FAO/WHO Symposium on Biotechnology and Food Safety

International Conference Hall

Makuhari Messe, 2-1, Nakase, Mihama-ku, Chiba City 261-0023, Japan

13 March 2000

FAO/WHO Symposium on Biotechnology and Food Safety

March 13, 2000
International Conference Hall
Makuhari Messe
Chiba City, Japan

Sponsored by

Food and Agriculture Organization of the United Nations
World Health Organization

Supported by

Food and Agriculture Organization of the United Nations
World Health Organization
International Life Sciences Institute (ILSI)
International Life Sciences Institute Japan

Patronized by

Japanese Ministry of Health and Welfare
Japanese Ministry of Agriculture, Forestry, and Fisheries

Scientific Planning Committee

Dr. Ezzeddine Boutrif, Food and Agriculture Organization of the United Nations
Dr. David Neumann, ILSI Risk Science Institute
Dr. Yasuyuki Sahara, World Health Organization
Dr. Jorgen Schlundt, World Health Organization
Dr. Makoto Tabata, Food and Agriculture Organization of the United Nations

FAO/WHO Symposium on Biotechnology and Food Safety

International Conference Hall
Makuhari Messe, 2-1, Nakase, Mihama-ku, Chiba City 261-0023, Japan

13 March 2000

Registration: 0900-1000 **Symposium: 1000-1730**

Introduction

Dr. Hartwig de Haen, Assistant Director General, Economic and Social, Food and Agriculture Organization of the United Nations

Session I:

Food Safety: Hazards, Risks, and Perceptions
Chairperson: Dr. Yoichi Konishi, Nara Medical University Cancer Center, Nara, Japan

Keynote Address – Distinguishing Between Hazard and Risk
Dr. Yuzo Hayashi, Kitasato University, School of Pharmacy, Kanagawa, Japan

Risk Perception and Public Expectations About Food Safety
Dr. Darryl Macer, Tsukuba University, Tsukuba Science City, Japan

Session II:

Foods Produced Through Biotechnology
Chairperson: Dr. Hartwig de Haen, Food and Agriculture Organization of the United Nations

Development of Transgenic Food Plants
Dr. Luis Rafael Herrera-Estrella, Centro de Investigacion y Estudios Avanzados del IPN, Irapuato, Mexico

Transgenic Food Plants: Traits, Transformants, and Deployment
Dr. Clive James, ISAAA, Ithaca, NY, USA

Detecting the Presence of Introduced DNA and its Protein Product
Dr. Elke Anklam, European Commission, Joint Research Center, Ispra, Italy

Session III:

Safety Assessment of Foods Produced Through Biotechnology
Chairpersons: Dr. Jorgen Schlundt, World Health Organization, Geneva, Switzerland and Dr. David A. Neumann, ILSI Risk Science Institute, Washington, DC, USA

FAO/WHO Consultation on the Safety Assessment of Foods Produced Through Biotechnology
Dr. David A. Jonas, WHO Consultant, Kent, United Kingdom

Fate of Ingested DNA
Prof. David E. Beever, University of Reading, Reading, United Kingdom

Assessing for Toxicity Associated With Foods Produced Through Biotechnology
Prof. Karl-Heinz Engel, Technische Universität München, Freising-Weihenstephan, Germany

Assessing the Allergenic Potential of Foods Produced Through Biotechnology
Dr. Samuel Lehrer, Tulane University, New Orleans, LA, USA

Regulatory Aspects of Foods Produced Through Biotechnology
Ms. Karen McIntyre, Health Protection Branch, Health Canada, Ottawa, Canada

Food Safety: Hazards, Risks, and Perceptions
Distinguishing Between Hazard and Risk

YUZO HAYASHI
Kitasato University School of Pharmacy
1-30-2-711 Unomori, Sagamihara-shi
Kanagawa 228-0801, Japan
81-427-46-3591 tel/fax

The purpose of this presentation is to illustrate that distinguishing between hazards and risks is a prerequisite for understanding of food safety issues and to adequately assess, communicate and manage risks attributed to foods, food additives or food contaminants.

Terminology and Logic

Hazard: A biological, chemical, or physical agent in or property of food that may have an adverse effect (FAO/WHO Expert Consultation, 1995).

Before the FAO/WHO Expert Consultation (1995), hazard was defined or understood as a set of inherent properties or potential properties of an agent capable of causing adverse effects. According to this definition, "hazard identification involved the determination of whether exposure to an agent can cause an increased incidence of adverse health effects such as cancer or birth defects, and characterization of the nature and strength of the evidence of causation" (US FDA Red Book, National Research Council 1994). The present paper is based on the definition by FAO/WHO Expert Consultation (1995).

Risk: A function of the probability of an adverse effect and the severity of that effect, consequential to a hazard(s) in food (FAO/WHO Expert Consultation 1995).

Risk = f (h_1, h_2, ...h_n ; e_1, e_2, ...e_n)

h_1, h_2, etc.: Variables determined during the process of hazard characterization.
e_1, e_2, etc.: Variables determined during the process of exposure assessment.

Safety: The practical certainty that there will be no adverse outcome under defined condition of exposure (Walker R, 1999).

–No adverse outcome
–Adverse outcome at acceptable or permissible rates/magnitudes

Considering these definitions, it is understood that food safety is a concept primarily related to risk, but not to hazard itself.

Risk Analysis

Risk analysis is regarded as the methodological basis for assessing and managing risks associated with the intake of foodborne hazards. In the context of the Codex Alimentarius Commission, risk analysis is defined as a process consisting of three components, risk assessment, risk management and risk commu-

nication. These three components are technically separate, but are integrated toward the final goal of developing food safety standards.

Risk Assessment

Risk assessment is generally defined as a scientific process to evaluate known or potential adverse health effects resulting from human exposure to foodborne hazards. The process consists of the following steps

(i) hazard identification, (ii) hazard characterization, (iii) exposure assessment, and (iv) risk characterization (FAO/WHO Expert Consultation, 1995).

i) Hazard identification: The identification of hazards (biological, chemical, or physical agents capable of causing adverse health effects) that may be present in a particular food or group of foods.

ii) Hazard characterization: The qualitative and/or quantitative evaluation of the nature of the adverse effects associated with hazards (biological, chemical of physical agents) that may be present in food.

iii) Exposure assessment: The qualitative and/or quantitative evaluation of the likely intake of hazards (biological, chemical, or physical agents) via food as well as exposure from other sources, if relevant.

iv) Risk characterization: The quantitative and/or qualitative estimation, including attendant uncertainties, of the probability of occurrence and severity of known or potential adverse health effects in a given population based on hazard identification, hazard characterization and exposure assessment.

Scientific Information Necessary for Hazard Identification

1) Epidemiological studies: Epidemiological studies can provide the most relevant information for hazard identification, simply because they involve observation of human beings, not laboratory animals (National Research Council, 1994). However, clinical and epidemiological data are unlikely to be available for most chemical agents. Negative epidemiological data may be difficult to interpret for risk assessment purposes because the statistical power of most epidemiological studies is inadequate to detect effects at relatively low levels in human populations (FAO/WHO Expert Consultation, 1995).

2) Animal studies: Scientific information on adverse effects of chemical agents can be derived from animal studies. Such studies provide the following advantages: (i) The quantitative relationship between exposure (or dose) and the extent of adverse effects can be established; (ii) The animal and animal tissues can be thoroughly examined so that the full range of adverse effects produced by a chemical can be identified; and (iii) The exposure duration and routes can be designed to match those experienced by the human population of concern (National Research Council, 1994).

Animal studies of a chemical are usually designed to identify a no observed effect level (NOEL), a no observed adverse effect level (NOAEL) or a benchmark dose, which may provide useful data for determination of a safe exposure level in humans. Exposure is conducted at levels high enough to reduce the likelihood of false-negatives while considering issues such as metabolic saturation

or cytotoxicity-induced cell proliferation (FAO/WHO Expert Consultation, 1995).

Points to Consider in Hazard Characterization

1) Extrapolation from high dose to low dose: The significance that the adverse effects detected in high-dose animal studies have for low-dose human exposure is the major question posed in the hazard characterization of chemical agents (FAO/WHO Expert Consultation, 1995).

2) Interspecies extrapolation from animals to humans: Information derived from pharmacokinetic studies and pharmacodynamic studies may provide a scientific basis for the extrapolation.

