6 February 2002
07/02

DRAFT ASSESSMENT REPORT
(FULL ASSESSMENT - s.15)

APPLICATION A388

OIL FROM BROMOXYNIL-TOLERANT CANOLA LINE WESTAR-OXY-235

DEADLINE FOR PUBLIC SUBMISSIONS to the Authority in relation to this matter:
20 March 2002
(see 'Invitation for Public Submissions' for details)

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EXECUTIVE SUMMARY

BACKGROUND

ANZFA received an application from Rhone-Poulenc Rural Australia Ltd (now trading as Aventis CropScience Pty Ltd after its merger with AgrEvo) on 29 April 1999 for the approval of food derived from bromoxynil-tolerant canola *(Brassica napus)*. This canola is tolerant to applications of the herbicide bromoxynil, and is known commercially as Navigator™ canola. This report describes the scientific assessment of the application.

ISSUES ADDRESSED DURING ASSESSMENT

(i) Safety evaluation

Food from bromoxynil-tolerant canola has been evaluated according to the safety assessment guidelines prepared by ANZFA. The assessment considered the following issues: (1) the nature of the genetic modification; (2) general safety issues such as novel protein expression and the potential for transfer of antibiotic resistance genes to microorganisms in the human digestive tract; (3) toxicological issues; and (4) nutritional issues.

Nature of the genetic modification

A single gene, *oxy*, was stably transferred to the bromoxynil-tolerant canola line Westar-Oxy-235 using the *Agrobacterium*-mediated transformation system. The *oxy* gene is derived from the soil bacterium *Klebsiella pneumoniae* subspecies *ozaenae* and encodes the enzyme nitrilase. When produced in canola, the bacterial nitrilase allows the normally bromoxynil-sensitive plants to effectively metabolise the herbicide to a non-toxic compound, thus enabling the plants to survive and grow in the presence of the herbicide. No antibiotic resistances genes were transferred to the bromoxynil-tolerant canola.

General safety issues

Canola is a genetic variation of rapeseed developed by plant breeders specifically for its nutritional qualities, particularly its low levels of saturated fat and naturally occurring toxins. Oil is the only food product of the canola plant that is being evaluated for human consumption as part of this application. Canola oil is routinely used in food and has an established history of safe use.

While nitrilase is readily detected in leaf tissue from bromoxynil-tolerant canola, it is only present in seeds at very low levels and no nitrilase protein could be detected in refined oil.

Toxicological issues

Canola contains two naturally occurring toxins - erucic acid and glucosinolates. The levels of these substances in bromoxynil-tolerant canola were found to be well below the respective mandatory and industry limits. There were no major differences between transgenic and control lines, indicating that the genetic modification process has not altered the levels of these compounds.

The potential toxicity and allergenicity of nitrilase was considered in the assessment. Nitrilase does not have any significant similarity to known protein toxins or allergens and is rapidly digested in conditions that mimic human digestion. The absence of toxicity of nitrilase has also been confirmed through acute toxicity testing in mice. Nitrilase, also cannot be detected in refined canola oil, therefore exposure to the protein, through consumption of refined oil from bromoxynil-tolerant canola, would be effectively zero. There is thus no evidence to indicate that there is any potential for nitrilase to be either toxic or allergenic to humans.

The potential toxicity of DBHA, the by-product of bromoxynil detoxification by nitrilase, was also considered. The evidence indicates that DBHA shows no potential to be toxic to humans at the predicted exposure levels.

Nutritional issues

Detailed compositional analyses did not reveal any consistent differences in key constituents between modified canola plants and control plants, or the oils produced from them. Treatment with bromoxynil also did not affect the levels of any of the key constituents measured. The results confirmed that the levels of key constituents in bromoxynil-tolerant canola are no different to those of non-modified canola varieties. An animal feeding study also confirmed that there is no difference between bromoxynil-tolerant and control varieties of canola in their ability to support typical growth and well being.

Conclusion

On the basis of the data submitted with the present application, refined oil derived from bromoxynil-tolerant canola line Westar-Oxy-235 is considered to be as safe and wholesome as refined oil derived from conventional canola varieties.

(ii) Labelling

The amended Standard for foods produced using gene technology (Standard A18 in Volume 1 of the *Food Standards Code*, Standard 1.5.2 in Volume 2 of the *Food Standards Code*) came into effect on 7 December 2001. Under the revised standard, food products made using oil from bromoxynil-tolerant canola will require labelling if it can be shown that novel DNA and/or protein is present in the final food.

(iii) Public submissions

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

CONCLUSIONS

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

- The introduced gene in bromoxynil-tolerant canola line Westar-Oxy-235 is not considered to produce any increased public health and safety risk;

- On the basis of the data submitted in the present application, oil from bromoxynil-tolerant canola line Westar-Oxy-235 is as safe and wholesome as oil derived from conventional canola varieties;

- On 7 December 2001, food products containing oil from bromoxynil-tolerant canola will require labelling if it can be shown that novel DNA and/or protein is present in the final food.

- The proposed amendment to the *Food Standards Code* is consistent with the section 10 objectives of the *Australia New Zealand Food Authority Act* 1991 and the conclusions of the regulatory impact assessment.

RECOMMENDATION

On the basis of the available evidence, ANZFA considers that oil from bromoxynil-tolerant canola line Westar-Oxy-235 is as safe for human consumption as oil from other commercial canola varieties and is therefore proposing an amendment to the *Food Standards Code* to give approval to the sale of such food in Australia and New Zealand.

ANZFA now seeks public comment on the proposed amendment in accordance with the procedures described in Section 17 of the *Australia New Zealand Food Authority Act 1991*.

FOOD STANDARDS SETTING IN AUSTRALIA AND NEW ZEALAND

The Governments of Australia and New Zealand entered an Agreement in December 1995 establishing a system for the development of joint food standards. On 24 November 2000, Health Ministers in the Australia New Zealand Food Standards Council (ANZFSC) agreed to adopt the new *Australian New Zealand Food Standards Code*. The new Code was gazetted on 20 December 2000 in both Australia and New Zealand as an alternate to existing food regulations until December 2002 when it will become the sole food code for both countries. It aims to reduce the prescription of existing food regulations in both countries and lead to greater industry innovation, competition and trade.

Until the joint *Australia New Zealand Food Standards Code* is finalised the following arrangements for the two countries apply:

- **Food imported into New Zealand other than from Australia** must comply with either Volume 1 (known as Australian *Food Standards Code)* or Volume 2 (known as the joint *Australia New Zealand Food Standards Code)* of the Australian *Food Standards Code,* as gazetted in New Zealand, or the New Zealand *Food Regulations 1984,* but not a combination thereof. However, in all cases maximum residue limits for agricultural and veterinary chemicals must comply solely with those limits specified in the New Zealand *(Maximum Residue Limits of Agricultural Compounds) Mandatory Food Standard 1999.*

- **Food imported into Australia other than from New Zealand** must comply solely with Volume 1 (known as Australian *Food Standards Code)* or Volume 2 (known as the joint *Australia New Zealand Food Standards Code)* of the Australian *Food Standards Code,* but not a combination of the two.

- **Food imported into New Zealand from Australia** must comply with either Volume 1 (known as Australian *Food Standards Code)* or Volume 2 (known as *Australia New Zealand Food Standards Code)* of the Australian *Food Standards Code* as gazetted in New Zealand, but not a combination thereof. Certain foods listed in Standard T1 in Volume 1 may be manufactured in Australia to equivalent provisions in the New Zealand *Food Regulations 1984.*

- **Food imported into Australia from New Zealand** must comply with Volume 1 (known as Australian *Food Standards Code)* or Volume 2 (known as *Australia New Zealand Food Standards Code)* of the Australian *Food Standards Code,* but not a combination of the two. However, under the provisions of the Trans-Tasman Mutual Recognition Arrangement, food may **also** be imported into Australia from New Zealand provided it complies with the New Zealand *Food Regulations 1984.*

- **Food manufactured in Australia and sold in Australia** must comply with Volume 1 (known as Australian *Food Standards Code)* or Volume 2 (known as *Australia New Zealand Food Standards Code)* of the Australian *Food Standards Code* but not a combination of the two. Certain foods listed in Standard T1 in Volume 1 may be manufactured in Australia to equivalent provisions in the New Zealand *Food Regulations 1984.*

In addition to the above, all food sold in New Zealand must comply with the New Zealand *Fair Trading Act 1986* and all food sold in Australia must comply with the Australian *Trade Practices Act 1974*, and the respective Australian State and Territory *Fair Trading Acts.*

Any person or organisation may apply to ANZFA to have the *Food Standards Code* amended. In addition, ANZFA may develop proposals to amend the Australian *Food Standards Code* or to develop joint Australia New Zealand food standards. ANZFA can provide advice on the requirements for applications to amend the *Food Standards Code*.

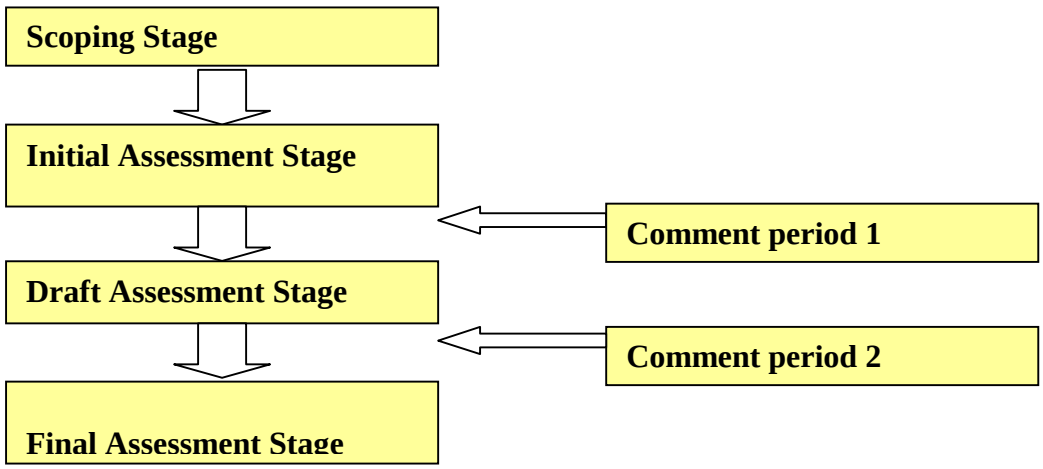
INVITATION FOR PUBLIC SUBMISSIONS

The process for amending the *Australia New Zealand Food Standards Code* (the Code) is prescribed in the ANZFA Act 1991. Open and transparent consultation with interested parties is a key element in the process involved in amending or varying the Code.

