REPORT OF THE

4th ASEAN-ILSI

Training Workshop on Safety and Risk Assessment of Agriculture-Related GMOs

August 31 – September 2, 2004
Sheraton Media Hotel & Towers
Jakarta, Indonesia

Organized by:

ASEAN FOUNDATION

ILSI International Life Sciences INSTITUTE

Departement of Agriculture
Indonesia

In collaboration with:

Food Standards Australia New Zealand

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CONTENTS

BREAKOUT SESSIONS

Workshop Overview – Framework and Objectives

Dr Paul Brent
Food Standards Australia New Zealand, Australia

This 4th ASEAN-ILSI Training Workshop on Safety and Risk Assessment of Agriculture-Related GMOs aims to (1) provide training in the safety assessment of genetically modified (GM) foods, leading to greater consistency of GM food safety assessment throughout the ASEAN region and possible harmonization of standards regulating GM foods; (2) provide the scientific background for the adoption of safety assessment methodology for GM foods into the technical infrastructure of the participating countries; and (3) assist in capacity building within the ASEAN region to enhance food safety through continuous training and identification of potential trainers.

The safety and risk assessment training is intended to utilize and review the international perspectives on GM food safety assessment, including approaches and guidelines established by CODEX and WHO/FAO, and a review of approval systems adopted internationally. Theoretical and practical experience in safety assessment methodology in Australia/New Zealand, USA and Japan, will also be presented and shared with the participants.

Important issues relating to the safety assessment of genetically modified organisms (GMOs) and foods derived from them will be discussed in the course of the Workshop. These include GMO product development; molecular characterization of the introduced gene; novel proteins; compositional characteristics; nutritional quality; potential for toxicants/anti-nutrients and potential allergenicity of new proteins introduced into a food; and substantial equivalence.

The focus of the Workshop is also to provide hands-on exercises with case studies that will give the participants opportunity to assess the safety of GM products. The case studies which will be used to demonstrate human and environmental safety assessment are MON 810 insect-resistant corn, high oleic acid soybeans and insect-resistant Bollgard II cotton.

Regulating Foods in Australia and New Zealand

Dr Paul Brent
Food Standards Australia New Zealand, Australia

Food Standards Australia New Zealand (FSANZ) is an independent, expert body responsible for public health protection throughout Australia and New Zealand by ensuring a high standard of food safety. Through the FSANZ Act 1991, FSANZ has the authority to make independent decisions, within statutory obligations and policy directions set by the Ministerial Council and other partnership agencies. FSANZ is mandated to perform the following functions:

- Development of standards (e.g., Food Standards Code)
- Development of codes of practices (e.g., Food Safety Codes of Practice)
- Provision of consistent interpretation for enforcement of standards
- Harmonization, both on the national and international levels (e.g., FAO, WHO, Codex Alimentarius (Codex))
- Conducting product recalls when warranted
- Monitoring and surveillance
- Provision of technical assistance to government, industry, and consumers

In Australia, the regulation of food products is governed by various laws, such as the Food Standards Code, State, Territory and New Zealand food/health laws, fair trading laws, import controls, and environmental and agricultural legislations. FSANZ is currently working on several food regulatory issues, including ongoing work on novel foods, GM foods, irradiated foods, health claims and fortification, food labelling, food additives and contaminants and primary production standards. With regards to the safety of GM foods and products, FSANZ aims to ensure that they are as safe as conventionally produced foods, based on internationally recognized risk-based approaches and the best scientific information available. The approval process is open, consultative and based on a scientific risk assessment undertaken by FSANZ. Public comment is also invited during the assessment process. This requirement for safety assessment applies to all foods on the Australian market, including imported foods.

Safety assessment requirements for food produced using gene technology are detailed in Standard 1.5.2, which prohibits the sale of GM foods unless such foods are listed in

the Food Standards Code. Pre-market safety assessment is also mandatory and the foods or products must comply with labelling provisions. Once the food or product has been approved, it can be used without further approvals as a whole food or as an ingredient in composite foods.

To date, FSANZ has completed and released full safety assessments on 30 GM foods for public comment. Out of these, 23 have been approved, 4 are under assessment, and 3 were withdrawn.

More information about FSANZ's processes for the regulation of GM foods can be found at FSANZ's website at http://www.foodstandards.gov.au.

FDA's Policy for Evaluating Bioengineered Foods

Dr Jeanette Glover Glew
Food and Drug Administration, Center for Food Safety and Applied Nutrition, USA

In the United States (US), evaluation of bioengineered foods encompasses foods for human consumption and animal feeds. In 1986, a coordinated framework for the regulation of genetically engineered foods was established between the United States Department of Agriculture (USDA), the Environmental Protection Agency (EPA), and the Food and Drug Administration (FDA). The USDA considers issues of agricultural safety during field trials, mostly concerns of an environmental or agronomic nature. EPA is responsible for ensuring that pesticidal substances introduced into plants are safe for human consumption and the environment, and sets tolerances or establishes exemption from tolerance for pesticides. The safety and proper labelling of all foods and food substances (e.g., cereals, fruits, vegetables, plant by-products such as starch and oils, milk, seafood, and other substances added to food such as enzymes and preservatives) comes under the purview of the FDA, except for meat and poultry which are regulated by USDA.

Within these agencies, it was agreed that the product, rather than the process by which it was developed, would be evaluated; that the products would be evaluated on a case by case basis; and that the products would be regulated under existing regulations.

The FDA derives its primary authority from the Federal Food, Drug, and Cosmetic Act (the Act). Three provisions of the Act are particularly important in securing food safety: Post-market adulteration provisions (Section 402), which gives FDA the authority to take legal action against a product or firm that violates the law; Pre-market approval of food additives (Section 409), which requires pre-market review and approval by FDA of additives unless the substance is Generally Recognized as Safe (GRAS); and Labelling provisions (Sections 403 and 201), which prohibit misbranding of food and misleading statements on food labels.

Genetically-engineered plant varieties regulations are evaluated under the 1992 FDA Policy Statement, published in the Federal Register, May 29, 1992, (57 FR22984). The Policy Statement considers the nature of the food (e.g., the intended characteristics or components of the food) rather than the fact that a new development method, including recombinant DNA, was used to produce the food, in regulating new plant varieties. In addition, these foods must also meet the same stringent safety standards as traditional counterparts on the market today.

This Policy Statement is intended to ensure that all safety or regulatory questions are resolved prior to the product entering the market; to provide guidance to industry on scientific and regulatory issues; and to recommend voluntary consultation with the FDA.

This voluntary consultation allows for communications between the FDA and the new product developer to discuss issues, such as potential safety, nutritional, and other regulatory issues, recommended tests and suggested data and information to include in the final consultation package. Under the Policy Statement, a multidisciplinary team, including nutritionists, molecular biologists, chemists, microbiologists, toxicologists, and veterinarians, evaluates the safety information provided on a new product. Both the new, intended modifications and any potential unintended modifications would be evaluated in the host organisms. The new product would also be subjected to agronomic and quality characteristics evaluation, assessment of the characteristics of new substances, genetic analysis, and chemical and nutritional analysis.

At this time, FDA has completed consultations on over 55 bioengineered food crops. While the most prominent traits introduced are agronomic in nature (e.g., herbicide tolerance, pest resistance, altered ripening, modified composition, and male sterility), it was expected that enhanced nutritional traits and "advanced-agronomic" traits - drought or salt resistance traits, for example - would be submitted for approval in the future.

FDA plans to continue to work with international bodies, such as WHO/FAO and Codex, and the industry to continually update the scientific information related to safety assessment of GM foods and crops. On the national level, FDA's Food Advisory Committee Food Biotech Subcommittee has been meeting to discuss complex issues related to the evaluation of bioengineered crops, such as the issue of allergenicity. FDA is also working closely with the National Academy of Sciences to assess unintended effects of genetically-engineered foods on human health.

More information about FDA's biotechnology program can be found at FDA's web page http://www.cfsan.fda.gov

An Update on Regulating Genetically Modified Plants (including Foods/Food Additives) in Japan – Assessment of Food Safety and Environmental Effects

Dr Hiroshi Kamada
University of Tsukuba, Japan

Regulations in Japan relating to the safety assessment of GM foods were enacted in 1986 and came under the purview of the Ministry of Health and Welfare. The regulations focused mainly on food additives such as enzymes. The enforcement of the guidelines for Safety Assessment of GM Food Additives began in 1991. The guidelines were later revised in 1996 to include products, concepts and procedures (standards) for safety assessment of GM seed plants. In 2001, mandatory pre-market requirement for safety assessment of GM foods/food additives was enforced under the Food Sanitation Law. The Pharmaceutical Affairs and Food Sanitation Council's Subcommittee on Biotechnology under the Ministry of Health, Labor and Welfare (MLHW) has the responsibility of conducting safety assessment of GM foods/food additives.

In July 2003, a new law, the Food Safety Basic Law, was enforced. Under this new law, the Food Safety Commission was established to conduct risk assessment of foods (including GM foods/food additives), to make recommendations to related administrative bodies, to monitor the implementation conditions of the recommendations, and to collate internal and external information on food-related hazards. The Commission members have varied expertise.

The safety assessment of GM foods/food additives includes main concepts such as "product-based assessment" and "application of substantial equivalence." The safety assessment was conducted for all factors added to the host by transformation, intended properties and unintended effects occurring as a result of the transformation. These are compared with those of the conventional counterpart and evaluated on characteristics and structure of host, vector, donor and inserted gene, properties of the insertion (expression pattern, stability of the expression, structure of the inserted gene and its surroundings, etc.), safety of the expressed proteins (allergenicity, toxicity, etc.), and others (nutrients, anti-nutrients, various constituents, unintended production of harmful substances through metabolism of the host (when the expressed protein is an enzyme), etc).

As of June 28, 2004, 58 GM foods (e.g., soybean, corn, potato, rapeseed, cottonseed and sugar beet) and 12 GM food additives (e.g., chymosin, amylase, and others) had been approved as safe foods/food additives, and 5 GM foods (e.g., papaya, cottonseed, corn) and 7 GM food additives (e.g., amylase, lipase, pectinase, phospholipase) were still under review.

On February 19, 2004, a new law concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms was enforced. With the new law, foods/food additives that are produced by self-cloning techniques are now subject to GM food safety assessment. Environmental safety assessment is also required for GM plants that are cultivated in Japan and foods/feeds that are imported into Japan.

Approved GM foods (except GM food additives) refer to foods where the proportion of the GMOs exceeds 5%. Japan has adopted many of the international standards of qualification and quantification methods and the MHLW and the Ministry of Agriculture, Forestry and Fisheries oversee compliance with such standards and methodologies. Moreover, to prevent the importation of non-approved GM foods into Japan, methods for qualitative detection of the non-approved foods have been developed and are used at National Quarantine Offices in Kobe and Yokohama.

Other issues related to GM foods in Japan are:

- Time lapse for approval
- Post-market monitoring
- Assessment of allergenicity
- Risk assessment and management of new GMOs (e.g., recombinant bacteria and recombinant fish)
- Risk communication of GM foods
- Capacity building for potential GM foods imported from developing countries
- Possible international collaboration

Further information can be gathered from the following websites:

- Ministry of Health, Labor and Welfare
  http://www.mhlw.go.jp/english/topics/food/index,html

- Food Safety Commission
  http://www.fsc.go.jp/english/index.html

- Japan Biosafety Clearing-House (Ministry of the Environment)
  http://www.bch.biodic.go.jp/english/e_index.htm

- Ministry of Agriculture, Forestry and Fisheries
  http://www.s.affrc.go.jp/docs/sentan/index.html

- Ministry of Education, Culture, Sports, Science and Technology
  http://www.mext.go.jp/english/index.html

Current GM Crops & Food Regulation in Brunei Darussalam

Masliana Yuliah binti Abdullah and Mulyadi Hj Mohammad Ali
Agriculture Department, Ministry of Industry and Primary Resources, Brunei

Mahani binti Haji Muhammad
Ministry of Health, Brunei

Brunei Darussalam has traditionally relied on oil and gas exploration as the country's main income source. However, the trend in other Southeast Asian countries in developing biotechnology as a potential industry sector has encouraged Brunei Darussalam to participate in a collaborative project to develop and introduce biotechnology in Brunei Darussalam. Biotechnology was first emphasized in 1990 during the Sixth National Development Plan, which later resulted in the development of infrastructure for tissue culture at Brunei Agricultural Research Centre (BARC) by the Ministry of Industry and Primary Resources.

Although Brunei currently does not have a biotechnology industry, BARC has been active in incorporating technology in agricultural research, such as tissue cultures. Recently, BARC also organized an awareness seminar at Bandar Seri Begawan, which was attended by more than 300 participants from various government departments, institutions and academics, as well as the general public and invited ASEAN delegates. In conjunction with the seminar, a book on "Frequently Asked Questions on GMOs" was published by the Agriculture Department and made available to all participants.

There are no separate regulations which govern GM foods in Brunei Darussalam. Rather, GM foods are required to comply with the existing food laws and legislations, the Public Health (Food) Act 1998 and Public Health (Food) Regulation 2000.