3) Genotoxic and non-genotoxic carcinogens: Since the early 1940s when it became evident that the initiating event in carcinogenesis could be a somatic mutation, it has traditionally been accepted that theoretically there may be no safe dose (no threshold) for a carcinogen that acts through genotoxic mechanisms. Recently it has become possible to identify non-genotoxic carcinogens, chemicals that are not capable of producing mutations themselves, but act at later stages of the carcinogenic process on target cells already initiated by other carcinogenic agents. Thus, genotoxic carcinogens are defined as chemicals that can cause genetic alterations in target cells, either directly or indirectly. While the major target of genotoxic carcinogens is genetic material, non-genotoxic carcinogens act at extra-genetic sites, leading presumably to enhanced cell proliferation and/or sustained hyperfunction/dysfunction of the target sites.

A large body of data indicates that quantitative differences exist in both genotoxic and non-genotoxic carcinogens with regard to species-specific effects. Certain non-genotoxic carcinogens, e.g., rodent-specific carcinogens, serve as examples of substances for which there are qualitative differences in the ultimate carcinogenic effects. In contrast, no such clear-cut examples have been reported for genotoxic carcinogens.

Food safety authorities in many countries now distinguish between genotoxic and non-genotoxic carcinogens. While this distinction cannot be applied in all instances due to insufficient information or knowledge on carcinogenesis, the concept can still contribute to the establishment of evaluation strategies for cancer risks posed by exposure to chemicals. In principle, non-genotoxic carcinogens may be regulated using a threshold approach, such as the "NOEL-safety factor" approach (FAO/WHO Expert Consultation, 1995).

Points to Consider in Risk Characterization

1) Risk characterization is performed by taking into consideration the results of the hazard identification, hazard characterization, and exposure assessment to estimate the likelihood of adverse health effects in human populations as a consequence of the exposure.

2) For risk management purposes, estimation of either the rate/severity of adverse effects likely to occur as a consequence of exposure to a hazard of interest at the actual daily dose; or the exposure level likely to cause adverse effects in the exposed human population at the acceptable or permissible rates/severity is often required.

3) As part of the risk characterization, the uncertainties involved in each step of the risk assessment process should be described. Compensation for uncertainties is an important procedure for implementation of risk assessment to deduce proper assessment outcomes.

Risk Perception and Public Expectations About Food Safety

DARRYL MACER
Director, IUBS Bioethics Program
Institute of Biological Sciences, Tsukuba University
Tsukuba Science City 305-8572, Japan
81-298-53-4662
81-298-53-6614 fax
email: Macer@biol.tsukuba.ac.jp

Modern society expects food to be simply "safe", and the improvements made in food processing and hygiene in recent decades mean that few people realize the inherent risks of the food that they eat. The most likely bad health experience most people in rich countries will have is a case of diarrhea from food kept too long in the refrigerator, or choosing a bad restaurant. Episodes of food poisoning are viewed as exceptions, traced to what people see are accidental rare events, like a bad catering experience. People in developing countries face more common bouts of food poisoning, but also may blame it on bad restaurants, and chance outbreaks.

In the 1990s, several well publicized events shook the confidence people have in the food safety systems, namely the bovine spongiform encephalophy (BSE) outbreak in UK, and the dioxin poisoning in Belgium. Although more people die from routine food poisoning in these countries, be it salmonella or *Listeria*, or *E. coli* 0157, the former two events led to a dramatic distrust in the authorities that monitor food safety. They show us that people, more than expecting food to be safe, expect the government regulatory authorities that monitor the food to be 100% accurate. Thus we need to separate these two elements, food safety itself, and trust in competent and transparent independent regulatory authorities.
Bioethics considers the ethical issues raised in biology and medicine, and especially those raised by human activity in society and the environment using biotechnology. The word "biotechnology" simply means using living organisms, or parts of them, to provide goods or services. All civilizations were formed needing food, clothes, and medicines, and in that sense biotechnology is not new. What is new is that we can now make new varieties much more quickly, and with greater variation—and some foodstuffs made from plants bred using genetic engineering are already being sold in parts of the world.

Bioethics is not just an academic endeavor or an applied part of philosophical ethics, it is rooted in describing the daily life and attitudes of all people. One way to examine the reasoning people have is to ask them in surveys of opinion. This paper will examine public perceptions of products of new biotechnology and the observations we have on the consumer acceptance of novel foods, from a global perspective. I will present results of surveys conducted in many countries. These include the 1993 International Bioethics Survey in Asia-Pacific countries, and the 1997 Eurobarometer survey with comparisons to Asia, North America, Japan and New Zealand. Surveys of public and scientists in Japan in 1991 and 1999 will also be discussed, to compare different groups' perceptions.

In all countries there is a positive view of science and technology, and it is perceived as increasing the quality of life by the majority in all countries. Less than 10% see it as doing more harm than good. When people are asked about

the benefits and risks of specific developments of technology, both benefits and risks are cited by many respondents. People do not have a simplistic view of science and technology, and can often perceive both benefits and risks. When specific details of an application are given there is generally greater acceptance, suggesting people have some discretion. This balancing of good and harm is one indicator of the bioethical maturity of a society. The introduction of "novel" foods is a great opportunity to make a more informed society.

People in the world are increasingly being given the same media coverage of technology, and education also has many similarities. Therefore, it is not surprising that the data also generally finds that most of the total diversity in all samples is found in any one country or group. In every society there are people who want to use new genetic techniques and those who do not. The issue goes deeper than religion or culture, and suggests that these issues will always be divided. However, one message is clear for the work of the United Nations agencies—they are more trusted than national governments in the regulation of biotechnology, and people expect to know how decisions are made on allowing food into the open markets, restaurants and supermarkets of the world.

Development of Transgenic Fod Plants

LUIS HERRERA-ESTRELLA
Departamento de Ingeniería Genética de Plantas
Centro de Investigación y Estudios Avanzados. Apartado postal 629, 36500
Irapuato, Guanajuato, Mexico
52-462-39600
52-462-45849 fax
Email: iherrera@irapuato.ira.cinvestav.mx

Ten thousand years ago, humans unconsciously initiated what we now know as agriculture by selecting seeds or plants with useful characteristics and planting them. Since then, the genetic manipulation of plants has been the basis for the production of improved varieties that have sustained food production for mankind. In the past 70 years or so, a more systematic selection of desirable traits by directed crosses of individuals of the same or related species (plant breeding) has produced the high yielding varieties which are currently being grown in many regions of the world. More recently, with the development of plant genetic engineering, new strategies, based on the direct manipulation of genetic material, have led to a new wave of plant varieties with improved characteristics and an enormous potential to reduce the production cost of crop plants and the use of agrochemicals. Examples of new traits are novel insect and disease resistance, longer shelf-life and improved nutritional quality.

Although the real potential of genetically modified plants is widely discussed, the non-expert knows little about the basic research needed to generate these plants, how these plants are produced and how they are tested before becoming available to farmers as commercial products. In this paper, I will describe the process of producing and testing transgenic plants. For this purpose, I will use two examples of transgenic plants that have been developed in our institute, namely, virus resistant potatoes and plants that require less fertilizer to grow. I will describe how basic research leads to the development of useful traits, the methods to introduce genetic material into plant cells, how the plant prototypes are tested and the final process of obtaining a commercial product.

Transgenic Food Plant: Traits, Transformants, and Deployment

CLIVE JAMES
Chair
International Service for the Acquisition of Agri-Biotech Applications
P.O. Box 427 SAV
Grand Cayman, Cayman Islands
Email: cjames@candw.ky

In the early 1990s many were skeptical that genetically modified (GM) crops could deliver improved products and make an impact in the near-term at the farm level. However, by the late 1990s the early promises of crop biotechnology were meeting expectations in both industrial and developing countries. The number of countries growing GM crops increased from 1 (China) in 1992, to 6 in 1996, to 9 in 1998, and 12 in 1999. The industrial countries grew 82 % of the global GM crop area in 1999 but with a significant and increasing proportion (18 %) being grown in the developing countries of Latin America, Asia and Africa. The four principal countries growing GM crops in 1999 were two industrial (USA and Canada) and two developing countries (Argentina and China), with USA growing 72% of global GM crop area, Argentina 17%, Canada 10%, and China 1%. The balance of GM crops was grown in eight countries: Australia, South Africa, Mexico, Spain, France, Portugal, Rumania and Ukraine. It is noteworthy that despite the continuing debate about GM crops in the European Union, farmers in three EU countries grew GM crops in 1999, and there is at least one developing country from each of the three continents in the South already commercializing GM crops. This is a notable achievement for the four countries from the South (Argentina, China, South Africa and Mexico) given the challenges related to technology acquisition, regulatory requirements, and the continuing disincentive related to public acceptance issues in countries of the European Union, which unlike developing countries have the luxury of surplus food production and a population that does not suffer from malnutrition.