Any individual or organization may make an 'application' to the Australia New Zealand Food Authority (the Authority) seeking to change the Code. The Authority itself, may also seek to change the Code by raising a 'proposal'. In the case of both applications and proposals there are usually two opportunities for interested parties to comment on proposed changes to the Code during the assessment process. This process varies for matters that are urgent or minor in nature.

Following the initial assessment of an application or proposal the Authority may decide to accept the matter and seek the views of interested parties. If accepted, the Authority then undertakes a draft assessment including, preparing a draft standard or draft variation to a standard (and supporting draft regulatory impact statement). If a draft standard or draft variation is prepared, it is then circulated to interested parties, including those from whom submissions were received, with a further invitation to make written submissions on the draft. Any such submissions will then be taken into consideration during the final assessment, which the Authority will hold to consider the draft standard or draft variation to a standard.

Comment opportunities in the usual assessment process to change the Australia New Zealand Food Standards Code
(Note: this process may vary for matters that are urgent or minor)



Content Of Submissions

Written submissions containing technical or other relevant information which will assist ANZFA in undertaking an assessment on matters relevant to the application, including consideration of its regulatory impact, are invited from interested individuals and organizations. Information providing details of potential costs and benefits of the proposed change to the Code from stakeholders is highly desirable. Claims made in submissions should be supported wherever possible by referencing or including relevant; studies, research findings, trials, surveys etc. Technical information presented should be in sufficient detail to allow independent scientific assessment.

Submissions may provide more general comment and opinion on the issue although those framing their submissions should bear in mind ANZFA's regulatory role specifically relates to food supplied for human consumption in Australia and New Zealand. The ANZFA Act 1991 sets out the objectives of the Authority in developing food regulatory measures and variations of food regulatory measures as:

(a) the protection of public health and safety; and
(b) the provision of adequate information relating to food to enable consumers to make informed choices; and
(c) the prevention of misleading or deceptive conduct.

In developing food regulatory measures and variations of food regulatory measures
The Authority must also have regard to the following:

(a) the need for standards to be based on risk analysis using the best available scientific evidence;
(b) the promotion consistency between domestic and international food standards;
(c) the desirability of an efficient and internationally competitive food industry;
(d) the promotion of fair trading in food.

Submissions addressing the issues in the context of the objectives of the Authority as set out in the *ANZFA Act 1991* will be more effective in supporting their case.
Written submissions containing technical or other relevant information which will assist the Authority in undertaking a final assessment on matters relevant to the application, including consideration of its regulatory impact, are invited from interested individuals and organisations. Technical information presented should be in sufficient detail to allow independent scientific assessment.

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

Following its draft assessment of the application the Authority may prepare a draft standard or draft variation to a standard (and supporting draft regulatory impact statement), or decide to reject the application/proposal. If a draft standard or draft variation is prepared, it is then circulated to interested parties, including those from whom submissions were received, with a further invitation to make written submissions on the draft. Any such submissions will then be taken into consideration during the inquiry, which the Authority will hold to consider the draft standard or draft variation to a standard.

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

Contact details for submitters are recorded so that the Authority can continue to keep them informed about progress of the application or proposal.

Deadlines
The deadlines for submissions are clearly indicated in the advertisements calling for comment and in the relevant Assessment Reports. While the Authority often provides comment periods of around 6 weeks, the periods allowed for comment may vary and may be limited to ensure critical deadlines for projects can be met. Unless the Project Manager has given specific consent for an extension, the Authority cannot guarantee that submissions received after the published closing date will be considered.

Delivery of Submissions
Submissions must be made in writing and should be clearly marked with the word 'Submission' and quote the **correct project number** and **title**. Submissions may be sent by mail, fax or email to the **Standards Liaison Officer** at one of the following addresses:

Australia New Zealand Food Authority
PO Box 7186
Canberra BC ACT 2610
AUSTRALIA
Tel (02) 6271 2258
Fax (02) 6271 2278
email: slo@anzfa.gov.au

Australia New Zealand Food Authority
PO Box 10559
The Terrace WELLINGTON 6036
NEW ZEALAND
Tel (04) 473 9942
Fax (04) 473 9855
email: anzfa.nz@anzfa.gov.au

Submissions should be received by the Authority by: 20 MARCH 2002

Submissions may also be sent electronically through the submission form on the ANZFA website www.anzfa.gov.au. Electronic submissions should also include the full contact details of the person making the submission on the main body of the submission so that the contact details are not separated.

Further Information
Further information on this and other matters should be addressed to the Standards Liaison Officer at the Australia New Zealand Food Authority at one of the above addresses.

Assessment reports are available for viewing and downloading from the ANZFA website or alternatively paper copies of reports can be requested from the Authorities Information Officer at info@anzfa.gov.au.

1. BACKGROUND TO THE APPLICATION

The herbicide-tolerant canola under consideration is known commercially as Navigator™ canola, and has been genetically modified to confer tolerance to bromoxynil – an herbicide belonging to the oxynil family - which is used for the control of broad leaf weeds common in canola fields.

The genetic change involved in the modification results in the transfer of one gene — the *oxy* gene from the soil bacterium *Klebsiella pneumoniae* subspecies *ozaenae*. The gene codes for nitrilase, an enzyme that breaks down oxynil herbicides into non-phytotoxic compounds.

Navigator™ canola is not currently grown in either New Zealand or Australia, and is only imported as a highly processed product. Canola seeds are processed into two major products, oil and meal. The oil from the seeds is the only human food product being assessed as part of this application. Canola meal is principally used as an animal feed. Canola oil is a premium quality oil and is used in a variety of manufactured food products including salad and cooking oil, margarine, shortening, mayonnaise, sandwich spreads, creamers and coffee whiteners. It can thus be imported as an ingredient of many processed foods.

The main benefits of bromoxynil-tolerant canola are agronomic in nature, and are therefore likely to accrue mainly to the primary producer. Canola weeds should be cheaper and easier to control, with lower expenditure on labour and herbicides. More general benefits may flow to the community as a result of reduced primary production costs.

2. PUBLIC CONSULTATION

ANZFA completed an Initial Assessment (Preliminary Assessment – section 13) upon receipt of the application and called for public comment on 3 November 1999. A total of 45 submissions were subsequently received. **Attachment 5** contains a summary of the submissions.

3. NOTIFICATION OF THE WORLD TRADE ORGANIZATION

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

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

4. ISSUES ADDRESSED DURING ASSESSMENT

4.1 Safety assessment

Food from bromoxynil-tolerant canola has been evaluated according to the safety assessment guidelines prepared by ANZFA[1]. The assessment considered the following issues: (1) the nature of the genetic modification; (2) general safety issues such as novel protein expression and the potential for transfer of novel genetic material to cells in the human digestive tract; (3) toxicological issues; and (4) nutritional issues.

On the basis of the available information, ANZFA concluded that refined oil derived from bromoxynil-tolerant canola line Westar-Oxy-235 is as safe and wholesome as refined oil derived from conventional canola varieties. The full safety assessment can be found at **Attachment 2** to this report.

4.2 Labelling of oil produced from bromoxynil-tolerant canola

On 28 July 2000 the Australia New Zealand Food Standards Council agreed to a revised standard which requires labelling of food where novel DNA and/or protein is present in the final food and also where the food has altered characteristics. The revised standard (A18 in the Australian *Food Standards Code*, 1.5.2 in the Australia New Zealand *Food Standards Code*) was gazetted on 7 December 2000, and came into effect on 7 December 2001.

Under the revised labelling provisions, oil derived from bromoxynil-tolerant canola line Westar-Oxy-235 will require labelling if it can be shown that novel DNA or novel protein is present in the final food.

4.3 Issues arising from public submissions

General issues

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

Specific issues

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

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

(i) Toxicity of bromoxynil breakdown products

Both the New Zealand Ministry of Health and the Public and Environmental Health Service in Australia raised the point that the ANZFA safety assessment should address the issue of whether residues of the herbicide degradation process are present, toxic and/or subject to a maximum residue limit (MRL). This is of relevance to bromoxynil-tolerant canola. The Consumers' Association of South Australia Inc. & National Council of Women of Australia raised similar concerns, suggesting that the persistence and toxicity of bromoxynil had not been adequately assessed by the US FDA, and that the breakdown product of bromoxynil (DBHA) may be more potent than bromoxynil itself.

Response

This issue has been fully addressed in the safety assessment report (**Attachment 2**).

Before the production of Navigator™ canola, bromoxynil use on canola would not have been possible, as the crop would have been damaged. There is currently no MRL for either bromoxynil or DBHA residues in canola in Australia. Similarly, in New Zealand no MRL exists, although a level of 0.1 ppm is allowed under default clause 6b of the regulation 257 (2A).

Residue analysis for both bromoxynil and the metabolite DBHA was done on samples of canola from field trials in Canada. All were below the level of quantitation of the analytical method (0.05 ppm), and very close to the limit of detection (0.02 ppm), meaning that none of them can be considered significant. A further study on the processed fractions of canola seed (oil and meal) found no detectable residues, even with rates 10 times that of the commercial rate, and no concentration of residues with processing. Overall, therefore, the residues expected to be present in refined canola oil are effectively zero.

The US EPA carried out a thorough toxicity assessment of bromoxynil, and produced a report in December 1998. They concluded that the risk from bromoxynil was "negligible". In addition they found that, based on an examination of the chemical structure of DBHA, that the toxicity of this metabolite would be similar to or lower than that of bromoxynil itself.

The consumption of oil produced from bromoxynil-tolerant canola is therefore not considered to pose a risk to human health.

(ii) Allergenic effects of novel genes

Diane Davie suggested that the use of herbicide-resistance genes could increase allergies.

Response

The safety assessment carried out by ANZFA has addressed the issue of the potential allergenicity of nitrilase in some depth. Data was evaluated on a comparison of the amino acid sequence of nitrilase to that of known allergens, its resistance to acid and protease digestion, and its presence in the food as consumed. Nitrilase does not come from a source that is known to be allergenic and has none of the characteristics that are common to food allergens, nor does it have any significant amino acid sequence similarity to known allergens.

This, combined with the fact that refined oil contains no detectable nitrilase, means that in the case of bromoxynil-tolerant canola, nitrilase has very limited potential to become a food allergen.

4.4 Risk management

Under the *Food Standards Code*, a GM food must undergo a safety assessment in accordance with ANZFA's safety assessment guidelines.

On the basis of the conclusions of the safety assessment, together with a consideration of the public submissions, it is recommended that Table 1 to Clause 2 of Standard A18/Standard 1.5.2 be amended to include oil from bromoxynil-tolerant canola line Westar-Oxy-235. The recommended variation is provided in **Attachment 1**.

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 GM 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.

4.5 Regulatory impact assessment

The benefits and costs associated with the proposed amendment to the *Food Standards Code* have been analysed in a draft Regulatory Impact Assessment (**Attachment 3**). The benefits of the proposed amendment to approve oil from bromoxynil-tolerant canola primarily accrue to the food industry and government, with potentially a small benefit to the consumer.