Foods sold in Brunei Darussalam, including GM foods, must: (1) comply with relevant regulations; (2) comply with labeling requirements; (3) be registered; (4) be licensed if sweetening substances/artificial sweetening substances are used; and (5) be licensed if the foods had been irradiated. The current issues with GMOs and GM foods in Brunei Darussalam stem from the lack of a national regulatory framework to evaluate the safety, detection methodology, labeling and monitoring system. As such, the ASEAN guidelines and Cartagena Protocol on Biosafety would be used as the reference for cultivation of GM crops. However, there has been, to date, no cultivation of GM crops in Brunei Darussalam.

The National Authority on Genetic Modification (NAGM) is being established in Brunei Darussalam to oversee the development and use of innovative genetic manipulation

techniques so that biosafety risk factors associated with GMOs are identified and managed. NAGM is expected to play a vital role in providing guidelines for a national framework on biosafety issues with regards to regulation, assessment and management or risks associated with the use and release of GMOs into the environment. It is also anticipated that the implementation on biosafety measures will be aimed mostly at GMOs imported from other countries.

A national regulatory framework would be important in regulating GMOs in the country, and both physical infrastructure as well as staff qualified in conducting the detection, labeling and monitoring of GMO products must be in place in order for the regulatory framework to be implemented.

In consideration of the fact that a majority of Brunei's population are Muslims, an emphasis on the development of capabilities to regulate the non-halal components in the GMOs should be taken into account.

Crop Improvement and Biotechnology in Cambodia

Mr Ty Channa
Cambodian Agricultural Research and Development Institute,
Ministry of Agriculture, Forestry and Fisheries, Cambodia

Mr Phiv Chin Theng
Department of Agronomy & Agricultural Land Improvement,
Ministry of Agriculture, Forestry and Fisheries, Cambodia

Mr Huy Veng
Department of Animal Health and Production,
Ministry of Agriculture, Forestry and Fisheries, Cambodia

Agriculture is the fundamental sector of the Cambodian economy. Contributing 39% to the country's GDP, agriculture is vital to the development of Cambodia. The majority of Cambodians (80%) are farmers, with rice as the primary crop. The government of Cambodia considers agriculture as its top priority and has invested in improving crops through conventional breeding and biotechnology.

Examples of conventional breeding techniques being practiced in Cambodia are mass and pure-line selection, conventional crossing, and grafting. At the Cambodian Agricultural Research and Development Institute, research on tissue culture on bananas is underway. It is acknowledged that the lack of resources hinders speedy adoption of modern biotechnology in Cambodia. Thus, agronomic improvement of Cambodian agriculture currently relies mainly on conventional methods.

At present, there are no regulations relating to biotechnology-derived crops and foods in Cambodia.

Safety Assessment and Regulation on Biosafety and Foods Derived from Genetically Modified Crops in Indonesia

Dr. Dedi Fardiaz
National Agency for Drug and Food Control, Indonesia

Indonesia's Food Law (Article 13, Law No.7, 1996 on Food) imposes compulsory pre-market food safety assessment for GM foods. This assessment should be conducted on a case-by-case basis, taking into consideration the various genetic modifications used to produce the GM product. The following components are included in the safety assessment of GM foods: (1) toxicity; (2) allergenicity; (3) components thought to have nutritional or toxic properties; (4) inserted gene stability; (5) nutritional effects, and (6) unintended effects.

Approval of GM foods is dependant on the completion of a stringent application process. The applicant must submit a written application, filled questionnaires, safety documentations, and commercial approval to the National Agency for Food and Drug Control (NAFDC), which will conduct safety assessment together with the Technical Team of Bio- and Food Safety Committee.

The written application must contain:

- Description of host organisms (e.g., the history of safe food use of the host organism; relevant phenotypic information; origins of the food crop; typical propagation of the host organism for food use; special processing requirement to render the food safe to eat; and role/significance of the food in the diet)

- Description of donor organisms (e.g., description of all donor organisms from which genetic material is derived; common and scientific names and taxonomic classification; information about any pathogenicity, toxicity, or allergenicity of relevance to the food; history of use of donor organism in food production or history of human exposure of the donor organism through other than the intended food use)

- Description of genetic modification (e.g., detailed information on genetic modification process; plasmid DNA elements size and functions (as promoter, intron, gene of interest, terminator, selection markers) and method of modification or system of transformation)

- Characterization of genetic modification (e.g., molecular characterization of inserted DNA through PCR, Southern and Western Blot analyses, or other methods)

The required safety documentations are:

- Substantial equivalence (e.g., origin of genes; phenotypic and genotypic characteristics of organism; chemical composition of unprocessed and processed products; intended use; and consumption data)

- Nutritional compositional analysis - including any potential change in the bioavailability of key nutrients (e.g., crude protein, crude fat, fiber, carbohydrate composition, amino acid composition, fatty acid composition, vitamin analysis, mineral analysis, and anti-nutritional factors)

- Allergenicity (e.g., amino acid sequence homology with known allergens; liability of the protein in simulated gastric fluids; and the history of safe use of the protein)

- Toxicity (e.g., comparison of amino acid sequences to known toxins and anti-nutrients, stability to heat, degradation in representative gastric or intestinal model systems, and appropriate oral toxicity studies)

- Other considerations (e.g., antibiotic markers)

In addition, the marketing of GM foods in Indonesia must comply with labeling requirements. The aim of labeling is to provide information to consumers, allowing them to choose products they prefer; the aim is not to provide safety information. Article 35 of Government Regulation No. 69/1999 on Food Labeling and Advertisement states that a food product derived from genetically modified products must include a written statement on its label. However, labeling is mandatory only when the maximum level of the cumulative GM products in a particular food product exceeds 5%.

Biosafety Regulation

In Indonesia, biosafety regulation was first established in 1997 through the decree of the Minister of Agriculture No. 85/Kpts/HK.330/9/1997 on the Provisions on Biosafety of Genetically Engineered Agricultural Biotechnology Products. In 1999, due to the lack of regulations on food safety, this decree was revised to the Joint Decree of Four Ministries (Ministry of Agriculture, Ministry of Forestry and Estate Crops, Ministry of Health, and State Ministry of Food and Horticulture) on Biosafety and Food Safety of Genetically Engineered Agricultural Products (GEAP). GEAP are organized into the four categories of General, Plants, Fish, Animal, and Micro-organisms. This joint decree is intended to regulate and supervise the utilization of GEAP. The scope of the joint decree covers the regulation of the varieties, requirements, procedures, rights and obligations, monitoring of and reporting on the utilization of GEAP and its supervision. Guidelines for the testing of the biosafety of GEAP have been developed.

In 2004, the joint decree was renamed the Government Regulation on Biosafety of Genetically Engineered Products (GEP). The final draft of the Government Regulation

has been signed by the Minister of Agriculture and other Head of Non-Departmental Institutions such as the Indonesian Institute of Sciences. This Government Regulation on GEP incorporates environmental safety, feed safety and food safety. The Guidelines on Food Safety Assessment of GEP is in its final draft. The Law on Ratification of Cartagena on Biosafety Protocol was approved by Parliament in July 2004.

To implement the regulation, the Biosafety and Food Safety Committee (BFSC) was formed to give suggestions, considerations or recommendations of GEAP to the relevant ministries. The Biosafety and Food Safety Technical Team (BFSTT) is responsible for the evaluation of the application and to carry out further technical studies or tests of GEAP in a biosafety containment or confined field.

To date, the BFSC has approved environmental multi-location tests for four transgenic crops: Bt corn resistant to stem borer, Roundup Ready (RR) corn, cotton and soybean tolerant of glyphosate herbicide. Recently, the BFSC approved the commercialization of Bt cotton resistant to bollworm. In addition, commercial release was also approved for two enzymes (Ronozyme and Finase P&L) derived from genetically modified organisms, for use as feed probiotics.

An Update on Implementing Safety Assessment Regulation and Procedure on Novel Foods/ Foods Produced Using Gene Technology

Nik Shabnam bt. Nik Mohd. Salleh
Food Quality Control Division, Ministry of Health, Malaysia

In Malaysia, consumers are still concerned about the food safety and health effects of GM foods. The Malaysian government has established biosafety procedures for genetic modification to ensure that the release, development and use of and commercial activities relating to GMOs are monitored and regulated.

The National Guidelines for Release of GMOs into the Environment, implemented by the Ministry of Science, Technology and Environment (MOSTE), provides a more defined procedure for risk assessment and management of the release of GMOs into the environment. It also addresses the need for capacity building in order to address safety in genetic modification research, development, use, release and placing on the market of GM foods. The guidelines cover the genetic modification of plants, animals, micro-organisms and products consisting of or containing GMOs and the implications on agriculture safety, public health, as well as environment and trans-boundary issues.

The general principles of the guidelines focus on:

- The organisms
- Characteristics of the parent organism and DNA donor organism
- Characteristics of the modified organism
- Ecological traits of the donor and recipient
- Interaction of GMOs with biological systems, stability of the engineered gene in GMOs, transfer capability, effects on target and non-target organisms, and effects on soil food web communities, plants and aquatic systems as well as sediments.

Application or Intended Use of the GMOs

Assessment of the receiving environment based on the organisms' traits and intended use. Risk management methodology depends on the GMOs and release activities

The Genetic Modification Advisory Committee (GMAC), consisting of officials from the relevant government agencies, was set up to monitor and implement the guidelines at the national level and to carry out the risk assessment and risk management associated with GMOs on a case-by-case basis. MOSTE has also prepared a Biosafety Bill to regulate

the import, export, release into the environment and contained use of GMOs in accordance with the precautionary principle of protecting human, plant, and animal health.

The Food Quality Control Division of the Ministry of Health (FQCD) is responsible for ensuring food safety, and is mandated, under the Food Act 1983, to ensure food sold in Malaysia is safe and that consumers are not cheated. It is also the Codex Contact Point for Malaysia.

The import, preparation, or advertisement for sale or sale of any GM foods in Malaysia is not allowed without the approval of the Director-General of the Ministry of Health. Approved GM foods, which have satisfied the pre-market approval process (which is in accordance with the Codex recommended safety assessment process) are gazetted, and are subject to labeling requirements.

Current GM Crops & Food Regulation in Myanmar

Tin Htut, Khin Maung Thet and Than Htun
Ministry of Agriculture and Irrigation, Myanmar

The government of the Union of Myanmar has designated the agriculture sector to be the main driving force for the national economy, recognizing the importance of agricultural development in enhancing the socio-economic development of the country. Myanmar thus applies appropriate agronomic techniques and modern crop varieties, including modern biotechnology, in order to meet the domestic and international supply and demand for agriculture products.

With regards to the use of biotechnology, human health and environmental risks are important safety factors. As the capacity to effectively safeguard biological and ecological resources against the presumed adverse effects of GMOs in Myanmar is still limited, capacity building on risk assessment and risk management in the development of national policy on the safe transfer, use and handling of GMOs are of priority.

On May 5, 2000, representatives from 11 respective government departments formed the National Authority on Genetic Modification (NAGM). Since Myanmar has yet to establish national biosafety regulations on GMOs, NAGM will carry out its responsibilities in accordance with the ASEAN Guidelines on Risk Assessment of Agriculture-Related Genetically Modified Organisms and the Cartagena Protocol on Biosafety.

Since July 2001, the National Biosafety Framework is being developed to overcome the inadequate institutional and manpower competence, lack of relevant legislations and low public awareness of GMOs. The National Coordinating Committee and the National Project Coordinators were formed to support the development of the Framework, with Ministry of Agriculture and Irrigation, Ministry of Forestry, and Ministry of Fisheries and Life Stock Breeding, as the three main government agencies involved. It is expected that the Framework will be ready by 2006.

Current GM Research and Regulation in the Philippines

Gemiliano D. Aligui
Philippine Council for Health Research & Development, the Philippines

Edison C. Renin
Cotton Development Administration, the Philippines

Jerry C. Serapion
Philippine Rice Research Institute, the Philippines

Cynthia Hedreyda
University of the Philippines, Diliman, the Philippines

The government of the Philippines has been consistent in its support for biotechnology, with early recognition of the need for biosafety. The first research and development institute on biotechnology was established at the University of the Philippines, Los Baños (UPLB) in 1979. Executive Order (EO) 430, issued in 1990, addresses safety issues related to modern biotechnology research and development. Through EO 430, the National Committee on Biosafety of the Philippines (NCBP) was established. The Agriculture & Fisheries Modernization Act, which was passed in 1997, provided the roadmap for biotechnology development in the agriculture and fisheries industry. President Macapagal-Arroyo declared in 2001 that the National Biotech Policy would "... promote the safe and responsible use of modern biotechnology and its products as one of the means to achieve food security, equal access to health services, sustainable and safe environment and industry development." Rules and regulations on the importation and release into the environment of plants and plant products derived from the use of modern biotechnology was outlined in the Department of Agriculture (DA) Administrative Order (AO) No. 8 in 2002 to address the risks of GM plant and plant products to human and animal health, as well as the environment.