The adoption rates for GM crops are unprecedented and are the highest for any new technologies by agricultural industry standards. Global acreage of GM crops increased from 1.7 million hectares in 1996 to 11.0 million hectares in 1997, to 27.8 million hectares in 1998, and to 39.9 million hectares in 1999; this is a substantial 23.5 fold increase in only four years. Soybean, corn, cotton and canola are the major GM crops on a global basis with potato, squash and papaya occupying less than 1% of the area. In terms of traits, herbicide tolerance is the most prevalent trait (71% in 1999) followed by insect resistance at 22%. In 1999, for the first time in the US, stacked genes for insect tolerance and herbicide tolerance in both corn and cotton occupied 2.9 million hectares, equivalent to 7% of the global GM crop area.

High adoption rates reflect grower satisfaction with GM crops that offer significant and multiple benefits ranging from more convenient and flexible crop management, higher productivity, to a safer environment through decreased use of conventional pesticides; collectively these contribute to higher net returns/hectare and a more sustainable agriculture. It is noteworthy that, with the exception of the delayed ripening tomato, the first generation of GM crops all have input or agronomic traits that have by and large benefited grow-

ers and the seed industry, almost to the exclusion of consumers. The first generation of GM crops have already demonstrated that incorporation of input traits have conferred beneficial control of biotic stresses that were not possible with conventional technology. For example, effective and targeted control of specific cotton and maize insect pests as well as papaya and potato virus diseases that was not possible through conventional crop improvement programs. Unlike the first generation input traits, the second generation GM crops, with output or quality traits, that are ready for deployment in the near-term, are capable of delivering significant nutritional and health benefits to consumers. Because of the evident benefits to consumers, they could have a significant impact on public acceptance of food produced from GM crops. For example high oleic soybeans, already approved in the USA, has 80% oleic acid versus 23% in its conventional counterpart. High levels of oleic acid have been shown to reduce the "bad" blood cholesterol without depressing the "good" cholesterol. Heart disease, which is closely linked to high cholesterol levels, is the major killer disease today and this clear benefit from food derived from GM crops should be very evident to consumers. With the support of the Rockefeller Foundation genes, encoding for beta-carotene, the precursor of Vitamin A, have been incorporated in rice. This technology has the potential to enhance the diets of 400 million people, of whom 180 million are children, in the developing countries who suffer from Vitamin A deficiency, and which results in the death of 2 million children annually. Priority should now be assigned to public awareness initiatives to share information and knowledge about potential nutritional and health benefits associated with foods derived from second generation GM crops. The R & D pipeline of GM crops is full of new and novel products that can be commercialized in the near term from 2000 onwards. GM crops projected for deployment in the next five years offer a rich mix of at least 20 new input traits and an equal number of output traits. Thus, GM crops will allow both the quantity and quality of food to be enhanced. This does not imply that GM crops are a panacea; biotechnology has limitations just like any other technology, must be managed responsibly and used in conjunction with other technologies.

In the next 50 years population will increase by 50% from 6 to 9 billion. A global strategy that integrates both conventional crop improvement and biotechnology, specifically including GM crops, will allow society to harness and optimize the contribution of technology to global food security. Biotechnology should be one of several essential inputs in a multiple thrust strategy, that includes improved distribution and population control, to ensure global food security; no approach dependent on a single input will succeed, it will require a strategy with multiple thrusts that addresses all the major issues. Failure to support a vigorous program in biotechnology, including GM crops could jeopardize and deny global society the opportunity of achieving food security in the new millennium. The recent report of the Nuffield Council on Bioethics, from the UK concluded that "there is a compelling moral imperative to make genetically modified crops readily available to developing countries who want them to help combat world hunger and poverty."

Detecting the Presence of Introduced DNA and its Protein Product

G. VAN DEN EEDE, M. LIPP, and E. ANKLAM
European Commission
DG Joint Research Centre
Institute for Health and Consumer Protection
Via Enrico Fermi
21020 Ispra (Varese), Italy
39-0332-78-5390
39-0332-78-5930 fax
email: elke.anklam@jrc.it

A genetically modified organism (GMO) can be distinguished from a non-GMO by the fact that it contains either unique, novel DNA sequences, and/or unique novel proteins. Currently, two different approaches are routinely applied for the detection of GMOs, according to the specific target chosen: DNA based detection systems (mostly PCR and related techniques) and protein based techniques (mostly ELISA and related techniques).

PCR stands for Polymerase Chain Reaction. This method allows the selective amplification of specific DNA sequences and can generate millions of copies of a single DNA molecule in just a few hours. Thus in theory, PCR should be able to detect the presence of, for instance, genetically modified soybean or maize, even if these are present at extremely low levels. The method involves the following three basic steps: 1) DNA extraction and purification, 2) PCR amplification of the sample DNA, 3) electrophoretic analysis of PCR products. Each of these steps influences both the reliability and the sensitivity of the assay, and a good method will include proper controls that allow the correct interpretation of the results and to assess their reliability.

Lipp et al.[1] provided the results of a validation study using the PLCR technique, that involved a large variety of European Member States laboratories, for the detection of GMOs in flour from Roundup-Ready® soybeans and from Maximizer® maize. The method was developed by Pietsch et al.[2], and is based on the detection of the control sequences flanking the newly introduced gene, the 35S promoter and the *nos*-terminator. The materials used had been prepared by the Joint Research Centre Institute for Reference Materials and Measurements (IRMM).

The results of this validation demonstrate that this screening method is suitable for the detection of GMO in raw material derived from Roundup-Ready® soybeans and BT-176® maize. All laboratories unequivocally and correctly identified samples containing 2% of transgenic soybean or maize. Furthermore, the same 100 % correct classification was achieved by analyzing the 35S promoter in samples containing 0.5 % GMO (soybeans). Enzyme-Linked Immunosorbent Assay (ELISA) is a method of analysis that relies on specific interactions between antibodies and antigens to measure a variety of substances. The key reagents in ELISAs are the antibodies, which are soluble proteins produced by the immune system in response to infection by a foreign substance (called an antigen). In the case of detection of GMOs, the antigen can be the newly synthesized protein. Antigen and antibody binding, can be visualized by colorimetric or fluorometric reactions.

The validation of an ELISA method, highly specific for Roundup-Ready® soybeans has also been completed by Lipp et al.[3]. This method is based on the use of antibodies directed specifically against the protein CP4-EPSPS (5-enolpyruvylshikimate-3-phosphate synthase, an enzyme from *Agrobacterium sp.* strain CP4). It is this protein that confers resistance against the herbicide Roundup® to the Roundup Ready® soybean. The collaborative trial study has been carried out with 38 laboratories from 13 EU Member States and Switzerland to evaluate the performance of a diagnostic kit to determine the relative amount of GMO present in defined mixtures of finely ground dried soybean powder. For this study, each participating laboratory received a set of standard samples together with 16 blinded samples, as produced by the IRMM. The ELISA-kit is produced by a private company and contains all necessary reagents together with the detailed method description.

In total, 37 laboratories sent their results back to the co-ordinator. The experiment was designed with a 2% GMO level as an arbitrary threshold to test the feasibility to determine for each given sample whether it contained at least 2% RR soybeans (classified as positive) or less than 2% (classified as negative) CP4-EPSPS. This threshold was established on the basis of technical feasibility and the availability of test materials, and in no way was intended to anticipate future European Community legislation. Statistical data interpretation revealed that with 99% confidence any sample scoring as negative contains less than 2% GMO and any positive sample contains at least 0.85% GMO.

This methodological approach provides an important step in developing the necessary quantitative tools to confirm compliance in those cases where a threshold level for a given GMO in food is established. It was demonstrated here by using the only current commercially available reference material for the Roundup-Ready® soybean (i.e. lyophilised finely ground soybeans powder). Depending on the food fraction to be tested, this ELISA-kit may require a modified extraction procedure.

Although the results obtained are encouraging, further data, along with the production of appropriate reference materials, are needed to prove the validity of the test for other key food fractions (e.g., protein concentrates, protein isolates, and lecithin preparation).