5. CONCLUSIONS

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

It is concluded that:

- The introduced gene in bromoxynil-tolerant canola line Westar-Oxy-235 is not considered to produce any increased public health and safety risk;

- On the basis of the data submitted in the present application, oil from bromoxynil-tolerant canola line Westar-Oxy-235 is as safe and wholesome as oil derived from conventional canola varieties;

- Food products containing oil from bromoxynil-tolerant canola will require labelling if it can be shown that novel DNA and/or protein is present in the final food; and

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

- The proposed amendment to the *Food Standards Code* is consistent with the section 10 objectives of the *Australia New Zealand Food Authority Act* 1991 and the conclusions of the regulatory impact assessment.

6. RECOMMENDATION

On the basis of the available evidence, ANZFA considers that oil from bromoxynil-tolerant canola line Westar-Oxy-235 is as safe for human consumption as oil from other commercial canola varieties and is therefore proposing an amendment to the *Food Standards Code* to give approval to the sale of such food in Australia and New Zealand. The proposed amendment is provided in **Attachment 1**.

ATTACHMENTS

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

ATTACHMENT 1 DRAFT VARIATION TO THE *FOOD STANDARDS CODE*

APPLICATION A388

OIL DERIVED FROM BROMOXYNIL-TOLERANT CANOLA LINE WESTAR-OXY-235

To commence: On gazettal

The Food Standards Code is varied by:

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

Oil from bromoxynil-tolerant canola line Westar-Oxy-235.

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

Oil from bromoxynil-tolerant canola line Westar-Oxy-235.

ATTACHMENT 2 DRAFT SAFETY ASSESSMENT REPORT

APPLICATION A388

OIL DERIVED FROM BROMOXYNIL-TOLERANT CANOLA LINE WESTAR-OXY-235

SUMMARY AND CONCLUSIONS

Oil from bromoxynil-tolerant canola line Westar-Oxy-235 has been assessed by ANZFA to evaluate its safety for human consumption. 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 allergenicity and toxicity of the newly expressed proteins.

Nature of the genetic modification

Bromoxynil-tolerant canola line Westar-Oxy-235 was generated by the transfer of the *oxy* gene from the soil bacterium *Klebsiella ozaenae*, using the *Agrobacterium*-mediated transformation system. The *oxy* gene codes for the enzyme nitrilase, which converts the herbicide bromoxynil (3,5-dibromo-4-hydrobenzonitrile) to its non-phytotoxic metabolite 3,5-dibromo-4-hydroxybenzoic acid (DBHA). No other genes were transferred and the transformed canola was shown to be phenotypically and genotypically stable by segregation and mapping studies.

General safety issues

Canola is a genetic variation of rapeseed developed by plant breeders specifically for its nutritional qualities, particularly its low levels of saturated fat and naturally occurring toxins. Oil is the only product of the canola plant that is being assessed for human consumption. Canola oil is routinely used in food and has a moderately long history of safe use.

The new protein, nitrilase, is an enzyme specific for oxynil herbicides. It was found to be easily detectable in leaf extracts from the modified plant, but was only present at very low levels in seeds. No detectable protein was found in refined oil.

The modification did not involve the transfer of any antibiotic resistance genes.

Toxicological issues

Analysis of naturally occurring toxins (erucic acid and glucosinolates) in bromoxynil-tolerant canola showed levels for both to be well below the respective mandatory and industry limits. There were no major differences between transgenic and control lines, indicating that the genetic modification process had not altered the levels of these compounds.

The potential toxicity and allergenicity of nitrilase was considered in the assessment. Proteins from the same family as nitrilase are ubiquitous throughout the animal and plant kingdoms, and are consumed by both animals and humans. Nitrilase itself does not have any

significant similarity to known protein toxins or allergens and is rapidly digested in conditions that mimic human digestion. The absence of toxicity of nitrilase has been confirmed through acute toxicity testing in mice.

Nitrilase, also cannot be detected in refined canola oil, therefore exposure to the protein, through consumption of refined oil from bromoxynil-tolerant canola, would be zero. There is thus no evidence to indicate that there is any potential for nitrilase to be either toxic or allergenic to humans.

The potential toxicity of DBHA, the by-product of bromoxynil detoxification by nitrilase, was also considered. The evidence indicates that DBHA shows no potential to be toxic to humans at the predicted exposure levels.

Nutritional issues

Detailed compositional analyses did not reveal any consistent differences in key constituents between modified canola plants and control plants, or the oils produced from them. Treatment with bromoxynil also did not affect the levels of any of the key constituents measured. The results confirmed that the levels of key constituents in bromoxynil-tolerant canola are no different to those of non-modified canola varieties. An animal feeding study also confirmed that there is no difference between bromoxynil-tolerant and control varieties of canola in their ability to support typical growth and well being.

Conclusion

No potential public health and safety concerns have been identified in the assessment of canola line Westar-Oxy-235. On the basis of the data submitted with the present application, refined oil derived from bromoxynil-tolerant canola line Westar-Oxy-235 is considered to be as safe and nutritious as refined oil derived from conventional canola varieties.

1. BACKGROUND

Aventis CropScience Pty Ltd has made an application to ANZFA to vary Standard A18 to include oil derived from canola, which has been genetically modified to be tolerant to the oxynil family of herbicides comprising bromoxynil and ioxynil. The genetically modified canola is marketed as Navigator™ canola.

The oxynil family of herbicides act by inhibiting electron transport in photosystem II in plants. Inhibition of electron transport causes superoxide production resulting in the destruction of cell membranes and an inhibition of chlorophyll formation, leading to plant death (Comai and Stalker 1986). Tolerance to either bromoxynil (3,5-dibromo-4-hydorxybenzonitrile) or ioxynil (3,5-di-iodo-4-hydroxybenzonitrile) is achieved through expression in the plant of a bacterial nitrilase enzyme that hydrolyses the herbicide to an inactive, non-phytotoxic compound. The nitrilase is derived from the bacterium *Klebsiella pneumoniae* subspecies *ozaenae* which is responsible for rapidly degrading bromoxynil in soil. The nitrilase enables the bacterium to utilise bromoxynil as a sole source of nitrogen (McBride *et al* 1986).

Bromoxynil is particularly effective on broadleaf weeds common in canola fields. The rationale for engineering canola to be bromoxynil-tolerant is to enable bromoxynil-containing

herbicides to be used for the post-emergence control of broadleaf weeds in canola crops without crop injury. The modified canola was developed for commercialisation in Canada, where it is grown for both domestic use and for export. Although the current level of trade of canola and its commodities between Canada and New Zealand and Australia is relatively small, some imported processed foods may contain genetically modified canola oil.

Canola seeds are processed into two major products, oil and meal with the oil being the only human food product being considered in this assessment. Canola meal is used principally as an animal feed. Canola oil is a premium quality oil and is used in a variety of manufactured food products including salad and cooking oil, margarine, shortening, mayonnaise, sandwich spreads, creamers and coffee whiteners. It can thus be imported as an ingredient of many processed foods.

2. DESCRIPTION OF THE GENETIC MODIFICATION

2.1 Methods used in the genetic modification

Canola (*Brassica napus* L. oleifera Metzg.) line Westar was transformed with plasmid pRPA-BL-150a using the method of *Agrobacterium tumefaciens*-mediated transformation. A disarmed (i.e. non phytopathogenic) strain of *Agrobacterium tumifaciens*, EHA 101 was used (Hood *et al* 1986). The *Agrobacterium*-mediated transformation system is well understood, and is widely used in plant biotechnology (Zambryski 1992).

Regeneration of transformed plants was done in the presence of bromoxynil as the sole selective agent. The transformation resulted in the selection of a single transformation event – Westar-Oxy-235 – which was subsequently used in sexual crosses with elite canola lines to generate the Navigator™ canola varieties used in commercial production.

2.2 Function and regulation of the novel genes

The transformation of canola with plasmid pRPA-BL-150a resulted in the transfer of a single gene expression cassette. The genetic elements contained within the gene expression cassette are described in Table 1 below and their organisation is depicted in Figure 1.

Table 1: Description of the gene expression cassette contained within pRPA-BL-150a

Genetic element	Source	Function
35S promoter	The cauliflower mosaic virus (CaMV) 35S promoter region (Gardner *et al* 1981).	A promoter for high-level constitutive (occurring in all parts of the plant and at all stages of development) gene expression in plant tissues.
Enhancer	The non-translated leader of a RuBisCO small subunit gene derived from maize (Lebrun *et al* 1987).	The non-translated leader sequence helps to stabilise mRNA and improve translation.
oxy	Gene isolated from *Klebsiella pneumoniae* subspecies *ozaenae* encoding the enzyme nitrilase (Stalker *et al* 1988).	Inactivates the herbicide bromoxynil and confers bromoxynil tolerance when expressed in plants.
NOS 3'	The 3' non-translated region of the nopaline synthase gene isolated from *Agrobacterium tumefaciens* plasmid pTi37	Contains signals for termination of transcription and directs polyadenylation.

(Bevan *et al* 1983).

The oxy gene

The *oxy* gene was isolated from the soil bacterium *Klebsiella pneumoniae* subsp. *ozaenae* and encodes an enzyme that metabolises the herbicide bromoxynil (Stalker and McBride 1987). The 1150 base pair *oxy* gene has been fully sequenced and its encoded enzyme, nitrilase, has been fully characterised (Stalker *et al* 1988). When transferred into plants, the gene, through its encoded protein, confers tolerance to the oxynil family of herbicides including bromoxynil and ioxynil. The mechanism of tolerance involves the detoxification of the herbicide by the nitrilase enzyme. This degradation effectively inactivates the herbicide and enables the normally bromoxynil-sensitive plant to survive and grow when treated with applications of the herbicide.

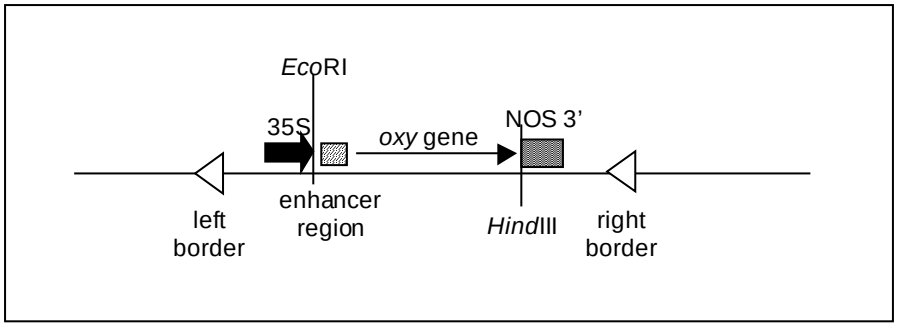
Other genetic elements

The plasmid pRPA-BL-150a is a double border binary plant transformation vector which contains well-characterised DNA segments required for the selection and replication of the plasmid in bacteria as well as the right and left borders delineating the region of DNA (T-DNA) which is transferred into the plant genomic DNA (Table 2). This is the region into which the gene expression cassette is inserted. DNA residing outside the T-DNA region does not normally get transferred into plant genomic DNA (Zambryski 1992). All DNA cloning and vector construction was carried out using the host bacterium *Escherichia coli* DH5α, a derivative of the common laboratory *E. coli* K-12 strain.

