Report of the

1st ASEAN-ILSI

Training Workshop on Safety and Risk Assessment of Agriculture-related Genetically Modified Organisms (GMOs)

July 18 - 20, 2001
Singapore

Organized by:

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ILSI
International Life Sciences Institute

AVA

In collaboration with

Health Canada
Santé Canada

REPORT OF THE
1ST ASEAN-ILSI
TRAINING WORKSHOP ON THE
SAFETY AND RISK ASSESSMENT OF
AGRICULTURE-RELATED GENETICALLY MODIFIED ORGANISMS
(GMOs)

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From Dr. Ngiam Tong Tau (Chief Executive Officer)
Agri-food and Veterinary Authority of Singapore (AVA)

The ASEAN Ministers of Agriculture and Forestry (AMAF) in their 21st Meeting in Brunei Darussalam in October 1999 endorsed the *ASEAN Guidelines on Risk Assessment of Agriculture-Related GMOs*. The Guidelines are aimed at providing ASEAN member countries with a common understanding and approach to undertake scientific evaluations of applications for the release of agriculture-related GMOs in their countries. The Ministers have noted the potential of biotechnology in increasing the productivity of agriculture and have recognised the need to have a better understanding of GM technology and risk assessment and to enhance capacity building in this area.

Subsequently, at their 22nd Meeting in Phnom Penh, Cambodia, the ASEAN Ministers of Agriculture and Forestry approved the proposal for Singapore to collaborate with the ILSI to organize a training programme for regulators and decision-makers of ASEAN member countries on the use of the ASEAN Guidelines on Risk Assessment of Agriculture-related GMOs. The proposed 2-year training programme would be an activity under the ASEAN Public Awareness Programme on GMOs which is currently coordinated by an Ad-Hoc Task Force chaired by the ASEAN Secretariat. As part of the Programme, a series of training workshops on the use of the *ASEAN Guidelines on Risk Assessment of Agriculture-related GMOs* will be held in 4 ASEAN countries commencing with Singapore followed by Malaysia, Thailand and Indonesia.

GM technology coupled with the necessary biosafety measures/ regulations has tremendous potential to improve the quality and supply of our food. It is essential to note that issues and concerns on GMOs demand a major commitment from governments. Both governments and scientists should do more to provide the public with clear, understandable and relevant information. More open access to information will be essential to convince concerned consumers regarding the transparency of safety assessments of GM foods. There is a real challenge for industry, academia and government to deliver on this.

Singapore and ASEAN is pleased to have the support of the International Life Science Institute (ILSI) and Health Canada for the organisation of this 1st ASEAN Workshop on risk assessment of agriculture-related GMOs. Officials from Health Canada and the Australia and New Zealand Food Authority (ANZFA) is able to share with us their approaches and experience in evaluating GMOs. The Workshop has been designed to provide participants with a hands-on exercise in the safety and risk assessment of agriculture-related GMOs. Case studies were used to illustrate the safety and risk assessment criteria established by Canada and various international organizations. I hope that through this training workshop and the future workshops planned, we will be able to build up a core of expertise in GMO risk assessment within ASEAN.

I would like to thank the ILSI for co-organizing this Workshop with Singapore. ILSI has been very supportive of ASEAN's capacity building efforts in GMO risk assessment. In addition, I wish to express our special thanks to Health Canada for their support and collaboration to make this Workshop possible.

I would like to express Singapore's and ASEAN's appreciation to ILSI and Health Canada for their support and contribution to the success of this Workshop.

MESSAGE

From Mrs. Yeong Boon Yee (Executive Director)
International Life Sciences Institute (ILSI) Southeast Asia

ILSI is pleased to work with Singapore and ASEAN to organise the 1st Workshop on the use of the *ASEAN Guidelines on Risk Assessment of Agriculture-related GMOs*. This Workshop is the first of a series of four workshops to be held in different ASEAN member countries under an ILSI-ASEAN 2-year collaborative programme to promote capacity building and public awareness in risk assessment of agriculture-related GMOs. ILSI is pleased with the collaboration given by Health Canada (HC) and Australia and New Zealand Food Authority (ANZFA) to facilitate this capacity building workshop series.

The coming together of this safety assessment training program sprang from the recognition of such need by AVA in early 1999 (previously known as the Primary Production Department, PPD), through two years of exploration and joint discussion with various bodies and the ASEAN Secretariat, to gaining the Ministerial approval in November 2000 at the special SOM-AMAF meeting in Brunei. I would like to thank Dr. David Neumann and Mr. Dale Good, whose early efforts have been instrumental in helping the realization of this initiative.

ILSI facilitates scientific exchanges among and between scientists by convening workshops, symposia, conferences and expert panels to examine the scientific basis for issues critical to improving human and environmental health. The objective is to ensure that the latest and most comprehensive scientific information is available to those who are responsible for health and safety decisions, and that the information are readily accessible to those that have the expertise and experience to transform them into easily understandable information to the non-specialists and the public.

As part of its mandate to address new and emerging scientific issues, ILSI has for over ten years, brought a balanced approach to facilitate activities related to the safety assessment of biotechnology-derived plants and foods.

Since 1998, ILSI has helped to facilitate scientific meetings on the safety assessment of GM foods in more than 20 countries in Asia, Australia, Europe, Latin and N. America and the Middle East, and published a substantial numbers of reports and proceedings.

The workshops address issues such as understanding of the concepts of risk assessments, substantial equivalence, testing and labelling guidelines, assessing for allergenic or toxic effects and how the scientific information is used to make decisions about safety.

ILSI and its partners have and will continue to play a significant global role in generating and disseminating scientific information about food biotechnology. The ILSI Southeast Asia branch with the regional office in Singapore was established in 1993 and now serves the ASEAN countries, Australasia and the pacific islands.

We are pleased to have this opportunity to work with ASEAN colleagues and to collaborate with other regional and international scientific organizations in our scientific and education endeavors. We hope this first Workshop, with a pertinent case study on the Round up Ready soybean will provide the practical example for your utilization of the Harmonized ASEAN Guidelines on Release of GMOs.

ILSI looks forward to working with ASEAN member countries to organise the remaining workshops.

INTRODUCTION

At the 19th Meeting of ASEAN Ministers of Agriculture and Forestry (AMAF) held in Bangkok, Thailand in September 1997, the Ministers endorsed Singapore's initiative to harmonise guidelines for agriculture biotechnology products in ASEAN. Singapore, designated as the lead country for this programme, led an ASEAN Task Force in 1998-1999 to draft the guidelines.

At the 21st AMAF Meeting held in Brunei Darussalam in October 1999, the Ministers endorsed the *"ASEAN Harmonised Guidelined on the Release of Agriculture–Related GMOs"* drafted by the ASEAN Task Force. In endorsing the Guidelines, the Ministers agreed that there is a need to improve public understanding and awareness on GMOs, and promote capacity building on risk assessment of GMOs. The ASEAN Guidelines would serve as a scientific basis to evaluate GMOs and to begin the education process.

At the 22nd AMAF Meeting held in Cambodia in November 2000**,** the Ministers approved the ASEAN training programme on risk assessment of GMOs proposed by Singapore and ILSI (International Life Sciences Institute) following extensive discussion with the ASEAN Secretariat, ASEAN Member Countries and other agencies since early 1999.

The ASEAN training programme consists of training workshops to be held in different ASEAN countries over 2 years, starting with the first workshop in Singapore. The objective of the programme is to build a core of expertise of regulatory scientists, administrators and decision makers in GMO risk assessment within ASEAN through the participation in case studies developed by leading international experts using the *ASEAN Guidelines on Safety and Risk Assessment of Agriculture-related GMOs*. The training programme will also provide a platform for ASEAN member Countries to learn and exchange views on the latest scientific developments related to the safety assessment of agriculture-related GMOs.