References:

1. Lipp M., Brodmann P, Pietsch K, Pauwels J, Anklam E (1999) IUPAC Collaborative trial study of a method to detect the presence of genetically modified soybeans and maize in food raw material. JAOAC 82:923
2. Pietsch K, Waiblinger HU, Brodmann P, Wurz A (1997) Screening Verfahren zur Identifizierung "gentechnisch veraenderter Lebensmittel". Dtsch. Lebensm.Rdsch. 93:35
3. Lipp M, Anklam E, Stave J (2000) Validation of an immunoassay for the detection and quantification of Roundup-Ready soybeans in food and food fractions by the use of reference materials. JAOAC, (in print)

FAO/WHO Consultation on the Safety Assessment of Foods Produced Through Biotechnology

DAVID A. JONAS
Consultant
Wayborough Bungalow, Wayborough Hill
Minster, Ramsgate, Kent, UK CT12 4HR
44-1843-821745
44-1843-822566 fax
email: 101451.2353@compuserve.com

In the last decade there have been several meetings of international experts aimed at developing strategies for the food safety assessment of genetically modified organisms. The presentation reviews the main conclusions arising from these meetings.

The first Joint Food and Agriculture Organization/World Health Organization (FAO/WHO) Consultation in 1990 reviewed the issues that needed to be considered in the food safety assessment and the specific safety assessment considerations. The Consultation concluded that: use of newer techniques (of biotechnology) does not result in food which is inherently less safe than that produced by conventional ones; all food process changes require examination of safety implications, the scope of evaluation should depend on perceived concerns; evaluation should cover safety and nutritional value, conventional foods should be used as a standard; and, comparative data on the closest counterpart are critically important in the evaluation of a new food.

Subsequently in 1993, the Organization for Economic Cooperation and Development (OECD) published its strategy for the safety evaluation of foods derived from biotechnology. The main features of the strategy are: the most practical approach to the determination of safety is to consider whether (food) products of biotechnology are *substantially equivalent* to analogous conventional foods; account should be taken of processing, intended use and exposure; and, the *concept of substantial equivalence* embodies the idea that existing organisms used as food can be used as the basis for comparison when assessing the safety of a new food.

A second FAO/WHO Consultation in 1996 endorsed the conclusions in the two earlier reports and those of a number of more specialized workshops organized by OECD and WHO. The conclusions of the second Consultation included: food safety concerns from organisms produced by biotechnology are basically the same as those from other ways of altering the genome; substantial equivalence is a basic tool to establish the safety of a food produced by biotechnology relative to that of an existing food; substantial equivalence is established by demonstrating that the characteristics assessed are equivalent to those of the comparator within natural variations based on an appropriate analysis of the data; determination of substantial equivalence entails consideration of the molecular characterization, phenotypic characteristics and key nutrients and toxicants; analyzing a broader spectrum is generally unnecessary but should be considered if there are indications of unintended effects of the modification; and, application of the substantial equivalence approach may have limitations but it provides equal or increased reassurance of safety compared to conventional foods.

When evaluating the status of a genetically modified organism, three situations can be envisaged. If substantial equivalence can be demonstrated then, in accordance with the OECD and FAO/WHO conclusions, no further testing is necessary to show that the genetically modified organism is as safe as the conventional counterpart. If substantial equivalence can be demonstrated apart from certain well-defined differences then, in accordance with the OECD and FAO/WHO conclusions, these differences should be the focus of an appropriate safety evaluation. If the differences are shown to be safe then it is presumed that the genetically modified organism is as safe as the counterpart. If substantial equivalence cannot be demonstrated either through lack of a comparator or because the differences are considerable, this does not necessarily mean that the genetically modified organism is unsafe but that a more extensive safety evaluation will be required.

The comparative approach is, essentially, a formalization of the approaches adopted previously by the developers of new food organisms by more traditional techniques. Determining substantial equivalence status does two things. Firstly, it identifies whether there are any differences that need to be evaluated for safety. Secondly, it helps to provide reassurance that the genetic modification has gone according to plan and there are no unexpected changes that need to be taken into account in the safety evaluation. In determining substantial equivalence status, a number of parameters should be examined and these will usually include genetic makeup, phenotype (agronomic characteristics), and chemical composition.

There would appear to be widespread international agreement that the comparative approach embodied in the OECD concept of substantial equivalence is a practical approach to the food safety assessment of genetically modified foods and the same approach is also being applied to other novel foods. However, there is less agreement concerning more practical implementation of the concept and, as experience grows, a number of groups are developing further guidance. Issues such as the choice of comparator, the material compared, and the parameters examined, together with questions relating to the statistical interpretation of results need further clarification. The application of the concept to genetic modifications that are more complex than those currently under investigation also requires further consideration.

Fate of ingested DNA

DAVID E. BEEVER

Centre for Dairy Research [CEDAR]
Department of Agriculture
The University of Reading
Earley Gate, Reading RG6 6AT. United Kingdom.
44-0118-9316504 tel
email: d.e.beever@reading.ac.uk

The possible introduction of genetically modified crops has raised concerns regarding safety issues over the insertion of foreign genes into plant genomes using recombinant DNA technology. This concern has been heightened in the UK where several food related issues, including Bovine Spongiform Encephalopothy [BSE], *E. coli* 0157 and *Salmonella*, have increased the public's attitude towards food safety and systems of food production. With the advent of genetically modified (GM) crops, albeit at this stage on a non-commercial basis, appropriate regulatory bodies have been established. These include the Advisory Committee on Release to the Environment (ACRE) and the Advisory Committee on Novel Food and Processes (ACNP), with both accountable to the Ministry of Agriculture of Fisheries and Food (MAFF), while overall responsibility resides with the Department of Environment, Transportation and the Regions (DETR). Through DETR and MAFF, there is close dialogue with regulatory bodies in the European Commission.

Of the various concerns being expressed, those of most immediate relevance to man are summarized as 1) could the DNA of inserted or modified genes or their products cause adverse health effects in animals consuming GM crops, 2) could the DNA fragments or proteins be transferred to and accumulate in products [milk, meat, eggs] of animals fed GM crops, and 3) will consumption of agricultural crop materials or animal products derived from GM crops lead to adverse health effects in humans.

The principal aim of this paper will be to consider the fate of DNA following ingestion by farm animals and attempt to establish the potential for foreign DNA fragments to be incorporated into the chromosomes of animal cells. In this respect both non-ruminant and ruminant species will be considered, bearing in mind the major anatomic and physiological differences in the gastrointestinal tracts of such animals. Being simple-stomached, pigs and poultry consume diets based on cereal [e.g. wheat, maize] and protein [e.g., soya] grains with some by-product feeds, ruminant diets comprise significant amounts of forage [e.g., grazed and ensiled grass, ensiled maize] as well as cereal grains and proteins. By-product feeds [e.g., sugar beet feed, rape seed meal] are used to a much greater extent in ruminant diets, and this may have long term importance in the utilization of feed residues after industrial processing of GM crops. Preliminary studies by Chiter et al. [1] at Leeds University have considered the effects of processing feeds for farm livestock on DNA fragmentation, including grinding and milling [as in the production of concentrate feeds] and heat treatment, with or without the application of high- or low-pressure steam. It was concluded that grinding and milling, using a range of experimental conditions, failed to affect the average molecular weight of the isolated DNA, which in all instances was 20kb or greater. Dry heat

treatment of wheat showed that DNA remained intact at temperatures of 90°C or less, but heat at 93°C applied for between 5 and 15 minutes resulted in some DNA fragmentation [fragment size; 2500 to 50bp]. However, at temperatures of 95°C or above, complete degradation of the DNA was established. Low and high pressure steam for various periods also resulted in DNA degradation provided the overall temperature was 95°C or above, with lower temperatures resulting in incomplete degradation. Subsequent examination of commercial feed stuffs confirmed that those which had been extensively processed [expelled linseed, soybean meal, extracted rapeseed] contained little no intact DNA [<100bp] but the ensiling of forage had no effect on the size of native DNA.

Following ingestion, part of the DNA will be digested within the oral cavity, by enzymatic catalysis with DNase I which is secreted by the salivary glands, and has an optimal activity at neutral pH. DNase II has been recently characterized and primarily functions in lysosomes within phagocytes, as well as fragmenting genomic DNA during apoptosis. In ruminants, nucleases are secreted by the microbial population present in the rumen, and McAllan [2] estimated more than 85% of the plant DNA consumed by ruminants was reduced to nucleotides or smaller fragments before entering the duodenum. Additionally the low pH of stomach contents in monogastrics or the abomasum in ruminants is known to remove adenine and guanine bases from naked DNA fragments in food, thus destroying the genetic information contained therein. A small portion of plant or microbial DNA remaining in the digests entering the intestines may be absorbed through the intestinal mucosal epithelia, especially if the epithelial surface has been previously damaged, but most of this DNA will be phagocytized by tissue macrophages or dendritic cells.