The AO 8 requires:

- Mandatory conduct of science-based risk assessment, to be carried out case-by-case and on the basis of transformation event
- Risk management through compliance with biosafety measures
- Transparency in risk communication

There are also different areas of safety assessment for genetically modified plants and plant products, depending on its intended use:

- *Importation for contained use in greenhouses and laboratories* - approval shall be based on compliance with safety requirements of the NCBP

- *Importation for field testing* - approval shall be based on the satisfactory completion of safety testing under contained conditions

- *Importation for propagation* - approval shall only be granted after field trials and risk assessment show no significant risk to human and animal health and the environment. Pest-protected GM plants must also be registered with the Fertilizer and Pesticide Authority (FPA)

- *Importation for direct use as food, feeds or processing* - approval will only be granted if it has been authorized for commercial distribution as food or feed, as the case may be, in the country of origin; and poses no significant risk to human and animal health

The application process for a permit to propagate any GM plant in the Philippines must follow the following stages:

- Contained experiments, under the authority of NCBP

- Confined field testing, under the authority of Bureau of Plant Industry (BPI)

- Multi-location field testing, under the authority of BPI

GM plants and plant products derived from modern biotechnology which have been approved through safety assessment by experts and regulatory agencies are compiled in the Approval Registry. At present, only MON 810 corn has been approved for propagation for 5 years within the prescribed 90-day period, subject to compliance with the insect-resistant management strategy, monitoring of the development of insect-resistance, and monitoring of other unintended effect(s), if any. For food, feed and processing propagation, the following GM plant varieties have been approved:

- Corn (MON 810, Bt 11, NK 603, MON 863, TC 1507, DBT 48, Bt 176, GA 21, DLL 25)
- Soybean (40-30-2)
- Canola (RT 73)

Implementation of AO 8 encompasses various organizations and divisions within the DA:

- Biotech Advisory Team - a multi-disciplinary team from various DA units for policy and technical advise

- Biotech Program Implementation Unit - the advocate for policy formulation, capacity building, assistance to R&D, information, education and communication

- BPI
- Bureau of Animal Industry
- FPA
- BAPHS
- Regional Field Monitoring Teams
- Scientific and Technical Review Panel (STRP)

The Philippines seeks the active cooperation from molecular biologists, biotechnologists, medical doctors, food technologists and nutritionists, and environmental scientists, to serve as a pool of experts to provide scientific information for education and communication. To continue with the capacity building skills training for related personnel, the Philippines also taps into national and international collaborators, such as USDA, FAO, ILSI, SEAMIC, AGILE/EGTA, ISAAA, Biotech Coalition of the Philippines, and the private sector.

Training provided includes:

- Biotech 101 training for biotech core teams at BPI, BAI, FPA, BAPHS and STRP
- Study tour of the US regulatory system for heads of risk assessment agencies and biotech core teams
- Local and international risk assessment training and workshops
- Technical assistance information sharing
- Laboratory skills in using DNA-based and immunological methods of detecting GMOs
- Planned training for DA Regional Office personnel on monitoring field trials and propagation
- Proposed degree programs for select members of biotech core teams at various agencies

The Philippines Rice Research Institute (PhilRice) and the Institute of Plant Breeding at the UPLB (IPB-UPLB), are among various institutions currently active in GMO research in the Philippines. At PhilRice, development of bacterial blight resistant, stem borer resistant, saline tolerant, and blast and sheath blight resistant rice varieties, are among the research topics. At IPB-UPLB, GM papaya and mango with delayed ripening traits, GM papaya resistant to ring spot virus, and GM sweet potato resistant to feathery mottle virus and weevils, are ongoing.

Singapore Update on Implementing Safety Assessment, Regulations and Procedure on Foods Containing GMOs

Airani Ramli
Genetic Modification Advisory Committee, Singapore

Khoo Gek Hoon, Koh Mong Chai and Emily Teo
Agri-food and Veterinary Authority, Singapore

To ensure public safety while allowing for the commercial use of GMO and GMO-derived products in compliance with international standards by companies and research institutions, a multi-agency committee, the Genetic Modification Advisory Committee (GMAC) was established under the Ministry of Trade and Industry. GMAC is responsible for providing advice on the release of agriculture-related GMOs, research on GMOs, labeling of foods containing GMOs, and public awareness. With regards to the regulation of GMOs, four regulatory agencies are involved: the Agri-food and Veterinary Authority of Singapore, the Ministry of Health, the National Environment Agency, and the Ministry of Manpower.

The approval process for the release of GMOs in Singapore includes submission of a proposal to GMAC for endorsement, approval from relevant agencies, and registration of the approved GMO with the GMAC Secretariat. Monitoring will be conducted by relevant regulatory agencies.

In accordance with the Animal and Birds Act, as well as the Control of Plants Act, the import and release of agriculture-related GMOs are regulated by the Guidelines on the Release of Agriculture-related GMOs. The Singapore Biosafety Guidelines for Research on GMOs, currently under working draft, include occupational health and safety guidelines for laboratories and production facilities in the biomedical sciences, and provide guiding principles for laboratory animal research.

Singapore also faces issues relating to GMO labeling, such as threshold levels, detection proficiencies and testing capabilities. The recently established Veterinary Public Health Centre enables Singapore to cater to the need for GM food testing, and to gather required reference materials and genetic information on GMOs. However, Singapore also recognizes the need for capacity building in risk assessment and risk management on GMOs and necessary infrastructure and capacity building in detection capabilities to ensure a balanced approach to regulating GMOs.

Status of Biosafety and Agriculture-related GMOs in Thailand

Payungsak Rauyaree
Biotechnology Research and Development Office, Department of Agriculture, Thailand

Thai Agricultural Commodity Standards closely follow that of Codex. The National Bureau of Agricultural Commodity and Food Standards follow the principles for risk analysis of foods and specify the guidelines for the conduct of safety assessment of foods, including those derived from transgenic plants, and the guidelines for the conduct of safety assessment of foods produced using recombinant-DNA micro-organisms. Advice on safety assessment is also provided by the National Center for Genetic Engineering and Biotechnology, under the Ministry of Agriculture and Cooperatives.

Thailand's National Policy Framework on biotechnology is currently under development. The National Biotechnology Committee was established to outline the national policy on GMOs and to draft biosafety policy for immediate implementation. The current national policy on GMOs include six topics, namely production, human resources and technical development, biosafety evaluation, trade, public relations, and participation.

With regards to production, Thailand has not produced GMOs for trade, although science-based risk assessment was conducted. Monitoring of long-term post-production/cultivation impacts to health and the environment is part of the biosafety evaluation. With laboratory facilities and available technical expertise, Thailand is able to support the research, development and production of GMOs. Thailand allows importation and domestic evaluation of GMOs, provided that the GMOs pass biosafety evaluation and risk assessment. However, importation of commercially-released genetically modified plants into Thailand is prohibited in accordance with the Plant Quarantine Act B.E. 2507 (1964) as amended in B.E. 2542 (1999)

Thailand does not as yet have specific laws governing biosafety. However, under various existing laws on plant quarantine and variety protection, GM plants are not allowed for registration.

Current assessment on GMOs and GMO derivatives in Thailand include transgenic vaccines, animals, micro-organisms and plants.

Current Status of Biosafety Regulations for GMOs in Vietnam

Vu Duc Quang
Agricultural Genetics Institute, Vietnam

Chu Hoai Hanh
Department of Science and Technology, Ministry of Agriculture and Rural Development, Vietnam

Doan Thu Thuy
Vietnam Agricultural Sciences Institute, Vietnam

Vietnam is an agricultural country with a population of approximately 81 million. The agriculture sector in Vietnam has grown steadily at an average rate of 4.5% per year, contributing 20.8% to the country's GDP. However, the country still faces many challenges in agriculture and rural development, such as a poverty level of 11.4%, high rate of population growth, decline of land areas for agriculture due to urbanization and industrialization, frequent natural disasters (typhoons, flood, or drought), and high production costs coupled with low product quality. Main agricultural output are food crops (rice, maize, cassava, and sweet potato), industrial crops (rubber, coffee, tea, cashew, pepper, and sugar-cane), vegetables and beans, fruit crops and other crops.

To guarantee food security and the sustainable development of agriculture in tandem with social-economic development, the Vietnamese government has focused on the research and development of biotechnology. Since 2001, funding for research and development in biotechnology has reached US$1.5 to US$2 million per year. Such funding is allocated to the development and production of transgenic plants in research institutions. However, Vietnam has not allowed for the commercial release of GM crops. The most important transgenic plants developed in Vietnam are rice (Bt, chitinase, pro-vitamin A, Xa-21), maize (Bt), cotton (Bt), soybean (herbicide resistance), papaya (resistant to ring spot virus, delayed ripening), flowers (chrysanthemum, gladiolus, carnation), tubers (potato, cassava, sweet potato), and forest plants. All of the transgenic plants developed above are tested inside protected fields in green houses.

It is acknowledged that some GM plants and seeds, namely maize, rice, soybean, cotton, and others, are unofficially imported or brought into Vietnam. Animal feeds containing GM derived products (mostly from milled grains of GM soybean and maize) and GM foods without GM-labeling have also been imported into the country. While these are unofficial imports, they are not illegal because Vietnam currently has no regulations governing GMOs.

Vietnam has been slow to enact regulations relating to GMOs. The government established a working group to draft biosafety regulations for GMOs and their products in 1999. This

working group comprised experienced and qualified experts from different institutions. Several conferences and workshops on risk assessment and formulation of biosafety regulations for GMOs were organized to address scientific and socio-political issues. At present, the latest draft decree on biosafety regulations for GMOs and their products is ready for review by different ministries, agencies and organizations. It was not until April 2004 that Vietnam ratified the Cartagena Protocol on biosafety.

The Decree on Biosafety Regulations for GMOs and Their Products aims to ensure the safe research, development and use of GMOs and their products. These biosafety regulations apply to all organizations and individuals conducting research, development, production, and use of GMOs in Vietnam. This includes the import, export and release of GMOs into the environment.

Upon the signing of the Decree, the National Biosafety Committee (NBC) will be established under the Ministry of Natural Resources and Environment. The members of the NBC will include representatives from the Ministry of Agriculture and Rural Development, Ministry of Aquaculture, Ministry of Natural Resources and Environment, Ministry of Science and Technology, Ministry of Public Health, and Ministry of Trade. The NBC is responsible for all matters related to overall biosafety policy relating to biotechnology, including biosafety review and subsequent biosafety management of GMOs used in laboratory and contained facilities, field testing of GMOs, commercial releases of GMOs, and import and export of GMOs. The NBC is also responsible for conducting risk assessment and management when applications for GMO approval are submitted.

In Vietnam, public awareness of GMOs is limited, and there is little public interest in GMOs. A survey of public opinions on GMOs reveals diverse opinions ranging from free utilization to limited use and even prohibition of GMOs and their products.

Safety Assessment of Food Derived from Biotechnology – Building Upon International Expertise

Dr Paul Brent
Food Standards Australia New Zealand, Australia

It has long been recognized that food is not inherently safe and that absolute safety of food is not an achievable goal. Food is considered to be safe based on experience, where there is no history of adverse effects and adequate knowledge within the community to address any food-related hazards. In 1993, the Organization for Economic Co-operation and Development (OECD) established the statement that "safety of food for human consumption is based on the concept that there should be reasonable certainty of no harm from the intended use."

Thus, the goal of GM food safety assessment is not to establish absolute safety. Rather, it aims to consider whether the genetically modified food is as safe as its traditional counterpart, where such counterpart exists (e.g., standard of safety equivalent to that applied to foods/feeds derived through traditional plant breeding). In June 2000 at the Joint FAO/WHO Expert Consultation on Foods Derived from Biotechnology, this safety assessment concept was also further elaborated.

General principles used internationally in safety assessment of GM foods are:

- Conventional foods generally considered to be safe, provided prepared and handled properly
- Novel foods, including GM food, are required to undergo mandatory pre-market safety assessment in some jurisdictions (e.g. Japan, Canada, Australia and New Zealand, UK, EU)
- An explicitly cautious approach is applied to foods, such as GM foods, with no history of safe use
- Safety assessments of GM foods undertaken according to key principles

These key principles were concurred following international discussion among OECD countries, within the FAO/WHO expert consultations, Codex Alimentarius Commission, and many regulatory agencies around the world. The key principles are:

- Based on science and risk-based methods, including identification of the potential adverse effects that GM foods may pose for human health, the process of determining

as accurately as possible the actual likelihood and consequences of the risks presented by exposure to identified hazards.

- Conducted on a case-by-case basis, such that subsequent genetic modification of a food commodity that has been genetically modified in different ways requires a separate safety assessment. However, approval given for food commodity can be applied to foods derived from that modified commodity (e.g., approval of modified corn applies to corn kernels, corn flour, corn syrup, and oil).

- Considers both intended and unintended effects of genetic modification, including identification of similarities and differences to the conventional counterparts and further scrutiny for identified differences.