The *1st ASEAN-ILSI Training Workshop on Safety and Risk Assessment of Agriculture-Related GMOs* was successfully held in Singapore on 17 – 20 July 2001. This Workshop was jointly organised by the Agri-food and Veterinary Authority of Singapore (AVA) and ILSI in collaboration with Health Canada (HC) and the Australia and New Zealand Food Authority (ANZFA). Through ILSI, regulatory scientists from HC and ANZFA, who had experience in conducting similar training workshops in Asia and Latin America, were invited as facilitators to conduct the workshop. A case study on the *Safety Assessment of Genetically Modified Herbicide Tolerant Soybean* was specially designed by ILSI and HC as training material for the Workshop.

WORKSHOP OVERVIEW

Dr. William Yan (Acting Head of the Office of Food Biotechnology, Food Directorate, Health Canada) opened the workshop with an overview of the workshop framework and objectives.

The training workshop was designed to include several presentations which highlight both Canada's and Australia's experience on Genetically Modified (GM) food regulation, including the principles of food safety assessment and environmental safety assessment of GM plants. Updates on international developments in GM food safety assessment (Codex, FAO/WHO, OECD) and the ASEAN guidelines on risk assessment of agricultural related GMOs, have also been included. A breakout session using Roundup Ready ® soybeans was used to give workshop participants a hands-on exercise on the safety assessment of GM products, and the workshop closes with presentations and a discussion session on the future challenges to the safety assessment of GM products.

The training workshop is aimed to address issues such as understanding the concepts of risk assessments, substantial equivalence, testing and labelling guidelines, assessing for allergenic or toxic effects and how the scientific information is used to make decisions about safety. It is hoped that this workshop, with a pertinent case study on the Roundup Ready ® soybean, will provide a practical example for the participants' utilization of the *Harmonized ASEAN Guidelines on Release of GMOs*.

Concepts and Principles of Food Safety Assessment of Genetically Modified (GM) Foods

Historically, our beliefs about the safety of foods have been based almost entirely on tradition and cultural experience. In practice, very few of the foods we eat today have been subjected to any toxicological studies, and yet they are generally accepted as safe. Even foods that contain toxins or anti-nutrients are considered safe, because of their long history of use. Dr. William Yan informed the group, that over the last decade international consultations involving the UN Food and Agricultural Organization (FAO), UN World Health Organization (WHO) and the Organization for Economic Co-operation and Development (OECD) have resulted in the conclusion that novel foods are not inherently less safe than those produced by more conventional techniques. Foods produced using GM crops have the same types of hazards as those produced from conventionally bred crops, and as such, the same food safety assessment principles and standards apply to novel foods.

Foods are complex mixtures of macro- and micro-nutrients, fibres, anti-nutrients, natural toxins and health-promoting substances. Therefore, it isn't possible to conduct safety evaluations of whole foods as they are performed with single food additives. Instead, the objective is to determine if the novel food presents any new or altered hazard in comparison with its traditional counterpart, or whether it can be used interchangeably with its traditional counterpart without affecting the health or nutritional status of consumers. This comparative approach, known as "Substantial Equivalence" is used to:

- structure the safety assessment relative to the counterpart food
- identify intended or unintended differences that would be the focus of further safety evaluation
- provide a flexible comparative process that can be applied at several levels along the food continuum (i.e. unprocessed food, individual processed fractions or final product) to allow the safety assessment to be targeted to the most appropriate level.

The goal of the approach is not to establish an absolute level of safety, but rather to establish with reasonable certainty that no harm will result from its intended use. Despite the obvious benefits, there are limitations in the use of the concept of "Substantial Equivalence" and these are:

- it's dependence on a comparator/traditional counterpart requiring sufficient analytical data be available for comparison
- misinterpretation of the concept.

Even considering its limitations, the concept of substantial equivalence, as a tool to help regulators structure the safety assessment process, has been reaffirmed on numerous occasions internationally. The WHO/ FAO Joint Expert Consultation on Biotechnology, 2000, re-examined the concept of substantial equivalence and concluded that this comparative approach was the most appropriate and practical strategy for evaluating the safety and nutritional quality of GM foods.

International regulatory cooperation is critical to ensure the safety and nutritional quality of GM foods, and to facilitate their acceptance and global trade. An understanding of the respective regulatory systems and requirements is required to facilitate a harmonized approach to food safety assessment. The Codex Alimentarius Commission has created a Task Force to develop specific guidance for the global community on the safety assessment of foods derived from biotechnology. The Codex Ad Hoc Intergovernmental Task Force on Foods Derived from Biotechnology has the following initiatives:

- Development of "General Principles for the Risk Analysis of Foods Derived from Recombinant DNA Plants"
- Development of "Guidelines for the Conduct of Safety Assessment of foods Derived from Recombinant DNA Plants"
- Compilation of identification and detection methodologies for GM foods.

Concepts and Principles of Environmental Safety Assessment of Transgenic Plants

Given the rapid increase in acreage of transgenic varieties, concerns have been raised about the potential environmental risks that these crops may pose. Ms. Mireille Prud'homme (Regulatory Officer, Food Policy Integration, Health Canada) introduced the concepts and principles for an environmental assessment of transgenic plants, using the approach adopted by the Canadian Food Inspection Agency (CFIA), to illustrate how the concepts are applied in Canada.

In Canada, transgenic plants are considered to be plants with novel traits (PNTs). Plants falling into this category are regulated on the basis of the characteristics of the product, not the specific process by which the product was made. This is because a novel trait, such as herbicide resistance, may be achieved through mutation breeding, selection of naturally occurring variants or by the use of recombinant DNA technology.

Each environmental assessment considers the following criteria:

- the potential for the PNT to become a plant pest (i.e. an agricultural weed)
- the potential for the PNT to be invasive of natural habitats
- the potential for the PNT to impact non-target species, (i.e. gene flow to weedy relatives causing them to become more weedy or invasive themselves)
- its potential impact on biodiversity.

Integral to the assessment of a PNT, is our knowledge of the environmental interactions of the unmodified crop. A determination of the environmental safety of a PNT is based on a thorough characterization of the novel trait and the resulting novel plant.

Mitigation measures are in place at the field testing stage, and include an initial assessment of the proposed trial protocol and PNT material prior to the approval of a field trial permit, imposed safety precautions during the trial, such as reproductive isolation, and conditions on future uses of the trial site. Once environmental release is approved, any identified risks are minimized by placing specific conditions on production and use of the PNT. For example, to minimize the likelihood for the development of pest resistance to an insect tolerant crop engineered to produce an insecticidal toxin, a pest resistance management plan is developed and put in place.

Regulating Novel Foods (Including Foods Derived from Biotechnology) in Canada

Mr. Brian Harrison (Office of Food Biotechnology, Health Canada) informed the audience that the Canadian approach to safety assessment is based upon principles developed through expert international consultation with the OECD, FAO, and WHO. International consultations held by these organizations concluded that the safety assessment of genetically modified food requires an integrated and stepwise, case-by-case approach, and re-affirmed that the concept of substantial equivalence is the most appropriate strategy for evaluating the safety and nutritional quality of genetically modified foods. The Canadian approach is also based on the premise that foods produced from modern biotechnology are not inherently less safe than those produced by more conventional techniques, and as such, the same strategy for safety assessment is used on all novel foods in Canada. Novel foods may include:

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- products that have no history of safe use as food in Canada,
- products produced by a process that has not been previously used on that food, and causes the food to undergo a major change,
- foods containing microorganisms that have not previously been used as food or to process food,
- foods that exhibit new or modified characteristics resulting from a genetic modification
- foods produced by organisms that exhibit new or modified characteristics.

