS n=7, GOX n= 7; Treated EPSPS n=9, GOX n= 9; Westar n=2.
[5]1993 Early post application plot of Roundup at 0.45 kg a.i./ha; 1994 Early post application plot of Roundup at 2 L/ha
[6]Expression of the novel proteins in Westar was not detected.

Processed Fractions

Analyses of the processed fractions of canola, refined, bleached and deodorised oil (RBDO) and toasted meal were also done (Table 3). It is widely accepted that many refined oils, do not contain any protein or only negligible amounts (Tattrie and Yaguchi, 1973; Klurfeld and Kritchevski, 1987). In the 1992 trial, the level of total protein present in canola oil was determined for both glyphosate-tolerant canola line GT73 and Westar. The total protein in both canola lines was present only in trace amounts (0.290 ppm in GT73 and 0.327 ppm in Westar) which was not considerably different to the level determined for an acid blank control sample (0.217 ppm).

Table 3: Total protein present in refine oil produced from the 1992 field trial

SAMPLE	Total protein present in refined oil (ppm)
GT73	0.290
Westar	0.327
Acid blank control	0.217

The trace protein in the oil represents less than 0.0001% protein and is at the limit of detection. This amount of protein is considered to be negligible. Given that the novel protein was present in unprocessed seed at very low levels and that all protein is virtually removed upon processing canola seed, the refined oil is not considered to contain any novel protein.

The amount of the novel proteins in toasted meal was found to be considerably reduced upon processing. In the 1992 and 1993 trials, the CP4 EPSPS protein was reduced by over 40% and the GOX protein was reduced by more than 20%. Additionally, the proteins were not found to have any enzymatic activity, as expected, since processing denatures the proteins and therefore its activity.

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

The human health considerations in this regard depend 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[3]/WHO Expert Consultation which looked at strategies for assessing the safety of foods produced by biotechnology (WHO 1991). It was concluded by that consultation 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. 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). There are concerns, however, that there could be horizontal gene transfer of the antibiotic resistance gene from ingested food to gut microorganisms and that if the microorganisms are able to express the transferred resistance gene this could lead to an increase, in the gastrointestinal tract, of microorganisms resistant to a specific antibiotic. This, in turn, might lead to an increased potential for the transfer of the antibiotic resistance gene to pathogenic microorganisms, thus compromising the therapeutic use of such antibiotics. There are further concerns that, if the antibiotic resistance gene is expressed in the plant, the expressed protein, when ingested, could inactivate oral doses of the antibiotic to which it confers resistance.

The glyphosate-tolerant canola line assessed in this application does not contain any antibiotic resistance genes as indicated by the Southern blot and specific PCR experiments. Only DNA contained within the Left and Right Borders of the *Agrobacterium*–based plasmid is transferred. This refers only to the genes conferring glyphosate tolerance which are not considered to pose any health risk.

Additionally, refined oil is the only product for human consumption derived from glyphosate-tolerant canola and there is virtually no protein present since it is removed during processing of the oil.

As discussed above, 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.

[3] Food and Agriculture Organization.

Given the information above, the horizontal gene transfer of any genetic material from the glyphosate tolerant canola, whether novel DNA or not, is not considered to pose any risk to public health and safety, particularly in relation to the development of antibiotic resistant pathogenic bacteria.

Conclusions regarding general safety issues

CP4 EPSPS and GOX are both expressed at relatively low levels in the seed. The only canola product intended for human consumption is the refined oil, which does not contain any detectable CP4 EPSPS or GOX protein. The CP4 EPSPS gene and protein have been well characterised and are considered similar to plant EPSPS genes which are readily consumed. The *gox* gene has been sourced from a common soil bacterium, which has no history of pathogenicity.

The risk of transfer of the novel genetic material to gut bacteria is considered negligible and additionally, there are no antibiotic resistance genes present in glyphosate-tolerant canola.

4. TOXICOLOGICAL ISSUES

4.1 Levels of naturally-occurring toxins

Rapeseed varieties naturally have very high levels of the toxic components erucic acid and glucosinolates both of which have dietary concerns. Erucic acid has cardiopathogenic potential and glucosinolates have goitrogenic properties, which makes rapeseed unsuitable for human consumption (McDonald, 1999). Canola refers to those varieties of rapeseed that must meet specific standards on the levels of erucic acid and glucosinolates.

Although refined oil is the only human food fraction derived from canola, data has also been presented for toasted meal. Canola meal is not considered to be a human food fraction and has been evaluated in this assessment to compare levels of major components to determine any potentially unintended effects. Canola meal, whether genetically modified or not, is not regarded as a food fraction due to the presence of natural toxicants, erucic acid and glucosinolates and the genetic modification does not change this pattern of consumption.

Erucic acid analysis

Erucic acid is a mono-unsaturated fatty acid (22:1), which is a natural constituent of rapeseed. High erucic acid rapeseed (HEAR) oil has been shown to have cardiopathic potential in laboratory animals (reviewed in ANZFA, 1999b). Canola has been developed from rapeseed and canola oil must conform to a standard defined as less than 2 percent erucic acid in oil and less than 30 micromoles of total glucosinolates in toasted meal to conform to CODEX standards (CODEX, 1993). Conformance to these standards ensures that canola oil is essentially free of cardiopathogenic potential. All canola varieties that meet CODEX specifications also meet specifications for canola oil as outlined in the Australian *Food Standards Code*.

Data for erucic acid in line GT73 has been statistically analysed to ensure that it does not exceed the 2% maximum level permitted in oil. The mean values for erucic acid in GT73 are well below the maximum limit allowed for canola and are also below the values determined for the control line Westar (Table 4). Breeding in canola continues to reduce the erucic acid levels and the fact that the glyphosate tolerant canola line has a low content is considered beneficial.

Table 4: Erucic acid levels in oil from glyphosate tolerant canola line GT73 and Westar[1]

	1992 seed	1993 untreated	1993 treated[4]	1994 untreated	1994 treated[4]
GT73[2]	0.12	0.04	0.00	0.10	0.12
Westar[3]	0.3-0.6	0.15-0.57	0.15-0.57	0.29-0.36	0.29-0.36

[1]Means of all samples taken from all locations except for 1992 where samples were taken from 3 of the 7 sites. Values for Westar samples from all trials were below the calculated limit of detection.
[2]1992 n=7; 1993 Untreated n=4, Treated n=5; 1994 Untreated n=2, Treated n=4.
[3]1992 n=7; 1993 n=7; 1994 n=2.
[4]1993 Early post application plot of Roundup at 0.45 kg a.i./ha; 1994 Early post application plot of Roundup at 2 L/ha

Glucosinolate analysis

There are over 100 known structural types of glucosinolates, nine of which are closely monitored in canola because they are reported as having toxic properties. Five compounds referred to as the alkyl glucosinolates are thought to have the anti-nutritional properties. The sum of four of these five alkyl glucosinolates (gluconapin, progoitrin, glucobrassicanapin and napoleiferin) must be less than a total of 30 μmoles/gram oil free meal for the seed to be classified as canola quality (the value is likely to be decreased 20 μmoles/gram). Of similar concentration but of less concern are the indol glucosinolates, two of which are monitored. Two types from a third group of glucosinolates, the thioalkyl glucosinolates are measured but are typically present in very low concentrations. Benzylglucosinolates are glucosinolates derived from phenylalanine and are also monitored in canola meal.

Glucosinolates are goitre-inducing when they are hydrolysed by myrosinase, an enzyme localised within cells of *Brassica* seeds. When the seed is crushed, the enzyme acts upon the glucosinolate to produce isothiocyanates, thiocyanates and possibly nitriles depending on temperature and moisture conditions. However, during processing, a cooking step inactivates myrosinase leaving glucosinolates intact. Some destruction and reduction of glucosinolates may occur in further processing steps. Breeders are encouraged to work towards the elimination of glucosinolates in canola.

During processing of canola seed to produce oil, the seed is flaked rupturing the oil cells and cooked at 75-85C. The cooking ruptures any remaining intact cells and compresses the flakes into cake fragments. These cake fragments are then solvent extracted to remove most of the remaining oil. Heal treatment of the processed fractions is important for removing volatile components which often are toxicants. The solvent is removed from the oil fraction which then undergoes a degumming process producing a semi-refined oil. These processing steps as well as the final refinement effectively remove glucosinolates from the refined bleached deodorised oil

(Genser and Eskin, 1979).

The applicant provided data for the analysis of glucosinolates in canola seeds and meal. Defatted meal from genetically modified canola line GT73 and the control Westar from the 1992 and 1993 field trials were analysed for glucosinolates by Agriculture Canada using standard methods of the Co-Op Test (Table 5). These analyses by Agriculture Canada (the Co-Op Test) allow a comparison of seed from GT73 to a much larger data set of values for Westar seed enabling an estimation of the considerable variation observed in the heterogeneous Westar genotype.

In the 1994 field trial, Cargill used an alternative technique to determine the glucosinolates content, which makes a direct comparison to previous years' values invalid.

The levels of glucosinolates in all samples from GT73 are well below the 30 µmole limit for defatted meal (Table 5). A comparison of mean levels of the alkyl glucosinolates in the genetically modified canola shows that all values except the 1992 GT73 value (16.8 µmol/g) are within the range of the Co-Op Test values (7.0-12.5 µmol/g). The level of glucosinolates in the genetically modified line is higher than in the control line but it is well below the accepted industry maximum limit (30 µmol/g).

Table 5. Glucosinolate composition in Westar and glyphosate tolerant canola line GT73 [1]

1992[2]	Westar		Westar Co-op		GT73	
	Mean	Range	Mean	Range	Mean	Range
Alkyl	8.75	6.11-11.4	9.66	7.0-12.5	16.8	13.8-19.8
Thioalkyl	0.26	0.18-0.40	0.36	0.2-0.8	0.46	0.38-0.55
Indolyl	11.4	9.8-13.4	11.0	7.0-13.7	11.6	11.55-11.63

1993[3]	Westar		Westar Co-op		GT73 Untreated		GT73 Treated[4]	
	Mean	Range	Mean	Range	Mean	Range	Mean	Range
Alkyl	8.93	6.7-11.1	7.56	5.3-9.4	10.56	7.97-12.9	10.8	5.57-13.2
Thioalkyl	0.28	0.2-0.37	0.30	0.2-0.4	0.28	0.23-0.33	0.28	0.13-0.37
Indolyl	11.5	11.0-12.5	11.5	10.7-12.5	11.4	10.9-12.0	11.4	10.5-12.5

1994[5]	Westar	GT73 Untreated	GT73 Treated[4]
Alkyl	10.6	11.6	10.8
Indolyl	3.92	4.06	4.67

[1]Values are in µmoles/gram of defatted meal.
[2]1992 Westar n=7, GT73 n=2 Co-op Westar n=13.
[3]1993 Westar n=5, Untreated GT73 n=5, Treated GT73 n=5, Co-op n=9.
[4]1993 Early post application plot of Roundup at 0.45 kg a.i./ha; 1994 Early post application plot of Roundup at 2 L/ha
[5]1994 Westar n=2, Untreated n=2, Treated n=2. Cargill used a different method of analysis.

Processed fractions – toasted meal

Independent laboratories at POS Pilot Plant Corporation of Saskatoon, Saskatchewan (POS) determined the glucosinolate content of the meal samples in 1992 and 1993 and at Cargill, Centre de Bolssay, Cedex in 1994. The content in GT73 in the 1992 trial was 9.9 μmol/g oil free meal and 4.4 μmol/g in Westar oil free meal. In the 1993 trial, glucosinolate content in untreated GT73 meal was also more than double that of Westar (10.5 and 4.7 μmol/g respectively). These values, although higher in the genetically modified line than in the control line are well below the 30 μmol/g defatted meal limit set by the industry in their definition of canola (McDonald, 1999).