Table 2: Description of other genetic elements contained within pRPA-BL-150a

Genetic element	Source	Function
Left border	A DNA fragment of the pTiA6 plasmid containing the 24 bp nopaline-type T-DNA left border region from *A. tumefaciens* (Barker *et al* 1983).	Terminates the transfer of the T-DNA from *A. tumefaciens* to the plant genome.
Right border	A DNA fragment from the pTiA6 plasmid containing the 24 bp nopaline-type T-DNA right border region from *A. tumefaciens*. (Barker *et al* 1983).	The right border region is used to initiate T-DNA transfer from *A. tumefaciens* to the plant genome.
Genta	Gentamicin resistance gene from plasmid pH1J1 (Hirsch and Beringer 1984).	Confers resistance to the antibiotic gentamicin. Used as a marker to select transformed bacteria from non-transformed bacteria during the DNA cloning and recombination steps undertaken in the laboratory prior to transformation of the plant cells.
ori-322	Origin of replication from *E. coli* plasmid pBR322 (Bolivar *et al* 1977).	Allows for autonomous replication of plasmids in *E. coli.*

Figure 1: Diagram of the T-DNA region transferred to Westar-Oxy-235.



2.3 Characterisation of the genes in the plant

Selection of plant lines

After the transformation of Westar with pRPA-BL-150a, regenerated plantlets were taken out of tissue culture and transferred to soil. The transformed plants were then assayed for herbicide tolerance, as well as other agronomic characteristics, in order to select the best transformation event. Line Westar-Oxy-235 was subsequently selected and used for all further studies, as well as for sexual crosses with elite lines.

Characterisation of inserted T-DNA

Southern blotting (Southern 1975) was used to characterise the inserted T-DNA in terms of insert number (number of integration events), insert integrity (gene size), and sequences outside the T-DNA borders (including the gentamicin resistance gene and the plasmid origin of replication).

Genomic DNA was isolated from leaf tissue of the non-transformed parental line, Westar and from the T_3 generation of the transformed canola line, Westar-Oxy-235. To determine the insert number of the T-DNA, genomic DNA was digested with either *EcoR*1 or *Hind*III, which reside at the 5' and 3' ends of the *oxy* gene, respectively (see diagram above). The number of hybridising bands detected will represent the number of copies of the *oxy* gene present in the plant genome, and hence serves as an indicator of the number of T-DNA insertions. With either restriction digestion, only a single hybridising band was detected, indicating that only a single copy of the *oxy* gene is present in Westar-Oxy-235. No hybridising bands were detected in genomic DNA isolated from the non-transformed control. Double digestion of the genomic DNA with both *EcoR*1 and *Hind*III resulted in a single hybridising band corresponding to the size of the coding region of the *oxy* gene (1150 bp). This indicates that the entire coding region has been transferred.

To determine if any sequences from outside the T-DNA borders had been transferred to the plant genome, genomic DNA from both Westar-Oxy-235 and the parental control were probed with a DNA fragment corresponding to the *ori-322* region of pBR322. No hybridising bands were detected, indicating that the bacterial origin of replication had not been transferred.

PCR analysis was used to determine if the gentamicin resistance gene had been transferred during the transformation process. DNA extracted from leaf tissue harvested from Westar-

Oxy-235 and the parental control line was used in the analysis. Plasmid DNA, containing the gentamicin resistance gene, was used as the reference substance and positive control for the analysis. No gentamicin-specific DNA fragment could be amplified from DNA extracted from Westar-Oxy-235, indicating that the gentamicin resistance gene had not been transferred.

Conclusion

A single copy of T-DNA, containing the *oxy* gene, has been integrated at a single site in Westar-Oxy-235. No rearrangements of the T-DNA were apparent and no sequences residing outside the T-DNA region, including the gentamicin resistance gene, were transferred during the transformation.

2.4 Stability of the genetic changes

The genetic stability (i.e., inheritance) and segregation of the bromoxynil-tolerant trait was monitored using data obtained from herbicide-sprayed plants and Southern blotting.

Progeny derived from the original transformation event, Westar-Oxy-235, were sprayed with oxynil herbicides at the T_2 and T_3 generations. By spraying seedlings with the herbicide and determining the Mendelian segregation ratios of the bromoxynil tolerant trait it is possible to determine the total number of functional (bromoxynil-tolerant) loci that have been integrated into an individual transformed plant. Ideally, a single genetic locus (i.e., a single insertion site) is preferred because, while not essential for the performance of the canola or the *oxy* gene, it simplifies the breeding of the trait into other elite commercial cultivars.

The segregation analysis done with the early generations derived from the original transformation event indicated the bromoxynil-tolerance trait is stably inherited by subsequent generations and that it segregates in a manner consistent with a single genetic locus.

Beyond the T_3 generation, lines homozygous for the bromoxynil-tolerant trait were selected. These lines no longer display segregation of the trait and oxynil spray screening is instead used to maintain and monitor seed purity. The maintenance of the tolerance trait over subsequent homozygous generations is thus a good measure of genetic stability. The bromoxynil-tolerant trait was found to be stably maintained over several generations produced from self-pollination, as well as in different genetic backgrounds produced through backcrossing with elite canola varieties. During the backcrossing program, the *oxy* gene was introgressed into a winter elite variety of canola called Samourai, producing Samourai-Oxy-235. Southern blotting was done on genomic DNA isolated from Samourai-Oxy-235 and compared to Westar-Oxy-235. The hybridisation patterns obtained were indistinguishable, confirming that the *oxy* gene is stably maintained in different genetic backgrounds.

Conclusion

Stability of the bromoxynil-tolerant trait was studied by backcrossing of plants containing transformation event Westar-Oxy-235 with elite canola varieties and by self-crossing followed by propagation. The bromoxynil-tolerant trait was found to segregate in a manner consistent with a single genetic locus and was also found to be stably inherited from one

generation to the next. Additionally, Southern blotting demonstrated that the *oxy* gene was stably maintained in a different genetic background.

3. GENERAL SAFETY ISSUES

3.1 History of use

Donor organism

Klebsiella ozaenae is a member of the *Enterobacteriaceae*, a group of facultative gram-negative bacteria. The European Federation of Biotechnologies has classified *K. ozaenae* as a Class 2 microorganism. This class contains microorganisms that could potentially cause disease in humans, however no known pathogenicity exists for the subspecies *ozaenae*. Bacteria of the *Klebsiella* class are widely distributed in nature, occurring naturally in the soil, water and in grain and are normal inhabitants of the intestinal tract (Krieg and Holt 1984).

Host organism

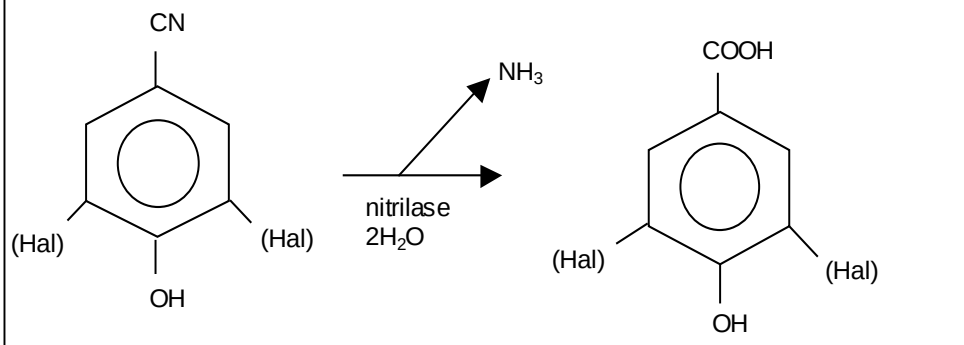
The plant species *Brassica napus* L. oleifera Metzg is more commonly known as oilseed rape, rape or rapeseed, with some cultivars referred to as canola. Rapeseed breeding began soon after the crop was introduced during the 1940s. Early rapeseed varieties were very high in the natural toxicants, erucic acid and glucosinolates, which made them unsuitable for consumption by either humans or animals. In the 1970s intensive breeding programs produced high quality varieties that were significantly lower in both erucic acid and glucosinolates. These varieties, largely *Brassica napus*, were called canola, the term denoting that these varieties contain an erucic acid level below 2% of total fatty acids and less than 30 micromoles of total glucosinolates. World production of oilseed rape in 1996-1997, was the third most important of oilseed crops behind soybean and cottonseed, but above peanut, sunflower and palm.

Presently, oilseed rape is grown primarily for its seeds, which yield about 40% oil and a high protein animal feed. Demand for canola has risen sharply, particularly the oil, which is used in margarine and other oil-based products. Canola oil-based products are routinely used in food and are considered to have a history of safe use.

3.2 Nature of the novel protein

The *oxy* gene was isolated from *Klebsiella pneumoniae* subspecies *ozaenae* (McBride *et al* 1986, Stalker and McBride 1987, Stalker *et al* 1988) and encodes a 37 kDa nitrilase (EC. 3.5.5.6). This enzyme hydrolyses the oxynil herbicides into non-phytotoxic compounds: 3.5-dibromo-4-hydroxybenzoic acid or 3,5-diiodo-4-hydroxybenzoic acid and ammonia (Figure 2).

Figure 2: Oxynil degradation by the *oxy*-encoded nitrilase. (Hal is either Br or I)



Oxynils

3,5-dibromo-4-hydroxybenzoic acid
3,5-diiodo-4-hydroxybenzoic acid

Purified nitrilase has optimal activity at pH 9.2 and at a temperature of 35˚C. The pH optimum remains relatively constant at different substrate concentrations. Nitrilase activity declines to 15% at pH 7.0 and also in temperatures of 10 and 55˚C. The *oxy*-encoded nitrilase is highly specific for its substrates, exhibiting a K_m of 0.31nM and a V_{max} of 15µmole of NH_3 released/min/mg protein for bromoxynil.