A variety of novel foods are being developed and introduced into the Canadian marketplace. To date, fifty novel foods have completed the regulatory process in Canada, including food products produced by genetically modified plants.

Canadian Regulatory Process

The *Novel Food Regulations* under the *Canadian Food and Drugs Act* require a pre-market notification in Canada for all novel foods, including food developed using biotechnology. Prior to sale, petitioners are required to make a submission to the Health Products and Food Branch of Health Canada regarding the novel food. This permits Health Canada to conduct a thorough safety assessment to determine whether the food is safe for consumption in Canada, and can be marketed for sale.

When a submission has been received, Health Canada is required to evaluate the submission and respond back to the petitioner within 45 days. If it is determined that additional information is necessary in order to assess the safety of the novel food, the

manufacturer must submit this information before the assessment proceeds any further. Once the additional information has been received, Health Canada then has 90 days to complete the review.

In Canada, food safety assessments are conducted on a case-by-case basis by Health Canada toxicologists, biologists, environmental scientists, chemists and nutritionists, following the *Guidelines for the Safety Assessment of Novel Foods,* established in 1994 by Health Canada. The guiding principle in the safety assessment is the comparison of molecular, compositional, toxicological, allergenicity and nutritional data for the modified organism with data from its traditional counterpart. A clear understanding of the methods used to develop the product, and a characterization of the product is required. As well, intended use and dietary exposure are examined. The guidelines were meant to provide a basis for the assessment and were not intended to explicitly define all of the data that might be required over the course of a safety assessment. As a result, developers are encouraged to consult with Health Canada during the developmental process to ensure that all potential concerns are addressed for the novel food.

Once the novel food has been considered to be as safe and nutritious as foods already on the Canadian market, these foods are approved and enter the marketplace in the same manner as traditional food products. They remain subject to the same post-market standards applicable to all foods in Canada, and it remains the responsibility of the manufacturer to ensure that the products sold are safe and comply with all regulatory requirements.

Labelling of GM Foods

In Canada, Health Canada and the Canadian Food Inspection Agency (CFIA) share the responsibility for food labelling policies under the *Canadian Food and Drugs Act*. Health Canada's responsibilities for food labelling falls within the Department's mandate for health and safety issues, and as such, mandatory labelling is required for genetically modified foods only when safety concerns such as allergenicity or composition and nutritional changes have been identified. Mandatory labelling alerts consumers or susceptible groups in the population to specific health and safety concerns.

Voluntary labelling of foods in order to provide consumer choice is permitted under current legislation. The CFIA is the leading federal agency on the development of general food labelling policies and regulations that are not related to health and safety. These policies and regulations are meant to protect consumers from misrepresentation and fraud with respect to food labelling, packaging and advertising, and for prescribing

basic food labelling and advertising requirements.

The Canadian General Standards Board has launched a project sponsored by the Canadian Council of Grocery Distributors to develop a Canadian standard for the voluntary labelling of foods derived from biotechnology. The voluntary labelling standard is being developed with participation from consumer groups, food companies, producers, environmental groups, general interest groups and government. The purpose is to ensure that labels found on foods are meaningful to the consumer, are verifiable, truthful and not misleading.

Regulating Novel Foods (Including Foods Derived from Biotechnology) in Australia and New Zealand

Dr. Paul Brent (Manager of Biotechnology, Product Standards, Australia New Zealand Food Authority) informed that the National food standards in Australia build on the level of food safety that is generally accepted by the community. An explicitly cautious approach is applied in cases where there is no established history of safe human consumption, as is the case for foods produced using gene technology. Novel foods, including genetically modified (GM) foods, must undergo a mandatory pre-market safety assessment. The approach used in Australia and New Zealand to assess the safety of foods produced using gene technology draws on concepts and principles that have been developed internationally by OECD, FAO/WHO and Codex Alimentarius Commission.

Food standards are developed in Australia and New Zealand by ANZFA and are approved by the Australia New Zealand Food Standards Council (ANZFSC; comprising the health ministers of the Commonwealth, States, Territories and New Zealand).

ANZFA undertakes the safety assessment of GM food according to the following key principles:

- safety assessments use scientific, risk-based methods;
- safety assessments are conducted on a case-by-case basis;
- both the intended and unintended effects of the genetic modification are considered;
- where appropriate, comparisons are made to conventionally produced foods.
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The pre-market assessment and approval process aims to ensure that food derived from biotechnology is as safe as conventionally produced food (ANZFA (2000)). Guidelines, explaining ANZFA's safety assessment process, are published on its web site[1]. The process established by ANZFA for the regulation of GM foods is one of the most transparent and consultative anywhere in the world today. Two full rounds of public consultation are built into the application process. All data, except for a small amount of commercial-in-confidence information, is available to the public for scrutiny.

GM foods are regulated in Australia and New Zealand under Standard A18 - *Food Produced Using Gene Technology* of the *Foods Standards Code* (also referred to as

[1] http://www.anzfa.gov.au

Standard 1.5.2 of the new Australian New Zealand Food Standards Code). The Standard covers two areas of the regulation of GM foods. Firstly, Standard A18 regulates the sale of foods and food ingredients, other than additives and processing aids, which are produced using gene technology. The Standard provides for a general prohibition on the sale of a food produced using gene technology unless it has been specifically approved as safe. A key provision of the Standard is the requirement for foods derived from biotechnology to undergo a mandatory pre-market safety assessment and approval. The Standard also recognises that some foods derived from biotechnology were already in the food supply when the Standard came into effect. Transitional arrangements were put in place to permit these foods to remain in the marketplace while the foods undergo the safety assessment.

The second area covered by the Standard relates to specific labelling provisions for GM foods. It is important to note that the labelling provisions of Standard A18 are intended to provide information to consumers, not to act as health warnings because unsafe foods, GM or otherwise, are not permitted for sale in Australia or New Zealand.

To date, the Australia New Zealand Food Standards Council have approved 12 GM foods to be imported into Australia and New Zealand and are considering approval of four more. All of these foods have been assessed as safe as the conventional counterpart foods with no additional risks. ANZFA is currently assessing the safety of five other GM foods and these assessments are in various stages of development.

Overview of ASEAN Guidelines on Risk Assessment of Agriculture-Related GMOs

Ms. Sumita G Thakurta (Head of Agribuisness Development Section, Agri-food and Veterinary Authority of Singapore) stated that in October 1999, the ASEAN Ministers of Agriculture and Forestry (AMAF) endorsed the *ASEAN Guidelines on Risk Assessment of Agriculture-related GMOs*. The Guidelines serve to provide ASEAN member countries with a common understanding and approach when conducting scientific evaluations for the release of agriculture-related GMOs. The Guidelines describe the procedures for notification, approval and registration of agriculture-related GMOs. Information on approved agriculture-related GMOs are deposited at the ASEAN Secretariat to provide a database and assist ASEAN member countries with the evaluation of received applications. The Guidelines also address the need for each country to establish its own National Authority on Genetic Manipulation (NAGM) along with the roles and responsibilities of this authority in regulating agricultural GMOs.

Discussion

The discussion session was chaired by Mr. Lee Yuen Tong (Director of Agrotechnology Division, Agri-food and Veterinary Authority of Singapore).