Although the level of glucosinolates in line GT73 seed and meal appear to be consistently higher than the average determined for Westar, it is consistent with the variability known to occur in the heterozygous canola variety (Downey, 1994). It is also important to note that canola meal is not considered a food fraction fit for human consumption.

4.2 Potential toxicity of novel proteins

The safety of the EPSPS protein used in this application has been addressed in previous assessments (A338 Roundup Ready Soybeans). This data has also been published in the scientific literature as cited in the text. Monsanto have submitted the following reports in support of the safety of the GOX protein:

Bishop, B.R. and M.E. Gustafson. 1993. Production of glyphosate oxidoreductase (GOX) in recombinant *E. coli*. Monsanto Company, USA 63198.

Kolacz, K.H. et al. 1994. *E. coli* vectors for the expression of plant-processed form of CP1-GOX and CTP1-GOXv247. Monsanto Company, USA 63198

Naylor, M.W. 1994. Acute oral toxicity study of GOX (M4-C1) protein in albino mice. Monsanto Company, USA 63198.

Naylor, M.W. 1994. Acute oral toxicity study of GOXv247 (M4-C1) protein in albino mice. Monsanto Company, USA 63198.

Nickson, T.E. et al. 1994. Preparation and confirmation of doses for acute oral toxicity studies in mice with glyphosate oxidoreductase GOX (M4-C1) and GOXv247 (M4-C1). Monsanto Company, USA 63198.

Harrison L.A., et al. 1993. Characterisation of microbially-expressed protein: CP4 EPSPS. Monsanto Company, USA 63198.

Harrison L.A., et al. 1994. Equivalence of plant- and microbially expressed proteins: CP4 EPSPS from glyphosate-tolerant canola and *E. coli*. Monsanto Company, USA 63198.

Bishop, B.R. 1992. Production of CP4 EPSP synthase in a 100 litre recombinant *Escherichia coli* fermentation. Monsanto Company, USA 63198

The potential for toxicity of the newly expressed proteins, CP4 EPSPS and GOX, were evaluated based on:

. the amino acid sequence similarity with known toxins

- acute toxicity testing in mice.
- the resistance to digestion by proteases and acids in the model digestive/gastric system
- their presence as a major protein component in a specified food.

The amino acid sequences of both the CP4 EPSPS and GOX proteins were compared to the amino acid sequences of 1935 known protein toxins. No significant similarity was found other than would be expected given that certain functional domains are generally conserved between proteins.

The acute oral toxicity of bacterially produced CP4 EPSPS, lacking the CTP (Harrison et al, 1996), GOX and GOXv247 proteins, was studied in groups of ten CD-1 mice/sex in order to directly assess the potential for toxicity associated with this protein. Physical and chemical integrity and identity between the bacterially-produced and plant-plant produced proteins was demonstrated using Western blot analysis, N-terminal amino acid sequencing and enzymatic activity. Thus the novel proteins that were produced by fermentation that were used in acute toxicity tests are equivalent to the novel proteins produced in the plant.

There were no adverse effects or mortalities noted in mice administered CP4 EPSPS protein by gavage at doses up to 572 mg/kg (Harrison et al, 1996). This data from application A338 Roundup Ready Soybean has been previously assessed by ANZFA (ANZFA, 1999c). The GOX protein used in the acute toxicity test included four amino acids of the CTP since evidence supports that processing of the mature protein includes these four amino acids. There were no adverse effects observed in mice administered the GOX protein by gavage at doses up to 100 and 104 mg/kg for GOX and GOXv247 respectively.

These doses are well above the level of expression of the proteins found in glyphosate-tolerant canola plants (refer to Table 2) and represent a test using an estimated 1300-fold and 5000-fold increase in exposure to CP4 EPSPS and GOX proteins respectively, that would be expected by consuming the genetically modified canola.

Clinical observations were performed and body weights and food consumption were determined. All surviving animals were necropsied at study termination (8-9 days). Mice were observed up to 9 days after dosing and no signs of toxicity were observed (ie no adverse effects for either protein on body weight, food consumption, survival, or gross pathology).

4.3 Levels of naturally occurring allergenic proteins

Canola oil has been shown in this application to contain negligible levels of protein (discussed in 3.3) and given that most allergens are proteins, its consumption is unlikely to cause an allergic reaction. Many refined oils have been shown not to be allergenic even if the source can be allergenic (Taylor *et al*, 1981; Tattrie and Yaguchi, 1973).

In all cases of documented allergies to foods including both common and unusual allergies, there is only a single entry for rapeseed and this is considered a very uncommon allergy (Bush and Hefle, 1996).

4.4 Potential allergenicity of novel proteins

Monsanto have submitted the following reports:

Astwood, J. 1995. Glyphosate oxidoreductase (GOX) shares no significant sequence similarity with proteins associated with allergy or Coeliac disease. Monsanto Company, USA 63198.

Ream, J.E., Bailey, M.R., Leach, J.N. and Padgette, S.R. 1993 Assessment of the *in vitro* digestive fate of CP4 EPSP synthase Monsanto Company, USA 63198. MSL-12949

Ream, J.E. et al. 1994. Assessment of the in vitro digestive fate of glyphosate oxidoreductase GOX and GOXv247 variant. Monsanto Company, USA 63198.

Although there are no 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. The CP4 EPSPS and GOX proteins were evaluated for potential allergenicity against these criteria.

On the basis that amino acid sequence similarity with known allergens is a useful indicator of allergenic potential, the amino acid sequence of the CP4 EPSPS and GOX proteins were compared to the amino acid sequences of 219 known allergens present in public domain databases (eg GenBank, EMBL, Swissprot, PIR). No significant similarity (i.e. a sequence of more than 8 consecutive amino acids) was found with any of these known allergens.

The CP4 EPSPS protein is one of many EPSPS proteins that occur in plants, fungi and bacteria. The EPSPS proteins are naturally present in foods derived from plants and microbes and have no history of being allergenic. The bacterially sourced CP4 EPSPS protein is 47.6 KDa.

The GOX and GOXv247 proteins are both 46.7 KDa (there is a 17 Da difference). Thus each protein fits the molecular mass criteria recognised for many allergens of 10–70 KDa. The GOX protein is a single polypeptide that has a narrow substrate specificity for glyphosate.

Protein allergens must be stable to the peptic and acidic conditions of the digestive system if they are to reach and pass through the intestinal mucosa to elicit an

allergenic response. A study of the digestibility of both proteins in model digestion systems was done using *in vitro* using simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) as mammalian digestion models. The method of preparation of the simulated mammalian gastric and intestinal digestive solutions used is described in the United States Pharmacopoeia (1989). The exposure of CP4 EPSPS and GOX proteins to SGF and SIF was conducted over a series of timed incubations at 37°C. The products of the digestion were analysed using gel electrophoresis, Western blot analysis and enzymatic activity assays.

Both the CP4 EPSPS and GOX proteins are digested by proteases present in the mammalian digestive system, suggesting that they would not survive peptic and tryptic digestion or the acidic conditions of the human digestive system. From the simulated digestion experiments and Western blot analyses, the CP4 EPSPS protein had a half–life of less than 15 seconds in the gastric system and 10 minutes in the intestinal system. The GOX protein had a half–life of less than 30 seconds in the intestinal system as determined by Western blot analyses.

Conclusions regarding toxicological issues

There is no evidence to indicate that there is any potential for the EPSPS or the GOX proteins to be either toxic or allergenic to humans. Proteins from the EPSPS family of proteins are naturally present in our food source. Although the GOX protein is not present in foods naturally, it does not possess characteristics or sequence homology common to many allergens or toxins. Furthermore, the proteins are expressed at relatively low levels in the canola and are rapidly digested in conditions that mimic human digestion. Additionally, neither protein had toxic effects on mice given acute doses of the equivalent bacterially produced proteins.

Finally, there is no protein present in refined oil as it is all removed during processing.

5. NUTRITIONAL ISSUES

Monsanto have submitted the following reports:

Nickson, T.E., and M.L. Taylor. 1994. Evaluation of seed from glyphosate-tolerant canola lines from the 1993 Canadian field trials. Monsanto Company, USA 63198.

Nickson, et al T.E., D.B. Re, B.G. Hammond, R.L. Fuchs and S.G. Rogers. 1994. Evaluation of glyphosate-tolerant canola lines from the 1992 Canadian field trials. Monsanto Company, USA 63198

Nickson, T.E., D.B. Re, B.G. Hammond, R.L. Fuchs and S.G. Rogers. 1995. Safety, compositional and nutritional aspects of glyphosate-tolerant canola: conclusion based on studies and information evaluated according to FDA's consultation process. Monsanto Company, USA 63198.

Taylor, M.L. 1995. The evaluation of seed from glyphosate-tolerant canola 1994 European field trials. Monsanto Company, USA 63198.

Taylor, M. and T.E. Nickson. 1995. The evaluation of refined, bleached, deodorised oil from glyphosate-tolerant canola. Monsanto Company, USA 63198.

5.1 Compositional analysis

Compositional analyses were done on the glyphosate-tolerant canola line GT73 and the control/parental line Westar. Comparisons were made to the database maintained by Agriculture Canada and Agrifood Canada (the Canadian Rapeseed Co-Op Tests). Three rounds of field trials of line GT73 were conducted according to Good Laboratory Practice (GLP) guidelines: 1992 Canadian trials grown in 7 field locations; 1993 Canadian trials grown in 4 field locations; and 1994 European trials grown in 3 field locations (France, Belgium and the UK). Seed grown from each of the sites were analysed and statistical analyses of the data were done. The seed, leaf and processed fractions were analysed by independent laboratories for compositional quality characteristics according to GLP using standardised analytical methods by either the Ralston Analytical Laboratories (RAL), St Louis, Missouri, the Grains Research Laboratory (GRL) and at the Agriculture Canada Research Station (Agriculture Canada) in Saskatoon.

Processed fractions: Analysis of refined, bleached, deodorised oil (RBDO)

All new varieties of canola oil must be analysed to ensure they meet CODEX specifications for canola. This includes 18 quality analyses that define canola oil and includes a fatty acid analysis and 17 other food chemical tests. The results for all analyses of glyphosate-tolerant canola line GT73 were within CODEX specifications except for the values for four minor fatty acids: arachidic acid (C20:0), behenic acid (C22:0), lignoceric acid (C24:0) and nervonic acid (C24:1) (Table 6). However, the value for these four fatty acids exceeded the CODEX specifications in both the control line Westar and GT73.

Table 6: Fatty acid profile for refined, bleached and deodorised oil.

Fatty Acid	Westar	GT73	Codex
Arachidic 20:0	1.02	1.06	<1.00
Behenic 22:0	0.51	0.52	<0.50
Lignoceric 24:0	0.24	0.23	<0.20
Nervonic 24:1	0.30	0.31	<0.20

This result is considered to reflect the natural variation within canola rather than any effect of the genetic modification on the canola line. Furthermore, there is no anti-nutritional or toxicological significance associated with these fatty acids. With the exception of four slightly elevated minor fatty acids, the oil derived from glyphosate-tolerant canola line GT73 is comparable to oil derived from Westar.