For the purpose of this review, a total of 35 animal feeding studies to compare GM and non GM crops have been identified. Different animal species [chickens, pigs, beef cattle, dairy cattle, sheep and catfish] crops [maize, soyabean, rapeseed and forages] and genetic inserts have been used to examine the possible occurrence of transgenic DNA and/or proteins in the products [milk, meat, eggs] of animals given diets containing GM crops. With poultry, comparison of maize grain with or without the Bt gene [insect resistance] fed for 14 days showed no occurrence of the Bt protein in white or dark muscle, liver or egg whites and yolks, and no adverse health effects. Beef cattle studies failed to identify either the Bt gene or Bt protein in muscle, spleen and milk, a dose rate study with male and female broilers fed maize grain containing the CP4 EPSPS protein [herbicide tolerance] failed to demonstrate any changes in growth rate compared with control chickens up to the highest inclusion rate of the transgenic protein. Other studies with conventional v GM soya have failed to establish any differences in amino acid composition, and similar findings have been reported for GM sugar beet and cotton. An initial concern over possible elevations in tryptophan levels, and the increased predisposition of animals to fog fever have not been substantiated. Meanwhile, a study with dairy cows fed Bt or conventional forage maize failed to detect any differences in feed intake, milk yield and composition or udder health, and further studies have shown no effects on diet digestibility or the processes of digestion in the rumen.

Despite such encouraging findings, to date no studies have reported on the sequential digestion of transgenic DNA through the digestive tract of farm livestock. Such studies are urgently required but analytical uncertainties with respect to the detection of transgenic DNA will make this a daunting task. A dairy cow consuming 24kg feed dry matter/d with 60% provided as GM maize grain or maize silage, was estimated to have a total DNA intake of 608mg/d, with 2.6 g/d

only as transgenic DNA [3]. This indicated GM DNA to be less than 0.00043% of total DNA with a ratio of transgenic DNA native DNA of 1:234,000. Suitable techniques exist for the acquisition of digesta samples from different parts of the alimentary tract of both ruminants and non-ruminants without need to slaughter the animal, but the challenge remains over the analytical uncertainty with respect to the identification and quantification of transgenic DNA. This must represent an *a priori* research issue, required to unequivocally demonstrate if transgenic DNA fragments are or are not capable of being incorporated into animal cells, continuing to be vigilant with respect to the possible occurrence of foreign proteins in the products of animals consuming GM crops. Occasional reports in the literature have suggested the occurrence of plant DNA fragments in white blood cells of a dairy cow fed a diet containing GM soya, and fragments of microbial DNA in mouse white blood cells when the DNA source was fed into the gastrointestinal lumen. However, doubt exists over these findings in relation to the use of unmethylated DNA as the test substance, when DNA in normal plant and animal cells would normally expected to be methylated.

These issues will be discussed in more detail within the presentation, and recommendations for future studies will be considered.

References:

1. Chiter A, Blair GE, Forbes JM (1998) Effects of processing on DNA fragmentation in feedstuffs. Report to MAFF, Project NO. CTF9702
2. McAllen AB (1982) The fate of nucleic acids in ruminants. Proceedings of Nutrition Society 41:309-317
3. Beever DE, Kemp CF (2000) Safety issues associated with the DNA in animal feed derived from genetically modified crops. Nutrition Abstracts and Reviews (Human and Animal Nutrition) (in press due March 2000)

Assessing for Toxicity Associated With Foods Produced Through Biotechnology

KARL-HEINZ ENGEL
Technical University of Munich, Food Technology
Am Forum 2
D-85350 Freising-Weihenstephan, Germany
49-81-61-714250
49-81-61-714259 fax
k.h.engel@lrz.tu-muenchen.de

In most cases, the insertion of a foreign gene into a plant via recombinant DNA techniques results in the expression of the corresponding protein, thus conferring a specific target trait to the host organism. Accordingly, the assessment of such foreign proteins plays a key role in the safety assessment of foods derived from genetically modified (GM) plants. If compositional analyses demonstrate the GM plants to be "substantially equivalent" to conventionally bred crops, except for the presence of the newly introduced protein, the subsequent safety assessment should be focused on the potential toxicity and allergenicity of the protein. Examples for commercialized protein/crop combinations for which this strategy has been applied are the 5-enolpyruvyl-shikimate-3-phosphate synthase (EPSPS) in glyphosate-tolerant soybeans, the phosphinothricin-acetyltransferase in glufosinate-tolerant rape, the CryIA (b) protein from *Bacillus thuringiensis* in insect-resistant maize, and the neomycin-phosphotransferase II in tomato.

Using the *Bacillus thuringiensis* (Bt) protein as an example, this contribution will examine protocols used to determine whether an introduced protein is "as safe as" proteins already present in foods [1-4].

Proteins are essential parts of the human diet. The vast majority of dietary proteins are rapidly degraded in the course of the digestion process and do not cause adverse effects when eaten. However, there are a few exceptions which should be noted. There are examples of bacterial toxins causing effects ranging from gastrointestinal discomfort to life threatening dehydration, paralysis and death. Soybeans are known to contain trypsin inhibitors which act as antinutrients and must be deactivated by cooking prior to digestion. Lectins/ hemagglutinins are glycoproteins that can also interfere with the bioavailability of nutrients.

The comparative approach to the safety assessment of proteins newly present in a crop includes data on:

- the history of the donor organism used as source for the gene,
- the expression level of the newly introduced protein in the host plant,
- the resulting dietary human exposure.

A major focus is on the comparison of the biochemical, physicochemical and immunological properties of the newly introduced proteins to known protein toxins, antinutrients or allergens. The following criteria have to be assessed:

- structural and functional properties/mode of action,
- amino acid homology to known mammalian protein toxins,
- stability under simulated mammalian digestion conditions,
- toxicity studies.

In most cases, the amounts of the newly expressed proteins in the GM plants are so low that their isolation in amounts sufficient for subsequent tests is not feasible. If GM microorganisms are used to produce the protein in higher amounts special care has to be taken in order to establish the chemical and functional equivalence of bacterial and plant protein.

The newly introduced proteins in GM plants presently in commerce are degraded under simulated mammalian digestion conditions as rapidly as common plant proteins. Acute oral gavage studies as well as short term (28 days) feeding studies did not show any adverse effects.

If the difference between a food produced through application of recombinant DNA techniques and existing foods cannot be solely focused on the presence of one or a few defined components (e.g., an additionally expressed protein), comprehensive toxicological and nutritional tests would be required to demonstrate its safety.

It is generally recognized, that the applicability of classical toxicological assessment procedures developed for single chemical substances, such as food additives, is limited. Safety and wholesomeness studies with whole foods have to be carefully designed in order to avoid nutritional imbalances causing artifacts and uninterpretable results. Alternative approaches, e.g., profiling techniques, *in vitro* assays, use of early biomarkers for toxicity, are explored.

References:

1. Fuchs, R.L. et al. Purification and Characterization of Microbially Expressed Neomycin Phosphotransferase II (NPTII) Protein and its Equivalence to the Plant Expressed Protein. Bio/Technology 11, 1537 (1993)
2. Lavrick, P.B. et al. Safety Assessment of Potatoes Resistant to Colorado Potato Beetle. in: Engel, K.-H., Takeoka, G.R., Teranishi, R. (Eds.) Genetically Modified Foods - Safety Aspects. American Chemical Society Symposium Series 605, Washington, DC, 1995, 148-158
3. Noteborn, H.P.J.M. et al. Safety Assessment of the *Bacillus thuringiensis* Insecticidal Crystal Protein CRYIA(b) Expressed in Transgenic Tomatoes. in: Engel, K.-H., Takeoka, G.R., Teranishi, R. (Eds.) Genetically Modified Foods - Safety Aspects. American Chemical Society Symposium Series 605, Washington, DC, 1995, 134-147
4. Sanders, P.R. et al. Safety Assessment of Insect-Protected Corn. In: Thomas, J.A. (Ed.) Biotechnology and Safety Assessment, 2nd ed., Taylor & Francis, 1998, 241-256

Assessing the Allergenic Potential of Food Produced Through Biotechnology

SAMUEL B. LEHRER
Research Professor of Medicine
Adjunct Associate Professor
of Microbiology and Immunology
Adjunct Professor of Environmental Medicine

Tulane University Medical Center
Department of Medicine, Section of Allergy & Clinical Immunology
1700 Perdido St., Room 321 (SL-57)
New Orleans, LA USA 70112
504-584-3677
504-584-3686 fax
email: sblehrer@tmcpop.tmc.tulane.edu

Allergies to foods are a significant public health concern throughout the world. Nearly 2% of adults and 4% to 6% of children have allergies to foods. Food allergies are defined as immune-mediated reactions to antigenic molecules present in foods. The immune response is mediated by immunoglobulin E (IgE), a class of antibody that is uniquely involved in allergic reactions. Antigenic molecules, or allergens, typically are proteins that stimulate IgE responses in certain individuals through as yet undetermined mechanisms. Food allergies are distinct from gluten sensitive enteropathy (celiac disease) and food intolerances which are due to nontoxic, nonimmune reactions to foods. Food allergy symptoms can range from mild discomfort to life-threatening anaphylactic shock.