1. A question was raised concerning the Canadian Food Inspection Agency (CFIA) and their monitoring and regulation practices for confined field trials containing genetically modified (GM) plants. Ms Prud'homme (of Health Canada) stated that in addition to the weekly monitoring done by the group conducting the field trial, CFIA inspectors visit the trial sites on a regular basis to check on field trial compliance. In the event a confined field trial does not meet the regulations for environmental safety set by the CFIA, the trial must be brought into compliance prior to flowering, or the field trial must be aborted and all of the GM plants must be destroyed. Should the trial be found non-compliant after flowering has commenced, additional restrictions are put in place at the trial site and the surrounding area. Also, in the year's following the trial, planting restrictions at the site exist for a set period of time, and the site continues to be monitored for volunteer plants to prevent their reoccurrence and possible escape of engineered traits.

Dr. Brent from the Australia New Zealand Food Authority, added that the penalty in Australia for non-compliance to the guidelines on the environmental risk assessment of agri-related GMOs can be as high as A$1 million. The only non-complying case was for the disposal of volunteered plants of the canola but the company involved had been dealt with.

2. Health Canada was asked to discuss the reason for choosing to use the terminology "novel food" rather than "gene technology" in their framework for safety assessment. Health Canada recognized the importance of international consensus on such definitions, but chose to adopt the broader term "novel food", so that the same framework for safety assessment would be carried out on all food with no history of safe use in Canada. The concept of novel foods includes food produced from genetically modified plants, but could also include foods derived from traditional breeding and mutagenesis if a major change has been made to the food itself. The reason for this broad definition comes from the concept that a safety assessment should be triggered by the traits of the

product and not by the process that produced it. The safety of food is of the prime concern, no matter how it was produced.

In the case of Australia and New Zealand, the standards for GMOs related food and novel food are defined separately. "Gene Technology" is as defined by the Organisation for Economic Co-operation and Development (OECD) and it refers to the “recombinant technology”. Novel food is classified as food without previous established history of safe human consumption.

3. When asked for recommendations regarding the public consultation process for the safety and risk assessment of GMOs, Health Canada indicated that sufficient information on GM food and its regulation should be provided to the public. However technical details may be too intricate for the public to understand, and it is necessary to present information in a public-friendly format. It was recommended that consultations be made early in the regulatory process so that the public has the opportunity to participate and present concerns and ideas from the very beginning. The framework for public consultations should consider what the regulator can realistically enforce, what industry can do to provide assurances during development and testing, and what the consumer’s needs are.

In Australia’s consultative framework, full assessment data is made available for public scrutiny. In general, adequate resources and infrastructures need to be invested to fine tune public communication and to balance the type of information to be released to the public. The discussion also highlighted that concerted effort is needed for countries to ensure transparency in their assessment process.

4. Guidelines for the safety and risk assessment of GM animals are currently being developed in Canada with an anticipated completion date in 2002. To date, no submissions have been made to Health Canada, though there is research ongoing in GM-salmon and GM-goat. Similarly, GM animals are still at the research and development stage in Australia and the guidelines for safety and risk assessment of GM animals have not been put in place.

5. A question was raised about environmental safety and risk assessments for GMOs

imported into Canada. The Plant Biosafety Office of the Canadian Food Inspection Agency is responsible for the regulation of imports and environmental release of plants with novel traits (PNTs) in Canada. Importation of PNTs, including the products derived from them, require a permit to import if the appropriate Environmental, Feed and Food approvals have not already been obtained. Import permits are issued only after a pest risk assessment has been conducted by the Plant Biosafety Office. As well, all PNT imports must also meet regular purity standards as required for non-GMO imports. Typically, permits are issued with specific conditions to limit the movement or use of the PNTs, upon entry into Canada. Environmental release of the import can only occur after an environmental risk assessment has been conducted by the Plant Biosafety Office. Applications for environmental release may be granted under either confined conditions, as in research field trials, or on an unconfined, unrestricted basis. For more information on the activities of the Plant Biosafety Office regarding importation of PNTs or environmental risk assessments for PNTs you are encouraged to visit the website (www.inspection.gc.ca).

6. The importance of having the sequence of the inserted gene included as a requirement for approval was raised, so that detection methods could be established. Health Canada agreed that the sequence of the inserted DNA is important and that it is now a requirement for all Canadian submissions. This information is provided by industry with the understanding that sequence information will only be released to a list of prescribed agencies with commercial confidence (such as the CFIA), and will not be available within the public domain. Information on the sequence of the inserted gene is required in Australian submissions as well, and is also considered confidential business information.

7. A representative of ILSI asked about the possible approaches to ensure public understanding on the objective of labelling GM food. ANZFA commented that in Australia consumers have been informed that implementation of a food labelling system for GM food is not about food safety, since this is already addressed by ANZFA's scientifically rigorous and transparent safety assessment process, but is about providing consumers with an informed choice about the food they eat. In Australia, it has been observed that the number of submissions received from the public on GM food

applications has greatly diminished following the implementation of GM food labelling. The chairman added that the labelling of GM food is a sensitive issue that requires the strong involvement of the government, the investment of abundant resources and infrastructures and substantial enforcement. ASEAN countries need to keep a watching brief on international developments and will have to make their own decision on this issue.

BREAKOUT SESSIONS – CASE STUDY: "NOVEL FOOD SAFETY ASSESSMENT OF A GENETICALLY MODIFIED, HERBICIDE TOLERANT SOYBEAN"

The breakout sessions were used to facilitate discussion within the group about the novel food safety assessment process. A case study using a genetically modified herbicide tolerant soybean provided the framework for examining a novel food evaluation within the Canadian regulatory context. In order to provide some insight into the type of data usually submitted for evaluation, the case study used excerpts from the applications for food safety assessment submitted to regulatory authorities in Canada, the UK and the US, by Monsanto for the genetically engineered soybean event GTS 40-3-2 and its progeny.

Four working groups were created, each containing approximately 12 participants. Workshop facilitators introduced each topic and guided the groups into discussion. The topics addressed by the working groups included the evaluation of data on: the host organism, donor organism, transformation system, molecular characterization of the inserted DNA, genetic stability of the introduced trait, expressed material/ effect, toxicity, allergenicity and nutrition. The groups reconvened and reported on their discussions as summarized below.

Development and Production of a Modified Soybean

The Host Organism

A thorough knowledge of the host organism and of the processing and properties of the final food products is important in order to establish appropriate data for comparison with the novel food. Dr. Yan emphasized the need for identifying the natural range and variation of key nutritional components, known toxicants, antinutrients, and potential allergens in the crop at various developmental stages and throughout it's processing.

In the case study, the participants generally agreed that the host organism, soybean (*Glycine max)*, had a long history of safe food use and has been widely consumed by humans. But, since the host organism is known to cause food allergies in some people, there was a general agreement that it must be assumed that the genetically modified soybean is allergenic as well, but the novel gene products would only need to undergo the normal assessment for allergencity. The participants also discussed the presence of naturally occurring antinutrients such as inhibitors, hemagglutinin, phytic acid, and phytoestrogens like genistein, diadzein and coumesterol, and discussed the presence of low molecular weight carbohydrates. Despite the presence of these compounds in the host soybean, it was accepted that there was no special cause for concern. However the levels of these components should be assessed during the safety evaluation of the genetically modified soybean to ensure that the levels fall within the range of natural variation found within the foods produced using the traditional soybean.

Participants highlighted the need to also assess the impact of the host organism on the environment and biological diversity. Questions raised included the need for information on the influence of the gene modification on such things as uptake of external contaminants (e.g. cadmium and aluminum) and the environmental impact of changes in pesticide practices. Dr. Yan informed the group that in Canada, a complete environmental risk assessment addressing these issues is conducted by the Canadian Food Inspection Agency and not Health Canada.