- Compares the new plant with conventionally produced foods, with history of safe use.

The safety consideration of GM foods includes evaluation of (i) the host organism that has been modified, including information on nutrient composition, known anti-nutrients, toxicants and allergenic potential, and any significant changes in these that may result from normal processing, (ii) the donor organism, including any known associated toxicity and allergenicity, and the introduced gene(s), (iii) molecular characterization of the genetic modification, including a description of the modification process and the stability of the introduced trait, (iv) identification of the primary and secondary gene products, including a description of the characteristics of the inserted gene, (v) evaluation of the safety of expected novel substances in the food, including an evaluation of any toxins produced directly by the modification, (vi) assessment of the novel food's potential allergenicity, and (vii) evaluation of the unintended effects on food composition, assessment of the changes in the concentration of nutrients or naturally occurring toxicants; identification of anti-nutrient compounds that are significantly altered in novel foods; and evaluation of the safety of compounds that show a significantly altered concentration.

Following the safety consideration, the concept of 'familiarity' is introduced. Familiarity is defined as knowledge about the characteristics of a species and experience with the use of that species, based on scientific literature and practical experience with the organism and similar varieties. Furthering this concept, many governments have developed an approach known as "substantial equivalence" as part of the risk assessment process.

Substantial equivalence is a general approach that involves detailed comparison of agronomic features and composition of the newly developed food with a suitable comparator food having a history of safe use. The purpose of evaluation is to identify similarities and differences between the new variety and its comparators in relation to agronomic and pleiotropic characteristics and compositional analysis of key nutritional components. Differences derived from such comparison are subjected to further investigation, in relation to human and livestock health. While "substantial equivalence" has been the subject of much debate by many expert bodies, it was recognized that "substantial equivalence" is a valid concept that contributes to a robust safety assessment framework.

Key initiatives to identify and address future needs have been undertaken by various international bodies:

- ***Codex Guidelines for Foods Derived from Recombinant DNA Micro-organism***

- The safety assessment of a food produced using a recombinant DNA microorganism follows a stepwise process of addressing relevant factors including: (1) description of the rDNA micro-organism; (2) description of recipient micro-organism and its use in food production; (3) description of donor organism; (4) description of the genetic modification(s) including vector and construct; (5) characterization of the genetic modification(s); and (6) Safety assessment of (i) expressed substances (assessment of potential toxicity and other traits related to pathogenicity; (ii) compositional analyses of key components; (iii) evaluation of metabolites; (iv) effects of food processing; (v) assessment of immunological effects and allergenicity; (vi) assessment of viability and residence of micro-organisms in the human gastro-intestinal tract; (vii) antibiotic resistance and gene transfers; (viii) nutritional modifications.

- ***OECD Task Force for Safety of Novel Foods and Feeds***

- To prepare consensus documents which provide guidance on critical parameters (e.g. key nutrients) of food safety and nutrition for each food crop;

- To identify the consequences of using (or avoiding the use of) various marker genes;

- To identify key elements in the safety assessment of transgenic fish;

- To improve the safety assessment of foods containing bioactive compounds;

- To address the safety assessment of whole foods with no documented history of safety consumption, e.g. exotic fruits and vegetables

- To facilitate outreach and capacity building/harmonization activities

- ***Codex Ad Hoc Intergovernmental Task Force on Foods Derived from Biotechnology***

- Has published two publications: "General Principles for the Risk Analysis of Foods Derived from Recombinant DNA Plants," and "Guidelines for the Conduct of Safety Assessment of Foods Derived from Recombinant DNA Plants and Micro-organisms"

- Will discuss and make decisions on issues related to food from transgenic animals and fish and food from cloned animals and their progeny

- ***FAO/WHO Expert Consultations***

- Consultation on Specific Aspects of Genetically Modified Foods of Plant Origin (Geneva, June 2000).

- Consultation on Allergenicity of Genetically Modified Foods (Rome, January 2001).

- Consultation on Safety Assessment of Foods Derived from Genetically Modified Micro-organisms (Geneva, September 2001).

- Consultation on Safety of Food derived from Transgenic Fish (Paris, November 2003)

- Proposal to establish international expert committee system for risk assessment and risk management which complements national regulatory capacities (JECFA).

In conclusion, concepts and principles developed by OECD, FAO/WHO and Codex have been used by countries assessing the safety of GMOs, or foods or food components derived from GMOs. Over the past 12 to 13 years, internationally conducted evaluations of genetically modified plant products have demonstrated that the concepts can be applied effectively in the safety assessment and approval of novel foods. The approach to the safety assessment of novel foods is continually evaluated, elaborated and expanded, with contribution from participating countries. International assistance and facilitation on adoption and adaptation of the updated approaches into individual countries' respective regulatory systems are available.

Safety Assessment Requirement of GM Plants in Indonesia – A Case Example

Inez H. Slamet-Loedin
Research Centre for Biotechnology, Indonesia Institute of Sciences, Indonesia

M. Herman
Indonesian Agency of Agricultural Research and Development,
Department of Agriculture, Indonesia

Article 13 of Food Law (1996), which states that "... any food derived from GEP must be evaluated before it can be commercialized," drives the biosafety regulation in Indonesia. Joint Ministerial Decree 1999 regulates biosafety and food safety of Genetically Engineered Agricultural Products (GEAP). The scope of this regulation covers the regulation of the types, requirements, procedure, rights and obligations, monitoring and reporting the utilization of GEAP. GEAP included in this Decree are transgenic plants, transgenic animals, transgenic fishes, and transgenic micro-organisms. Guidelines on biosafety testing have been developed since 1998 to include general GEAP, plant GEAP, animal GEAP, fish GEAP, and micro-organism GEAP. Food Safety Testing of GEAP and Feed Safety Testing of GEAP guidelines are being drafted. The Government Regulation No. 69/1999 and Joint Ministerial Decree 1999 outline mandatory GMO labeling regulation.

The Biosafety and Food Safety Committee (BFSC) was established to suggest or recommend technical aspects on biosafety and/or food safety of GEAP to the related Ministries (Agriculture, Forestry, or Health). The BFSC comprises scientists and experts from the Research Centre for Biotechnology, Indonesia Institute of Sciences (LIPI), AAAT (BPPT), Agricultural Forestry Research and Development, Indonesia Agency of Agricultural Research and Development (AARD), AHRD (Health), AFRD (Fishery), National Agency for Food and Drug Control (NAFDC), Ministry of Environment, professional associations, farmer associations, and non-government organizations (NGOs).

The Biosafety and Food Safety Technical Team (BFSTT), under the authority of BFSC, carries out the evaluation, appropriate technical study, and testing on biosafety and/or food safety of GEAP. BFSTT comprises senior scientists in the areas of biochemistry, food science, entomology, genetics, microbiology, molecular biology, nutrition, physiology, and plant pathology and breeding, from various institutions, including Bogor Agricultural University, Indonesia University, LIPI, AAAT (BPPT), AARD, AFRD (Forestry), AHRD (Health), AFRD (Fishery), and NAFDC. The teams are grouped into various teams, based on their expertise: animal, fish, plant, microbe, and food.

The risk assessment conducted by BFSTT includes evaluation of questioner and documents, literature studies, interview of proponent, biosafety containment (BC) test,

evaluation, and interview, isolation field (IF) test, evaluation, interviews, and recommendation of biosafety. The BFSC then makes the decision on whether or not to approve the GEAP.

The following GEAP have been approved by BFSC:

- Bt cotton (2000)
- RR Cotton (2000)
- Bt Corn (2000)
- RR Corn (2000)
- RR Soybean (2000)
- Ronozyme-P for feed, an enzyme derived from transgenic fungus (2001)
- Finase L and Finase P for feed, enzymes derived from transgenic fungus (2001)

Indonesia also recently passed the Ratification Law on the Cartagena Biosafety Protocol in July 2004. Establishment of the Biosafety Clearing House to streamline the approval process of GEAP is also being discussed.

Using Bt rice as a case example for approval of GEAP in Indonesia, the following safety assessment process will have to be complied with. Questionnaires must be completed and submitted by the proponent to address the following issues:

- The plant species
- Reproductive method
- Transformation method
- New trait(s) introduced
- Origin of the introduced traits
- Detailed description of the vector
- Location
- Design of the experiments

Following the approval for a field trial, experiments were carried out in collaboration and under control of the Rice Research Institute in Sukamandi. The field trial was conducted outside of the growing season on the vegetative and seedlings phases. Having addressed the safety issue on biodiversity, including impact on non-target insects and soil microbes, the Bt rice must be confined to reduce the potential crossing to wild relatives. The research on Bt rice will continue to select non-hygromycine gene lines. In addition, the food safety test on this GEAP will also be conducted.

Introduction to Molecular Biology and GM Plant Development

Bronwyn Dixon
Food Standards Australia New Zealand, Australia

For centuries, plant breeders have cross-bred similar varieties of plant to produce new crops or crops with new desirable traits such as increased yield. Genetic engineering allows scientists to isolate a specific gene for a particular trait, such as resistance to insect attack, in one organism and transfer it into another unrelated organism. This is possible because the genes of all organisms are made up of the same building blocks - deoxyribonucleic acid or DNA.

DNA is made up of a phosphate backbone and combination of four chemical bases (adenine, cytosine, guanine, and thymine). Segments of DNA that encode the information necessary for assembly of specific proteins are called genes. When DNA is transcribed, the intermediary compound is known as messenger RNA (mRNA), which can be further translated to protein. Proteins function as enzymes to catalyse biochemical reactions, or as structural or storage units of a cell, to contribute to phenotype.

Among the most important tools in the genetic engineer's tool kit are enzymes that perform specific functions on DNA. Restriction enzymes recognize and cut DNA strands at specific sites. With restriction enzymes, DNA can be cut into various fragments of different sizes, which can be compared and separated through a process called gel electrophoresis. Other enzymes known as ligases join the ends of two DNA fragments. With ligases, two different fragments of DNA can be joined together into a recombinant DNA. These and other enzymes enable the manipulation and amplification of DNA, which are essential techniques in molecular biology.

Once a gene that codes for a particular characteristic in one organism has been identified, it is possible to transfer that gene into the cells of a different organism. The gene becomes incorporated into the genome of the recipient organism. The resulting organism will be genetically modified to produce the desired characteristic.

There are a number of steps involved in the development of a GM plant:

- Identification of the gene(s) that govern the desired trait (gene of interest).
- DNA isolation - isolation of the gene of interest from its source (the donor organism).
- Cloning of the genes - the gene of interest is amplified in the laboratory, usually in a bacterial plasmid.

- Designing genes - the relevant regulatory elements, such as plant promoter and termination sequences are added to the gene of interest, to ensure the gene will function in the plant cells. This is called the gene construct.

- Transformation and tissue culture - the gene construct is inserted into the cells of the recipient plant (either by Agrobacterium mediated gene transfer or by biolistic transformation, see below). The plant cells are grown and tested to ensure the gene construct is functional and stably incorporated into the plant's genome.

- Plant breeding - including field tests and breeding of the new variety.

There are two main methods of genetic transformation in plants, namely the "gene gun" method (also known as microprojectile bombardment or biolistics) and the Agrobacterium method. The gene gun method, as the name implies, includes the process of firing tiny particles of gold or tungsten coated in recombinant DNA at plant cells through the cell wall without destroying the cell. This technique has been especially useful in transforming monocot species such as corn and rice. The Agrobacterium method is a technique to deliver the recombinant DNA through infecting plant cells using a bacterium (Agrobacterium tumefaciens). Transformation via Agrobacterium has been successfully used in dicot and monocot species. This "nature's engineer" method is less likely to lead to multiple DNA insertions than the biolistic transformation method.

When the modified cells are allowed to divide and grow into plants in a growth medium, the trigger ("promoter") activates the desired gene, causing the growing plant to develop the desired trait.

The success of the genetic transformation is measured through a "marker gene," an auxiliary responsible for an easily-identified trait. There are two types of marker genes available: selectable marker genes and visual marker genes. Selectable marker genes include antibiotic resistance genes or herbicide resistance genes, which allow the transformed cells to grow in the presence of the relevant antibiotic or herbicide. Visual marker genes allow identification of the transformed cells following a specific treatment.

Successfully transformed plant cells are cultivated in a selective medium to allow growth, and then transferred to soil. Until further testing and assessment of phenotypic characteristics can be observed, the GM plants are grown in the glasshouse. Should the GM plants be considered fit for field trial, they will be grown in field conditions for assessment of agronomic performance.

Crops such as corn and cotton that are severely affected by insect pests can be genetically modified to produce a protein that acts as a natural insecticide. An example is Bt corn, which was used as a case study in this Workshop. DNA of the Bt gene is separated from the DNA of all the other genes in the Bt bacterium. The DNA of a marker gene for either antibiotic or herbicide resistance is fused to the DNA of a Bt gene. The modified Bt gene

is inserted into plant cells. The plant cells are grown in a medium containing the antibiotic or herbicide to which the marker gene confers tolerance. Cells that survive have antibiotic or herbicide resistance controlled by the selectable marker gene and the attached Bt gene are grown into mature transgenic plants that produce seed. Plant breeders cross the transgenic plants with elite parents that have other desired traits, such as high yield. Elite offspring from the cross that have Bt gene and other desirable traits are then selected as varieties for commercial production.