3.3 Expression of the novel protein in the plant

Expression levels of the *oxy*-encoded nitrilase were determined by immuno-blotting techniques using a rabbit polyclonal antibody specific to nitrilase. Analyses were done on leaf and seed tissue extracts as well as processed fractions (oil and meal) from homozygous Westar-Oxy-235 and the non-transformed parental control. A positive nitrilase signal on the immunoblot consists of a single band at 37 kDa. The protein level was quantified by comparing the intensity of the signal in the protein extracts with known amounts of purified nitrilase. The detection limit for the assay was 20 ppb nitrilase. Nitrilase was not detected in any of the protein extracts from the non-transformed parental control line. The results are summarised in Table 3 below.

Table 3: Nitrilase expression levels in tissue from Westar-Oxy-235

	Nitrilase expression levels		
Sample	**ng/mg total protein**	**% tissue**	**Parts per million (ppm)**
Leaf	1000	0.002	20
Seed	<10	<0.0003	<3
Meal	5	0.0002	2
Refined Oil	Not detected		

The results show that the levels of nitrilase are highest in the leaf tissue, with only relatively low amounts of nitrilase able to be detected in the seeds. In refined oil, which is the only

human food product derived from canola being assessed in this application, nitrilase could not be detected (detection limit of 20 ppb).

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 cells in the human digestive tract is with antibiotic resistance genes. Antibiotic resistance genes can be present in some transgenic plants as a result of their use as marker genes to select transformed cells. It is generally accepted that there are no safety concerns with regard to the presence in the food of antibiotic resistance gene DNA *per se* (WHO 1993).
There have been concerns expressed, however, that there could be horizontal gene transfer of antibiotic resistance genes from ingested food to microorganisms present in the human digestive tract and that this could compromise the therapeutic use of antibiotics.

As no antibiotic resistance gene was transferred to Westar-Oxy-235 during the transformation process, this issue will not be considered further in the assessment.

4. TOXICOLOGICAL ISSUES

4.1 Levels of naturally occurring toxins

Canola contains two naturally occurring toxic compounds – erucic acid and the glucosinolates. High levels of erucic acid, a long-chain fatty acid, are considered to have cardiopathic potential based on laboratory studies with rats and the glucosinolates have been found to possess goitrogenic properties. Because of this, canola must meet specific standards on the levels of erucic acid and glucosinolates – these are less than 2% erucic acid in the oil and less than 30µmoles of total glucosinolates in the meal.

The levels of erucic acid and the glucosinolates were measured in the oil and meal derived from seed samples taken from field trials with Westar-Oxy-235 canola and the non-transformed parental control grown at various sites in Canada and France in 1992-1995. Data was also obtained from field trials in France in 1994 – 1995 with French canola elite lines that had been crossed with Westar-Oxy-235. Data was obtained for both bromoxynil-sprayed and unsprayed plants. These data are presented in Tables 3 and 4 below.

[3] Food and Agriculture Organization.

Erucic acid

Table 3: Erucic acid content[1] of oil from Westar-Oxy-235 and elite crosses

Line	Bromoxynil treatment	Erucic acid level (% total fatty acids)
Control (n=21)	unsprayed	0.04 (0 – 2.2)
Westar-Oxy-235 (n=8)	unsprayed	0.01 (0 – 0.1)
Westar-Oxy-235 (n=5)	120 g/ha	0.0
Westar-Oxy-235 (n=5)	240 g/ha	0.0
Westar-Oxy-235 (n=5)	480 g/ha	0.0
French elite lines (n=8)	unsprayed	0.08 (0 – 0.5)
Westar-Oxy-235 x French elite lines (n=8)	480 g/ha	0.0
Literature range	-	0.0 – 2.0

[1] mean values with range in parentheses

Mean values of erucic acid in oil from Westar-Oxy-235 and elite lines expressing the bromoxynil tolerant trait were found to all be well below the limit specified for canola and comparable to that found in oil from the parental control lines. The application of bromoxynil to the plants did not result in any changes to the levels of erucic acid.

Glucosinolates

The glucosinolates are converted to more toxic compounds upon hydrolysis by myrosinase, an enzyme localised within the 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. Nonetheless, breeders are encouraged to work towards the elimination of glucosinolates in canola.

There are over 100 known structural types of glucosinolates, nine of which have been monitored in canola because of the known potential toxicity of their metabolites. A group called the alkyl glucosinolates are monitored particularly closely – the sum of four of them must be less than a total of 30µmoles/g seed for the seed to be classified as canola quality – this is an industry standard agreed by various canola associations worldwide. 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.

Table 4: Glucosinolate content[1] of canola meal from Westar-Oxy-235 and elite crosses

		Glucosinolates (µmol/g seed)		
Line	**Bromoxynil treatment**	**Alkyl**	**Indol**	**Total**
Control (n=21)	unsprayed	10.27	5.21	15.48

		(5.88 – 20.47)	(1.57 – 8.04)	(11.58 – 25.05)
Westar-Oxy-235 (n=5)	unsprayed	8.12	6.51	14.63
		(5.76 – 10.99)	(5.04 – 8.4)	(13.45 – 16.39)
Westar-Oxy-235 (n=5)	120 g/ha	8.79	6.15	14.94
		(7.06 – 11.29)	(4.53 – 7.25)	(11.82 – 17.59)
Westar-Oxy-235 (n=5)	240 g/ha	9.19	6.29	15.48
		(7.06 – 13.61)	(4.92 – 8.28)	(12.29 – 19.55)
Westar-Oxy-235 (n=5)	480 g/ha	8.22	5.73	13.95
		(5.17 – 13.17)	(4.28 – 6.72)	(11.59 – 19.83)
French elite lines (n=8)	unsprayed	8.46	3.33	11.75
		(7.1 – 11.5)	(2.8 – 4.1)	(10.2 – 15.4)
Westar-Oxy-235 x elite lines (n=8)	480 g/ha	8.59	3.44	12.03
		(4.3 – 15.7)	(2.8 – 4.4)	(7.2 – 20.1)
Literature range		7.28 – 14.4	1.82 – 11.4	6.70 – 18.50

[1] mean values with range in parentheses

The levels of total glucosinolates in the bromoxynil-tolerant canola lines were found to be well below the 30µmole maximum limit for oil-free meal and were also comparable to the levels found in the corresponding parental control lines. The application of bromoxynil to the plants did not result in any changes to the levels of glucosinolates in the meal.

Some differences were apparent in the levels of the different classes of glucosinolates. In particular, the bromoxynil-tolerant canola lines exhibit a pattern of slightly higher levels of the indol glucosinolates, compared to the parental control. This contrasts to the slightly reduced levels of the alkyl glucosinolates, compared to the parental control. Overall, this balances out to very little difference in the levels of total glucosinolates, which as stated above, are well below the industry standard of 30µmoles. As the indol glucosinolates are much less of a concern than the alkyl glucosinolates, the slightly increased levels are not considered to pose a hazard, particularly as the meal is not intended for human consumption.

4.2 Potential toxicity of novel protein

The protein expression data demonstrates that Westar-Oxy-235 expresses a single novel protein – nitrilase. This section of the report will therefore assess the potential toxicity of nitrilase based on the following:

- the potential for human exposure to nitrilase;
- its amino acid sequence similarity to known toxins;
- an acute oral toxicity study in mice;
- prior history of human ingestion of similar enzymes; and
- potential toxicity of bromoxynil metabolites.

Potential for human exposure to nitrilase

Refined canola oil from Westar-Oxy-235 was analysed for the presence of nitrilase, which could not be detected down to a detection limit of 20 ppb (see Section 3.3). Therefore, it is highly unlikely that humans ingesting refined oil derived from bromoxynil-tolerant canola would be exposed to any appreciable amounts of nitrilase.

Similarity to known protein toxins

Astwood, J.D. (1997). *Klebsiella ozaenae* nitrilase (BXN) has no significant sequence similarity to known allergens or toxins. Monsanto Study Report No. MSL-15120 – submitted with Application A379 – Bromoxynil tolerant cotton.

A database of protein toxin amino acid sequences was assembled from the public domain genetic databases, which included GenPept ver. 92 (a protein database extracted from GenBank and EMBL), PIR ver. 45, and SwissProt ver. 31. Amino acid sequences were retrieved from the databases using the STRINGSEARCH program supplied with the GCG sequence analysis package version 7 (Devereux *et al* 1984). Using the DATASET program, the sequences of toxins were combined into a single database called TOXIN3.

The keyword "toxin" identified and retrieved 2662 amino acid sequences from the public domain genetic databases – this comprised the TOXIN3 database. There were no toxins in the TOXIN3 database that showed significant similarity to nitrilase.

Acute oral toxicity

Dange, M. (1996) Nitrilase: sub-acute oral toxicity study in the mouse. Rhône-Poulenc Study SA 96267 – submitted with Application A379 – Bromoxynil tolerant cotton.

To obtain sufficient quantities of nitrilase for toxicity testing, the enzyme was expressed in *Escherichia coli* BL21 and subsequently purified as an inclusion body pellet.

An acute oral toxicity study was planned to be performed using doses up to 2000mg/kg body weight, using a suspension of nitrilase at 200mg/ml. However, the consistency of the suspension once prepared did not allow the total dose to be administered at one time. Therefore, the suspension was administered over four consecutive days at 500mg/kg body weight/day.

Four consecutive oral doses (500mg/kg body weight) of nitrilase (Batch No. JHJ0001) were administered to groups of OF1 mice (5/sex) at a dose volume of 20ml/kg. The purified nitrilase was suspended in 0.25% methylcellulose in distilled water.

All animals were checked daily for clinical signs over a period of 15 days, and their body weight recorded weekly. At termination of the study period, all animals were killed and subject to necropsy. The necropsy included the macroscopic examination of abdominal and thoracic cavities, major organs and tissues.

No clinical signs were observed during the study and there were no unscheduled deaths. The body weight gain of the animals was unaffected by the treatment and no gross findings were recorded at necropsy. The LD_{50} was designated as >500 mg/kg body weight.

History of ingestion

Nitrilase enzymes, similar to that encoded by the *oxy* gene from *Klebsiella pneumonia,* have been found in a number of plant and microbial species. Although substrates and pathways differ, it appears as though nitrilases share common functions such as hydrolysis of nitriles to carboxylic acids. Plant nitrilases can also confer resistance to some of the nitrile containing herbicides. Nitrilases have been found in a number of important food crops such as wheat, cabbage, barley, and bananas (Buckland *et al* 1973, Thimann and Mahadevan 1964), therefore, humans have a history of exposure to similar types of proteins with no apparent ill effects ever being documented.

Potential toxicity of bromoxynil metabolites

Bromoxynil-tolerant canola plants inactivate bromoxynil by hydrolysing it to 3,5-dibromo-4-hydroxybenzoic acid (DBHA), a carboxylic acid. As this metabolite is a by-product resulting from the activity of an introduced enzyme it is important that a consideration of its safety be included in any evaluation of bromoxynil-tolerant canola. Two issues are relevant. Firstly, the actual toxicity of DBHA, and secondly, the residue levels of DBHA likely to be present in food derived from bromoxynil-tolerant canola varieties.