Processed fractions: Analysis of toasted meal

Samples of toasted meal from glyphosate-tolerant canola line GT73 were sent to RAL for proximate analysis, amino acid composition, nitrogen solubility indexes and a mineral screen. The results for all analyses of toasted meal from glyphosate-tolerant canola were comparable to the samples derived from the Westar line and consistent with published values.

Proximate analysis for major constituents

Proximate analysis was done on genetically modified and control canola seeds at both

RAL and the protein and oil components were also done at the Agriculture Canada in the 1992 and 1993 field trials. Components measured were protein, fat, moisture, fibre, ash and carbohydrates as well as calories and are all reported on a dry weight basis except for moisture (Table 7).

The proximate analyses were done on GT73 canola from all years including analyses on seeds from herbicide treated and untreated plants in 1993 and 1994. In all of the component analyses of line GT73, there were no significant differences between the glyphosate-tolerant canola and the control line Westar, nor for the seeds from plants treated with herbicide (p=0.05).

Table 7: Mean values and ranges for the Proximate Analyses of Canola from three field trials

1992	Westar[2]		GT73[2]			
	Mean	Range	Mean	Range		
Protein[1]	23.4	21.0-26.1	25.4	25.4-25.7		
Fat[1,2]	46.5	42.3-49.9	45.8	44.6-47.1		
Fibre[1]	8.21	7.16-9.90	7.37	6.26-8.19		
Moisture[3]	4.39	3.69-4.86	4.85	4.32-5.38		
Calories Kcal/100g[1]	551	536-567	546	539-554		
Ash[1]	3.68	3.44-3.91	3.59	3.39-3.79		
Carbohydrate[1]	26.4	23.6-28.0	25.2	23.4-26.9		
1993	Westar[2]		Untreated[2]		Treated[2,4]	
	Mean	Range	Mean	Range	Mean	Range
Protein	23.8	22.8-26.7	23.4	22.3-26.2	23.5	22.7-25.5
Fat	45.7	43.3-47.2	46.4	42.7-48.8	46.2	44.3-47.4
fibre	8.62	8.07-9.59	8.36	7.98-8.77	8.38	8.1-8.94
Moisture	10.4	8.44-11.6	9.22	8.49-9.49	9.67	9.20-10.1
Calories Kcal/100g	513	495-533	523	501-534	520	507-528
Ash	4.07	3.58-4.26	4.00	3.72-4.47	3.93	3.49-4.30
Carbohydrate	26.4	25.8-27.9	26.1	24.9-27.1	26.4	25.7-27.2
1994	Westar[2]		Untreated[2]		Treated[2,4]	
	Mean	Range	Mean	Range	Mean	Range
Protein	27.5	26.3-28.6	25.6	23.9-27.2	25.6	24.5-27.1
Fat	39.3	39.0-39.6	42.4	42.1-42.8	43.2	42.3-44.2
fibre	10.9	10.5-11.2	10.7	10.5-11.0	10.1	9.7-10.6
Moisture	8.30	8.18-8.43	8.43	8.34-8.52	8.63	7.68-9.31
Calories Kcal/100g	495	494-496	510	507-513	512	505-517
Ash	4.83	4.76-4.90	4.26	4.22-4.31	4.25	4.18-4.40
Carbohydrate	28.4	27.6-29.2	27.8	26.4-29.1	24.6	23.9-25.4

[1]Data as a percentage of dry weight
[2]1992: Westar n=7; GT73 n=2; Westar fat n=6; 1993 n=4; 1994 Westar n=2; Untreated GT73 n=2; Treated GT73 n=3.
[3]Equilibrium moisture value
[4]1993 Early post application plot of Roundup at 0.45 kg a.i./ha; 1994 Early post application plot of Roundup at 2 L/ha

% Fat and % Protein

Additional analyses (protein and oil) by Agriculture Canada (the Co-Op Test) allowed a comparison of seed from GT73 to a much larger data set of values for Westar seed. This enabled an estimation of the considerable variation observed in the heterogeneous Westar genotype. Statistical analyses on the fat content (whole seed, dry weight basis) and on protein content (defatted meal) noted one significant difference in line GT73 compared to Westar (p=0.05) (Table 8). The mean fat values in 1993 (Untreated GT73: 45.8% and Treated GT73: 45.5%) were significantly higher than Westar. These findings were not consistent year to year and nor were they consistently noted in the proximate analyses and could be attributed to the natural range of variation that occurs in canola. The fat values, even though different to those for the control, were within the range reported for Westar grown during the field trial (fat: 42.4-47.3% and protein: 38.5-44.9%) and were also within the range reported for canola varieties from the Co-op Test Database (fat: 37.9-51.1% and protein: 34.0-50.8%).

Table 8: Mean values for % protein and % fat in canola seed

	Westar		Co-op Westar		GT73			
1992[1]	Mean	Range	Mean	Range	Mean	Range		
% Protein[1,2]	41.1	38.4-42.9	43.3	34.8-48.0	44.8	42.9-46.6		
% Fat[1,3]	44.8	41.9-47.7	42.8	37.7-47.6	44.8	44.1-45.4		
1993[4]	Westar		Co-op Westar		Untreated		Treated[5]	
% Protein[1,2]	41.2	38.3-45.0	42.3	34.0-50.8	41.8	39.6-44.8	42.2	40.2-44.7
% Fat[1,3]	45.1	42.4-47.3	44.8	37.9-51.1	45.8	43.7-47.1	45.5	42.8-48.5
1994[6]	Westar		Co-op Westar		Untreated		Treated[5]	
% Protein[1,2]	39.4	37.8-41.0	-		38.2	36.0-40.5	38.6	37.1-40.2
% Fat[1,3]	39.3	39.0-39.6	-		42.4	42.1-42.8	43.2	42.3-44.2

[1]Westar n=7; Co-op Westar n=52; GT73 n=2. Analyses done at Ag Canada.
[2]% Protein in defatted meal on samples ≤3% moisture
[3]% Fat on a whole seed basis dried to constant moisture (≤3%)
[4]Westar n=5; Co-op Westar n=87; Untreated GT73 n=4; Treated GT73 n=5. Analyses done at Ag Canada.
[5]1993: Early post application plot of Roundup at 0.45 kg a.i./ha; 1994: Early post application plot of Roundup at 2 L/ha
[6]Westar n=2; Untreated GT73 n=2; Treated GT73 n=2. Analyses done at RAL.

Fatty acid analysis

Canola has a high content of long-chain unsaturated fatty acids. Refined canola oil is about 90% unsaturated C18 fatty acids which make it ideal for human consumption. Erucic acid (C22:1) content is monitored to ensure the canola maintains its GRAS (generally regarded as safe) status. Canola oil has considerable natural variation in fatty acid composition and thus some variation in the composition of commercial canola oil is acceptable.

Two methods of comparison of canola oil from GT73 and Westar seed using standard methods of the Co-Op Test were done. The first method was based on profile: total saturated (eg. 16:0, 18:0, 20:0 and 22:0), mono-unsaturated, di-unsaturated and tri-unsaturated fatty acid esters. There were no differences in fatty acid profiles between mean values for the treated or untreated GT73 and Westar seed.

Individual fatty acid esters were also monitored and compared (Tables 9.1 and 9.2). The components measured were palmitic acid (C16:0), palmitoleic acid (C16:1), stearic acid (C18:0), oleic acid (C18:1 cis), linoleic (C18:2), and linolenic (C18:3), arachidic acid (C20:0), eicosenoic acid (C20:1), eicosadienoic acid (C20:2), behenic acid (C22:0), and erucic acid (C22:1).

Table 9.1 Fatty acid ester profiles for GT73 and Westar canola for the 1992 and 1993 trials

Fatty	1992[2]			1993[3]			
Acid	Westar	Co-op	GT73	Westar	Co-op	Not treated	Treated[4]
16:0	3.9-4.2	3.7-4.8	3.98	3.8-4.3	4.0-4.3	4.1	4.1
16:1	0.3-0.4	0.0-0.6	0.32	0.2[5]	0.2-0.3	0.2	0.2
18:0	1.4-2.0	1.2-2.1	1.72	1.4-1.9	1.7-1.9	1.7	1.8
18:1	58.8-62.5	57.4-63.4	61.4	60.1-62.8	61.9-63.1	62.9	62.8
18:2	18.9-20.2	18.3-22.1	18.9	18.8-20.6	18.4-19.8	18.7	18.7
18:3	8.1-12.1	8.2-13.0	10.8	8.6-10.13	8.5-9.8	9.65	9.73
20:0	0.6-0.8	0.4-0.9	0.72	0.6-0.7	0.6-0.7	0.65	0.68
20:1	1.7-2.0	1.3-2.3	1.58	1.57-2.0	1.4-1.9	1.49	1.51
20:2	0.1[5]	0.1-0.2	0.17	0.1[5]	0.1[5]	0.09	0.1
22:0	0.3-0.4	0.3-0.4	0.40	0.4-0.5	0.4[5]	0.4	0.43
22:1[6]	0.3-0.6	0.1-1.4	0.12	0.15-0.57	0.1-0.5	0.04	0.0

[1]Values are % of fatty acid ester profile. Analysis by Ag Canada.
[2]Westar n=7; Co-op Westar n=13; GT73 n=2;.
[3]Westar n=15; Co-op Westar n=8; Untreated GT73 n=12; Treated GT73 n=15.
[4]Treated: Early post application plot of Roundup at 0.45 kg a.i./ha
[5]Single value obtained for all samples.
[6]Erucic Acid

In 1994, the fatty acid analysis also included docosadienoic acid (C22:2), lignoceric acid (C24:0) and nervonic acid (C24:1) (Table 9.2). In all years, the values for fatty acid esters from GT73 were within the range for Westar from the Co-Op Test except erucic acid which was below that for Westar (Tables 9.1 and 9.2) in 1993. Since canola continues to be bred for lower erucic acid content because of its adverse cardiopathic potential, this difference is considered to be a positive attribute. Erucic acid is discussed in greater detail in Section 4.1 Naturally Occurring Toxins.

Table 9.2 Fatty acid ester profiles for GT73 and Westar canola from seed from the 1994 trial[1]

1994			
Fatty Acid	Westar	Not treated	Treated[2]
16:0	4.52	4.51	4.50
16:1	0.24	0.24	0.24
18:0	1.90	1.5	1.89
18:1	62.6	64.8	64.4
18:2	20.2	19.0	19.1
18:3	7.11	6.94	7.00
20:0	0.77	0.78	0.74
20:1	1.46	1.16	1.17
20:2	0.1	0.1	0.1
22:0	0.36	0.36	0.34
22:1	0.32	0.1	0.12
22:2	0.1	0.1	0.1
24:0	0.20	0.18	0.18
24:1[6]	0.18	0.14	0.15

[1]Westar n=2; Untreated GT73 n=2; Treated GT73 n=3.
[2]Treated: Early post application plot of Roundup at 2 L/ha

Amino acid analysis

Amino acid analyses were done on glyphosate-tolerant canola seeds from line GT73 in 1992 and from untreated plants and plants treated with glyphosate in 1993 and 1994. The results are reported as a dry weight and per protein basis (i.e. the amino acid value divided by the percent protein as determined from proximate analyses).

Of the 18 amino acids analysed, the values for each year were comparable for treated or untreated glyphosate-tolerant canola plants and the control line Westar with few exceptions. Table 10 lists the amino acids that were found to be slightly lower in the genetically modified canola plants. In 1992, the only exception was the mean value for proline on a per unit protein basis in GT73 (6.61%), which exceeds the range for Westar (mean value of 6.24% and a range of 6.09-6.36%). However this difference between the genetically modified and control line is consistent with previously reported values (up to 7.79%, Baidoo and Aherne, 1985).