The Donor Organism

Information about the donor organism is required to determine if it exhibits characteristics of pathogenicity or toxin production, or have other traits that affect human health. For example, when the genetically engineered food contains genes from a donor organism known to contain allergens, the novel gene product is assumed to be allergenic unless proven otherwise. In the case study, the participants noted that the only novel

gene present in the GM-soybean was CP4 EPSPS, donated from *Agrobacterium* species. *Agrobacterium* is a naturally occurring soil bacterium and the protein produced by this gene would therefore already be present in all plant, microbial and fungal food sources. Further analysis or toxicological tests of the donor species would not be warranted because only the specific sequenced gene encoding EPSPS was transferred to the soybean.

Concern was raised over the use of antibiotic and bacterial marker genes (i.e. *nptII*) which have been used in the selection of plasmids in *Escherichia coli*. These genes confer resistance to aminoglycosides antibiotics (i.e. kanamycin or neomycin) and their use is an internationally debated issue. Dr. Yan noted that in Canada, companies have been encouraged to use alternative markers for plant transformation in the development of future products of biotechnology. Health Canada and numerous national and international scientific organizations have concluded however, that the risk of developing widespread antibiotic resistance through the use of these genes as markers is negligible. When assessing foods containing antibiotic resistance markers, the clinical use and importance of the antibiotic along with the safety of the gene expressed product would be assessed for risk to human health. Dr. Brent highlighted that there is no known evidence of gene transfer from food into the human gut cells or microorganisms. Nevertheless, it is a requirement for the applicants to identify all foreign genetic elements involved or incorporated in GTS 40-3-2 including the EPSPS gene.

The Modification Process

It is important to have a detailed understanding of the method by which the novel traits are introduced into the host plant, because it determines, in part, the information requirements for the assessment of the molecular biology of the plant. The two principal methods for introducing new genetic material into plant cells currently are microparticle bombardment and *Agrobacterium*-mediated transformation. Each technique presents specific issues that need to be addressed when examining the molecular characterization of the inserted DNA. The participants indicated that the necessary information describing the modification process (micro-projectile bombardment) used to introduce the CP4 EPSPS gene into the soybean was sufficient for the safety assessment process.

Molecular Characterization of the Inserted DNA

Molecular characterization of a transgenic plant provides information about the

composition and integrity of the inserted DNA; the number of copies of the inserted DNA; the number of sites of insertion; and the level of expression of the novel protein(s) over time and in different tissues. Dr. Yan commented that a detailed description on the molecular characteristics of the genetically modified plant is required to demonstrate that the developer has critically analyzed the plant and its products, including all novel genes and novel proteins. A detailed molecular characterization may also by able to address issues related to positional effects, pleiotropic effects and gene silencing. It is recommended therefore, that the safety/ risk assessment team be comprised of at least one molecular biologist to look at the details and clarify any missing or confusing data. Participants felt that the data presented in the case study allowed for a determination of the genetic change caused by the modification process.

Questions were raised by the workshop participants concerning the data provided in the training manual for this section. Some copies of the gels from the Southern blot analyses and the PCR analyses were difficult to read and interpret, and contained bands that were unexplained in the text. Although some of these problems were the result of the difficulty in reproducing these gels for the purpose of the training manual, Dr. Yan reiterated that regulators reserve the right to request additional information and clarification from the applicants should the submission be incomplete, confusing or have inadequate data. Mr. Harrison confirmed that for the purpose of a submission, high quality copies or original photographs along with restriction map/ plasmid maps would be necessary for a proper assessment of the data.

Introduction to Product Information

Genetic Stability of the Introduced Trait

The inheritance and stability of each introduced trait that is functional in the transformed plant must be determined. In the case study, the stability of the introduced trait or the stable integration of the CP4 EPSPS gene into the genome of GTS 40-3-2 was demonstrated through a combination of molecular and phenotypic trait segregation analyses. This included the examination of the segregation patterns of progeny produced from crosses between GTS 40-3-2 and non-transgenic cultivars, and testing for glyphosate tolerance. A consistent 3 tolerant to 1 sensitive ratio was observed among all F_2 progeny, indicating that the glyphosate tolerance in GTS 40-3-2 is conferred by a single dominant gene. It was reaffirmed that up to six generations of the GTS 40-3-2 progeny was actually generated for Southern blot analysis to confirm the genetic stability of the CP4 EPSPS trait. The participants felt that the data provided sufficient information to demonstrate that the gene was stable in the soybean genome.

Expressed Material/ Effect

A food safety assessment requires an analysis of which introduced genes are expressed, and an identification of the characteristics, the concentration, localization and impact of the expressed products. The participants in the workshop identified some inconsistent statistical data and incomplete methodology in the case study. Dr. Yan explained that this was the result of reducing the submitted data to subsets and summaries for the purpose of creating the course material, and that the actual application contained the appropriate information for the assessment. Dr. Yan complimented the participants for their thoroughness in identifying the missing information.

The participants were in doubt if the analysis of the introduced gene was done for both sprayed and unsprayed plants. Dr. Brent revealed that CP4 EPSPS protein expression in the sprayed and unsprayed herbicide resistant soybean was studied in the data package reviewed by regulators. On the safety concern on the herbicide (i.e. glyphosate) residue, Dr. Brent raised the common criticism in Australia and internationally that the farmers would tend to spray more glyphosate, on the herbicide resistant soybean. Dr. Brent also added that the limit for the usage of glyphosate in Australia was much lower, at 0.1 mg/ kg, than that of the Codex (20 mg/ kg). All foods sold in Australia and Canada must comply with relevant maximum residue limits, whether a food is genetically modified or not.

Nutritional Data

All plant breeding methods, traditional and modern, have the potential to alter the nutritional value of the plant or lead to unexpected or unintended changes in the concentrations of various natural toxicants and anti-nutrients. The objective of the nutritional assessment is to consider the potential for any change in nutritional composition or bioavailability of key nutritional components in the modified product. It should also determine if there have been any unintentional changes in the levels of natural toxicants or anti-nutrients that would adversely affect the health or nutritional status of the consumer, including specific sub-groups.

Based on the information provided in the workshop materials for this topic, the participants raised concerns over the inconsistent and incomplete data submitted for the safety assessment. For example, some of the analyses were made using soybean seed, while others were made using soy protein products and toasted product without an explanation for why they used these different forms for the compositional analysis. Dr. Yan explained that the workbook was a summary of the information that was provided to Health Canada for the nutritional assessment of GTS 40-3-2, and that the actual submission contained additional information than what could be provided in the workbook. He also stated that normal practice was to initially focus the nutritional assessment on the crop itself, and if necessary perform additional analyses on the processed products typically consumed by the population. Such studies can be time consuming and costly for the developer, so applicants are encouraged to consult the regulators throughout the product development stage for advice on the types of studies and data that will be needed for the safety assessment.

Dr. Brent added that in Australia, it is also a good educational experience for the regulators. In its first safety assessment of agri-related GMOs involving GM potatoes, the applicants highlighted the fact that there was no need to analyse all the vitamins and minerals since potatoes contain mainly of carbohydrates and Vitamin C.

In this case study, the results for the fatty acid comparison showed a significant difference in the seed C22:0 composition between GTS 40-3-2 and the control soybeans. When determining how important this difference is, regulators must consider 1) the trial design, 2) the variability of the data, 3) the consistency of the result, 4) the reported literature values and 5) the significance of the component to the profile. Carefully constructed studies conducted across a range of environmental conditions will often show that the statistical differences found within a site are dwarfed by the differences found between sites due to environmental influences. A consistent difference in a component across several environments is more reflective of an actual difference than its occurrence

at only one site. However, if the data from the transgenic variety falls within the accepted literature range for that crop, and it is a minor component of the profile, there is really not much cause for concern. Component C22:0 of the fatty acid profile represents less than 0.6% of the total fatty acid fraction, and for GTS 40-3-2, the C22:0 fatty acid profile fell within the accepted literature range for all soybean varieties.