CASE STUDY 1: MON 810 Insect-resistant Corn

Introduction

The MON 810 Insect-resistant Corn Case Study was used as a hands-on exercise for food safety and risk assessment of plant GMO. The introduction to the case study was presented by Dr Paul Brent and Ms Bronwyn Dixon of Food Standards Australia New Zealand (FSANZ). The organizers acknowledge the contribution of Health Canada and FSANZ for the case study material.

The Workshop breakout sessions aimed to provide participants with hands-on training in food safety and risk assessment on plant GMOs using MON 810 Insect-Resistant Corn as a case study. The participants were divided into four working groups, each consisting of about 12 participants from different countries and background, to discuss the case study. Each group was guided by a facilitator to review and assess the data and information provided in the case study material.

The case study material consists of the following data and information:
- The plant and its characteristics
- Genetic modification
- Characterization of the genetic modification
- Modified plant
- Safety assessment of expressed substance - toxicity & allergenicity
- Nutritional data
- Decision and management

The working groups then reported on their review and assessment on the MON 810 insect-resistant corn for each of the above topics and made a decision on whether or not to approve the use of the GM corn.

Bacillus thuringiensis (Bt) is a rod-shaped soil bacterium, which naturally has crystalline (Cry) protein that releases a toxin called delta-endotoxin. In certain insects, this toxin can stop digestion and cause death. Different types of Cry protein can be fatal to different insect orders. For example, the target pest of Bt corn is European corn borer, for which CryIA(a), CryIA(b), and CryIA(c) proteins are toxic. Bt has been commercially used as pest control agents for decades. In the development of MON 810 Bt corn, the Bt genes, together with a selectable marker gene, are inserted through the particle bombardment technique. As the result, insect-resistant variety MON 810 corn contains CryIA(b) protein.

The purpose of the GM corn is to recover the 5% to 10% of harvest losses due to European corn borer. The transformation is intended for the variety mainly used as animal feed, although it is also assumed that the GM corn will find its way into the food chain.

The Plant and Its Characteristics

In the development of a new GM plant variety, it is important to know the conventional

variety's history, including the genotype, phenotype, cultivation practices, usages (as foods and non-foods), processing, and others. Knowledge from a molecular perspective may provide information on possible direct and indirect consequences of a genetic modification.

For the host plant, it is important to include the history of safe use as a food product. The information can be gathered through the origins of the food crop, how the plant is typically cultivated, transported, and stored, special processing prior to consumption, and the role of the crop in the diet. In such regards, food consumption pattern, nutritional profile, genotype and phenotype related to safety of the crop, known toxicity and allergenicity, should be included.

The host organism in this case is corn (Zeal Mays), which has been cultivated for over 8,000 years in Mexico and Central America. It has also been widely used in other regions of the world, including in Asia where it has become, in some countries, the staple food. Corn is also noted for its industrial importance as a source of oil and starch. Upon perusing the information provided, the groups agreed that in order to arrive at a conclusion that the modified plant or its product is "as safe as" its conventional counterpart, a comprehensive description of the host plant must be made available. In this instance, for the new corn product to be considered safe, the host organism must have an established long history of safe use as food or feed.

Information on donor organisms should include data on naturally occurring toxins, anti-nutrients, allergens, pathogenicity and the relationship with known pathogens. Common and scientific names and taxonomic classifications should also be enclosed. To establish safe history of use, previous use of the donor organism or products derived from the donor organism in food and food production must be taken into consideration.

The donor is the Bacillus thuringiensis subsp kurstaki which can produce specific protein that is toxic to Lepidopterans by virtue of the delta endotoxin it produces. Bacillus thuringiensis has been used for many years as a bacterial biopesticide without deleterious consequences. Considering that the Bt protein is activated in the insect gut by alkaline pH and only Lepidopterans have the Bt delta endotoxin receptor, the effect of consuming Bt protein is deemed safe to both humans and animals which consume the GM corn.

While it can be argued that donor organism with a long history of safe use can be deemed as safe when its trait is transferred into another organism, the group warned that new product safety assessment should not be based simply on the characteristics of donor or host organisms. Familiarity of the genetic modification process is just as important.

Genetic Modification

The method by which novel traits are introduced into the host organism determines, in part, the requirements for the assessment of the novel organism and its products. Knowledge from a molecular perspective may provide information on possible direct and indirect consequences of a genetic modification. There have been established guidelines

outlining criteria for the safety assessment of recombinant DNA-derived plants by FAO/WHO, OECD, and Codex.

It was anticipated that for the modified plant to be "as safe as" the conventional plant, only the desired trait, which was earlier described to already have a long history of safe use, should be transferred. It was inferred that the integration of other elements with the desired gene into the transformed material may later on complicate assessment of food safety, as food safety assessment of other product characteristics may be necessary. The group thus investigated the results of Southern blot analyses, along with other presented information in tables and graphs, to discover and ascertain that only the desired gene, CryIA(b), was integrated into the modified plant.

There are three aspects to consider in the genetic modification of plants:

- The transformation system (Agrobacterium-mediated or microparticle bombardment)
- Molecular characterization of the inserted DNA (insert number, insert composition)
- Genetic stability of the introduced trait (Segregation analysis, stability of the inserted DNA (maintenance of border or junction sequences, no loss of sequence through recombination events, etc))

The modification was done using the biolistic method. Two plasmid constructs used, PV-ZMBK07 (7794 bp) containing the CryIA(b) gene, and PV-ZMGT10 (8427 bp) containing two marker genes used for selection on glyphosate, were intended to create the necessary genetic modification of the Bt corn. However, after backcrossing, it was apparent that only a portion of PV-ZMBK07 plasmid vector was present in the final product. It is presumed that the genes which allow for selection of glyphosate in plasmid PV-ZMGT10 were originally incorporated into the plant genomic DNA but were lost by segregation during backcrossing. It may also be that these genes were integrated at separate loci from the cryIA(b) gene and segregated out during the crossing.

Characterization of the Genetic Modification

Using methods for molecular characterization, such as Polymerase Chain Reaction (PCR), Southern and Western Blot analyses, the number of insertion sites and organization of inserted genetic material within insertions can be determined. MON 818, the conventional corn, was used as negative control.

To determine the number of insertion sites, a restriction enzyme NdeI was used in both PV-ZMBK07 and PV-ZMGT10 plasmids. NdeI does not cleave within either the plasmids, thus both plasmids will be inserted as intact. A single band at approximately 5.5 Kb was observed, indicating one insertion site at the modified plant.

Upon evaluating the result of Southern blot analysis, the probe applied to the plasmid PV-ZMBK07 - the CryIA(b) gene - was detected at the molecular weight of 3.1Kb. Since

the expected size of CryIA(b) gene is 3.46 Kb, the insert appeared to be a "close copy" of the CryIA(b). To confirm that the 3.1Kb fragment is indeed CryIA(b), analysis on PV-ZMGT10 plasmid, containing CP4 EPSPS and gox genes, were conducted using Southern and Western Blots. The results confirmed that only CryIA(b) genes were present in the modified host plant. Genes of PV-ZMGT10 plasmid were not present in the final modified plant.

The group also perused the information provided to establish the genes in the 5.5 Kb fragment. NptII and ori-(UC probes were used in both MON 810 and Plasmid PV-ZMBK07. It was established that genes coding for nptII and ori-pUC are not present in MON 810, which leaves a single integrated DNA fragment of E35S promoter, maize hsp 70 intron and the truncated CryIA(b) gene in MON 810.

Modified Plant

To address the efficacy of CryIA(b) protein produced by its truncated genes in MON 810 to eliminate the targeted insect pest, further studies were conducted. The expression of HD-1 protein and its corresponding trypsin-resistant core protein were evaluated, both in conventional corn lines and MON 810. While the full length of HD-1 protein (~131 KD) is observed in conventional corn lines, it was expected that a smaller size 92 KD HD-1 protein will be produced by the truncated CryIA(b) protein in MON 810. However, 92 KD HD-1 protein was not observed, probably due to low expression of rapid degradation to the trypsin-resistant product during the extraction process. The active, trypsin-resistant core of HD-1 protein observed in all corn lines, including MON 810, however, is 63 KD. It was concluded that the CryIA(b) protein produced by the gene fragment in MON 810 is as effective as the original bacterium source, as far as activities against insect pests are concerned.

The expression of Bt protein is expected to be present in all plant tissues during the life of the plant. Analysis with ELISA and Western blots reveal that low level of CryIA(b) in various corn tissues, such as leaf, pollen and grain were detected in MON 810. However, CP4 EPSPS, gox and nptII proteins were not detected. In the grain, the novel protein range from 0.19 to 0.39 g/g fresh weight. As CryIA(b) protein does not have specific breakdown products in plants and are only active in the alkaline environment of the corn borer gut, there are no specific risks of digestion of CryIA(b) protein or its respective metabolites in humans and animals.

Stability of the insert was determined by crossing MON 810 into diverse corn genotypes for several generations. The efficacy of the lines has been maintained throughout seven generations of backcrossing, consistent with the laws of inheritance (Mendelian genetics). These were demonstrated by Southern blot analysis (genotypic analysis) and segregation analysis (phenotypic analysis).

One point raised by the group was related to the acceptable significant level of 5%. The group noted that in making decisions for food safety purposes, where human health is at stake, a stricter measure may be necessary.

Safety Assessment of Expressed Substance - Toxicity and Allergenicity

Very few foods consumed today have been subjected to rigorous toxicological assessment. The general assumption for new foods in the market has been that if individual ingredients are safe, then new combinations of these are equally safe. Similarly, it was agreed that the dose makes the poison (consumption of large amounts of single foods would likely result in adverse effects).

When a substance is a new component of food, conventional toxicology testing on the isolated or synthesized substance is necessary. In the development of GMOs, introduced genes and their products may have historically been consumed in large or small amounts by humans. The principal focus of toxicity evaluation is the protein expression product(s) of the inserted gene(s). Data evaluated were focused on comparison of amino acid sequences to known toxins and anti-nutrients, stability to heat or other processing methods, degradation in the presence of gastric or intestinal model systems, and appropriate oral toxicity studies. It is important to stress that any indications of potential toxicity would require the need for additional studies on a case-by-case basis.

Various toxicity tests may be undertaken for safety assessment of expressed novel protein(s). Acute Oral Toxicity tests are designed to test for mammalian toxicity (LD50). While almost no proteins are orally toxic, there are a few which cause problems, mostly through acute mechanisms. The test is done through a single, large acute dose in a 14-day observation. While it does not specifically address toxicity issues, animal feeding studies conducted in conjunction with compositional analysis may provide an idea of the wholesomeness of the food.

It is important to note that with regards to toxicity, very little is known about long term effects of consumption of any foods. Long-term studies are difficult to design, as nutritional imbalance from overfeeding on a single whole food, which itself can lead to adverse effects, may be unavoidable. However, it is necessary for any foods that are subjects of toxicity studies to be taken, if warranted, in multiples over anticipated dose of human intake. Margins of safety of 1-3 times have to be accepted, to account for the possibility of unintentionally modifying metabolic pathways of the plant, as a consequence of gene insertion, thus affecting concentrations of endogenous toxicants.

Another important note is that protein produced in a GMO is of exactly the same physical and biochemical characteristics as conventionally-produced protein. Thus, as with conventionally-produced protein, it is expected that proteins produced in a GMO would follow the same, predictable metabolic fate. Any adverse effects specifically attributable to GMOs is highly unlikely. Toxicological assessment is determined through comparison to known toxicants at the level following the model of metabolic fate. Proteins that are resistant to digestion, as protein toxins and allergens tendency are, does not imply that resistant protein provides a higher risk.

Upon evaluating the safety of Bt protein expressed in MON 810 corn, the group first learned of the metabolic fate of Bt protein. The CryIA(b) protein is in its crystalline form in neutral or acidic pH and is only solubilized in alkaline condition - as it is in the gut of

larval insects. Only in its solubilized form does the CryIA(b) protein release delta-endotoxins, which can bind to specific, high affinity receptors on the surface of the mid-gut epithelium. From the above metabolic fate, it can be derived that the acidic pH in the human stomach will not activate delta-endotoxins of CryIA(b) protein. In addition, because mammalian intestinal cells do not have similar receptors, they are not susceptible to these proteins. The long history of safe use of Bt proteins also supported the safety of Bt protein for humans.

HD-1 protein sequence, the expressed Bt protein in MON 810, is identical with CryIA(b) protein sequence. Comparing the CryIA(b) protein with any known toxins also reveal no homology. An acute mouse gavage study also showed no adverse effect observed. The LC50 of the HD-1 protein is greater than 4000 mg/kg and NOEL for this protein is set at this value.