In the 1993 trials, amino acid mean values (g/100g seed dry weight) for line GT73 were within the ranges determined for Westar except the means were higher for cysteine (0.43 versus 0.33 and a range of 0.20-0.42 for Westar) and methionine (0.35 versus 0.26 and a range of 0.16-0.32 for Westar) in untreated plants and proline in treated plants (1.46 versus 1.38 and a range of 1.28-1.45 for Westar). Upon statistical analysis, the mean tryptophan value was significantly different ($p=0.05$) in untreated GT73 (0.24 versus 0.26) to that for Westar. All values however, were within the range for canola (0.24-0.29) and the differences are considered within the natural variation range known for canola.

Table 10. Amino Acid values that were different between GT73 and Westar.

	Westar	Westar range	GT73	GT73 range
1992				
Proline[1]	6.24	6.09-6.36	6.61	6.46-6.70
1993				
cysteine[3]	0.33	0.20-0.42	0.43	0.29-0.57
methionine[3]	0.26	0.16-0.32	0.35	0.23-0.51
proline[4]	1.38	1.28-1.45	1.46	1.31-1.64
tryptophan[5]		0.24-0.29	0.24	0.23-0.28
1994[1]				
glutamic acid	17.7	17.3-18.1	16.5	16.0-16.9
histidine	2.36	2.32-2.40	2.26	2.24-2.29
proline	5.69	5.60-5.78	5.46	5.39-5.54

[1]Value is mean value on a per unit protein basis
[2]Value is g/100g seed dry weight
[3]untreated plants
[4]Treated plants. 1993 Early post application plot of Roundup at 0.45 kg a.i./ha; 1994 Early post application plot of Roundup at 2 L/ha
[5]Significantly different p=0.05.

In the 1994 trials, the values for glutamic acid, histidine and proline were all lower than those found for Westar. However, all values were within the range found for Westar. The values for glutamic acid (16.5 versus 17.7 and a range of 17.3-18.1 for Westar), histidine (2.26 versus 2.36 and a range of 2.32-2.40 for Westar) and proline (5.46 versus 5.69 and a range of 5.60-5.78 for Westar) in treated and untreated GT73 seeds were all lower than the mean value found for Westar but were within the range found for Westar.

5.2 Levels of anti-nutrients

Canola has been through extensive breeding programs to become one of the most widely used oils for human consumption. Canola has been bred from rapeseed for reduced anti-nutritional factors.

Sinapine analysis

Sinapines are a family of choline esters that naturally occur in canola and can be found in canola meal. Sinapines are known to render an off-odour to chicken eggs if the chickens are fed canola meal and have some significance to the poultry feed industry. The analysis for sinapines was done by Agriculture Canada using published methods. The mean value for sinapine content in line GT73 (12.7) was determined in the 1992 and 1993 trials and was the same as that for Westar (12.7).

Mineral/phytic acid analysis in processed fractions

Canola meal is rich in many essential minerals but their content in meal can be influenced by environmental factors. As phytic acid can adversely affect the uptake of phosphorous, calcium, magnesium and zinc, all of these constituents were assessed in untreated canola line GT73 and the control Westar. The values for all minerals and phytic acid were determined in the 1992 and 1993 trials and were comparable to those found in canola.

Conclusion regarding compositional data

Analysis of the compositional data of the canola seed and processed fractions indicates that there were no meaningful differences in the levels of major constituents, nutrients, anti–nutritional factors or natural toxicants between glyphosate-tolerant canola line GT73 and the control canola line Westar. Since new varieties of canola must undergo assessment to ensure that it meets the compositional standards required for canola (eg CODEX standards), a valuable resource is available for comparison. The glyphosate-tolerant canola line GT73 assessed in this application has been analysed by Agriculture Canada and the results compared to the database (the Canadian Rapeseed Co-Op). In terms of the anti-nutrients erucic acid and glucosinolates, GT73 seeds were found to be well below the maximum acceptable limit for both of these compounds and comparable to Westar.

Genetically modified canola plants that were treated with the herbicide Roundup during growing were also analysed and found to be comparable to Westar canola.

Additionally, an analysis of oil derived from GT73 and Westar seeds found a negligible amount of protein in the refined canola oil, which was at the limit of detection for both lines. There was no meaningful difference between oil derived from the genetically modified and control lines. Proximate analyses and some compositional studies of the toasted meal were also done and no meaningful differences to toasted meal from Westar were found.

5.3 Ability to support typical growth and well-being

Monsanto have submitted the following reports:

Brown, P.B. 1994. Evaluation of glyphosate-tolerant canola as a feed for rainbow trout. Monsanto Company, USA 63198.

Cambell, S.M. et al. 1993. Glyphosate-tolerant canola seed meal, a dietary toxicity study with the Northern bobwhite, Wildlife International Ltd. Monsanto Company, USA 63198.

Cambell, S.M. and J.B. Beavers. 1994. A dietary toxicity study with glyphosate-tolerant canola seed meal in the bobwhite. Monsanto Company, USA 63198.

Naylor, M.W. 1994. One month feeding study with processed and unprocessed glyphosate-tolerant canola meal in Sprague Dawley rats. Monsanto Company, USA 63198.

Naylor, M.W. 1995. One month feeding study with processed canola (line GT73) in Sprague Dawley rats. Monsanto Company, USA 63198.

In assessing the safety of a genetically modified food, 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. 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 glyphosate-tolerant canola, the applicant submitted data from several feeding study trials in order to demonstrate wholesomeness of the canola meal. Although canola meal is not a human food fraction, the studies have been assessed as supporting data for the wholesomeness of the genetically modified canola. These include a four-week rat study on processed and unprocessed meal, a ten-week trout study on processed meal and a five-day quail (Northern Bobwhite) study on unprocessed meal.

Rat feeding study

Six-week-old Sprague-Dawley rats (10/sex/group) were fed either 0, 5 or 15% w/w ground (unprocessed) and processed (toasted and defatted) glyphosate-tolerant canola (which was a composite of two genetically modified lines GT73 and GT200) and Westar canola meal and a diet control (commercial rodent chow with no added canola meal). The canola seed was incorporated into a balanced diet for four weeks. All test diets were formulated as Purina test diets to be as similar as possible in composition to commercial Purina rodent chow.

Mild but significant decreased weight gains were observed in male rats given the 15% dose level of unprocessed seed or processed meal from glyphosate-tolerant canola compared to those fed Westar meal. There were no differences in food consumption between any of the groups that would account for the variable weight gain. These results may be attributable to higher level of glucosinolates in the glyphosate-tolerant canola line compared to the level in the parental line.

For groups fed both glyphosate-tolerant and parental line canola meal, the absolute and/or relative liver and kidney weights were increased approximately 5-20% when compared to diet controls. However there were no differences in absolute or relative organ weights between the glyphosate-tolerant canola and parental line groups.

The experiment was repeated for the processed (toasted and defatted) GT73 and Westar canola meal. Six-week-old Sprague-Dawley rats (10/sex/group) were fed either 0, 5 or 15% w/w processed (toasted and defatted) glyphosate-tolerant canola (line GT73 only) and Westar canola meal and a diet control (commercial rodent chow with no added canola meal).

No meaningful differences were observed in body weights and body weight gains in the second rat study between groups fed processed glyphosate-tolerant canola meal and parental line canola meal. Liver weights were however increased approximately 12-16% for both sexes fed 15% GT73 meal. Livers appeared normal at gross necroscopy. This increase in liver weight has been attributed to a higher level of alkyl glucosinolate toxicants in the glyphosate-tolerant canola line GT73 which was 4 g/kg compared to 1.8 g/kg for the parental line.

Liver weights can vary and this can be an adaptive change that is indicative of a higher level of metabolic activity. Increased liver weight is commonly observed in toxicity studies, when it is often considered a physiological adaptation (if dose

related), that reaches a steady state with continued dosing and is reversible after cessation of treatment. It is not necessarily harmless in itself (Glaister, 1986).

Glucosinolates have been linked to enlargement of the thyroid, adrenal gland, kidney and liver in feeding studies using rapeseed (Verkerk et al, 1998). There is an industry limit of 30 µmol glucosinolates per gram of defatted canola meal (which is equivalent to 12 g/kg) to which this canola line meets. As canola meal is not considered a human food fraction, there are no standards for canola meal in the Australian *Food Standards Code*.

Quail feeding study

Thirty northern bobwhite (*Colinus virginianus*) chicks (three groups of ten each) were fed glyphosate-tolerant canola meal for five days and observed for a further three days. Treatment groups were fed a basal diet, Westar or glyphosate-tolerant canola (both line GT73 and GT200) incorporated at a rate of 20% of the total weight of the diet.

There were no effects on body weight or feed consumption between birds in the control or treatment groups. There were no mortalities or overt signs of toxicity in either treatment or control groups.

A second similar study was also done on the Northern Bobwhite. No treatment related mortality or differences in food consumption, body weight or behaviour occurred between birds fed 20% weight/weight glyphosate-tolerant canola or control canola meal.

Trout feeding study

Triplicate groups of 15 fish rainbow trout (*Oncorhynchus mykiss*) were fed canola meal at 0, 5, 10, 15 or 20% weight of the dry diet for 10 weeks (ie 45 fish/treatment). There was statistical overlap in weight gain of fish fed each dietary treatment and no differences were detected between glyphosate-tolerant canola (both line GT73 and GT200) diets and control diets at individual level of incorporation. Fish fed the glyphosate-tolerant canola did not exhibit any adverse effects of the sample as the level of inclusion increased. These results support the safety of meal from glyphosate-tolerant canola as a component in fish diets.

Conclusions from the feeding studies

All of the feeding studies examined the wholesomeness of glyphosate-tolerant canola meal for animal feeds. Although these studies are limited in terms of the information they provide about the human food fraction (oil), they provide support for the wholesomeness of the genetically modified canola meal.

The glyphosate-tolerant canola meal contains a higher level of glucosinolates than in the control line. The observed increase in liver weights in rats was attributed to this higher level of glucosinolates. The higher level of glucosinolates present in glyphosate-tolerant canola was not attributed to the genetic modification.

An important factor in the assessment of glyphosate tolerant canola is that only highly refined, bleached and deodorised oil is for human consumption. The feeding studies establish the nutritional adequacy of canola meal for animal feeds and represent a worse case scenario in terms of canola consumption by humans. In the processing of canola seed to oil, the erucic acid content is reduced to a very low level that meets Australian regulations and glucosinolates are removed. Consequently, the refined oil constitutes an even lower risk than processed and unprocessed meal.

Conclusions regarding nutritional issues

Nutritional qualities for the glyphosate-tolerant canola line GT73 were determined by compositional analyses of the major components of the seed and processed fractions and were found to be comparable in all respects to the conventional control line Westar.

Changes at the whole food level (canola meal only) have been assessed by the wholesomeness studies and these studies support that the glyphosate-tolerant canola meal is nutritionally comparable to meal from the parent line.

There is a long history of safe use of canola oil. Based on the data submitted in the present application, canola oil derived from glyphosate-tolerant canola line GT73 is considered to be equivalent in terms of its safety and nutritional adequacy to parent varieties.