A concern was raised about the high amount of variability found in the isoflavone data. Again, because higher levels of variability make it more difficult to declare a significant difference, the trial design should be carefully examined and the statistical analysis may be better conducted within sites rather than making the comparison by grouping the data from all of the sites. In this case, it was determined that the variability found in the data was due to the influence of the different environments on the formation of these compounds in plants.

The credibility of the Substantial Equivalence (SE) concept for use in the safety assessment process was questioned by the participants in response to the effects of environmental variability on nutrient composition as demonstrated in the case study, and as raised by Greenpeace at the last OECD meeting. The participants were reminded that the SE concept is not a safety assessment in itself because it does not characterize hazard. SE is used to structure the safety assessment to compare the GM and non-GM plants to identify differences that would require further analysis in order to establish if the statistical difference is biologically relevant. It was noted however, that there are limitations to the use of SE, for example, there must be sufficient analytical data for the traditional counterpart in order to have a meaningful comparison.

Participants were satisfied with the range of data presented for GTS 40-3-2 to allow for a compositional and nutritional comparison with traditional soybeans. It was established that key micro and macro-components were found to within the acceptable limits of natural variation for soybean and that GTS 40-3-2 was of the same nutritional quality as the traditional counterpart.

Toxicity

The prime focus of the toxicity evaluation is on the gene products of the inserted gene(s). The inserted DNA, in itself, does not pose a food safety concern. Another key issue is the

potential for increases in levels of natural toxicants or allergens associated with the novel food. In determining which data would be required, it should first be established whether the novel protein(s) will be expressed in the edible tissue, and if present, whether the anticipated processing conditions will result in the removal or denaturation of proteinaceous material. If a concern remains, then data will be required to address the safety of the novel protein.

There are now numerous examples of GM plants used as food that express novel protein as a result of the transfer of new genes. Examples of such novel proteins include plant virus coat proteins used to protect plants against virus infection, bacterial proteins used to protect plants against insect attack, and various enzymes responsible for detoxifying a number of different herbicides.

A large number of proteins are ingested as part of the normal human diet without any adverse effects, although a small number have the potential to impair health, e.g., are allergens or anti-nutrients. As proteins perform a wide variety of functions in organisms, different possible effects have to be considered during the safety assessment including potential toxic, allergenic and nutritional effects. To effectively identify any potential hazards requires knowledge of the characteristics, concentration and localisation of all novel proteins expressed in the new organism as well as a detailed understanding of their biochemical function, fate and phenotypic effects.

Very few foods consumed today have been the subject of toxicological studies. When a novel food is compared with a conventional counterpart, the intention is to determine whether the new food is as safe as the counterpart. If the GM food differs from its traditional counterpart by the presence of one or a few novel proteins, it is usually possible to assess the potential toxicity of these proteins in a manner analogous to traditional toxicity testing (WHO 2000). That is, the assessment is applied to the novel protein itself, rather than the whole food.

In considering the potential toxicity of a novel protein it is first important to determine whether it is likely to be present in the food as consumed, and thus whether exposure is

likely[2]. Once likely human exposure to a novel protein is established, a number of different pieces of information can collectively be used to demonstrate there is a reasonable certainty that no harm will result from that exposure.

- An assessment of potential toxicity of a novel protein should consider the following:
- whether the novel protein has a prior history of safe human consumption, or is sufficiently similar to proteins that have been safely consumed in food;
- whether there is any amino acid sequence similarity between the novel protein and known protein toxins and anti-nutrients;
- whether the novel protein causes any adverse effects in acute oral toxicity testing;
- whether the novel protein is resistant to heat and/or processing;
- whether the novel protein is resistant to degradation in simulated digestion models.

It should be noted that, unlike many other substances that are added to foods, the majority of proteins have a predictable metabolic fate in the digestive system, that is, they are typically broken down into their constituent amino acids and then assimilated. For novel proteins, it is therefore important to establish that they will behave like any other dietary protein. One method that can be used to demonstrate this is an *in vitro* digestibility assay. This assay should be able to establish if a novel protein has any characteristics unusual in dietary protein, such as resistance to digestive fluids.

Acute oral toxicity testing is an important component of the safety assessment of novel proteins and is particularly useful in circumstances where there is no prior history of safe consumption of the protein. Acute tests should be sufficient since – if toxic – proteins are known to act via acute mechanisms and laboratory animals have been shown to exhibit acute toxic effects from exposure to proteins known to be toxic to humans (Sjoblad *et al* 1992). The acute toxicity tests are done using purified protein that is administered at very high dose levels, usually orders of magnitude above what the human exposure level would be. Ideally, the protein to be tested should be that which has been directly purified from the new organism. Where this is not possible, usually because it is difficult to obtain sufficient quantities of purified protein, it is essential to ensure that the protein tested is biochemically and functionally equivalent to that present in the GM food.

[2] Even if it can be demonstrated that a protein will not be present in the edible portion, proteins known to be toxic to humans should never be deliberately introduced into another organism to be used for food because of the risk of

If a novel protein is found to have no significant sequence similarities to known protein toxins, is not stable to heat and/or processing and is readily digested in conditions that mimic mammalian digestion and either has a prior history of safe human consumption and/ or does not cause any toxic effects in acute toxicity testing then it can be reasonably concluded that the protein is non-toxic to humans and no further toxicological investigations would be required.

If a novel protein fails one or more of the criteria discussed above then further investigation of the novel protein may be required. For example, if adverse effects were noted in acute toxicity testing then additional toxicity testing would be required to determine a safe level of human exposure.

As part of the assessment of the potential toxicity of a novel protein it is important to also determine if the activity of the novel protein in the organism is likely to produce any secondary effects, such as the accumulation of other substances. If other substances are found to accumulate as a result of the activity of a novel protein, e.g., the accumulation of a metabolite as a result of the detoxification of a herbicide in a plant, it is important to also include an assessment of the potential toxicity of such substances.

Usefulness of long-term animal toxicity studies

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 characterized, 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

accidental carryover into the edible portion.

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.

GTS 40-3-2 Case Study

The results of the studies completed by the applicant to establish potential toxicity concerns were as follows:

- Purified CP4 EPSPS from bacterial cultures was used as the test material for the acute mouse gavage and protein digestibility studies because of the relatively low level of expression of CP4 EPSPS protein in GTS 40-3-2;
- Functional equivalence between *E. Coli* expressed CP4 EPSPS and plant expressed protein was based on the criteria of molecular weight, immunological cross-reactivity, absence of glycosylation, N-terminal amino acid sequence and enzymatic activity;
- The CP4 EPSPS protein showed no amino acid sequence similarity to known protein toxins, is rapidly degraded *in vitro* under conditions simulating the digestive conditions in the mammalian stomach or intestinal tract, and displays no indications of acute toxicity as measured by treatment-related adverse effects in mice administered CP4 EPSPS protein by oral gavage.

For the case study, the participants were satisfied with the conclusions reached by the studies undertaken on the history of safe use of the EPSPS family of proteins and potential toxicity of the novel protein.