In relation to toxicity, the US Environment Protection Agency (EPA), in its evaluation of bromoxynil, also evaluated the toxicity of the DBHA metabolite and concluded "there was no concern that DBHA would exhibit significant toxicity over that of the parent bromoxynil" and that bromoxynil "poses negligible risk to human health at expected exposure levels" (US EPA 1998). Bromoxynil and DBHA are extremely similar in structure, varying only in that bromoxynil has a cyano (-CN) group that has been converted to a carboxyl (-COOH) group in the DBHA metabolite. Conversion to a carboxyl group is generally considered to decrease the toxicity of a molecule (US EPA 1998). The conversion to the carboxyl group should cause the DBHA to be more polar and therefore more soluble in water and less in fats. This increased water solubility, combined with the decreased fat solubility means that DBHA should be eliminated faster from the organism than its parent compound, bromoxynil. It is likely that these characteristics would also limit the amount of DBHA residue likely to be present in canola oil.

The Pest Management Regulatory Authority of Canada has recently agreed (February 2000) to the registration of bromoxynil for use on bromoxynil-tolerant canola varieties. To support this registration, a number of field trials were conducted on bromoxynil-tolerant canola between 1996 and 1997. The field trials monitored maximum residue levels of bromoxynil, as well as DBHA. The maximum residues of bromoxynil and DBHA in canola seeds, collected 71-119 days after the last application of bromoxynil, were less than 0.05 ppm each, that is, below the limit of quantitation for the method used. A further study, done with the processed fractions (oil and meal) of the seed, found no detectable residues, even with application rates 10 times that of the commercial rate, and therefore no concentration of residues with processing. Overall, the residues expected to be present in refined canola oil are effectively zero.

Conclusion

The evidence from the sub-acute toxicity study in mice does not indicate that there is any potential for nitrilase from *Klebsiella pneumoniae* subsp. *ozaenae* to be toxic to humans. Furthermore, humans are extremely unlikely to be exposed to this enzyme through the consumption of refined oil from bromoxynil-tolerant canola as the refined oil has been shown to be devoid of any detectable protein. The metabolite of bromoxynil, DBHA, also does not show any potential to be toxic to humans at the predicted exposure levels.

4.3 Potential allergenicity of novel proteins

The concerns regarding potential allergenicity of novel proteins are two fold. Firstly, there are concerns that the ability to express new or different proteins in food will result in the transfer of allergens from one food to another, thereby causing some individuals to develop allergic reactions to food they have not previously been allergic to. Secondly, there are concerns that the transfer of novel proteins to food will lead to the development of new allergies in certain individuals. The former is more easily addressed than the latter because if an allergen is already known it is possible, using human sera or human skin tests, to test if it has been transferred. There are no reliable tests or animal models, however, which enable the prediction of the allergenic potential of novel proteins.

Instead, potential allergenicity can only be indicated by examination of a number of characteristics of the novel protein, such as whether it is derived from a known allergenic source, its physical/chemical characteristics (resistance to acid and protease degradation, amino acid sequence similarity with known allergens) and whether it is likely to be present in large amounts in the food as consumed and therefore have potential for allergic sensitisation.

Notwithstanding the lack of any detectable nitrilase in refined oil, the allergenic potential of nitrilase has been assessed according to the following:

- potential for human exposure to nitrilase;
- similarity to known allergens; and
- digestibility in simulated mammalian digestion fluids

Potential for human exposure

Refined oil from bromoxynil-tolerant canola has been found to contain no detectible nitrilase therefore humans would be extremely unlikely to be exposed to nitrilase through consumption of the oil.

Similarity to known allergens

Astwood, J.D. (1997). *Klebsiella ozaenae* nitrilase (BXN) has no significant sequence similarity to known allergens and toxins. Monsanto Study Report No. MSL-15120 – submitted with Application A379 – Bromoxynil tolerant cotton.

A search for amino acid sequence similarity with known allergens and gliadins is a useful first approximation of potential allergenicity and potential association with coeliac disease (Fuchs and Astwood 1996, Metcalf *et al* 1996). Many protein allergens have been

characterised and their amino acid sequences are known, and importantly, their IgE binding epitopes have been mapped (Elsayad and Apold 1983, Elsayad *et al* 1991, Zhang *et al* 1992). The binding epitopes are generally between 8 and 12 amino acids in length.

To undertake the amino acid sequence comparison between nitrilase and known protein allergens and gliadins, a database of allergen and gliadin sequences was assembled from the standard public domain databases containing protein sequences (GenPept ver. 86.0, PIR ver. 41, SwissProt ver. 30). In addition, DNA sequences were retrieved from GenBank/EMBL ver. 86 as some allergen sequence entries do not appear in the protein sequence databases. The amino acid sequences of the allergens retrieved from the GenBank/EMBL database were either obtained from the GenEMBL flat files or were obtained by translation of the open reading frames in the DNA sequences. Therefore the assembled database consisted of two parts: (1) a dataset of protein sequences and (2) a supplemental database of protein sequences initially retrieved as DNA sequences. Duplicates were deleted from the assembled database and irrelevant sequences were identified by examining complete flat files or by reference to the scientific literature. The resulting database of 219 allergens and gliadins has been published in the scientific literature (Astwood *et al* 1996).

The allergen and gliadin database was then searched for sequences similar to nitrilase. A significant sequence similarity was defined as a sequence identity of greater than seven contiguous amino acids. No significant similarity between nitrilase and any of the known allergens or gliadins was identified.

Digestibility

Aasen, E., *et al* (1997). Assessment of the digestibility of purified BXN nitrilase protein *in vitro* using mammalian digestive fate models. Monsanto Study Report No. MSL-15148 – submitted with Application A379 – Bromoxynil tolerant cotton

If proteins are to be allergenic they must be stable to the peptic and tryptic digestion and acid conditions of the digestive system if they are to pass through the intestinal mucosa to elicit an allergenic response.

The digestibility of nitrilase was determined experimentally using *in vitro* mammalian digestion models. *In vitro* studies with simulated digestion solutions have been used as models for animal digestion for a number of years and have had wide application.

To obtain sufficient quantities of purified nitrilase for testing, the enzyme was expressed in *Escherichia coli* from a cloned *Kelbsiella ozaenae* DNA fragment and purified to homogeneity (Stalker *et al* 1988). The coding region used to express nitrilase in *E. coli* was therefore identical to that transferred into Westar-Oxy-235. The molecular mass of nitrilase is approximately 37 kDa, however, the active form of the enzyme is as a dimer composed of two identical 37 kDa subunits.

Nitrilase was added to simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) and incubated at 37ºC over a series of time points. The time points for SGF were 0 sec, 15 secs, 30 secs, 1 min, 5 mins, 10 mins, 30 mins, 1 hour and for SIF the time points were 0 sec, 1 min, 5 mins, 15 mins, 30 mins, 1 hour, 2 hours, 4 hours, 8 hours and 24 hours.

Analysis of nitrilase after incubation in SGF showed that the protein is degraded to below the limit of detection within 15 seconds. Nitrilase was found to be stable in an inactive test

system over the time period tested confirming that the degradation of nitrilase in the active test system is due to proteolytic activity, not to any molecular instability of nitrilase.

In SIF, nitrilase was degraded within 5 minutes of exposure. Once again, nitrilase was shown to be stable in an inactive SIF system.

The results of these studies demonstrate that nitrilase is rapidly degraded in conditions that mimic mammalian digestion, greatly minimising any potential for intact nitrilase to be absorbed by the intestinal mucosa.

Conclusion

Humans are highly unlikely to be exposed to nitrilase through the consumption of refined oil from bromoxynil-tolerant canola. Moreover, nitrilase does not possess any of the characteristics of known allergens. Therefore nitrilase has very limited potential to become a food allergen.

5. NUTRITIONAL ISSUES

5.1 Nutrient analysis

There are concerns that genetic modification will affect the overall nutritional composition of a food, or cause unintended changes that could adversely affect the safety of the product. Therefore a safety assessment of food produced from transgenic plants must include analysis of the composition of the food, based on a comparison with other commercial varieties of the crop. Generally, comparisons are made not only with the parental line but also with other non-transformed lines. If the parameter for the transformed line is within the normal range for non-transformed lines, this is considered acceptable (Hammond and Fuchs 1998).

Compositional analyses of key constituents were done on the seed, and its derived meal and oil fractions, harvested from field trials with Westar-Oxy-235 canola and its non-transformed parental control grown at various sites in Canada and France in 1992 – 1995. Data was also obtained from field trials in France in 1994 – 1995 with French canola elite lines that had been crossed with Westar-Oxy-235. Data was obtained for both bromoxynil-sprayed and unsprayed plants.

Proximate analysis

Proximate analysis was done on seed from Westar-Oxy-235, Tanto-Oxy (a hybrid between Westar-Oxy-235 and Tanto, a spring elite line used in France), and the respective parental control lines grown in field trials in Canada and France during 1995. All the bromoxynil-tolerant canola lines were treated with bromoxynil at 330 g/ha. The combined results are summarised in Table 5 below.

Table 5: Proximate analysis of seed harvested from Westar-Oxy-235 canola lines and control canola grown in Canada and France in 1995

Analysis	Parental control Lines Mean ± SE (n=6)	Westar-Oxy-235 canola lines Mean ± SE (n=6)
Dry matter (%)	92.85 ± 1.44	92.85 ± 1.76

Mineral content (% dry weight)	7.33 ± 1.66	8.18 ± 1.89
Nitrogen (2 reps)	4.35 ± 0.32	4.33 ± 0.20
Protein in seed (% D.W.)	27.03 ± 2.07	26.89 ± 1.26
Protein in meal (% D.W.)	45.91 ± 3.76	44.65 ± 2.84
Fat/oil (% D.W.)	41.10 ± 0.50	39.53 ± 1.76
Soluble sugars (% D.W.)	3.25 ± 0.95	2.90 ± 0.51
Total carbohydrates (% D.W.)	24.54 ± 3.76	25.40 ± 3.13
Gross energy (seed, Kcal/kg)	6491 ± 60	6494 ± 109
Gross energy (meal, Kcal/kg)	4894 ± 131	4802 ± 137

No significant differences were evident between the bromoxynil-tolerant canola lines and their parental controls in any of the major constituents.

Fatty acid analysis

New varieties of canola oil are analysed to ensure they meet certain specifications – this includes the fatty acid content. Canola oil has considerable natural variation in fatty acid composition and thus some variation in the composition of commercial canola oil is acceptable. The individual fatty acids measured were palmitic acid (C16:0), palmitoleic acid (C16:1), stearic acid (C18:0), oleic acid (C18:1 cis), linoleic acid (C18:2), and linolenic acid (C18:3), arachidic acid (C20:0), eicosenoic acid (C20:1), and behenic acid (C22:0). Values for erucic acid (C22:1) are presented in Section 4.1, Table 3. The results are summarised in Tables 6 and 7.