6. OTHER ISSUES

The significance and metabolism of AMPA in plants and animals

The GOX protein, encoded by the transferred *gox* gene, confers glyphosate tolerance by breaking down glyphosate to glyoxylate and aminomethylphosphonic acid (AMPA), which effectively reduces cellular levels of glyphosate. AMPA is the primary plant metabolite of glyphosate and does not have herbicidal activity. The applicant has provided additional data for the evaluation of the metabolism and toxicology of AMPA. This data addresses the issue that residues would be expected to be higher in some GM crops such as canola line GT73 that can withstand over-the-top application of herbicide as opposed to conventional methods of herbicide application.

6.1 AMPA metabolism in the plant

The metabolism of glyphosate is the same in tolerant or non-tolerant plants: glyphosate is metabolised to AMPA. The only difference between glyphosate metabolism in tolerant and non-tolerant plants is that the relative distribution of metabolites depends on the speed and extent to which glyphosate is converted to AMPA. AMPA has one of three fates in a plant: it is either non-selectively bound to natural plant constituents, further degraded to one-carbon fragments that are incorporated into natural products or conjugated with naturally occurring organic acids to give trace level metabolites.

6.2 AMPA residues in the plant

The metabolism of glyphosate (and AMPA) metabolism in canola line GT73 was investigated using two sequential applications of ^{14}C-glyphosate, each applied at a rate of approximately 0.90 kg a.e./ha at 14 and 22 days after planting. The treatments used, simulate expected commercial treatments but the total application rate of 1.80 kg a.e./ha exceeds the maximum proposed application rate of 0.90 kg a.e./ha. Canola seed was harvested 79 days after the last application. Maximum AMPA residues found in canola seed were 0.97 mg/kg. The amount of radioactivity was determined in processed fractions that had undergone processing that simulated commercial oil extraction (i.e. hexane-extracted oil, aqueous extract, extracted meal) as well as in the initial seed.

The radioactivity in the oil was due to the presence of fatty acids that had incorporated one-carbon fragments that were breakdown products of the labelled glyphosate. No glyphosate or glyphosate related metabolites were present in the oil derived from canola seed that had been treated as described above. Up to 70-80% of the total radioactivity in the unextracted seed remained in the extracted meal, with the remainder present in the aqueous extract. Further investigations characterised the non-extractable bound radioactive residues and the fate of glyphosate in the plant.

Overall, glyphosate metabolism in canola occurs as follows: as a result of the action of the GOX enzyme, glyphosate is rapidly degraded to AMPA which is conjugated to secondary metabolites (N-glyceryl-AMPA and N-acetyl-AMPA). The results suggest that AMPA accounts for at least 15% of bound radioactivity due to unspecific adsorption and binding. In addition, AMPA is further degraded to one-carbon fragments that become broadly incorporated in a wide variety of natural products and plant constituents. Simulated digestive and gastric system studies showed that less than 8% of the bound ^{14}C-activity was released and that therefore only a very small fraction of the bound components would be biologically available if ingested by animals.

Because the level of AMPA was expected to be higher than in other canola lines, an evaluation of the animal metabolism and toxicology of AMPA has also been assessed.

6.3 AMPA metabolism in animals

AMPA metabolism studies were conducted by administering rats intravenously with ^{14}C-AMPA at a rate of 6.7 mg/kg body weight. These studies demonstrated that AMPA is not metabolised in animals and that greater than 90% of the administered dose is rapidly eliminated (i.e. within 48 hours) in faeces and urine.

Glyphosate metabolism studies were conducted by administering rats orally or intravenously with ^{14}C-glyphosate at a rate of 10 or 1000 mg/kg body weight. These studies demonstrated that glyphosate is absorbed to the extent of 30-36% and that its recovery in the excretia accounts for 98-99% of the administered ^{14}C-glyphosate. The metabolism of glyphosate was very minor regardless of whether it was administered orally or intravenously.

In all cases described above, after 120 hours post-administration, less than 0.7% of the administered dose remained in the tissues and organs, demonstrating that AMPA does

not bio-accumulate in these tissues.

6.4 Toxicology of AMPA

Structure analysis shows AMPA to be very similar to the parent molecule glyphosate which has been extensively tested by the applicant and found not to be oncogenic and has a low order of chronic toxicity. Both compounds are poorly absorbed orally and if absorbed, is rapidly excreted unmetabolised via the urine. The toxicity profile is similar between the two compounds and neither compound bioaccumulates.

The major toxicology endpoints have been investigated for AMPA and the results demonstrate a very low order of toxicity. The acute toxicity of AMPA is low, with an oral LD_{50} of 8300 mg/kg.

Subchronic toxicity of AMPA is also low in studies using rats and dogs. AMPA was administered orally to dogs (5 per sex per group) for three months at concentrations of 0, 10, 30, 100 and 300 mg/kg/day. No treatment related effects were observed at doses up to and including the highest dose tested (analytically determined to be 263 mg/kg/day).

Several subchronic exposure in rats were conducted: a 14 day study on groups of rats (5 per sex per group) using doses of 0, 1000, 2000 and 4000 mg/kg/day and a 90 day study on groups of rats (20 per sex per group) using doses of 0, 400, 1200 and 4800 mg/kg/day.

In the first rat study, reduced body weight gain and food consumption were observed at the highest dose tested. No other effects were observed. The NOEL (no observed effect level) was determined to be 2000 mg/kg/day.

In the second study, body weights were reduced in mid and high dose animals. There was no effect on food consumption or haematology at any dose level. There were differences in some blood chemistry parameters (i.e. increase in mean lactic dehydrogenase and SGOT levels) at the high dose level. Hyperplasia of the urinary bladder epithelium was observed at the mid (low incidence) and high dose level. Thus exposure to very high dose levels results in kidney toxicity. However the NOEL in this study was set quite high at 400 mg/kg/day.

Additional chronic and reproductive studies have been conducted to determine the toxicity of glyphosate where the presence of AMPA, as a metabolite of glyphosate, can be deduced. These include a two-generation rat reproduction study and a rat teratology study. The two-generation rat reproduction study found a decrease in pup weight at the high dose, which also produced toxicity to the parents. At the NOEL in this study, animals were exposed to approximately 3 and 740 mg/kg/day of AMPA and glyphosate, respectively. In the rat teratology study, AMPA did not produce birth defects even at levels which produced maternal toxicity.

6.5 Livestock feeding studies

Livestock feeding studies were conducted with swine, poultry and lactating cows. Test groups of animals were fed a daily ration containing a nine to one mixture of

glyphosate and AMPA at total combined daily dietary levels that represent 1X, 3X and 10X the maximum expected residue levels of both compounds in the diet (i.e. 40, 120 and 400 ppm glyphosate and 4, 12 and 40 ppm AMPA respectively).

For all three species, AMPA residues were less than 0.05 ppm (non-detectable) in all fat and muscles samples from all treatment levels. At the 1X dose level, AMPA residues were less than 0.05 ppm in all liver samples and did not exceed 0.07 ppm in all kidney samples. Small residues levels were detected in liver and kidney at the 3X and 10X dose levels. AMPA residue levels in the kidney at the 10X dose level were 0.96, 0.33 and 0.94 ppm in swine, poultry and cows respectively. AMPA residues in liver at the 10X level were 0.39, 0.38 and 0.17 ppm in swine, poultry and cows respectively. Analysis of tissues following the 28 day depuration (i.e. cleansing) period demonstrated that AMPA is rapidly eliminated, with residues less than 0.05 ppm in all samples from all species.

AMPA residues were less than 0.025 ppm (non-detectable) in all egg samples collected from hens dosed at the 1X and 3X levels. With the exception of two eggs which had less than 0.035 ppm AMPA, residues in eggs were less than 0.025 ppm in all egg samples from hens dosed at the 10X level. Analysis of eggs following the depuration period demonstrated that AMPA is rapidly eliminated , with residues less than 0.05 ppm in all egg samples.

AMPA residues were less than 0.025 ppm (non-detectable) in all milk samples collected from cows dosed at the 10X levels. Since AMPA was not detected in the 10X milk samples, the 1X and 3X samples were not analysed.

6.6 Metabolism and distribution in livestock

Lactating goats exposed orally to glyphosate and AMPA (in a combined nine to one ration dose level, contained only low residue levels in the edible tissues. The highest ^{14}C residues among all edible tissues was found in the kidneys (representing 0.13% of the total administered dose) and milk contained less than 0.01% of the total administered dose. Similarly in laying hens exposed orally to glyphosate and AMPA, almost all radioactivity was found in the excretia. The total radioactivity in eggs and tissues accounted for less than 0.02 and 0.1% respectively of the administered dose.

Thus the results from both the feeding and metabolism studies show that AMPA residues will not be present in meat, milk or eggs of animals that consume feed containing expected or exaggerated residues.

6.7 Conclusions

Oil derived from glyphosate-tolerant canola has been shown not to contain any residues of AMPA (or glyphosate).

AMPA has only minimal toxicity in acute and subchronic toxicity studies. Animal metabolism and feeding studies demonstrated that AMPA is rapidly eliminated and does not bio-accumulate in edible tissues, milk or eggs.

Acknowledgements

ANZFA gratefully acknowledges the expert comments of Professor Geoff Fincher in the Department of Plant Science, Waite Institute, University of Adelaide in the preparation of this safety assessment report.

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ATTACHMENT 3

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[4]. This is equivalent to 0.51% of turnover in Australia and 0.19% in New Zealand.

[4] 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.

It is considered that these Full Assessments do constitute a potential Technical Barrier to Trade or a Sanitary/Phytosanitary matter. Matters raised in these Full Assessments therefore will be notified to the WTO.

ATTACHMENT 5

SUMMARY OF FIRST ROUND PUBLIC COMMENTS

The Authority received the first six applications for foods produced using gene technology from Monsanto Australia Ltd. Due to commonalities in these applications, a combined Notice of Application (formally referred to as the Preliminary Assessment Report) was advertised on 28 October 1998, which called for public comment on the applications. A total of 58 submissions were received in response to the combined Notice of Application, of which 53 relate to this application.

Jean Adams (Aust)

- does not want these experimental foods in the common food supply until they have been long–term tested for undesirable side–effects related to public health or to environmental damage;
- questions the legality of forcing such genetically modified foods onto the public and the intention to remove labelling of such foods.

Robert Anderson (member of Physicians and Scientists for Responsible Application of Science and Technology)

- knowledge about the nature of the promoter, genes and the type of antibiotic resistance genes is crucial to a proper assessment;
- the applications should be rejected because most of the New Zealand population does not want to eat genetically engineered food. There are real dangers of allergic reactions, the Maori people are opposed to genetic engineering and these products are all an unknown risk to human health because they have not been tested.

Aoraki Greens and the Organic Garden City Trust (NZ)

- opposed to the amendment to the *Food Standards Code* to permit the foods in the applications;
- claim there is no alternative but to decline the acceptance of these products until they are clearly labelled and can be differentiated from their conventional counterparts;
- believe consumer choice is being violated;
- consider that because the science is new, potential problems or long term implications are yet to be made apparent.

Elaine Attwood (Aust)

- supports Option 1 in the combined Preliminary Assessment - that is, to maintain the status quo and not approve any of the six applications;
- re: A338 - considers 4 weeks of laboratory animal testing inadequate and doubts the applicant's claim that the need for herbicide will be reduced. Comments on proposed increase in the MRL for glyphosate;
- re: A355, A362 and A346–genetically modified material will enter the food chain via cotton seed meal and hulls and corn waste being fed to animals;
- re: A363 – canola free of genetic modification would be marketable overseas;
- re: A341 – the results of laboratory feeding studies in rats are of concern. Long term safety is uncertain and therefore the genetically modified cotton should not

be permitted;
- trade considerations should not prevail over consumer rights to have all genetically modified foods labelled as such.