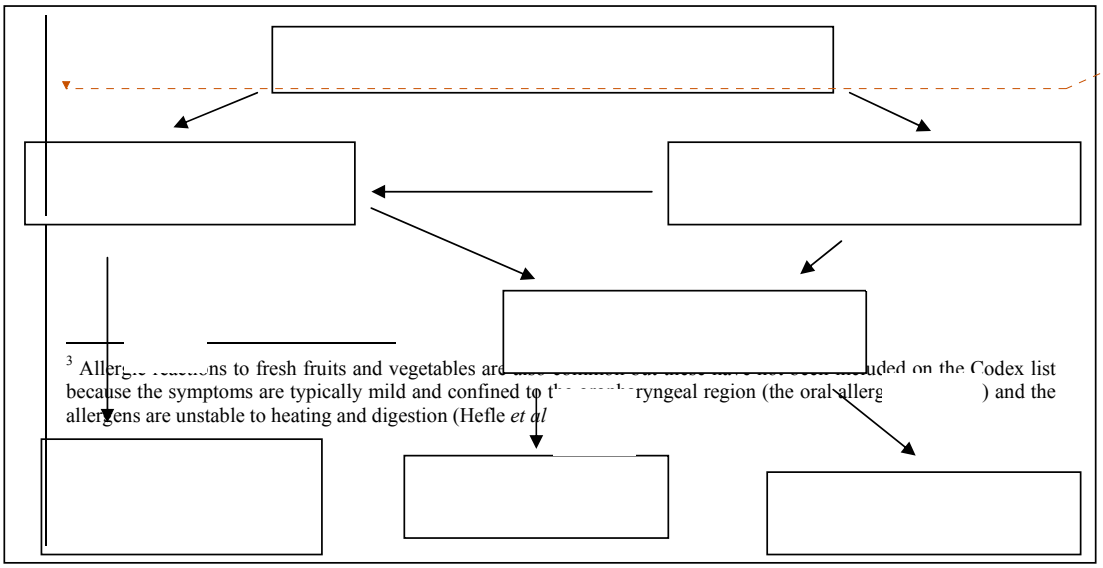
Allergenicity

Food allergy is an issue of considerable concern to consumers and has been the subject of a relatively recent FAO technical experts meeting (FAO 1995). Food allergies are caused by abnormal immunological responses to particular substances in food and affect between 1 and 2% of the population. The Codex Alimentarius Commission has adopted a list of the

most common allergenic foods – these include peanuts, soybeans, milk, eggs, fish, crustacea, cereals, and tree nuts. These foods account for over 90% of all moderate to severe allergic reactions to foods[3].

Virtually all food allergens are proteins, but only a small fraction of the many proteins found in food are allergenic. Therefore, even though foods can contain tens of thousands of different proteins, relatively few are allergenic. As the use of gene technology can result in additional protein diversity being added to the food supply, the potential allergenicity of any new protein should be a part of the safety evaluation. It should be noted that additional protein diversity could also be introduced into the food supply through conventional breeding techniques. For example, the recently introduced conventionally bred kiwi fruit has proven to be an additional source of food allergens.

Prediction of allergenic potential of novel proteins is not a simple matter. There are presently no reliable animal models for the assessment of allergenicity. In 1996, the International Food Biotechnology Council, in conjunction with the Allergy and Immunology Institute of the International Life Sciences Institute, developed a decision-tree approach for the assessment of the potential allergenicity of GM foods (Metcalfe *et al* 1996). A simplified version of the decision tree is reproduced below.



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[3] Allergic reactions to fresh fruits and vegetables are [illegible] included on the Codex list because the symptoms are typically mild and confined to the oropharyngeal region (the oral allergy) and the allergens are unstable to heating and digestion (Hefle *et al*

The strategy behind the decision tree focuses on the following:

- source of the gene – particular caution should be exercised if the source organism of the gene contains known allergens, e.g. peanuts;
- amino acid sequence similarity of the newly introduced protein to known allergens – the amino acid sequence of many allergens are readily available through public domain databases. The current criteria to determine significant sequence similarity is a match of at least eight contiguous, identical amino acids (Metcalfe et al 1996);
- stability to digestion – most allergens are resistant to gastric acidity and to digestive proteases. The ability of food allergens to reach and cross the intestinal mucosal barrier in immunologically intact form appears to be a prerequisite to allergenicity (Metcalfe et al 1996). Simulated gastric and intestinal digestive models of mammalian digestion have been used to assess the digestive stability of proteins (Astwood et al 1996);
- heat or processing stability – labile allergens in foods that are eaten cooked or undergo other processing before consumption are of less concern;
- immunological reactivity of the newly introduced protein – if a novel protein is derived from a known allergenic source or if it has sequence similarity to a known allergen, then the reactivity of the novel protein with IgE from the blood serum of appropriate allergic individuals can be tested.

Many food allergens, especially those in common allergenic foods, are present as major protein components, typically ranging between 1.0 and 80% of total protein (Metcalfe *et al* 1996). Allergic sensitisation is thus considered more likely to occur to the major proteins that exist in foods (Taylor 1997). Most novel proteins, on the other hand, are expressed in comparatively low amounts in the food and are therefore considered to have limited potential for allergic sensitisation. Greater scrutiny though would be warranted of GM foods that contain novel proteins at significant levels. On the other hand, novel proteins expressed

in the non-edible portions of an organism (for example in the leaves of potatoes but not in the tubers) are not a concern in terms of food allergy.

When new proteins are produced from genes derived from known allergenic foods, tests can be conducted both *in vitro* (using sera from sensitive individuals) and *in vivo* (using skin tests on sensitive individuals). In the case of negative results, no further action would be necessary. In the case of positive results from *in vitro* and *in vivo* tests, appropriate regulatory action would need to be taken to manage the risk to susceptible population groups. This could involve either withholding approval of the product, or prescribing appropriate labelling to inform the public of the hazard. The appropriate risk management approach would need to be determined on a case-by-case basis but it is unlikely that approval would be recommended for a new, allergenic food that is likely to be widely distributed throughout the food supply.

Likewise in cases where doubt exists about the potential allergenicity of a novel protein a cautious approach may be warranted until such time as more certainty exists about the potential allergenicity of the product. For example, regulatory concern might be appropriate in circumstances where a novel protein is expressed at high levels in the edible part of the GMO and is resistant to digestion and/or processing even if it is from a non-allergenic source and has no sequence similarity to known allergens.

GTS 40-3-2 Case Study

The potential allergenicity of the CP4 EPSPS protein expressed in transgenic GTS 40-3-2 soybeans was assessed by examining:

- the immunoreactivity of separated soybean proteins with IgE antibodies from sera obtained from soybean allergic individuals;
- the physiochemical properties of CP4 EPSPS in relation to known allergenic proteins;
- the lability of CP4 EPSPS in simulated gastric and intestinal fluids;
- amino acid sequence similarities with other naturally occurring plant derived EPSPS enzymes and with known protein allergens; and
- estimated dietary exposure to CP4 EPSPS based on its concentration in food.

The results of the predictor tests for potential allergenicity demonstrated the CP4 EPSPS protein does not pose any significant risk of allergenicity for human consumption. This conclusion was based on the findings that CP4 EPSPS protein is not derived from a known allergenic source, does not possess immunologically relevant amino acid sequence homology with known allergens, and does not possess the characteristics of known protein allergens (e.g. molecular weight, heat stability, propensity for glycosylation). This information, coupled with the information that CP4 EPSPS protein is present in very low levels in soybean seed (and even less in food fractions derived from seed such as oil), together with the extremely rapid digestion of this protein under *in vitro* digestive conditions that mimic human digestion, established that there is little likelihood that plant expressed CP4 EPSPS protein would pose any significant allergenic risk from consumption of food derived from GTS 40-3-2 soybeans. Participants generally agreed with the conclusions reached by the studies. One important point raised by the participants was soybean consumption varied greatly from culture to culture, and therefore the likely exposure in a particular country to the novel protein should be taken into account when considering potential for toxicity and allergenicity.