Table 6: Fatty acid content (%total fatty acids) of seeds from Westar-Oxy-235 canola and control canola grown in Canada in 1992 – 1994. (see Table 7 for Codex ranges)

Fatty acid	**Lines**				
	Control (Unsprayed) (n =21)	**Oxy-235 (Unsprayed) (n=5)**	**Oxy-235 (120g/ha) (n=5)**	**Oxy-235 (240g/ha) (n=5)**	**Oxy-235 (480g/ha) (n=5)**
Palmitic acid	4.5 (3.9-5.9)[1]	4.4 (3.6-5.3)	4.2 (3.5-4.7)	4.1 (3.5-4.7)	4.1 (3.8-4.4)
Stearic acid	1.7 (1.2-2.5)	1.6 (1.3-1.9)	1.5 (1.4-1.6)	1.5 (1.3-1.7)	1.5 (1.3-1.7)
Oleic acid	61.9 (59.8-64.7)	63.8 (63.1-64.6)	64.0 (63.0-65.3)	63.7 (62.3-65.7)	64.4. (63.2-66.0)
Linoleic acid	19.5 (17.7-21.0)	18.4 (17.5-19.3)	17.9 (16.8-19.0)	18.3 (16.5-19.7)	17.8 (17.1-19.0)
Linolenic acid	9.0 (6.7-10.5)	9.1 (7.6-10.3)	9.6 (8.6-10.1)	9.4 (8.5-10.3)	9.5 (8.5-10.5)
Arachidic acid	0.7 (0.5-0.8)	0.7 (0.6-0.7)	0.6 (0.6-0.7)	0.6 (0.6-0.7)	0.6 (0.6-0.7)
Eicosenoic acid	1.5 (1.2-2.4)	1.4 (1.2-1.6)	1.5 (1.3-1.6)	1.4 (1.3-1.6)	1.4 (1.3-1.6)
Behenic acid	0.4 (0.3-0.5)	0.4	0.4	0.4 (0.3-0.4)	0.4 (0.3-0.4)

[1] mean value, range in parentheses

Table 7: Fatty acid content (% total fatty acids) of seeds from French elite

lines crossed with Westar-Oxy-235 grown in France in 1994 – 1995

Fatty acid	CODEX Ranges	Line	
		French elite lines (Unsprayed) (n=8)	Westar-Oxy-235 X French elite lines (480g/ha) (n=8)
Palmitic acid	2.5-7.0	5.7 (5.1-6.6)[1]	5.5 (4.8-6.2)
Palmitoleic acid	0.0-0.6	0.15 (0.1-0.2)	0.15 (0.0-0.2)
Stearic acid	0.8-3.0	1.55 (1.2-2.0)	1.5 (1.2-1.9)
Oleic acid	51.0-70.0	61.4 (58.1-65.3)	60.5 (50.6-64.4)
Linoleic acid	15.0-30.0	20.9 (19.0-23.0)	21.1 (19.0-26.0)
Linolenic acid	5.0-14.0	8.4 (7.6-9.5)	8.65 (7.3-11.8)
Arachidic acid	0.2-1.2	0.5 (0.2-0.8)	0.6 (0.5-0.8)
Eicosenoic acid	0.1-4.3	1.2 (0.8-1.9)	1.2 (0.9-1.7)
Behenic acid	0.0-0.6	0.3 (0.0-0.5)	0.3 (0.2-0.5)

[1] mean value, range in parentheses

All the fatty acids measured were within the ranges specified by Codex (Table 7) for canola quality oilseed rape (Codex Alinorm 99/7 Appendix II 3.1), and no major differences between modified and control crops were identified. Treatment with bromoxynil had no significant effect on the fatty acid content.

Sterol and tocopherol analysis

The levels of sterols and tocopherols were measured in seed from control and Westar-Oxy-235 canola grown in France and Canada in 1995 as well as from an elite line (Samourai), also grown in France in 1995. The bromoxynil-tolerant canola lines were all treated with bromoxynil. The results are summarised in Table 8 below.

Table 8: Total sterol and tocopherol levels in bromoxynil tolerant canola and control canola grown in field trials in Canada and France in 1994 - 1995

Trial and crop		Bromoxynil treatment	Total Sterols (mg/100g oil)	Total Tocopherols (µg/g oil)
Canada (1995)	Control	-	777.3	876.0
(n=2)	Westar-Oxy-235	-	753.8	785.0
	Westar-Oxy-235	330 g/ha	760.8	808.5
France (1995)	Control	-	828.2	955.0
(n=2)	Westar-Oxy-235	-	851.2	1015.0
	Westar-Oxy-235	450 g/ha	840.2	1007.0
France (1995)	Control (Samourai)	-	922.3	739.88
(n=8)	Samourai-Oxy-235	450 g/ha	943.1	716.13
		Literature values:		424.0 – 1054.0

No major differences were evident in total sterol and tocopherol content between control and bromoxynil tolerant canola. Treatment with bromoxynil had no significant effect on either the total sterol or total tocopherol content.

Unsaponifiable matter

The Codex specification for unsaponifiable matter states that the level must be not higher than 1.5%. This component was measured for oils produced from the 1995 French and Canadian trial crops. All were below the specified level, and no significant differences were seen between control and modified crops.

5.2 Ability to support typical growth and well being

In assessing the safety of food produced using gene technology, a key factor is the need to establish that the food is nutritionally adequate and will support typical growth and well being. In most cases, this can be achieved through an understanding of the genetic modification and its consequences, together with an extensive compositional analysis of the food. 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 oil derived from bromoxynil-tolerant canola there is adequate compositional data to demonstrate the nutritional adequacy of the oil. However, a feeding study on canola meal was provided as additional supporting information and is evaluated below.

Feeding study in rats

A 28-day feeding study was carried out in rats to compare the effects of ingestion of canola cake made from both non-transgenic (Westar and Tanto) and transgenic (untreated and that treated with bromoxynil) canola. The study was performed in accordance with the OECD Principles of Good Laboratory Practice (OECD, 1982):

From days 1 to 28, each type of cake was administered *ad libitum* at a 10% concentration to groups of five male and five female rats. Clinical signs were recorded at least once a day throughout the study. Additional detailed physical examination was performed weekly. Body weights were measured on days –1, 1, 8, 15, and 22 and at final sacrifice. The weight of food supplied to each animal and that remaining at the end of the food consumption period was recorded for each week throughout the treatment period. From these records, the mean weekly consumption was calculated for each rat. Food spillage was also noted. For clinical pathology studies, blood samples were collected before necropsy. At necropsy macroscopic examination of the external surfaces, all orifices and all major body cavities, organs and tissues was carried out. Any significant macroscopic findings were recorded and the tissues (adrenal gland, heart, kidney, liver and spleen) samples taken.

Results

There were no mortalities and no clinical signs of toxicity in any of the groups. Neither the mean body weight, mean daily intake, haematology nor clinical chemistry was affected by the type of canola administered. Likewise, no differences were seen in the macroscopic observations, or the microscopic examination of the organs sampled.

At a level of 10% inclusion of canola cake in feed, therefore, there was no difference between the control and the transgenic canola in their ability to support growth and well being of rats.

5.3 Conclusion

Analysis of the compositional data of the canola seed and processed fractions indicates that there were no significant differences in the levels of key nutrients between Westar-Oxy-235 line and control lines. This was true for both untreated plants and those treated with bromoxynil.

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ATTACHMENT 3 DRAFT REGULATORY IMPACT ASSESSMENT

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 ORGANIZATION 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 phytosanitary measure applied:

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

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

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

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

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

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

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

TBT Notifications

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

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

Instances of non-alignment with international standards which could result in trade barriers must be identified and, if questioned, justified.

Voluntary codes of practice are not expected to generate technical barriers to trade except where compliance with a code of practice or some aspect of a code of practice is expected. Consequently, it is possible for a voluntary code of practice to be viewed by the WTO as mandatory and subject to all the notification and other provisions applying to mandatory regulations.

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

ATTACHMENT 5 SUMMARY OF PUBLIC SUBMISSIONS

1. National Genetic Awareness Alliance (Australia)

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

2. Pola Lekstan and Anna Clements (Australia)

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

3. Arnold Ward (Australia)

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

4. Australian GeneEthics Network

- Believes that the data provided is insufficient to make an assessment, and clock should be stopped on the applications. Concerns include:
  - Direct health effects of pesticide residues
  - Possibility of transfer of antibiotic resistance marker genes leading to resistant bacteria
  - The possibility that transfer of other traits e.g. herbicide tolerance to bacteria, could lead to horizontal spread of unfavourable traits
  - Insertion of viral DNA could create new and virulent viruses
  - The possibility that approval could lead to the growing of GMOs in Australia – ecological concerns including effects of, and increases in resistance to, Bt-toxins and the encouragement of increased herbicide use resulting from herbicide-tolerant crops
  - The threat to GE-free status export markets
- Believes that the term 'substantial equivalence' is not useful– compositional data alone does not establish equivalence

5. Public and Environmental Health Service (Australia)

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

6. David Grundy (Australia)

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

7. Leesa Daniels (Australia) Member of the Genetic Engineering Action Group

- Believes that:
  - Scientific research although limited, has brought concerns to light
  - Substantial equivalence is a subjective principal
  - Comprehensive and mandatory labelling must be urgently implemented
  - The cauliflower mosaic virus (CaMV) promoter could enhance the capability to transfer genes horizontally and has the potential for activating dormant or new viruses
  - Antibiotic marker genes could lead to increase in antibiotic resistance
  - Several of the transformations encourage the use of pesticides, all of which have shown to be harmful.

8. Australian Food and Grocery Council

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

own safety assessment. In the absence of such an agreement it supports the ANZFA safety assessment process.

- Believes that an appropriate information and labelling scheme would enable consumers to make an informed choice.