Australian GeneEthics Network

- Monsanto's proposals should all be rejected as inadequate;
- there should be pre–market human testing to provide data for a precautionary approach on safety and nutritional efficacy;
- there should be full labelling of all approved foods in keeping with the Ministerial decision;
- there should be public review of the MRLs for Roundup in these foods;
- there should be public review of the toxicity of the quantities of Bt toxins likely to enter the human and animal food supplies, taking cultural, social, ethnic and age diversity into account;
- an adverse reactions register should be established to enable systematic monitoring of any impacts of these foods;
- all proposals should be submitted for GMAC assessment and recommendation including an updated and public review of Bt cotton and Roundup Ready soy for environmental and health impacts;
- GMAC's assumption that AQIS regulations would keep imported soy out of the Australian environment does not apply to the other commodities, and the geographical limits and performance of Bt cotton need public review;
- Monsanto has not studied the dietary implications of these products and presents no evidence that the company considered the diversity of diets among different cultures, social or ethnic groups;
- RR soy and corn crops are very different in containing novel DNA, proteins at elevated levels, and new levels of synthetic chemical residue not in food before;
- RR canola and cotton seed oils are so extensively processed before human consumption that no DNA or proteins will remain. This ignores, for example, the use of whole seeds for sprouting, the inclusion of whole seeds in uncooked foods, and the cold pressing of oils;
- Bt cotton and corn are substantially equivalent to parental lines in composition, safety and wholesomeness, yet Bt has never been in the food supply in such quantities before;
- the toxicological studies of RR foods are brief and insufficient as no chemical residue studies are cited, proteins created by inserted genes have only been checked against known protein toxins and allergens, no human, and very few animal testing of the products has been done, whole genetically engineered soybean, corn, canola or cotton were not checked in simulated gastric and intestinal fluids;
- no toxicological studies were carried out on the Bt crops as Monsanto asserts that "regulatory agencies world-wide have determined that the use of registered B.t.k products pose no significant risks to human health, non-target organisms or the environment." Believes this is grossly misleading as it refers to the topical use of a whole organism which quickly disappears from the environment following spraying, whereas Bt crops express large amounts of toxin throughout their systems.

Berylla (NZ)

- these foods will be in 60–80% of all processed foods therefore freedom to choose will be compromised;
- as these foods will also be fed to animals, choices will be restricted even further and if the animals were eaten then the degree of risk will increase;
- support the submissions of the Natural Law Party and Clive Elwell.

Willi Borst (NZ)
- wants all genetically modified foods to be labelled and if not they should all be banned;
- concerned about antibiotic resistance, viral recombination and environmental pollution;
- all genetically modified food should be deemed unsafe until proven otherwise;
- submits that ANZFA not amend the *Food Standards Code* to permit foods derived from genetically modified crops.

Jim Chapple (NZ)
- strongly opposed to all six applications on the grounds that approval of these foods may create a market monopoly for the applicant in the supply of agrochemicals and that gene technology is potentially unsafe;
- very strongly objects to the term "substantially equivalent" as a play on words;
- genetically modified foods are not identical to their conventional counterpart and therefore all such products must carry labelling.

Commerce Commission (NZ)
- no issues raised by the applications on which the Commission has any comments.

Consumers' Association of South Australia Inc. (Aust)
- supports comments made by Elaine Attwood.

Clive Elwell (NZ)
- the applications should be rejected because Maori people find genetic engineering in conflict with their beliefs and values, the overwhelming majority of people in Australia and New Zealand do not want to eat genetically modified food, there is a danger of allergic reactions, and genetically modified food is insufficiently tested and so cannot be regarded as safe for human consumption;
- the foods cannot be sufficiently tested because it is impossible to carry out appropriate tests; the tests that are carried out are limited and inappropriate.

Consumers' Federation of Australia Inc.
- not supportive of these applications being approved at this stage;
- questions the safety of soya milk as infant food because of the presence of trypsin inhibitor and other anti–nutrients after heat processing, and also the presence of isoflavones;
- refers to a reference (no details supplied) which has shown that the isoflavone levels may differ from the levels in conventional soybeans;
- application A338 does not provide sufficient evidence of anti-nutrients to prove that the soybeans are safe for processing into infant formula. In light of this, interprets ANZFA's safety assessment guidelines as requiring a full toxicological and nutritional assessment of the soybeans. Believes these

concerns are serious enough to warrant a recall of foods containing Roundup Ready soy ingredients;
- no evidence is presented by the applicant on glyphosate residues in A338, A362, and A363, despite a specific requirement to do so in ANZFA's safety assessment guidelines;
- does not accept the assertion by the applicant that there is only one novel protein in the Roundup Ready soybeans;
- does not believe that testing for homology of protein structure is a sufficient test for allergenicity. At the very least these foods should be fed to human volunteers in closely monitored trials before they are released generally;
- traces of the introduced proteins could be present in cold–pressed oils at levels sufficient to precipitate allergic reactions, if there is an allergic potential. At the very least, such oils should carry precautionary labels warning of the possibility of allergic reactions;
- the approval of Roundup Ready maize will facilitate even greater use of high fructose corn syrups in Australian processed foods. The end result of this could well be that consumption of high energy products by Australians will rise and that the current excessive levels of nutritional diseases such as obesity, diabetes and heart disease will increase further;
- ANZFA needs to be satisfied that anti–nutrient levels in canola are safe and that they will not rise over time;
- expresses concern about the decreased weight gain by laboratory rats in the first week of a 4 week feeding trial with INGARD cotton seed. Believes that further feeding trials on a range of animals should be performed before this product is released;
- approval of foods produced using gene technology should be deferred until a national coordinating system for regulatory approvals is in place so that a global assessment of their likely impacts can be made;
- a system for monitoring adverse reactions to these foods should be established before they are released into the diet of Australians;
- approval and release of these foods should not occur until the system of labelling agreed to by Health Ministers is established;
- Australia should not be bullied by other countries to accept their exports of unsegregated mixtures of genetically modified and non–modified foods.

Francela Davies (NZ)
- concerned about the addition of food additives in the form of genetically engineered foods that have not been given adequate testing of their benefits or side effects to human health;
- wants ANZFA to address the long term effects of the consumption of foreign proteins, antibiotic resistant marker genes and viruses;
- the applications should be rejected because there is no evidence that these foods are contributing anything positive to the food supply or the environment.

Food Technology Association (FTA) Victoria Inc.
- the risk assessment must be completed and reported to ANZFA stakeholders prior to any decision on the Applications;
- it is unclear from Standard A18 as to the labelling that would apply to these products;
- wants to know what special conditions might apply to these products;

- the option to not permit the sale of these foods is the preferred option;
- the application needs more detail and background information such as a Full Assessment report, details on special conditions and labelling and a complete risk assessment.

Friends of the Earth (NZ)

- share the same concerns as expressed in the submission of the Natural Law Party and Clive Elwell;
- glyphosate has not been included among the residues tested, and there is no awareness of any program that monitors for glyphosate residues in food;
- Treaty of Waitangi obligations have not been considered in ANZFA processes;
- the New Zealand Bill of Rights provides that no New Zealand may be subjected to experimentation without providing informed consent, therefore full disclosure of all transgenic foods and ingredients via labelling is the only way this can begin to be achieved;
- Monsanto has not done any long term studies on health effects;
- submit that ANZFA should approve these foods for a period of 6 months only conditional on a requirement for immediate, prominent labelling of all food products and a warning logo. This should be followed by a moratorium on any further approval of genetically engineered foods.

Noeline Gannaway (NZ)

- supports labelling of all food containing genetically engineered products;
- there may be risks of toxic or allergic reactions;
- oppose the transfer of genetic material between different species as unethical and potentially unsafe.

Goodman Fielder (Aust)

- is fully supportive of developments in the agri–food industry through the application of gene technologies provided that consumer benefits are clearly defined and communicated;
- urges ANZFA to undertake wide consultation with all affected parties, including growers, crushers (in the case of oilseeds), food industry users and consumers before these modified plants are introduced.

Nathan Green (NZ)

- objects vehemently to the further introduction of genetically modified foods, specifically the applications by Monsanto;
- there have not been sufficient tests to prove safety;
- NZ should exploit the GMO free market opportunities;
- there has not been adequate public debate on the introduction of genetically modified foods;
- does not agree with the concept and use of substantial equivalence.

Mike and Jeanne Gregory (NZ)

- the public has not been properly consulted or informed by Government or ANZFA on the introduction of genetically modified foods;
- strongly opposed to genetically modified foods on grounds that these are not adequately tested;

- there is significant and growing scientific concern worldwide about the technology and the processes undertaken to evaluate the safety of genetically modified foods;
- NZ would have a market advantage if genetically engineered foods were prohibited altogether.

Martin Hartman and Cornelia Baumgartner (NZ)
- object to genetically modified foods;
- call for mandatory labelling of all genetically modified foods.

Karen Hunt (NZ)
- demands that all genetically modified foods be labelled;
- states that consumer rights are violated if products are deemed substantially equivalent and consequently are not subject to mandatory labelling.

InforMed Systems Ltd (NZ)
- the transfer of EPSPS genes to soybean, maize, cotton and canola is acceptable;
- the transfer of the gox gene to canola and the use of the cry1Ac gene are also acceptable;
- noted that no mention was made of any maker genes in the applications for soybeans, corn or canola;
- noted that the nptII gene is used in cotton and one insect resistant corn variety. Considers that there are remaining questions with regard to the use of antibiotic resistance genes. It would be reassuring if independent biomedical advice were available to reassure us that this does not pose a risk to the future use of these or related antibiotics in the management of human disease;
- notes that none of the modified plants provides any nutritional or functional benefit for the consumer. It is unfortunate that the first applications should not demonstrate benefits to the consumer, who may thus feel that failure to permit the use of such foods will have no measurable effect on them.

Oraina Jones (NZ)
- genetically engineered foods have not been adequately tested for their benefits or side effects to human health;
- what are the long term effects of the consumption of foreign proteins, antibiotic resistant marker genes and viruses;
- questions whether Monsanto supplied any evidence of long term trials;
- requests that the application be declined as the foods are not contributing in any way to the food supply or environment.

Michael Karas (Aust)
- is opposed to applications A338, A355, A362 and A363 because they are for herbicide resistant crops;
- is concerned about the potential for Roundup residues to be increased in human food supply;
- is concerned about the out–crossing of herbicide resistant crops to create ‘super–weeds’.

Colin Kell (NZ)
- criticises some of the wording used in the preliminary assessment report;

- claims that genetically altering food decreases the nutritional value;
- the application provides no proof that glyphosate does not cause long term effects;
- there has been insufficient testing of these genetically modified foods;
- balanced information on genetic modification needs to be made available and the rights of everyone taken into consideration;
- imported commodities should be segregated at source;
- the applications do not indicate the source of the genes being used - believes that genes from fish and animals are being used which is unethical and against nature.

Janine Kelly (NZ)
- concerned about the depth of investigation into the safety of genetically modified foods and the apparent lack of concern by regulatory authorities for the opinions of informed members of the general public and some scientists;
- ANZFA puts too much faith in the integrity of companies who are producing genetically modified foods;
- urges ANZFA to consider the long–term implications of allowing the sale of genetically modified foods;
- if they are allowed, they should all be labelled.

Kristen Khaine (NZ)
- consumer rights include the choice not to eat any genetically modified foods, therefore labelling is of paramount importance;
- trade barrier issues are secondary to public health and safety.