Studies were also conducted to establish the possible unintentional modification of metabolic pathways of the plant. Aflatoxin and DIMBOA levels assessed to reveal no significant changes. The group, however, expressed concerned that only one mycotoxin level was assessed at one period of harvesting (1993). As mycotoxin levels are dependent on environment and post-harvest handling, studies on changes in mycotoxin levels of GM plants due to these factors should be conducted over the course of many harvesting periods.

Stimulated gastric and intestinal fluids to measure metabolic degradation of HD-1 protein was conducted to measure protein bioactivity. Using an insect bioassay, 90% HD-1 protein was shown to be degraded and have dissipated quickly (74 - 90%) within 2 minutes in the insect stomach. In intestinal fluid where trypsin proteases are abundant, the tryptic core of HD-1 protein was not degraded substantially, even after over 19 hours of incubation. These tests show that HD-1 protein in MON 810 corn can be an effective measure against the European corn borer, without posing toxicity to humans. The group did note, however, that the test of specificity of the toxin directed at the European corn borer was inferred using tobacco budworm. It could be argued that the test organism for this purpose was probably inappropriate and that studies using the direct target species should be conducted.

In measuring allergenicity, a decision tree and weight of evidence approaches are necessary due to the absence of definite tests. ILSI/IFBC developed the decision tree approach, which have since been elaborated and enhanced by an expert committee of FAO/WHO.

The following considerations in assessing potential allergenicity will be necessary:

- Source of the gene or protein, including consideration of possible transfer of allergenicity should the donor protein be a known allergen

- Amino acid sequence homology with known allergens

- Degradation in gastrointestinal fluids, including consideration of pepsin-resistant, pH-resistant, temperature-resistant proteins.

- Heat stability, including consideration of heat introduced during food processing

- Level of expression in the food

For proteins from sources known to be allergenic, specific serum screening may be necessary to assess the availability of the protein in human sera. In addition, as the insertion of the target trait may cause modifications of protein expression of endogenous allergens- allergens that are present in the conventional counterparts - assessment may be necessary.

The group concluded that Bt protein poses no great concern in terms of allergenicity due to the following considerations: (1) it does not have a history of causing allergies; (2) the protein is quickly digested in the human stomach; (3) present at low level; and (4) has no homology with known allergens.

While assessment of toxicity and allergenicity of the expressed protein through comparisons to known toxins and allergens are widely accepted, the group was concerned with the appropriateness of the database used. In addition, it is not known if the presence of the degradation products of the delta-endotoxins in the human digestive system would pose safety concerns, as the case study materials presented no such data. Detection studies following gastric enzyme digestion of Bt protein are thought to be necessary. The group also felt that the duration of observation of the mouse assay of only 7 days is not sufficient, and would require the standard observation duration of 15 days and chronic toxicity study (90 days observation). Additional missing information from the case study material was the data on thermal stability of the CryIA(b).

Nutritional Data

All plant breeding methods, traditional and modern, have the potential to alter the nutritional value of the plant, both in terms of the concentration of a certain nutrient or the bioavailability of such nutrient, or lead to unexpected changes in the concentrations of various natural toxicants or anti-nutrients. GM plants that were not developed to have intentionally altered nutritional values should have same levels of nutrients and anti-nutrients as their conventional counterparts. Nutritional assessment will also confirm the nutritional quality of the GM plants.

When assessing the nutritional value of GM plants, palatable plant components such as the proportion of the diet should be taken into consideration. To this effect, dietary exposure data may be necessary. One should also consider the possibility for plants to have varying nutritional values due to natural variations, effects of food processing, the bioavailability of the nutrients and level of anti-nutrients, and various types of nutritional factors as assessment is done for different plant types.

Nutritional compositional analysis should include:

- Crude protein
- Crude fat

- Fiber
- Carbohydrate composition
- Amino acid composition
- Fatty acid composition
- Vitamin analysis
- Mineral analysis
- Anti-nutritional factors

Consumption of corn kernels or processed corn products is not a significant part of human diet, although corn-based ingredients, such as corn starch and corn oil, are widely used. Again, a conventional counterpart and MON 818 corn are directly compared for nutritional value. In addition, nutritional data, as reported in the literature, were also compared to nutritional values of MON 810 corn.

Nutritional composition data showed no significant difference in protein, fat, ash, carbohydrates, calories, and moisture. Values of eight amino acids in MON 810 corn were different compared to MON 818 corn, although the means of 6 amino acids fall within literature ranges. The other two amino acids are comparable with MON 800/801 corn, which have similar genetic backgrounds. Crude fiber in MON 810 corn is found to be significantly higher, although it falls within literature range. Tocopherols are found to be similar to that of the control, although (-tocopherol is found to be higher. Since the human body only recognizes (-tocopherol, a higher level of (-tocopherol does not pose food safety concerns. Phosphorous levels are comparable between MON 810 corn and conventional varieties. Calcium level in MON 810 corn is found to be higher, although it falls within ranges of MON 800/801 corn. The case study materials, however, do not enclose assays of other vitamins and minerals. The group is of the opinion that for complete nutritional comparison, it is important to determine the presence and levels of other vitamins and minerals.

Caution is advised in examining and accepting data relating to the factors which determine the safety of GM food consumption, namely the nutritional value, consumption pattern and processing methods of the GM food. The group agreed that nutritional assessment of GM corn should be made against the conventional, parent variety, and not just any other corn lines. The group also felt that the presence of transcriptional factor for nutrients and anti-nutrients in GM plants should be assessed because such presence would result in different levels of expressed proteins. Further, animal feeding studies to discover if the nutrients behave in the exact expected physical and biochemical properties in vivo would also be useful to determine the safety of the GM plants.

Decision and Management

The group consensus after reviewing the information provided in the case study material was to accept the propagation and use of MON 810 corn as feed and food. The group concurred that the safety of the GM-corn has been established based on the acceptable molecular modification, which results in the encoding for an active delta-endotoxin, which is non-toxic to humans, and the biological equivalence of the GM-corn with that of conventional field corn.

CASE STUDY 2: High Oleic Acid Soybeans – Safety Assessment and Approval

Bronwyn Dixon and Dr Paul Brent
Food Standards Australia New Zealand, Australia

Soybeans genetically modified to have higher levels of oleic acid compared to conventional soybeans were approved in Australia and New Zealand in November 2000. This transgenic soybean consistently produces a high level of oleic acid (exceeding 80%), compared to traditional soybean oil, which has approximately 23% oleic acid. This trait was produced by the suppression (gene silencing) of the soybean gene coding for the enzyme (fatty acid desaturase), which converts oleic acid to linoleic acid, resulting in the accumulation of oleic acid instead of linoleic acid.

The oil produced by the GM high oleic acid soybean is more heat-stable than conventional soybean oil and can be used for deep fat frying without the need for hydrogenation. It was intended to replace hydrogenated soybean oil or palm- or vegetable-oil blends. Similar products - developed through conventional plant breeding and selection techniques - are already available on the market and have been successful in replacing a proportion of palm oil blends used in food manufacture and retail frying. High oleic acid soybean has the potential to reduce the need for hydrogenation - thus reducing the possibility of forming trans-fats.

Safety assessment of the transgenic soybeans conducted by FSANZ follows the generally accepted review of information required:

- The host and donor organisms
- The nature of the genetic modification
- Molecular characterization of the plants
- Compositional analysis of the plants
- Nutritional impact of the transgenic soybean

The Host and Donor Organisms

The host organism is elite cultivar A2396 (high yield) soybean (Glycine max), which has a long history of safe use. Soybean seeds, oil and meal are widely used in food products, including noodles, breads, flours, sausage casings, pastries, crackers, meat substitutes, milk substitutes, confectionery, etc. Unprocessed soy products contain toxicants and anti-nutrients, which are effectively destroyed by heat processing. Soybean proteins are known to cause allergies in some individuals.

One of the introduced genes, the GmFad 2-1 gene, comes from soybean, and the other gene, the dapA gene, from Corynebacterium. Therefore the safety assessment focused on the use of Corynebacterium as an organism with no previous history of use for food production.

The Nature of the Genetic Modification

Through biolistic transformation, two genes (GmFad 2-1 and dapA) were transferred, along with two marker genes, bla gene and uidA gene. The endogenous GmFad 2-1 gene converts oleic acid to linoleic acid, but a second copy of the gene causes gene silencing (both copies turned off). The dapA gene encodes the enzyme dihydrodipicolinic acid synthase to increase lysine.

Molecular Characterization of the Plants

Typical methods for characterising the inserted DNA, including Southern blot analysis, PCR and DNA sequencing, were used to identify all transferred genetic material and to determine whether it has undergone any rearrangements. The number of insertion sites and the number of copies at each insertion site were determined as was the arrangement of inserted DNA at each insertion site. Any unexpected open reading frames that could potentially be expressed and yield unexpected results were analysed.

A small number of plants with the high oleic acid phenotype were selected and it was decided that the high lysine trait would be dropped. Based on Southern blot analysis, high oleic acid soy lines G94-1, G94-19 and G168 were identified as containing the Gm Fad 2-1 gene.

Genotyping and phenotype analysis were conducted to ensure the stability of inserted DNA across multiple generations. Southern analysis over 6 generations and phenotypic analysis of the high oleic acid trait in soybean lines G94-1, G94-19 and G168 showed the inserts are stable over a number of generations.

Two copies of the bla gene (ampicillin resistance) are present as marker genes in the high oleic soybean. It is important to consider the likelihood that DNA will be present in the final food fractions (e.g. the oil, meal, flour, etc.) and the clinical and veterinary importance of such antibiotic resistance. However, when novel protein analysis was done, the result shows that bla gene, as well as any other novel proteins resulting from gene insertions, were not expressed (Gm Fad 2-1 turns off the endogenous gene; partial dapA gene is not expressed, uidA gene is switched off following transformation).

Compositional Analysis of the Plants

Information on the range of natural variation for levels of key nutrients, toxicants and anti-nutrients was measured in the new GM variety and was compared to those in the non-transformed control (the conventional counterpart). Comparative analysis was also conducted for downstream metabolic effects. As soybean has naturally occurring allergenic proteins, the levels in the GM variety were compared to the conventional counterpart.

Two separate field studies were conducted to compare the composition of high oleic acid soy lines G94-1, G94-19 and G168 with the parental line (A2396) at six locations. Proximates, amino acids, fatty acids, vitamins and minerals, trypsin inhibitor, tocopherols,

raffinose, stacchyose, phytic acid and isoflavones were analysed. No significant differences were reported for amino acids, vitamins and minerals (including tocopherols), phytic acid and trypsin inhibitor (anti-nutrients), and stacchyose and raffinose (oligosaccharides). Small, significant differences were detected in the level of isoflavones (increased glycitein) and lectin, although both are within literature ranges and do not present safety concerns. The fatty acids composition in GM soybean, as expected, is statistically different from its conventional counterpart.

The major difference in the fatty acid composition is the high level of oleic acid in the GM soybean. High levels of oleic acid are found in other edible oils (e.g. olive oil, high oleic sunflower and canola oils) and therefore this is not a safety concern in itself. Increased oleic acid has led to decreases in some of the other fatty acids, most notably linoleic acid (9, 12 and 9, 15 isomers) and linolenic acid.

Trace amounts (<1%) of an isomer of linoleic acid (9, 15) were found in the GM soybean oil, but absent from the control. It was postulated that the isomer is the result of the (-15 (n-3) desaturase (GmFad3) enzyme. The GmFad3 enzyme normally inserts a (-15 double bond into 9,12-linoleic acid, but may have inadvertently created a small amount of the 9, 15 isomer. Commonly used oils and fats have varying levels of linoleic 9, 15 isomer. It was concluded that the presence of linoleic 9, 15 isomer in the GM soybean oil at a level of 0.5% of the total fatty acids is not considered to pose any safety concerns.

Nutritional Impact of the Transgenic Soybean

The transgenic soybean was found to be nutritionally adequate and will support typical growth and well being. However, data on animal feeding studies and specific dietary modelling to estimate human nutritional impact of the new food in the diet may be informative.

With the thorough information examined and the safety assessment conducted, FSANZ concluded that food derived from transgenic high oleic acid soybeans was as safe for human consumption as conventional soybean oil. In Australia and New Zealand, food derived from high oleic acid soybeans is required to be labelled as being produced from soybeans genetically modified to contain elevated levels of oleic acid.

Regulation of Gene Technology in Australia

William Tucker
Office of the Gene Technology Regulator, Australia

Australian gene technology legislation, the Gene Technology Act 2000 (GT Act) and Gene Technology Regulations 2001, and corresponding State and Territory legislation, aim to protect the health and safety of people, and to protect the environment, by identifying risks posed by or as a result of gene technology and by managing those risks through regulating certain dealings with GMOs. The legislation also aims to provide nationally consistent, transparent, efficient and accountable, science-based assessments.