More than 90% of food-induced allergic reactions observed in children and adults can be attributed to exposure to eight foods or food groups. These include eggs, fish, shellfish, milk, peanuts, soybeans, tree nuts, and wheat. Virtually all allergens are proteins; yet of the enormous numbers of proteins occurring in foods, only a very few are allergenic and only in certain people. Most known protein allergens are stable to digestion and processing, and many of the major allergens are generally major proteins in the allergenic food. Many of the known food allergens have been molecularly cloned and characterized.

Most food allergens share several common properties. Food allergens are proteins or glycoproteins with an acid pI, and generally are in the molecular range of 10,000 to 80,000 daltons. They are usually fairly resistant to industrial processing, heating and cooking as well as showing resistance to the digestive enzymes of the gut. It is felt that these properties may aid in the allergenicity of those molecules. It has been demonstrated that substantial cross-reactivity can occur among foods and between foods and other allergens. This can occur among closely related foods (crustacea and legumes) and foods and seemingly unrelated substances (pollens or latex with fruits and vegetables).

Modern biotechnology provides methods for the identification and selection of genes encoding for specific proteins. A gene from any source (e.g., microorganism, plant, or animal) that confers a specific trait can be selectively and precisely introduced or transferred into the genome of another organism where the expression of the transferred gene will confer that trait on the host organism. This type of genetic engineering has been used to introduce genes into various microorganisms and plants that are sources of foods and food components.

Introduced traits include insect and virus resistance, herbicide tolerance, and changes in composition or nutritional content. Typically the amount of protein expressed by the introduced gene is small and, in some cases, inactivation of a native gene that results in the absence of a specific protein yields the desired trait (e.g., the tomato genetically engineered to delay ripening). This technology has also been used to reduce the expression of a major allergen found in rice.

Because of concern that a protein encoded by an introduced gene may have allergenic properties, an expert scientific panel was convened to develop scientific approaches to assess the allergic potential of foods derived from genetically engineered crop plants. The initiative resulted in the development of a report that addressed the cell biology, symptoms, and treatment of food allergy; developed a catalog of allergenic foods, and characterized major food allergens from the perspective of the plants and methods used to genetically modify food crops. This information served as the background for the development of a decision tree for assessing the allergic potential of foods derived from genetically engineered plants (Critical Reviews in Food Science and Nutrition in 1996). Eight commonly allergenic foods and more than 160 less commonly allergenic foods were identified. The report summarized the frequency of allergy associated with each, the symptoms, and the methods and outcomes of confirmatory testing (when performed). Based on this information, it was recommended that food biotechnologists should avoid the transfer of known food allergens. Genes transferred from sources known to be allergenic should be assumed to encode for an allergen, until proven otherwise. In addition, the allergenic potential of all introduced proteins should be assessed. For genetically engineered foods entering the marketplace, consumers should be informed by appropriate labeling that the food contains known or suspected allergens.

The safety assessment decision tree begins with the characterization of the source of the introduced gene. Is it from a commonly allergenic or less commonly allergenic source or does the source have no history of allergenicity? If there is no history of allergenicity associated with the gene source, its protein product should be subjected to amino acid sequence analysis. The sequence should be compared with those of the more than 180 known allergens that have been deposited into various electronic databases, e.g., GenBank, EMBL, SwissProt, PIR. If this evaluation fails to provide evidence suggesting allergenic potential, the protein should then be subject to physical/chemical testing to establish its stability to digestion and processing. Proteins that are labile to digestion are unlikely to be allergenic. A food containing a protein for which there is no concern based on amino acid sequence or on chemical analysis would not be considered to have allergenic potential.

If the protein originates from a known allergenic source or its amino acid sequence analysis raises concern about the allergenic potential of the molecule, the protein is then evaluated to determine whether it is recognized by serum from individuals with known food allergies. Standard statistical methods can be used to estimate the number of sera samples that need to be tested to have a high probability (95.5% to 99.9%) of detecting both major and minor allergens. Equivocal results would necessitate conducting stability testing of the protein, while negative results would indicate that the protein's allergenic potential is negligible. If the protein product of an introduced gene exhibits similarities to known allergens and/or yields positive results in serological analysis, the appropriate regulatory authority should be consulted to determine if and what further testing might be performed.

Genetically engineered foods containing those proteins that tested positive in the serologic analysis should be labeled as to the protein's source. In addition, for proteins considered to be commonly allergenic based on the serological analysis, confirmatory skin prick testing is recommended. If these tests are positive, double-blind placebo-controlled food challenge testing should be conducted in accord with Institutional Review Board-approved protocols for the use of human subjects. Foods containing proteins confirmed as allergenic in the skin prick and/or food challenge studies could be brought to market with appropriate labeling, although foods confirmed to be allergenic by challenge testing would likely have only a very limited place in the market.

The assessment of the allergenicity of proteins from unknown allergen sources continues to be a challenge to the food industry. All evidence suggests that for proteins introduced into foods from sources with no history of allergenicity, that have no amino acid sequence similarities to known food allergens, that are rapidly digested, and that are expressed at low levels relative to the expression of major allergens, there is essentially no concern about their allergenic potential. The recommended approach, by sequence comparison and enzymatic digestion resistance, is based on current technology. Future efforts must be directed at refining this technology through continued allergen identification and characterization to increase the databank of protein sequences, refinement of the properties that define the amino acid sequence of allergenic epitopes to develop more precise amino acid sequence screening criteria, and development of an animal model that can recognize food allergens in a manner similar to that which occurs in human disease.

List of Recommended Reading:

1. Metcalfe DD, Sampson HA, Simon RA. Food Allergy: Adverse Reactions to Foods and Food Additives, Second Edition. Blackwell Science, 1996.
2. Lehrer SB, Horner WE, Reese G. Why are some proteins allergenic? Implications for biotechnology. Critical Review in Food Science and Nutrition 1996;36(6):553-564.
3. Taylor S, Lehrer SB. Principles and characteristics of food allergens. In: Critical Reviews in Food Science and Nutrition, Allergenicity of Foods Produced by Genetic Modification. 1996;36(S):S91-S118.
4. Bush RR, Hefle SL. Food allergens. In: Critical Reviews in Food Science and Nutrition, Allergenicity of Foods Produced by Genetic Modification, IFBC/ILSI 1996;36(S):S119-150.
5. Metcalfe DD, Astwood JD, Townsend R, Sampson HA, Taylor SL, Fuchs RL. Assessment of the allergenic potential of foods derived from genetically engineered crop plants. In: Critical Reviews in Food Science and Nutrition, FM Clydesdale, Ed., Allergenicity of Foods Produced by Genetic Modification, IFBC/ILSI 1996;36:S165-S185
6. Lehrer SB, Taylor S, Hefle S, Bush R. Food Allergens. In: Allergy and Allergic Diseases. A.B. Kay, Ed., Blackwell Scientific Publications, London, UK 1997;961-980.
7. Lehrer SB, Reese G. Biosafety of genetically modified plants and microorganisms: Recent developments in approaches to evaluation of allergenicity. In: The Fourth International Symposium on the Biosafety Results of Field Tests of Genetically Modified Plants and Microorganisms. 1997:1-12.
8. Reese G, Lehrer SB. Toxicants in food: Food Allergens. In: Nutrition and Chemical Toxicity. C. Ioannides, Ed., Wiley, England 998:81-114
9. Lehrer SB, Reese G. Food Allergens: Implications for biotechnology. In: Biotechnology and Safety Assessment, 2nd Ed., J Thomas Ed., Taylor and Francis, 1998:127-150.