Hilde and Kristin Knorr (Aust)
- advocate a prohibition on genetically modified foods altogether, but otherwise strongly demand mandatory labelling.

Susie Lees (NZ)
- not enough information has been provided in these applications;
- the public do not want to eat these products;
- if the products are approved, we will be at risk of unknown toxins and allergens.

Margaret and Leonard Krohn (Aust)
- opposed to genetically modified foods on the grounds that insufficient scientific testing has been done and the effects on public health are unknown.

C. Lamprecht (Aust)
- concerned about the possible detrimental health effects of genetically modified foods;
- concerned about increased pesticide residues in food;
- advocates full mandatory labelling of all genetically modified foods.

Hannah Levy (Aust)
- strongly opposed to genetically modified foods because of the limited knowledge concerning the risks associated with the technology;
- demands full labelling.

Mahikari Australia

- strongly advocates the mandatory labelling of all foods or food ingredients produced using gene technology to allow consumer choice;
- disagrees with validity of "substantial equivalence" as a basis for labelling because of a lack of scientific rigor;
- completely opposed to all six applications because of the potential long term risks;
- concerned about increased levels of glyphosate in food;
- considers gene technology unethical;
- considers the outcomes of gene technology scientifically unpredictable because of the possibility that DNA can readily transfer between species.

Nadine McRae and others (NZ)

- opposes all of the six applications on the grounds that gene technology is unpredictable, unsafe and harmful to the environment;
- demands that all food with some genetically modified food content be labelled.

National Council of Women of Australia

- requests that ANZFA maintain the status quo and not amend Standard A18 to permit the sale of the indicated foods;
- no deliberations on applications should be made under this Standard until the situation with labelling is resolved;
- there is no mention of monitoring pesticide residue increase in the final product as a result of a greater tolerance to what is an obvious need to increase the pesticide used;
- for the soybean applications there should be absolutely no doubt about the safety of the source of the soybean if it is to be used in the Australian food supply;
- only two out of the six foods have been tested by feeding to laboratory animals and then only for 6 weeks;
- no evidence was provided about herbicide residue levels in any of the soybean foods despite there being an application to increase the MRL for glyphosate in soybeans;
- although the CP4 EPSPS protein may be inactivated on processing, the application does not take into account the use of raw soybeans to grow sprouts. This could represent an allergy problem and therefore the foods should be labelled;
- ANZFA has not taken into consideration the considerable consumer backlash that is occurring;
- there must be scientific certainty that humans are not exposed to any newly expressed proteins;
- objects to the commercial-in-confidence aspects of A362;
- concerned about the feeding of genetically modified seeds to animals as this is another source for these products entering the human food supply;
- there is no justification for using glyphosate–tolerant canola;
- Australia should be able to prohibit the import of genetically modified foods if it wishes;
- if ANZFA allows genetically engineered foods to be imported into Australia unlabelled, consumers will be affected by a lack of choice.

Natural Law Party (NZ)

- in the absence of a moratorium on genetically modified food, demands labelling of all genetically modified foods on the grounds that there has been no long term pre–market testing or screening for risk factors associated with this technology and that unlabelled products deprive individuals of their basic freedom of choice;
- rejects the notion of substantial equivalence on the grounds that differences at the DNA level make them substantially different;
- concerned about the potential for increased glyphosate levels;
- the effects of glyphosate on health and on phytoestrogens in genetically engineered soy has not been addressed;
- genetically engineered soy contains genes from a virus, a soil bacterium and from petunia, none of which has been in our food before;
- the technology is being introduced in the total absence of an informed public debate about the general acceptance of GMO technology;
- believe that there is significant potential for environmental or health disasters associated with the current introduction of this technology. Believes that serious liability implications exist and need to be explored;
- recommends that, until long term independent safety and risk assessment studies on genetic technology in food production have been completed and their safety to human health and the ecosystems that support human life is established, approvals for these foods should be declined;
- no further applications should be considered until proper public debate has occurred.

New Zealand Nutrition Foundation

- submission identical to InforMed Systems Ltd

Office of Regulation Review (Aust)

- comments on the preparation of the RIS for the full assessment report;
- ANZFA should discuss, in the background section of the report, why products such as the Roundup Ready soybeans, which previously entered the commercial markets without segregation from the non–transgenic counterpart, now require an approval process. Questions whether the regulation is to address health and safety and/or consumer information concerns;
- the problem section of the RIS should outline the characteristics of food produced using gene technology and why these characteristics might give rise to the need to list special conditions. The RIS should specifically canvass the possible special conditions which could apply and fully discuss the varying costs and benefits that each set of conditions entails;
- the material present in the sections on potential regulatory impacts and identification of affected parties should be summarised in the RIS in matrix form;
- when the RIS is fully developed it will need to include a conclusion section which summarises the views elicited from the main affected parties, a conclusion and recommendation option section which states what the preferred option is and why this option was accepted and the others rejected, and an implementation and review section which outlines how the proposal will be administered, implemented and enforced.

Martin Oliver (Aust)

- opposes all six applications on the grounds that the long term safety of eating foods from herbicide tolerant or insect resistant crops has not been adequately established;
- all genetically modified foods should be labelled in order for consumers to choose;
- claims that the foods have not been tested for any health impact on humans.

The Pacific Institute of Resource Management/Revolt Against Genetic Engineering (NZ)

- all genetically modified food should be labelled so that there can be post-market monitoring for new allergens or toxic effects in consumers;
- strongly opposed to the technology because of a range of concerns about public health and safety;
- raised a number of concerns in relation to Application A338 specifically:
  - the bacterial EPSPS is unlike any protein that humans have ever eaten and there is no reliable method for predicting its allergenic potential;
  - a major allergen, trypsin inhibitor was found to be 26.7% higher in transgenic soybeans;
  - the compositional analyses of the soybeans were not done on soybeans that had been treated with the herbicide;
  - there were significant increases compared to controls in the milk fat of cows fed transgenic soybeans; and
  - the applicant did not submit any data on glyphosate residues in the transgenic soybeans.

Sara Parsons (NZ)

- objects to the applications because she is a vegetarian;
- it is harmful to be introducing genetically modified soybeans, corn, canola oil and cottonseed into the NZ food chain;
- these products are a threat to the safety and well being of animals and humans and are of no benefit to society;
- the testing of genetically modified foods on animals and the harm that may be caused to animals in the wider environment is unacceptable;
- the lack of labelling of genetically modified foods means that NZ consumers have no way of making appropriate choices if they wish to avoid eating such foods which may cause allergic reactions and offend ethical beliefs.

Eric Phimister (NZ)

- is concerned about the importation of unlabelled genetically modified food;
- does not wish to consume soybeans with a higher pesticide level than the previously allowed maximum. This alone should make it not substantially equivalent.

Marja Rouse (Aust)

- opposes all six applications on the grounds that the genetically engineered crops pose a major environmental hazard and human health hazard;
- claims that the technology promotes unsustainable farming practices;
- believes consumers have the fundamental right to be informed about all the ingredients in foods and therefore demands mandatory labelling;

- the safety assessment for the applications should not be based on information provided by the applicant in these cases, as the company has a vested interest in having the applications approved.

Dean Scahill (NZ)
- is opposed to the foods which are the subject of Monsanto's applications on the grounds that the costs in terms of potential risk to health, risk to organic crop contamination, and current inability of consumers to identify such foods, greatly outweighs the benefits;
- if NZ remains GMO–free is represents an opportunity to create a niche market;
- a labelling system should be developed which would provide consumers with a choice so that they can retain the right to not eat genetically modified food should they choose;
- ANZFA should address the large public concern associated with the introduction of genetically modified foods onto the market.

Emma Subue-Timson (Aust)
- opposed to foods produced using gene technology on the grounds that the technology contravenes nature.

Christine Taylor (Aust)
- opposes all applications because of the presence of new genes, new proteins and increased herbicide residues in genetically modified foods;
- concerned about the potential for herbicide resistance genes to transfer to other plant species, creating undesirable effects.

Bridget Thrussell (NZ)
- supports regulatory option 1- to not permit the sale of any of the foods in the applications;
- no long term safety tests have been done;
- worried about antibiotic resistance increasing because of the antibiotic resistance marker genes in A355;
- concerned about gene transfer between Roundup Ready canola and other Brassicas.

E.M. Trevelyan (NZ)
- does not believe that genetically modified foods can be assessed as safe because of the possibility of "gene flow";
- crops containing the Bt gene will inevitably lead to resistant insect populations;
- envisages an enormous marketing advantage to NZ if it maintains a clean, green image by not allowing genetically modified food onto the market;
- all genetically modified food products should be labelled.

Richard van Wegen (Aust)
- supports the restricted use of genetically modified plants for food production;
- strongly supports mandatory labelling as a democratic right to make informed decisions about food purchases.

Arnold Ward (Aust)
- opposed to all applications on the grounds that long term safety has not been

established;
- ANZFA only concerns itself with public safety rather than adopting a 'holistic' approach which takes into consideration the broader issues to do with genetic engineering
- Roundup herbicide contains other chemicals which are harmful. Considers that the acceptable daily intake of glyphosate does not take into account the higher toxicity of the surfactant POEA in Roundup, on individuals with increased susceptibility such as children, immune compromised individuals or the elderly;
- notes examples of scientific evidence which show glyphosate can increase levels of plant oestrogens, which are known to affect humans. Very concerned about the potential health effects, particularly in children, of higher levels of oestrogens;
- feeding experiments in cows indicate a change in the milk fat production in animals fed on Roundup Ready soybeans versus non-transgenic soybeans;
- where resistance to Bt toxin occurs because of a widespread use of insect resistant crops, this would mean that organic farmers, who now rely on Bt formulations, could lose an important pest control agent;
- expresses concern about the possibility of recombination and horizontal gene transfer resulting in environmental catastrophies;
- glyphosate does not degrade in soils as efficiently as claimed by the applicant;
- all transgene products should be given the same testing applicable to pharmaceuticals;
- the seeds from genetically engineered crops could spread due to natural disasters;
- plant viruses can acquire viral DNA from a transgenic plant;
- Bt cotton is not very effective in controlling bollworm infestations;
- calls for a moratorium of 10 years on the introduction of genetically modified foods.

Joyce Weatherhead (NZ)
- opposes approval for the applications on the grounds that genetically modified foods have not undergone an independent scientific testing;
- calls for a moratorium on genetically modified foods in NZ for ethical and religious reasons;
- demands mandatory labelling of all genetically modified foods;
- believes that approval for herbicide resistant soybeans will result in a huge increase in the level of contaminating herbicides in foods derived from these crops.

Western Australian Food Advisory Committee
- a safety assessment of the foods is lacking along with the absence of any supporting scientific evidence;
- post–market monitoring to confirm the results of risk assessment and establish evidence of a safe history of use is an unacceptable alternative to a full scientific evaluation, with the results being available for public scrutiny;
- the claim that CP4 EPSPS is destroyed in heat processing requires independent scientific validation and it is unclear from ANZFA's papers whether this evidence has been provided and reviewed;
- insufficient evidence has been provided in the discussion document to support claims that these products are safe or that the Authority has undertaken a

rigorous analysis or comprehensive scientific evaluation of these products;
- the issue of decreased availability of food choices in the marketplace listed under both Options 1 and 2 is not nearly as important as the safety issue;
- given the heightened public concern about genetically modified foods it is essential that scientific information relating to compositional variance due to novel gene expression, toxicology, potential for allergenicity, nutritional and dietary properties for each of the foods proposed by Monsanto, is publicly available;
- the Committee recommends the adoption of Option 1 at this time.