The GT Act covers:

- GMOs, which are defined as organisms modified by gene technology, or progeny which inherit modified traits (but does not include human beings and cloning)
- Dealings with GMOs, including research, manufacture, production, propagation, growth, breeding and import

The GT Act does not cover:

- Intellectual property
- Economic and social impact
- Cost/benefit considerations
- Trade and marketability
- Food safety and labelling

The Gene Technology Regulator was appointed under the authority of the GT Act to administer the legislation, supported by the Office of the Gene Technology Regulator (OGTR). The GT Act also provides for accreditation of organisations; certification of containment facilities; establishment of three key committees (Technical, Community, Ethics); a public record of GMOs and GM product dealings; and monitoring and enforcement powers.

The OGTR complements the work of other Australian regulatory agencies, such as the Australian Pesticides & Veterinary Medicines Authority (APVMA), Food Standards Australia New Zealand (FSANZ), and the Therapeutic Goods Administration (TGA).

The GT Act also prohibits all dealings with GMOs in Australia unless they are:

1. Licensed - either as dealings involving intentional release of GMOs into the open environment (DIR), or dealings not involving intentional release of GMOs into the open environment (DNIR)); or

2. Notified - notifiable low risk dealings (NLRDs) include non-toxic, non-pathogenic low risk work in contained facilities, for instance, work on plants in a glass house; or

3. Exempt - being on the list of exempt dealings using host/vector systems shown over time to be of very low risk; or

4. Registered - on the Register of GM products (none as yet).

The presentation will focus on the assessment process for DIR applications. The OGTR conducts case by case science-based risk assessments which take into consideration both long and short term risks. Effects of introduced changes in the GMO are compared with the non-modified parent organism. The assessment follows the Risk Analysis Framework developed by OGTR (www.ogtr.gov.au/pdf/public/raffinal.pdf, currently under review), which describes the steps of hazard identification, risk assessment, risk management, and risk communication. The legislative time-frame for these assessments is 170 working days, including extensive consultation with prescribed expert groups, key stakeholders and the public.

Hazard Identification

A hazard is the potential for the GMO to produce an adverse effect on human health or the environment. Both direct and indirect hazards are considered. The OGTR considers hazards to human health such as toxicity, allergenicity and pathogenicity, in the context of both occupational health and safety and safety of the general public. Consideration of hazards to the environment includes flora and fauna, habitat and biodiversity, soil, air and water. Commonly identified hazards are: toxicity and allergenicity for humans; toxicity for other organisms; pathogenicity; weediness; and gene transfer (with adverse impacts).

Risk Assessment

Risk combines likelihood and impact for each identified hazard, relative to the parent organisms. The OGTR evaluates the likely level and pathway of exposure to a particular hazard (exposure), the probability that in a certain timeframe an identified hazard will arise (likelihood) and how severe the identified adverse outcome is (impact).

In conducting the risk assessment, the OGTR takes into consideration uncertainty (Precautionary principle - "where there are threats of serious or irreversible environmental damage, a lack of full scientific certainty should not be used as a reason for postponing cost-effective measures to prevent environmental degradation" - GT Act), the complex nature of biological systems, rapidly advancing technology, long and short term, direct and indirect effects, determinations of other regulatory agencies and results from previous releases in Australia and overseas.

Applicants are required to supply information in support of their application, and the OGTR also makes an independent assessment of relevant scientific literature. Information

considered includes: details of the parent organism and of the GMO; the nature of the proposed dealings; interactions between the GMO and the environment; risks the GMO may pose to health and safety of people; and proposed risk management measures.

Analysis of human toxicity and allergenicity would include assessment of exposure routes and characteristics of the introduced protein (considering data such as expression levels, acute oral toxicity, sequence similarity to known toxins and allergens, digestive stability, history of safe use) and potential pleiotropic (unintended/unexpected) effects (considering data such as animal feeding studies, compositional analysis and analysis of gene insertion site). Toxicity to other organisms would additionally consider specific studies on sensitive/ indicative species.

If pathogenicity were identified as a potential hazard, data would be required on host species, transmission, survival in the environment and diseases caused, and how the genetic modification may have altered these.

If weediness were identified as a potential hazard, information would be required on the weediness of the parent organism and of related species, how the genetic modification may have altered life history traits associated with weediness (such as seed production, dissemination, persistence, competitiveness) and the potential impact (such as loss of biodiversity, ecosystem disruption).

If gene transfer (with adverse impacts) were identified as a potential hazard, data on pollen movement, out-crossing/selfing rates, sexually compatible species, hybridisation and introgression, and the potential impacts (such as altered weeds, spread of toxicity, food supply) would be considered.

Risk Management

Risk management involves the identification, evaluation, selection and implementation of options to manage identified risk. Risk management measures are put into effect by licence conditions imposed. Examples of licence conditions include requirements to: work in certified contained facilities; surround GMOs with buffer rows to trap pollen and limit spread from a trial site; the removal of related weedy species from around a trial site.

Risk Communication

Good risk communication ensures that the risk assessment is a transparent process, the public is adequately informed about the risks and their management and confidence in the regulatory system is maximised.

Risk Assessment for Commercial Release of Bollgard II Cotton in Australia

To illustrate the risk assessments conducted by the OGTR, a case study of Bollgard II cotton is presented:

Details of the Parent Organism

Cotton (Gossypium hirsutum) is exotic to Australia. It is naturally a perennial shrub but is commercially cultivated as an annual. Cotton has various uses. Lint is used for yarn, fabric, clothing. Linters (short fibres) are used in foods and for industrial purposes. Cotton seed is used for oil production for human food. All of these products are free of DNA and protein. Whole cotton seed or cotton seed meal is used for stock feed. Gossypol and cyclopropenoid fatty acids are natural toxicants of cotton, which limits its use for food and feed.

Details of the GMO

Bollgard II cotton is modified for insect-resistance, containing two inserted genes from the bacterium Bacillus thuringiensis (Bt). It is resistant to Lepidopteran caterpillar pests, including Helicoverpa armigera (cotton bollworm) and Helicoverpa punctigera (native budworm). Bollgard II cotton is derived from Ingard (Bollgard) cotton, which has one Bt gene (the cry 1Ac gene) introduced by Agrobacterium-mediated transformation. The second Bt gene (cry2Ab) was introduced into Bollgard II cotton by particle bombardment.

Ingard cotton was commercially released in Australia in 1996, being approved by the APVMA as an agricultural chemical product, but its growth was limited to south of latitude 22º South. An insect resistance management plan was also enforced by the APVMA, which included limiting its use to 30% of the total cotton crop.

Bollgard II cotton was licensed by the OGTR for commercial release and approved for food use by FSANZ in 2002, and registered as an agricultural chemical product by APVMA in 2003. It was also approved in the USA and Canada for food, feed and environmental release in 2002, and in Japan for food use in 2002 and feed use in 2003. It has been extensively trialed prior to commercial release in both Australia and the USA, with no reports of adverse impacts on human health and safety or the environment. There is a statutory requirement for applicants and licence holders to report adverse events.

Molecular characterization was conducted both for Ingard and Bollgard II cottons through Southern blot and PCR analysis. The analysis shows a single insertion site (single locus) of one intact copy of the CryIAc gene present in Ingard cotton, while Bollgard II cotton has additionally a single copy of the cry2Ab gene. Other introduced genes present are antibiotic resistance markers (nptII gene, encoding the NPTII protein, and aad gene which is not expressed in the cotton) and a visual marker (uidA gene, encoding the GUS protein), which were used in the laboratory to help generate the genetic modifications. Both genetic modifications have been shown to be stable throughout several generations of backcrosses.

Hazard Identification and Risk Assessment

Potential hazards identified were allergenicity, toxicity (humans, mammals, non-target invertebrates), weediness (increased over conventional cotton) and gene transfer (to other cotton crops or related species, with adverse impact).

Allergenicity: CryIAc and Cry2Ab proteins have no similarity to known allergens, are present in small amounts in the GMO, rapidly degrade in the mammalian digestive system and have a history of safe use in Bt insecticide formulations. These proteins are not present in cotton seed oil, which is the only product consumed by humans, and occupational exposure will be low as cotton pollen in not wind dispersed. Thus exposure and the overall risk of allergenicity is 'very low'.

Toxicity: Potential for toxicity was considered as a direct result of the introduced proteins (CryIAc, Cry2Ab, NPTII and GUS) and as an indirect result of the genetic modification, through changes in gossypol or cycloprenoids or other compositional changes.

NPTII and GUS are very frequently used in GM plants, have no similarity to known toxins or allergens and are expressed at very low levels relative to their LD50s. Cry proteins are naturally expressed in the common soil bacterium B. thuringiensis, and exert their insecticidal activities through binding to specific receptors in the larval insect gut. There is no evidence of mammalian toxicity. The proteins have a long history of safe use in Bt insecticidal formulations and are expressed at low levels relative to their LD50s. Thus the risk of mammalian toxicity is 'very low' to 'negligible'.

Toxicity of CryIAc is highly specific for lepidopteran insects. High doses of purified CryIAc given to a range of insects and other arthropods demonstrate that only lepidoteran species are susceptible. There is also no effect of high doses of CryIAc on micro-organisms in vitro or in soil.

The Cry2A class of proteins are highly specific for both lepidopteran and dipteran insects. Cry2Ab from B. thuringiensis var galleriae was found to be toxic to mosquitos (Diptera). However, data suggest that Cry2Ab from B. thuringiensis var kurstaki (from which the Cry2Ab gene in Bollgard II cotton is derived) is not toxic to dipterans such as lacewings. Cry2Ab is not toxic to other insect orders (for example honey bees, ladybird beetles) or earthworms. No direct data is available on Cry2Ab on micro-organisms but Cry2A proteins occur naturally in soil.

Compositional studies demonstrate that Bollgard II cotton is comparable to commercial/ parental varieties for gossypol, cycloprenoids, protein and amino acids, fat, fatty acids carbohydrates, crude fibre and minerals, indicating no unintended effects and no increase in natural toxicants. Feeding studies found no effects of the genetic modification on cows, quail or catfish.

Field observations were also presented for assessment of non-target toxicity. Non-target insect abundance in Bollgard II cotton fields was compared to conventional and Ingard

cotton fields in Australia over two seasons. In the first season, no effect was detected on any insect order at any sampling time. In the second season, reduced dipterans were seen at two sampling times. These data are possibly explained by inherent variability or premature senescence in Ingard and conventional crops, leading to increased detritus dwelling dipterans. In a study in the USA, diversity of arthropods was unaffected.

Thus, the conclusions of the toxicity assessment for CryIAc and Cry2Ab were that there is no evidence of mammalian toxicity, no non-target effects for CryIAc and equivocal results for Cry2Ab effect on dipterans. Therefore the overall risk to non-target organisms was assessed as 'very low'.

Weediness: In southern Australia, cotton is not considered a weed in cultivated areas and does not possess weedy characteristics such as seed dormancy, persistent seed banks, rapid vegetative growth and high seed output and dispersal. It does occur as a road side volunteer but does not develop self perpetuating feral populations. It is limited by frost, low temperature, water availability and soil fertility.

In northern Australia, it is not considered an invasive weed but feral populations do exist and volunteers occur in disturbed environments. Grazing, fire and plant competition seem to be the main limiting factors. Insect pressure may also be limiting (grasshoppers, not Lepidoptera).

In southern Australia, Bollgard II cotton has no alteration in life history traits that might lead to weediness (compared to parental varieties). Insect resistance is unlikely to increase weediness. In northern Australia, data also suggest that Bollgard II cotton is unlikely to be weedy (germination and seedling survival not enhanced) but results were equivocal for reproductive performance (seed production) and net population growth index (invasiveness) were greater than conventional cotton at some sites. Therefore there is some uncertainty about weediness in northern Australia.

Gene Transfer: Cotton is mostly self-pollinating. Pollen is heavy and sticky, and insect, not wind, pollinated. Outcrossing rates are mostly estimated at around 10%, however in Australia the rates are very low at 0 - 1% for adjacent rows.

Gene transfer is most likely at very low rates between commercial cotton fields and could occur to feral cotton populations in northern Australia. G. barbadense is another cotton species cultivated in Australia, representing 3% to 4% of commercial cotton production, and feral populations exist in northern Australia and southern Queensland. G. barbadense is sexually compatible with G. hirsutum. Outcrossing would pose the same risks as Bollgard II cotton itself. Thus, although the likelihood is high, the impact is very low, resulting in an assessment of 'very low' risk.

Australia has a number of native Gossypium species, some with distributions which overlap with commercial cotton growing regions. However these all have different genome types, resulting in genetic incompatibility. Thus the likelihood of gene transfer is negligible and the impact is very low, leading to a risk assessment of 'negligible'. Similarly, gene

transfer to unrelated species is prevented by genetic incompatibility. Transfer of antibiotic resistance to bacteria is the only identified possible adverse outcome, however this is negligible relative to the natural prevalence of resistance genes. Thus, the risk of gene transfer to unrelated species was assessed as 'negligible'.

Risk Management / Licence Conditions

Commercial Production: To manage the identified uncertain risk of weediness, commercial production was limited to southern Australia (south of latitude 22º for Ingard cotton), seed transported to northern Australia for stock feed must be contained, transport routes monitored and further research into weediness conducted.