9. New Zealand Ministry of Health

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

10. Nestle Australia Ltd.

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

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

- Believe that current testing procedure is inadequate and that human trials are the only adequate method, as with testing of new drugs. Also that physiological and neurological effects as well as the toxicological and allergenic effects should be looked at, and that an independent body should be responsible for testing
- Do not support the use of antibiotic markers, since they believe they may pose a threat to efficacy of antibiotics in humans
- State that new research has shown that GM soybeans may be a less potent source of phytoestrogens than conventional soybeans confirming the inadequacy of the term 'substantial equivalence'
- Raise the point that although these crops have been approved elsewhere, this situation may change with consumer pressure
- Do not accept that it is impossible to source food to ascertain whether or not it contains GM ingredients. Believe that if McCain and Sanitarium can do it, then others should also be able to
- State general concern about the risk that MRLs will be raised as a result of herbicide-tolerant crops being developed, and feel that the calculations used are flawed and are not based on safety criteria
- Believe that the use of GM crops in animal feed should also be regulated. A378
- State concern over possible increase in glyphosate use (it is apparently confirmed in one reference that herbicide use increases with herbicide resistant crops), referring to studies that link the chemical to Hodgkin's lymphoma, and the possibility that Europe may ban it due to adverse effects on beneficial insects**.** They are particularly concerned that glyphosate is not looked at by the same regulatory body as that looking at GM foods

A379, A388

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

A372, A375, A380, A381, A386

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

A380, A382, A383, A384, A385, A386

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

A387

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

12. Health Department of Western Australia

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

13. Meat New Zealand

A379

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

14. BRI Australia

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

15. Food Technology Association of Victoria Inc.

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

16. Diane Davie (Australia)

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

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

- Believe that most Australians and New Zealanders do not want GM foods, there are no benefits, and deferral would not be disadvantageous. Approval should be delayed until they are proven safe.
- Feel that there is insufficient time to assess these applications thoroughly, and there are so many products under development that there is a high overall risk of a major disaster
- Believe that GM foods encourage pesticide use, and applications have made for commercial purposes only, and also that here could be commercial benefit to Australia and New Zealand in remaining GM-free.

18. Richard and Sharon Moreham (see also above)

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

19. Vicky Solah (Australia)

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

20. Dr Rosemary Keighley (Australia)

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

21. Nicola Roil (Australia)

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

22. Ian and Fran Fergusson (Australia)

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

23. Lyndal Vincent (Australia)

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

24. Fay Andary (Australia)

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

25. John and Francesca Irving (Australia)

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

26. Diana Killen (Australia)

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

27. Sheila Annesley (Australia)

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

28. David and Edwina Ross (Australia)

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

29. Beth Schurr (Australia)

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

30. Beth Eager (Australia)

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

31. Bruce Pont and Ljiljiana Kuzic-Pont (Australia)

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

32. Chitta Mylvaganum (Australia)

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

33. John Stevens (Australia)

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

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

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

35. Jan Kingsbury (Australia)

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

36. Teresa Sackett (Australia)

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

- Asks the question of whether workers in the food industry are to be better informed, and also why no 'verification documents' are to be required by retailers? Believes that certification schemes should be on a par with those for Kosher foods and organics.

37. John and Sandy Price (Australia)

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

38. John Scott (New Zealand)

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

39. R A Randell (New Zealand)

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

40. National Council of Women of New Zealand

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

41. Safe Food Campaign (New Zealand)

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

42. Jocelyn Logan, Caroline Phillips (New Zealand)

- Oppose all 13 applications for the following reasons:
  - Testing has not been long-term or independent, precautionary principle should apply. Approval can happen later if GM is proven safe.

- No clear public benefit, and lack of opportunity for informed choice (immoral and undemocratic). Labelling regulations also unsatisfactory in this respect.
- Environmental concerns (increase in pesticides, threat to organic farming, Bt resistance).

43. Robert Anderson (member of Physicians and Scientists for Responsible Genetics – New Zealand)

- Considers that the GM issue should be reconsidered in the light of the release of internal FDA documents made available for a recent lawsuit aimed at amending their policy. Attached document (presentation given by Steven Druker, Alliance for Bio-integrity) suggests that:
  - Scientist's warnings have been ignored
  - FDA policy may be illegal, violating the Food, Drugs and Cosmetic Act – Mr Druker believes that the term generally-regarded-as-safe (GRAS) cannot apply to foreign DNA.

44. Stephen Blackheath (New Zealand)

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

45. Claire Bleakley (New Zealand)

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

ATTACHMENT 6 GENERAL ISSUES RAISED IN PUBLIC SUBMISSIONS

The majority of submissions received in response to the Section 14 Gazette Notice, express general views against the use of gene technology and assert that food produced using this technology is unsafe for human consumption, irrespective of the food concerned or the particular genetic modification. A number of general issues were raised in these submissions that 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/Standard 1.5.2 is to establish that the new food is at least as safe as the existing food. 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 constantly under review to ensure that the process reflects both recent scientific and regulatory developments and are consistent with protocols developed internationally.

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 laboratory 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 feeding studies is the need to maintain the nutritional value and balance of the diet. A diet that consists entirely of a single food is poorly balanced and will compromise the interpretation of the study, since the effects observed will confound and usually override any other small adverse effect which may be related to a component or components of the food being tested. 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 cases, studies up to 14 days have also been performed. These can provide additional reassurance that the proteins will have no adverse effects in humans when consumed as part of a food.

While animal experiments using a single new protein can provide more meaningful information than experiments on the whole food, additional reassurance regarding the safety of newly-expressed protein can be obtained by examining the digestibility of the new protein in laboratory conducted *in vitro* assays using conditions which simulate the human gastric system.

3. Substantial equivalence

A number of submitters express concern regarding the use of the concept of substantial equivalence as part of the assessment process. Some reject 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. This is partly because differences at the DNA level occur with every breeding event and often arise also as a result of certain environmental factors.

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*'. Since this time, the concept has been integrated into safety assessment procedures used by regulatory authorities worldwide. It has thus been in use for approximately ten years and has been an integral part of the safety assessment of some 40 products.

Although the concept of *substantial equivalence* has attracted criticism, it remains as the most appropriate mechanism for assessing the nutritional and food safety implications of foods produced using gene technology. It is generally agreed also that continual review of the concept, in response to the criticism, provides a useful stimulus to ensure that safety assessment procedures are kept at the forefront of scientific knowledge (Nick Tomlinson, Food Standards Agency, United Kingdom: Joint FAO/WHO Expert Consultation on Foods Derived from Biotechnology, Geneva, 2000).

4. The nutritional value of food produced using gene technology

A small number of submitters express 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 express 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 raise concerns about an increase in antibiotic resistance resulting from the use of gene technology. Some consider that it would be reassuring if independent biomedical advice were available to inform 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 express 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 focus on this issue. Specifically, the submissions call for comprehensive labelling of foods produced using gene technology, regardless of whether they are substantially equivalent to conventional foods. The submitters base their demands for full labelling on the presumption that all foods produced using gene technology are unsafe, even where no novel genes are present, and on consumer "right to know" arguments. It is stated that full labelling is the only means of identification of foods produced using gene technology available to consumers.

Evaluation

In response to consumer sentiment on this issue, on 28 July 2000, Health Ministers (from New Zealand, the Commonwealth, States and Territories of Australia) agreed to new labelling rules for genetically modified foods. Amendments to the Standard were subsequently confirmed by the Ministerial Council on 24 November 2000 and finally gazetted on 7 December 2000. The amended Standard A18 (Volume 1) is now also known as Standard 1.5.2 in the joint Australia New Zealand Food Standards Code (Volume 2). To allow adequate time for compliance to the new provisions of the Standard, it will come into effect on 7 December 2001, twelve months after the date of gazettal.

The new Standard requires the labelling of food and food ingredients where novel DNA and/or protein is present in the final food and where the food has altered characteristics.

Exempt from these requirements are:

- highly refined food, where the effect of the refining process is to remove novel genetic material and/or protein;
- processing aids and food additives, except where novel genetic material and/or protein is present in the final food;
- flavours which are present in a concentration less than or equal to 0.1 per cent in the final food; and
- food prepared at point of sale (e.g. restaurants, takeaway food outlets).

In addition, the new Standard allows for a maximum of 1 per cent of unintended presence of genetically modified product, as ascertained by laboratory testing, before labelling would be required. The comprehensive provisions of the new Standard represent the culmination of extensive consultation between government, consumers and the food industry to ensure practical and relevant information is available to all in relation to the sale of genetically modified foods.

A User Guide has been prepared by the Authority under direction of the Ministerial Council, to assist with compliance with the amended labelling provisions of the Standard. A copy of the guide is available on the ANZFA website (www.anzfa.gov.au).

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

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

Evaluation

Surveillance of potential adverse or beneficial effects of GM foods is seen by many as a logical follow-up to the initial scientific risk assessment. Nevertheless, it is recognised that there are limitations to the application of epidemiology studies, particularly in relation to food components. A key requirement for post-market surveillance systems is that a clear hypothesis be identified for testing. Establishing a system for the surveillance of potential health effects of exposure to novel foods requires monitoring of the consumption patterns of novel foods in the population, and health effects in both “exposed” and “non-exposed” individuals/populations, so that risk estimates can be derived. For any such monitoring system to be useful, there needs to be a range of exposures, otherwise, any variation in health outcome would be unexplainable by that exposure. Variations in exposure could be apparent over time (temporal trends), space (geographical trends) or both.

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

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

11. Public consultation and information about gene technology

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

Evaluation

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

Although Standard A18 came into force in May 1999, the public have a continuous and ongoing opportunity to provide comment in relation to applications under the standard. ANZFA's statutory process for all applications to amend the *Food Standards Code* normally involves two rounds of public comment. Furthermore, all the documentation (except for commercial in confidence information) relating to these applications is available in the public domain, including the safety assessment reports. There is ample evidence that the provision of such information by ANZFA has already significantly stimulated public debate on this matter.

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

In response to the concerns raised in public submissions with regard to gene technology and GM foods, ANZFA has prepared a public discussion paper on the safety assessment process for GM foods[5], available at no charge on request. Since completion, this document has been widely distributed 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 as part of the comprehensive assessment processes of the Office of the Gene Technology Regulator (OGTR) in Australia, and the Environmental Risk Management Authority (ERMA) in New Zealand. Since June 2001, OGTR regulates all GMOs and any 'gap' products (i.e. products for which no other regulator has responsibility).

[5] Gm foods and the consumer – ANZFA Occasional Paper Series No.1, Australia New Zealand Food Authority, June 2000.

The Australia New Zealand Food Authority (ANZFA) does not have the mandate to assess matters relating to environmental risks resulting from the release of foods produced using gene technology into the environment. However, links exist between ANZFA and these other regulatory agencies in both Australia and New Zealand, and a large degree of information sharing occurs.

In Australia, the current regulatory system includes a number of other agencies 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).

All GM foods continue to be assessed and regulated by ANZFA under the direction of Commonwealth, State and Territories Health Ministers and the New Zealand Health Minister, sitting as the Australia New Zealand Food Standards Council (ANZFSC). However, an interface between ANZFA and OGTR has been established through amendments to the ANZFA Act arising from the Gene Technology Bill 2000. These amendments to the ANZFA Act require the Authority to advise OGTR of recommendations to ANZFSC regarding the standard for foods produced using gene technology (Standard A18/1.5.2).

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

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

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.

Response

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

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