S. and L. Wintergraas
- ANZFA should stop all genetically engineered foods from entering into any food products in NZ, as it will destroy the clean green image;
- ANZFA is not able to guarantee safety of these foods - cites DDT, nuclear power and antibiotics as examples;
- ANZFA should protect the consumer, not big business.

SUMMARY OF SECOND ROUND PUBLIC COMMENTS

The Authority received four applications from Monsanto Australia Ltd. (A346, A355, A362, A363) and one from Dupont/Pioneer (A387) for foods produced using gene technology. A draft Risk Analysis Report (formally referred to as the Full Assessment Report) was released for a 10 week period of public comment on 19 June 2000. At the end of the public comment period (30 August) a total of 26 submissions had been received.

J Coburn (NZ)
- does not want these experimental foods in the common food supply until they have been long–term tested for undesirable side–effects related to public health;
- questions the fairness of the ANZFA response to the concerns expressed in the first round of public submissions;
- comments on the risk of spread of antibiotic resistance due to the use of antibiotic resistance marker genes;
- objects to any trace of herbicide residues in general;
- submits that the Draft Regulatory Impact Assessment is flawed.

Commerce Commission (NZ)
- concerned that labelling and advertising of GM foods is not misleading or deceptive;
- concerned whether by-products from the processing of GM foods could be fed to animals.

National Agenetic Awareness Alliance (Aus)
- believe that there has been no independent scientific research conducted by ANZFA in the risk assessment process;
- request ANZFA to set up analytical techniques to measure DNA or protein in GM-crop-derived oils;
- object to the use of viral promoters such as cauliflower mosaic virus (CaMV) promoter
- believe that GM crops yield less than conventional crops and require more

herbicides.

InforMed Systems (Aus)

- comment that the use of antibiotic resistance marker genes should be phased out;
- the absence of any perceived benefit to the consumer of the modifications is not relevant to their safety, but can only increase public resistance to the technology.

Teresa Sutton (Aus)

- opposes the approval of GM crops into the Australian environment;
- GM techniques not reliable; need for long-term testing; antibiotic resistance marker genes risky;
- believes substantial equivalence inappropriate; risk of horizontal transfer of gene traits; risks from use of viral promoters; risks from use of chemicals in foods;
- suggests the establishment of an adverse reactions register.

Food Technology Association (Aus)

- recommend long-term feeding trials;
- question whether all "novel chemicals" have been "identified/discovered".

Australian GeneEthics Network

- recommends rejection of all applications on GM food;
- Monsanto's proposals should all be rejected as inadequate;
- questions the relevance of substantial equivalence;
- believes ANZFA should adopt the precautionary principle in its risk assessment process;
- suggest that insect-resistant crops should be considered an insecticide;
- labelling of GM food should be encouraged;
- believes the research conducted by Ewen and Pusztai should be considered in the assessments;
- objects to the use of antibiotic resistance marker genes;
- believes precautionary principle should be applied to the use of viral promoter sequences;
- recommend long-term feeding studies be undertaken;
- believe that gene silencing and its potential repercussions are not fully understood;
- state that ANZFA needs to take into account the variation in diet between different cultural and ethical groups.

Environmental Health Branch – SA Department of Human Services (Aus)

- state that the approval of a food produced using gene technology for human consumption in Australia should not depend on the GMO from which it is derived being cleared for general release in Australia. However, if clearance for general release of a GM crop is sought from GMAC and rejected, ANZFA should take account of the reasons for rejection in assessing any application received by the Authority in relation to any food produced using gene technology for human consumption derived from the GM crop.
- applicants should identify which food products produced using genetic

modification contain novel DNA and/or protein so labelling requirements can be determined;
- draft variations to Standard A18 should be specific as to which foods are permitted.

National Council of Women of Australia
- believe that the safety evaluation used by ANZFA is not the best suited to the evaluation of GM food;
- do not support the concept of substantial equivalence;
- objects to the use of antibiotic resistance marker genes;
- believe that animal feeding studies and human feeding studies should be conducted before GM foods are approved;
- post-market surveillance should be carried out since there is no long-term history of safe use of novel foods;
- all food derived from, or processed using genetic engineering, whether any DNA or protein remains in the finished product or not, should be labelled.
- believe that many statements made in the reports are not decisive;
- believe that the public's concerns are being over ridden by trade and other commercial interests;
- want the Office of the Gene Technology Regulator to be the overall regulator on all gene technology matters;
- believes that ANZFA does not deal with the issue of potential allergenicity appropriately; unknown allergens are not tested for;
- states that the Regulatory Impact Assessments for the applications are misleading and that there are no benefits to consumers;
- warn about the risks of using viral promoters such as CaMV;
- support continuing public consultation and information regarding gene technology;
- object to any chemical residues in foods.

Australian Competition & Consumer Commission
- the Commission believes that consumers have a right to purchase products that reflect their own personal preferences. Consumers must be able to rely on disclosures on packaging in order to make purchasing decisions;
- the Commission recommended the delay in the approval of the applications until the ANZFSC labelling decision of 28 July;
- column 2 of the table to clause 2 of Standard A18 could be used to require positive initiatives be undertaken by the applicant such as public information about the food in question or GMOs generally.

Institute of Environmental Science & Research Limited (NZ)
- ESR believe the ANZFA safety assessment process is consistent with current international "best practice" for this area;
- ESR's review of the data supporting the applications for approval of GM foods concluded that there was no reason to disagree with the ANZFA assessment that these foods are safe for human consumption;
- Greater toxicological testing is desirable to improve the data supporting the safety of GM foods, although it is acknowledged that there are practical difficulties in testing whole foods.

Consumers' Institute of New Zealand Incorporated

- expressed concerns over whether ANZFA had established that the evidence provided by the applicant has not been superceded by subsequent research;
- audit processes should be established to ensure that if new knowledge suggests there is any risk associated with the foods that approval can quickly be withdrawn;
- ongoing monitoring of the long-term effects of the foods should also be established;
- expressed concern on the lack of independent verification of testing carried out by the developers of the products;
- believe the concept of substantial equivalence is not rigorous;
- comment that the language in the risk analysis documents gives the impression that uncertainty remains about the products;
- believe that GM foods should be treated in the same way as medicines in relation to tests required to establish safety.

G C Morgan (NZ)

- raised concerns regarding the use of pesticides on crops;
- comments that there is little evidence of any benefit of the introduction of GM foods to the consumer.

Consumers' Association of South Australia Inc. (Aus)
- strongly support the submission of the National Council of Women.

Dieticians Association of Australia
- supports full labelling of GM food;
- comments that the broader environmental impacts of GM foods are not being addressed in the evaluations of the applications;
- believes that the recent decision on labelling of foods produced using gene technology should be extended further to require labelling of purified foods from GM sources, such as oils from glyphosate tolerant canola, even if there are no nutritional or safety concerns with the food;
- noted that very few of the studies that are relied upon in the evaluations have been published in peer-reviewed journals;
- comment that for a number of the applications there are no feeding studies.

I P Hancox (NZ)
- expressed general concerns regarding the environmental impact of GM foods.

P Gilgenberg (NZ)
- expressed general concerns regarding the safety of GM foods.

Food Technology Association of Victoria Inc (Aus)
- recommend long-term feeding trials;
- labelling of foods noting the presence of a GMO should only apply where more than 1% of any food contains a GMO present.

Canberra Consumers Incorporated (Aus)
- comments that none of the reports were peer reviewed;
- expressed concern over the use of antibiotic resistance marker genes;
- recommend long-term feeding trials;
- expressed concerns that GM foods used as stock feeds for animals are not safe for livestock.

National Council of Women of New Zealand (Te Kaunihera Wahine O Aotearoa)
- the Council recommends that where substantial differences are detected in GM foods these products must be labelled;
- the Council advocate that an adequately funded independent scientific body to evaluate data be established as soon as possible.

University of Auckland, Food Science Postgraduate Programme (NZ)
- recommend long-term studies be conducted
- expressed concern over the use of antibiotic resistance marker genes;

Monsanto Australia Limited
- there are many formulations of the herbicide Roundup and not all have the surfactant POEA in them;
- some formulations e.g. Roundup Biactive is actually registered for use in waterways because the surfactant is approved with a good aquatic toxicological profile;

Arnold Ward (Aus)

- believes that ANZFA largely ignores submissions from the general public and is in league with large biotechnology companies;
- believes that there is a conspiracy between ANZFA and the US government and the FDA regarding the introduction of GM foods;
- wants ANZFA to exercise the precautionary principle and not approve GM food until it is proven to be safe;
- states that GM foods may not be as nutritional as conventional foods;
- objects to the concept of substantial equivalence;
- recommends long-term feeding studies in animals and human studies be conducted;
- recommends caution on the use of promotors such as CaMV;
- recommends that GM foods be treated the same as drugs in terms of testing requirements.

Carolyn Kitson

- recommends that ANZFA guidelines for data requirements on safety of GM foods be consistent for every application.

Ministry of Health (NZ)

- considers the ANZFA safety assessment process is consistent with international "best practice" in this area and that all the applications were subject to this process;
- in relation to the assessments themselves, and by way of summary, MoH agree with the conclusion reached in each assessment, that these foods are safe for human consumption;
- the concentration of newly expressed proteins were generally very low as the refinement processes involved removal of these proteins;
- consider that the applications closely considered the potential allergenicity of the newly expressed proteins on the basis of the physical and chemical nature of these proteins, and the similarity of their amino acid sequence with known allergens;
- compositional analyses of the nutrients in control and GM food indicated no substantial differences in the levels of major nutrients; and
- toxicological effects of the modified foods were evaluated (although the estimated dietary intakes of the newly expressed proteins were not determined).

The following submissions were received after the end of the consultation period of 30 August 2000:

Public Health Association of Australia (PHAA) (part submission received 28 September 2000)

- believe that all studies submitted by industry should first be published by peer reviewed journals before undergoing the regulatory process;
- believe that there is a conflict of interest in an applicant company doing its own safety assessments and studies should be reproduced by independent laboratories;
- comment that the statistical analyses on the compositional studies is inadequate;

- contend that these foods undertake at least thorough animal testing, and at least the first phase of the four phases of a clinical trial before being released;
- contend that the issue of likely horizontal gene transfer has not been adequately resolved.

Australian Food and Grocery Council (received September 2000)

- The AFGC supports approval of each the applications A346, A355, A362, A363 and A387 on the basis that they do not raise any public health and safety concerns;
- Labelling of these foods should be according to the 28 July decision of the ANZFSC to enable consumers to make an informed choice.

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 and asserted that food produced using this technology is unsafe for human. A number of general issues were raised in these submissions and are addressed 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. Establishing a dose-response relationship is a pivotal step in toxicological testing. By determining the level of exposure at which no adverse effects occur, a safe level of exposure for humans can be established which includes 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 a need to examine 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 when consumed as part of a food. Such experiments can provide more meaningful information than experiments on the whole food. Additional re-assurance regarding the safety of newly-expressed protein can be obtained by examining 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 as part of the assessment process. 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 between the new food and traditionally-produced food. This can include physical characteristics and compositional factors, as well as an examination of 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 characteristics for 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 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 analytical 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, genetic modification may be used intentionally to improve the nutritional value of food. In this regard, GM foods may be able to assist in addressing the general nutritional needs of the community and also specific dietary needs 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 is in the process of preparing a public discussion paper on the safety assessment process for GM foods. This will be 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.

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 of agriculture/veterinary chemicals

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.

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 Food Regulations (1984) in New Zealand.