It was noted by Dr. Yan and Dr. Brent that the information requirements relating to the potential allergenicity of novel proteins are likely to be revised to reflect the deliberations of the Codex Ad Hoc Intergovernmental Task Force on Foods Derived from Biotechnology, who are examining the outcomes of the recent Joint FAO/WHO Expert Consultation on Allergenicity of Foods Derived from Biotechnology, held in Rome in January 2001. This may result in a revised decision-tree approach and some refinements to the current system for assessment of potential allergenicity of the novel protein.

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The workshop concluded with presentations on the future challenges facing GM-food safety assessment. Dr. William Yan and Dr. Paul Brent presented regulatory perspectives while Dr. Anthony Huggette (Nestle R&D Centre, Singapore) presented an industry perspective.

A Regulatory Perspective

Dr. Yan indicated that there were general as well as specific challenges all regulators will have to face in the future. The first general challenge regulators need to face is the development of effective communication strategies for public education. In the past, Canada has not communicated technical issues related to the regulatory system well to the public, and the public has generally not been keen to learn about the regulatory system unless there was a specific cause for concern. The regulation of GM-food has however, triggered a lot of public interest over the last few years. In response to the need for increased public education and communication about GM-foods, the Canadian government has made a number of changes to their web site, making it more structured and user friendly, and Health Canada has conducted numerous seminars across Canada for a variety of groups including ecologists, consumers, nutritionists, and academia.

In Australia, the approach has been similar, having acquired the assistance of journalists to maintain their web site in a user-friendly format. They are also required by law to consult the public at two stages during the safety assessment process. The two mandatory public consultations are used to provide consumers an opportunity to express their views, which are then incorporated into the assessment process. The final safety assessment however, is still science based. Despite the transparency of this approach, it still faces criticism and requires much more time and effort for it to gain public acceptance.

A second general challenge is the need for capacity building within individual countries. Dr. Brent indicated that it is a difficult process to predict what infrastructure will be needed for the future. In Australia, it has been recognized that there is the need to train scientists and economists for risk benefit analysis, and in Canada, the federal government has budgeted C$90m for biotechnology development and capacity building for GM safety assessment. Conducting workshops and sharing regulatory experiences are also excellent ways to build regulatory capacity across the globe, and also provide a forum for collaboration and guideline harmonization.

A specific challenge for our future is the development of safety assessment criteria for molecular farming or "pharming" products. Despite being in the early stages of research and development, the consultation process for the development of safety assessment criteria for GM–pharmaceuticals has already been started in Canada by Health Canada and the Canadian Food Inspection Agency. Australia will be using a similar approach for safety criteria development.

Dr. Yan also indicated that the development of guidelines for the safety assessment of GM live-stock and fish is another specific challenge regulatory agencies now face. Canada is currently in the process of drafting guidelines for GM live-stock and fish because the safety assessment criteria will be different from those used for GM crops. The current draft target date for these new guidelines is June 2002.

Health Canada and the Ministry of Health Council in Australia are both currently in the process of developing standard codes and safety guidelines for the safety assessment of functional foods. In both cases, the emphasis is on the safety of the product and on the health claims these foods possess rather than the technology used to create it.

As discussed during the workshop, research needs to be continued in the area of food allergens and predictive models, in order to make improvements to allergenicity assessment criteria. Dr. Brent noted that a WHO consultation had derived a new set of criteria that is yet to be confirmed for its practicality in September in Vancouver.

According to Dr. Brent, the application of profiling techniques such as proteomics seem exciting as more facilities were being setup in the academic laboratories. However, major issues remained with how the data are interpreted, managed, validated and used. It will in no doubt create a lot of data and work for the regulators in the future.

Dr. Brent also indicated that Australia although they are not mandatory animal feeding studies are considered highly useful to assist with the safety assessment of GM foods. Such testing is considered useful to compare animal health after consuming the GM food versus the traditional counterpart. International consensus on protocols for such studies is desirable.

Another issue that needs to be addressed is the development and implementation of post-

market monitoring guidelines for GM products to address long-term effects. In Britain, a feasibility study, known as the Post Market Surveillance, was being conducted by the Advisory Committee for normal food and processes under the Food Standard Agency. It was a survey on the consumption of normal and GM food, however, considerable problems were encountered during the planning of the survey. The difficulty with monitoring programs is the inability to relate an observed effect to the consumption of GM foods and not some other variable.

Another challenge is identifying the time frame for which GM products are given a time limited approval. Time limited approvals are common for other products like drugs and pesticides, and takes advantage of the advancements in technology and assessment over the years, leading to a more effective safety evaluation. Generally, it would be the responsibility of the company to monitor the GM product for safety and resubmit the product for evaluation and further approval.

An Industry Perspective

The introduction of gene technology in food production holds a great promise to improve the quality and nutritional value of our food as well as to increase food production. However, as for all novel foods, the introduction of raw materials produced from genetically modified crops into the food chain should only be permitted after a thorough safety assessment. The food industry has a key role to play in this process since it has the ultimate responsibility for food safety. Consequently large food producers cannot rely solely on assurances given by suppliers, but must have the expertise to evaluate the safety of the raw materials that they use.

The food industry has played an important role in providing information and expertise to international agencies such as WHO, FAO and OECD which have contributed to the development of strategies for the safety evaluation of foods derived from genetically modified organisms. There is a general consensus amongst the international organizations, major regulatory agencies, and food industry on the strategy and extent of evaluation required before a food containing constituents derived from a genetically modified organism can be marketed.

Food safety is just one of many issues faced by major food companies with respect to agriculture-related GMOs. Regulatory, quality assurance, ethical, and consumer

preference considerations, amongst others, have to be addressed.

Many GMOs are still in the development and assessment phase (e.g. undergoing field trials), and there has been at least one case (Starlink) whereby a GMO has received approval for use in animal feeds but not human foods. It is therefore essential for a food company to have intimate knowledge on the traceability of its raw materials to ensure that no products derived from unapproved or untested GMOs enter the food supply. This can only be achieved by working in partnership with all other parties in the food chain (e.g. farmers, suppliers, distributors, retailers, etc.). Traceability systems must ensure that the identity of raw materials is preserved throughout the food chain and certification should be backed up by verification.

Some governments have introduced mandatory labelling requirements for foods containing ingredients derived from GMOs. Adventitious cross-contamination of crops occurs throughout food production (seeding, harvesting, transport, milling, processing). The recognition that it is impractical and virtually impossible to guarantee the complete absence of traces of materials derived from GMOs in certain ingredients led to the development of thresholds for labelling by some regulatory agencies. There has been a wide variation in the labelling requirements enforced by different governments and in most cases these are unrelated to food safety aspects. This diversity and the potential for a lack of consumer understanding of the rationale for labelling can pose an important challenge to a multinational food company, both in terms of meeting legal requirements and with respect to communication.

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Ms. Lee Siew Mooi	Agri-food & Veterinary Authority (AVA)	Singapore
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Ms. Tan Wei Ling	Health Promotion Board	Singapore
Dr. Lena Chan	National Parks Board	Singapore
Dr. Leo Tan	National Parks Board	Singapore
Dr. Yvonne Chow	National Science & Technology Board	Singapore
Ms. Pauline Tay	National Science & Technology Board	Singapore
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Mr. David Tan Tuang Hong	Ministry of Environment	Singapore
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Dr. Philip Barlow	National University of Singapore	Singapore
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Ms. Esther Chong	Cerebos Pacific Limited	Singapore
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