Regulatory Aspects of Foods Produced Through Biotechnology

KAREN E. MC INTYRE

Office of Food Policy Integration
Health Protection Branch, Health Canada
Tunney's Pasture
Ottawa, Ontario, Canada. K1A 0L2. P.L. 2203G3
613-957-0349
613-952-6400 fax
email: Karen_McIntyre@hc-sc.gc.ca

Introduction

Under the *Food and Drugs Act and Regulations*, Health Canada is responsible for provisions related to public health, food safety and nutrition. Health Canada's responsibility regarding food is to establish science-based policies and standards ensuring that all foods, including those foods derived from biotechnology, are safe and nutritious. The department has recently established a new regulation (Novel Foods Regulation, October, 1999) that defines the concept of a "novel food" and requires notification prior to the sale or advertising for sale of such products in Canada. This permits Health Canada to conduct a thorough safety assessment for each product. Novel foods include, but are not limited to, food products derived from biotechnology. Since 1994, forty-three genetically modified plant products have completed the regulatory process in Canada.

Canadian Regulatory Framework for Biotechnology Products and Departmental/Agency Responsibilities

In 1993, a Canadian Federal Regulatory Framework for the regulation of biotechnology products was announced by the Government. The framework is intended to ensure that the benefits of biotechnology products and processes are realized in a way that protects health, safety, and the environment. The principles adopted by the regulatory departments include:

- maintaining Canada's high standards for protecting the health of Canadians and the environment;
- using existing laws and regulatory departments to avoid duplication;
- developing clear guidelines for evaluating biotechnology products that are in harmony with national priorities and international standards;
- providing a sound, scientific knowledge base on which to assess risk and evaluate products
- ensuring that the development and enforcement of Canadian biotechnology regulations are open and include consultation, and
- contributing to the prosperity and well being of Canadians by fostering a favorable climate for investment, development, innovation and the adoption of sustainable Canadian biotechnology products and processes.

Current regulatory authority for food products derived from biotechnology falls under several federal departments and agencies including the following:

Health Canada is responsible for assessing the human health safety of foods, drugs, cosmetics, medical devices and pest control products.

The Canadian Food Inspection Agency (CFIA) shares responsibility for the regulation of products derived from biotechnology including plants, animal feeds and animal feed ingredients, fertilizers and veterinary biologics. For genetically modified crop plants, the CFIA assesses the potential risk of adverse environmental effects; authorizes and oversees import permits, confined trials, unconfined release and variety registration.

As of September 1, 1997, new products of biotechnology including foods, drugs, cosmetics and medical devices are regulated by *Environment Canada* under the New Substances Notification Regulations of the Canadian Environmental Protection Act (CEPA). CEPA can be described as a "safety net" because new products of biotechnology not covered by any other federal statutes are assessed for adverse human health or environmental effects by this department before being released into the Canadian environment. Products that fall under this legislation include microorganisms used in bioremediation, waste disposal, mineral leaching or enhanced oil recovery.

The Canadian Biotechnology Advisory Committee

A cornerstone of the renewed Canadian Biotechnology Strategy is a commitment to open, transparent regulatory processes and public participation surrounding biotechnology issues. Health Canada, under its mandate for health and safety, reviews products using a science based assessment process. The Canadian Biotechnology Advisory Committee (CBAC) will advise on broader policy directions but it will not be involved in specific regulatory decisions regarding new products. Issues that will be considered by CBAC include those social, ethical, economic, scientific, regulatory, environmental and health aspects of biotechnology.

CBAC is an expert, arm's-length committee formed to advise Ministers with responsibilities in the area of biotechnology on those related issues. This committee will work to raise the public's awareness of the regulatory processes and provide an ongoing forum for the public to voice their views.

Expert Scientific Panel

An independent expert science panel has been established (February, 2000) to examine future developments in biotechnology. The panel will advise Health Canada, the Canadian Food Inspection Agency and Environment Canada on the science capacity and related regulatory aspects that the federal government will require to continue to ensure the safety of new products being developed through the application of biotechnology into the 21st century.

Canadian Regulatory Process

The sale of food in Canada is controlled by several regulatory mechanisms under the Canadian Food and Drugs Act and Regulations. These mechanisms include pre-market notification, pre-market approval and food standards. However, a variety of new foods are being developed and introduced into the Canadian marketplace. These foods may originate from new or unusual sources, be produced using new processes and include foods derived through genetic modification. Pre-market notification is the approach that is applied to foods derived through biotechnology. This approach requires the submission of information regarding the product in question to the Health Protection Branch of Health Canada so that a determination can be made with respect to its acceptability as food prior to sale.

Health Canada has recently promulgated a new piece of legislation, the Novel Foods Regulation (Part II of the Canada Gazette, October, 1999) under the Food and Drugs Act in order to address the safety of such new foods and food ingredients. Foods derived from plants that have been genetically modified trigger the notification requirement when a new characteristic has been introduced or the composition of the product has been substantially altered.

In addition to the proposed Novel Foods Regulation, the Health Protection Branch has issued Guidelines for the Safety Assessment of Novel Foods. These Guidelines are based upon the Organization for Economic Cooperation and Development (OECD) approach of substantial equivalence. Substantial equivalence embodies the concept that if a new food or food component is found to be substantially equivalent to an existing food or food component, it can be treated in the same manner with respect to safety. These Guidelines are flexible in that they allow the waiver of data requirements that are not relevant to the product under consideration. This is important considering the broad range of products that are being developed.

The approach that we use is sequential. It begins with a review of the information available on the development of the modified plant itself followed by a characterization of the actual product. Then, dietary exposure to the product is considered. Lastly, where relevant, we consider nutritional and toxicological data. In the case of food components consisting of single chemical products or well-defined mixtures, procedures for safety assessment are relatively straight forward. In the case of undefined mixtures or whole foods the safety assessment is more complex. The review may include a toxicological and nutritional assessment of the product that may include a combination of in-vitro and in-vivo tests.

The safety assessment proceeds until a determination is made as to whether the product is as safe as its traditional counterpart. Once reviewed, these foods enter the marketplace in the same manner as traditional food products, and remain subject to the same post-market standards applicable to all foods in Canada.

References

1. Health Canada. Guidelines for the Safety Assessment of Novel Foods, Food Directorate Publication, Health Protection Branch, Health Canada: Ottawa, 1994.

2. Organization for Economic Cooperation and Development. Safety Evaluation of Foods Derived by Modern Biotechnology: Concepts and Principles, OECD: Paris, 1993.

For Additional Information:

Health Canada's website: www.hc-sc.gc.ca/food-aliment
Expert Scientific Panel: www.rsc.ca/english/index.html
Canadian Biotechnology Advisory Committee: www.cbac.gc.ca

Biographical Sketch

YUZO HAYASHI

Yuzo Hayashi is visiting professor, Kitasato University School of Pharmacy, Tokyo, Japan. He served on the faculty of medicine at the Tokyo Medical and Dental University, where he was awarded his M.D. and Ph.D. degrees. Prior to his present position, Dr. Hayashi was a senior investigator at the Shionogi Research Institute, Osaka; project associative at the Department of Pathology, University of Wisconsin Medical School, Madison; director at the Department of Pathology and Toxicology, Food and Drug Safety Center, Hatano Research Institute, Hatano, Kanagawa; and director, Biological Safety Research Center, National Institute of Hygienic Sciences, Tokyo.

Dr. Hayashi is a member of the Japanese Cancer Association, Japanese Society of Pathology, Japanese Society of Toxicology, European Society of Toxicology, and the Society of Toxicologic Pathologists. Dr. Hayashi serves on a number of international and domestic committees, including the Joint FAO/WHO Expert Committee on Food Additives, for which is an advisor.

Biographical Sketch

DARRYL MACER

Darryl Macer is currently Associate Professor at the Institute of Biological Sciences, University of Tsukuba, Ibaraki, Japan, where from 1990-1995, he held the position of Foreign Professor. He teaches and researches bioethics, both environmental and medical ethics. He is director of the Eubios Ethics Institute, based in New Zealand and Japan, which includes an international network on bioethics and genetics. He is also director of the IUBS Bioethics program, a member of the HUGO Committee on Ethics, and a Board member of the International Association of Bioethics.

Dr. Macer completed a Bachelor of Science with first class honors in Biochemistry from Lincoln College, University of Canterbury, Christchurch, New Zealand in 1983. He received his Ph.D. in biochemistry at the MRC Laboratory of Molecular Biology, and Trinity College, University of Cambridge, England. In 1988-1989 he was a Cambridge Commonwealth Trust Prince of Wales Scholar.