In northern Australia, limited and contained release was allowed, with the following conditions to limit dissemination of the GMO and its genetic material:

- Reproductive isolation (pollen traps/isolation zones)
- Precise location of trial (GPS coordinate to be notified the OGTR)
- Stringent transport and storage conditions
- Monitor for, and destroy, volunteers prior to flowering/seed set
- No other cotton on location until free of volunteers
- Monitoring by OGTR of compliance with licence conditions

An insect-resistant management strategy is also enforced by the APVMA as a condition of registration as an agricultural chemical. This condition is imposed by the APVMA because insect resistance is an agricultural efficacy issue (not a human health or environmental risk which is covered by the OGTR). The cotton industry's Transgenic Insect Resistance Management Strategy (TIMS) committee, in conjunction with the APVMA, developed an insect resistance management plan, which included refugia to ensure survival of some susceptible insects, and limiting the area or proportion of the total cotton crop which can be Bollgard II (or Ingard). Ingard cotton is also being phased out in favor of Bollgard II to reduce evolution of insect resistance to the Bt proteins. (The limit on the proportion of the total cotton crop which can be Bollgard II has been removed for the 2004/05 growing season, in conjunction will the withdrawal of Ingard cotton. Other insect-resistance management requirements remain).

Safety Assessments of GTS 40-3-2 Soybean, MON 810 Corn and High Oleic Acid Soybean – A Comparison

Ruud Valyasevi
National Center for Genetic Engineering and Biotechnology, Thailand

The concept of safety assessment of transgenic plants remain unchanged for various organisms. The three varieties of GM crops evaluated in this Workshop show similarities in the application of safety assessment concepts.

Phenotypic Differences, Donor Organisms and Intended Uses

GTS 40-3-2 Soybean is a herbicide-tolerant variety intended for use as human food and animal feed. The gene CP4 EPSPS, which is resistant to glyphosate, is derived from Agrobacterium sp. strain CP4 and genetic transformation is achieved through particle bombardment.

GM Corn line MON 810 is an insect-resistance variety, with particular resistance to the European corn borer. It is intended mainly for use as animal feed. The novel gene is CryIA(b) from Bacillus thuringiensis subsp. Kurstaki strain HD-1. The genetic transformation is also achieved through particle bombardment.

High oleic acid soybean is a nutritionally-enhanced variety, with higher levels of oleic acid at the expense of linoleic and linolenic acid content. It also has an increased ratio of glycinin to beta-conglycin and has low level of a 9,15 isomer of linoleic acid. The Desaturase gene (Gm Fad 2-1) is isolated from the soybean seed and the DapA gene is derived from Corynebacterium. High Oleic Acid Soybean is mostly used for the production of soybean oil, which is widely used in the production of snacks or deep fried food products.

All of the above host organisms have established histories of safe use.

Molecular Characterization, Identification and Analysis of Novel Proteins

In the genetic make-up of GTS 40-3-2 Soybean, CP4 EPSPS and gox genes are present. Npt II under the bacterial promoter (used as molecular markers) is not found in the final product. CP4 EPSPS protein was detected either in the seed or leaf tissue, causing the positive enzymatic activity of glyphosate-tolerant EPSPS. No GUS protein was detected.

In the MON 810 corn, the CryIA(b) gene was detected, although the marker genes, CP4 EPSPS, gox and Npt II were not present in the final product.

The high oleic acid soybean incorporates additional copy of Gm Fad 2-1 gene, with no expressed novel protein. Marker genes GUS and Bla were eliminated during backcrossing.

Toxicity Studies and Allergenicity

Mouse acute oral gavage using different, higher doses than calculated dietary exposure of novel protein was used to determine the LD50 level. Comparison of amino acid sequence to known protein toxins was also conducted. Following the metabolic fate of the novel protein, metabolic degradation in simulated gastric and intestinal fluids was conducted. These tests revealed that more than 90% of CryIA(b) protein was degraded within 2 minutes, thus posing little risks of toxicity and allergenicity to humans. In the intestinal fluid of an insect, however, purified CryIA(b) protein did not degrade after 19.5 hours and still retained its insect-resistant activity. The protein is also stable against peptic and tryptic digestion.

Allergenicity testing is conducted through comparison of at least 8 to 12 contiguous amino acid sequence homology to known food allergens.

The high oleic acid soybean does not contain any novel protein, although it has a slightly altered seed storage protein profile. RAST reactivity (Radioallergosorbent) was conducted to determine if changes in protein profiles changed their allergenicity relative to the parental soybean line.

Compositional Analysis

Compositional analysis was conducted for key nutrients, natural toxicants, and anti-nutrients. Samples for analysis were gathered from various growth seasons. However, caution must be exercised when gathering samples as nutrients have been shown to vary depending on the growth season and the environment.

GTS 40-3-2 soybean, MON 810 corn, and high oleic acid soybean are found to have compositions comparable to their respective parental lines.

Animal Feeding Studies

Nutrient bioavailability using feeding studies of rats, broiler chickens, catfish, dairy cows and bob white quail were conducted for GTS 40-3-2 soybean and MON 810 corn. Test animals were sacrificed at the end of the studies and necropsied. Internal organs were weighed and body weight, cumulative body weight gain and food consumption were evaluated. No statistical differences were detected between the GM-group and control.

Animal feeding studies were conducted using livestock species (namely, pigs, chickens) to determine the wholesomeness of the GM plant. The amount of GM-feed consumed in order for the livestock to put on 1 lb of bodyweight is used to measure the ability to support typical growth and well-being of the livestock, as compared to non-GM, conventional feed.

Conclusion

Following the review of expression of inserted genes (toxicity and allergenicity), nutritional assessment and dietary exposure, and the remnants of molecular markers, it was concluded that GTS 40-3-2 soybean, MON 810 corn, and high oleic acid soybean are as safe as their respective conventional counterparts. Higher levels of oleic acid, as seen in the high oleic acid soybean, may have a positive health impact on the population.

ABOUT THE ORGANIZERS

As a special initiative of ASEAN Leaders, the main objectives of the ASEAN Foundation, established in 1997, are to generate greater awareness of ASEAN, and promote greater interaction and participation by member countries in ASEAN activities. Additionally, the ASEAN Foundation carries out human resource development efforts to enable the people of the region to realize their full potential and capacity towards progress as productive and responsible members of society. The Foundation is also directed at the evolution of a development cooperation strategy aimed at providing mutual assistance and equitable economic development, and alleviating poverty. Activities under the Foundation are funded by member countries and through donations from various sources.

One of the sources of fund came from the Government of Japan, through the ASEAN-Japan Solidarity Fund aimed to support capacity building projects on science, technology, social development, culture and information within ASEAN countries. Among others, the "3rd and 4th ASEAN-ILSI Training Workshop on GMOs" is one of the projects supported by the ASEAN Japan Solidarity Fund.

The Department of Agriculture is responsible for administering part of the Government's duties in the field of agriculture and plantation. It implements governance affairs in the field of agriculture and plantation, promote and coordinate the implementation of duties and administration service, carry out researches and applied development, education and training, coordination to stabilize food resilience in the framework of supporting the policy in the field of agriculture and plantation, and is in charge for carrying out national surveillance. The Center for Plant Variety Protection (CPVP) was established in 2002, and is expected to encourage the involvement of private sector in the development of new, better plant varieties. It is the Center's aim, that the involvement of private sector will consequently boost the development of new plant varieties, which in turn help improve farmers welfare as well as the economic development.

The International Life Sciences Institute (ILSI) is a nonprofit, worldwide foundation based in Washington, DC established in 1978 to advance the understanding of scientific issues relating to nutrition, food safety, toxicology, risk assessment, and the environment. ILSI branches include Argentina, Brasil, Europe, India, Japan, Korea, Mexico, North Africa and the Gulf Region, North America, North Andean, South Africa, South Andean, Southeast Asia Region, the Focal Point in China, and the ILSI Health and Environmental Sciences Institute. ILSI also accomplishes its work through the ILSI Research Foundation (composed of the ILSI Human Nutrition Institute and the ILSI Risk Science Institute) and the ILSI Center for Health Promotion. Established in 1993, ILSI Southeast Asia Region, located in Singapore currently serves as the regional office for the coordination of scientific programs, research and information dissemination in ASEAN, Australia, New Zealand and the Pacific. By bringing together scientists from academia, government, industry and the public sector, ILSI seeks a balanced approach to solving problems of common concern for the well-being of the general public. ILSI receives financial support from industry, government, and foundations.

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PARTICIPANTS

Name	Organization	Country
William Tucker	Office of the Gene Technology Regulator	Australia
Paul Brent	Food Standards Australia New Zealand	Australia
Bronwyn Dixon	Food Standards Australia New Zealand	Australia
Mulyadi Haji Mohamad Ali	Department of Agriculture (Ministry of Industry and Primary Resources)	Brunei Darussalam
Masliana Yuliah Abdullah	Department of Agriculture (Ministry of Industry and Primary Resources)	Brunei Darussalam
Veng Huy	Ministry of Agriculture, Forestry and Fisheries	Cambodia
Chin Theng Phiv	Ministry of Agriculture, Forestry and Fisheries	Cambodia
Channa Ty	Cambodian Agricultural Research and Development Institute	Cambodia
Amy Estiati	Research Center for Biotechnology	Indonesia
Adi Santoso	Research Center for Biotechnology	Indonesia
Hajrial Aswidinoor	Bogor Agricultural University	Indonesia
Agus Purwito	Bogor Agricultural University	Indonesia
Siswanto	Indonesian Biotechnology Research Institute for Estate Crops	Indonesia
Nurita Toruan Mathius	Indonesian Biotechnology Research Institute for Estate Crops	Indonesia
Karden Mulya	Indonesian Center for Agricultural Biotechnology and Genetic Resources Research and Development	Indonesia
Inez H Loedin	Research Center for Biotechnology	Indonesia
Bahagiawati	Indonesian Center for Agricultural Biotechnology and Genetic Resources Research and Development	Indonesia
Kartika Adiwilaga	PT Nestle Indonesia	Indonesia
Harsi DK	Bogor Agricultural University	Indonesia
M Herman	Indonesian Center for Agricultural Biotechnology and Genetic Resources Research and Development	Indonesia
Feri Kusnandar	Bogor Agricultural University	Indonesia
Sugiono Moeljopawiro	Center for Plant Variety Protection	Indonesia
Bambang Purwoko	Bogor Agricultural University	Indonesia
Wisnu Broto	National Agency for Drug and Food Control	Indonesia
Tumpal Silalahi	Monsanto Indonesia	Indonesia
Alfi Puruhita	PT Swaco Prima Windotama	Indonesia
Fadjar Ayu Tofiana	National Agency for Drug and Food Control	Indonesia
Hiroshi Kamada	University of Tsukuba	Japan
Tanthaphone Chanphasouk	Ministry of Agriculture and Forestry	Lao PDR

Laila Rabaah Bt Ahmad Suhaimi	Ministry of Health	Malaysia
Nik Shabnam Bt Nik Mohd Salleh	Ministry of Health	Malaysia
Khin Maung Thet	Myanmar Agriculture Service	Myanmar
Tin Htut	Agriculture Research Department	Myanmar
Than Tun	Ministry of Agriculture and Irrigation	Myanmar
Gemiliano Alugui	Department of Agriculture	Philippines
Edison Rinen	Department of Agriculture	Philippines
Cynthia Hedreyda	University of the Philippines	Philippines
Jerry Serapion	Department of Agriculture	Philippines
Lara Vivas	Bureau of Agriculture and Fisheries Product Standards	Philippines
Mong Chai Koh	Agri-Food & Veterinary Authority of Singapore	Singapore
Boon Yee Yeong	ILSI Southeast Asia Region	Singapore
Emily Teo Huey Shyan	Agri-Food & Veterinary Authority of Singapore	Singapore
Veronita Rusli	ILSI Southeast Asia Region	Singapore
Cheau Jen Lee	ILSI Southeast Asia Region	Singapore
Airani Ramli	Agency for Science, Technology & Research	Singapore
Evelyn Kuah	Quest International	Singapore
Tin Tan Seow	Nestle R&D Center	Singapore
Gek Hoon Khoo	Agri-Food & Veterinary Authority of Singapore	Singapore
Payungsak Rauyaree	Department of Agriculture	Thailand
Anadi Nitithamyong	Institute of Nutrition, Mahidol University	Thailand
Ruud Valyasevi	National Center for Genetic Engineering and Biotechnology	Thailand
Ayuth Harintharanon	Bureau of Biotechnology for Animal Production	Thailand
Sukun Kunawasen	National Center for Genetic Engineering and Biotechnology	Thailand
Oratai Silapanapaporn	Ministry of Agriculture and Cooperatives	Thailand
Jeanette Glover Glew	United States Food and Drug Administration	USA
Vu Duc Quang	Ministry of Agriculture and Agriculture and Rural Development	Vietnam
Chu Hoai Hanh	Ministry of Agriculture and Agriculture and Rural Development	Vietnam
Doan Thu Thuy	Ministry of Agriculture and Agriculture and Rural Development	Vietnam