Dr. Macer is a founding member of the UNESCO International Committee on Bioethics (1993-1998). He has published more than 10 books and 100 papers on bioethics.

Biographical Sketch

LUIS HERRERA-ESTRELLA

Dr. Luis Herrera-Estrella was born in Mexico City. He graduated with a B.Sc. degree in Biochemical Engineering from the Mexican National Polytechnic Institute in 1978. In 1984, he received a Ph.D. from the State University in Gent, Belgium.

Dr. Luis Herrera-Estrella has made important contributions to the field of plant molecular biology, especially in the study of gene regulation and in the development of gene transfer methods. While still working as a Ph.D. student he published the first report on the genetic manipulation of plant cells. He also pioneered the development of dominant selectable markers and the use of reporter genes for plant systems, which later became the two most important tools to develop gene transfer systems for economically important crops. His current research is primarily focused to the development transgenic plants better adapted to marginal soils.

Dr. Herrera-Estrella has been awarded several national prizes, among them the award in biology from the Mexican Academy of Sciences and the Lazaro Cardenas medal from the National Polytechnic Institute. He has also been honored with international awards such as the Minuro and Ethel Tsutsui Distinguished Graduate Research Award of the New York Academy of Sciences and the Javed Husain prize for young scientists from UNESCO.

Biographical Sketch

W. CLIVE JAMES

Dr. Clive James is Chair of the International Service for the Acquisition of Agri-biotech Applications (ISAAA), USA. ISAAA is a non-profit organization established to facilitate the acquisition and transfer of agricultural biotechnology applications from the industrial countries, particularly proprietary technology application from the private sector for the benefit of the developing world.

He has served as senior agricultural biotechnology advisor to the Canadian Bilateral Aid Agency (CIDA, FAO, and consulted for many international development agencies including the UNDP and World Bank.

Biographical Sketch

ELKE ANKLAM

Dr. Elke Anklam is Head of the Food Products and Consumer Goods Unit of the Institute for Health and Consumer Protection of the European Commission's Joint Research Centre in Ispra, Italy. She received a food chemistry degree in 1980 from the University of Münster, Germany, and her Ph.D. degree in organic chemistry in 1984 from the University of Hamburg, Germany.

Dr. Anklam was grant holder for a post-doctoral position (Alexander von Humboldt Grant) in the University Louis Pasteur of Strasbourg, France in 1985. From 1986-1989 she was a grant holder for a position in the Hahn-Meitner Institute in Berlin, Germany, and professor for food chemistry at the Engineering School of Fulda, Germany, from 1990–1991.

Dr. Anklam is member of the Society of German Chemists (GDCh), AOAC International, the IUPAC Food Commission and of the advisory board of the journal *European Food Research and Technology*. She is author or co-author of more than 150 articles, abstracts and papers.

Biographical Sketch

DAVID A. JONAS

David Jonas is a chemist by training and he received his PhD in organic chemistry from the University of Wales in 1969. After several years in several research posts in industry, he joined the Food Science Group of the UK Ministry of Agriculture Fisheries and Food (MAFF) in 1975 where he became Head of the Novel Foods Branch. For ten years he was Scientific Secretary of the UK Advisory Committee on Novel Foods and Processes and was responsible for advising Ministers on the safety of a wide range of novel foods including those obtained from genetically modified plants.

Dr. Jonas was intimately involved in the discussions leading to the adoption of the EU regulation on Novel Foods and has worked with the European Commission's Scientific Committee for Food in developing guidelines for the safety assessment of novel foods. He has been a member of many national and international committees responsible for food safety and has advised various UN agencies on procedures for the safety evaluation of foods obtained by biotechnology.

Dr. Jonas retired from MAFF in 1995 and is now an independent consultant advising on scientific and regulatory aspects of novel foods and food biotechnology.

Biographical Sketch

DAVID E. BEEVER

Dr. David Beever is Director of the Centre for Dairy Research (CEDAR), Department of Agriculture, The University of Reading, in Reading, England. He received his B.Sc. (with honors) in agricultural biochemistry, from Dunelm, and his Ph.D. in the same subject from Newcastle upon Tyne.

From 1969-1992, Dr. Beever was associated with the Grassland Research Institute, Berkshire and Head of the Ruminant Nutrition and Metabolism Department from 1985-1992. In 1992, Dr. Beever was Chair of Animal Science at the Swiss Institute of Technology, Zurich.

Dr. Beever's research interests include nutrition of ruminant livestock initially with sheep, then growing cattle and more recently involved with dairy cows. Specific interests include: digestive fate of ingested nutrients in the reticulo-rumen with particular reference to the fate of dietary proteins and the synthesis of microbial biomass; the post-ruminal fate of nutrients entering the small intestine and gut metabolism of glucose and amino acids; hepatic metabolism of nutrients and the impact on the supply of nutrients to peripheral tissues; factors affecting the partition of nutrients between milk and body tissue synthesis; overall energy and protein metabolism; manipulation of product composition by nutritional and endocrinological means; mathematical modeling of biological processes and development of models to describe nutrient requirements and responses; recent interests in reductions in methane emissions from ruminant livestock in relation to global warming and the potential of genetically modified crops to improve food security and reduce the environmental consequences of intensive livestock production.

Dr. Beever has authored or co-authored almost 400 scientific papers, conference proceedings and book chapters.

Biographical Sketch

KARL-HEINZ ENGEL

Dr. Karl-Heinz Engel is professor and chair of the General Food Technology unit at the Technical University of Munich, Germany. He received a food chemistry degree in 1977 from Karlsruhe University and his Ph.D. degree in 1984 from the Technical University of Berlin. His major fields of research are the safety assessment of novel foods and the development of methods for the detection of food modified by means of genetic engineering.

For four years Dr. Engel served as research officer and head of the Novel Food Section of the German National Food Agency (BgVV) in Berlin. He is a member of the Working Group on Novel Foods of the German Research Council (DFG) and was involved as an ad hoc-expert in the elaboration of the "Opinions on the Assessment of Novel Foods" developed by the Scientific Committee for Foods (SCF) of the European Commission.

Dr. Engel is author or coauthor of more than 70 articles, abstracts, book chapters, and papers, co-editor of several books, and coeditor of the journal *Food Reviews International.* He is member of the Society of German Chemists, the Society of German Food Technologists, and the American Chemical Society.

Biographical Sketch

SAMUEL B. LEHRER

Dr. Samuel B. Lehrer is currently a Research Professor of Medicine, Adjunct Associate Professor of Microbiology and Immunology, Adjunct Professor of Environmental Health Sciences, and Member, Center for Bioenvironmental Research at Tulane University School of Medicine. Dr. Lehrer has been associated with Tulane since 1975.

Dr. Lehrer graduated from Upsala College (1966) and received his Ph.D. from Temple University, School of Medicine in 1971. He served as a Postdoctoral Fellow at Scripps Clinic and Research Foundation in LaJolla, California.

His research interests are in the areas of biotechnology and food allergy, immunopathogenesis of food allergy, genetically modified foods, control mechanisms in IgE antibody production, environmental fungal allergens, effects of environmental pollutants on respiratory disease, and occupational allergies. He has published or collaborated on over 400 articles, book chapters, and abstracts on these topics. Dr. Lehrer has lectured and participated in seminars, symposia and workshops around the world on a variety of subjects. Currently, he serves as an editorial board member for the *International Archives of Allergy & Immunology.* He participates as a reviewer for several scientific journals such as the *Journal of Biological Chemistry, the Journal of Pediatrics, Chest,* and *The European Journal of Allergy and Clinical Immunology.* Dr. Lehrer is currently the recipient of a research grant award, "Demonstration and Characterization of Corn Induced Allergic Responses". He is a member of the American Academy of Allergy, the American Association for the Advancement of Science, the Institute of Food Technologists, and the Collegium Internationale Allergologicum.

Biographical Sketch

KAREN MC INTYRE

Karen McIntyre is the Acting Associate Director in the Bureau of Food Policy Integration, Food Directorate, Health Canada. Her responsibilities include the development of policy related to foods derived from biotechnology. Karen is Chair of the Food Directorate Working Group on Biotechnology which is responsible for the development of Guidelines for the Safety Assessment of Novel Foods.

Karen is involved international activities aimed towards the harmonization of approaches to safety assessment of foods derived from biotechnology. She currently heads the Canadian Delegation of the Organization for Economic Cooperation and Development—Task Force on Novel Foods and Feeds.

She has a B.Sc. and an M.Sc. in microbiology from the University of Guelph.