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REPORT OF THE TASK FORCE FOR THE SAFETY OF NOVEL FOODS AND FEEDS

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EXECUTIVE SUMMARY

1. The techniques of genetic modification are having a major impact on the development of new varieties of crops, vegetables and fruits, starting with major trading commodities such as maize, rice, soybean – whether for human consumption or as livestock feed. There are systems in place in the majority of OECD countries for the safety assessment of genetically modified (GM) foods and feeds. Most participants in the OECD's **Task Force for the Safety of Novel Foods and Feeds** work in national ministries or agencies whose responsibility is to ensure consumer safety.

2. Regulatory bodies in some of the OECD countries have approved approximately 40 GM foods, and more approvals are expected in the near future. The main issues addressed by food safety assessors are the implications on human health, including the impact of genes which code for antibiotic resistance, the identification of toxicological or allergenic properties of new food components introduced through genetic modifications; and nutritional impacts.

3. Safety assessors use a number of internationally established scientific principles, including *substantial equivalence*, in their work. Although substantial equivalence is not the only such principle, there is detailed description given in the report, partly because it was a concept elaborated at the OECD, and partly because there is high level of interest in the topic at the present time.

4. Much experience has been gained in the safety assessment of the first generation of foods derived through modern biotechnology, and those countries that have conducted assessments are confident that those GM foods they have approved are as safe as other foods. Nevertheless, some have raised concerns about the adequacy of existing test methods. For example, more standardised procedures to establish substantial equivalence are needed, as well as improved methods to assess the allergenicity of proteins new to the diet (together with their digestibility and toxicity) taking regional differences in diet into account. In this respect the Task Force has recognised the need for capacity-building to assess the safety of novel foods as a priority activity. This is the reason why work continues internationally on the development of Consensus Documents on individual crop species. **Food and feed safety assessors should address these issues. In this context it is important to note that the concept of substantial equivalence is being addressed in a number of international fora and will need to be kept under review.**

5. Looking at regional and national experience, the report states that there are differences in risk analysis among OECD countries. One example is that the application of the concept of substantial equivalence is not necessarily identical in regional and national legislation. It is evident that differences exist in risk management and the way other legitimate factors (such as socio-economic and ethical concerns) are taken into account.

6. A major issue for the future is the development of strategies for managing the safety assessment of the **"next generation"** of GM products (i.e. those expected to be marketed during the next decade). One category of these new products, **agronomic applications**, includes crop varieties with the ability to withstand specific environmental stresses. For example, researchers are developing new varieties that can resist drought, salt or heat stress.

7. A second category of new products, **food and public health applications**, includes crop varieties with improved levels of specific nutrients. An example is the new "golden rice" variety that expresses a Vitamin A precursor.

8. A third category, **medical applications**, includes fruits and vegetables (such as bananas or potatoes) that are being genetically modified to produce edible vaccines or novel forms of pharmaceuticals.

9. A fourth category, **industrial and environmental applications**, refers to new crop plants being developed for use in the production of textiles, fuel oils, or other forms of industrial chemicals, as well as methods of bio-remediation and waste control.

10. These "next generation" products will raise additional food safety issues for several reasons. Perhaps most importantly, some will involve more complicated modifications (with several genes) than the "first generation" products. Since this will make the application of established principles such as substantial equivalence even more difficult, evaluating these products' safety is likely to require that more sophisticated testing strategies and methods be developed. Even in the case of products (i.e. medical and industrial) not intended to be consumed as food, safety assessors need to be certain that effective measures are in place to keep these products from entering the food chain. In preparation for the new generation of GM products, **food safety assessors should keep the concept of substantial equivalence under review and should continue to exchange experience with the development of new testing methods and strategies as well as harmonising data needs**.

11. This report shows that some differences exist among OECD countries. One issue on which there is disagreement concerns the detection of any possible long-term effects through post-market surveillance. Post-market surveillance implies the continuing need to monitor GM foods' impact on human health following marketing. Some OECD countries believe that, because new food products should not be placed on the market until safety of the product has been established, there is no scientific basis on which to require special surveillance for foods derived using modern biotechnology. For other countries, post-market surveillance is one of the ways to demonstrate the absence of possible long-term or unintended effects that might result from the consumption of a novel food or feed. **Safety assessors should continue to review this issue by evaluating feasibility studies related to post-market surveillance.**

12. Although food safety assessment is based on sound science, there is a clear need for increased transparency and for safety assessors to communicate better with the public. Much progress has already been made in this regard. For example, some authorities invite public comments on safety evaluations and some publish the results of the work of their advisory committees. (In this context, the Internet has become a powerful tool for disseminating safety information.) Some authorities have included consumer representatives on committees responsible for safety assessments. However, more could be done in this area. An important first step would be for authorities to compare experiences, with a view to developing "good practices" for public involvement in safety assessments. **Safety assessors in different countries should continue to exchange experiences on mechanisms for public involvement in the safety assessment process. OECD's BioTrack Online site should be further developed, to ensure that this information is readily available.**

13. A number of references are made to the work of other intergovernmental organisations, particularly FAO, WHO and that of the Codex Alimentarius Commission. The Task Force, which works with these organisations to ensure an effective global system for food safety assessment, welcomes their participation in its work. **It also welcomes the work of the Inter-Agency Network for Safety in Biotechnology (IANB), which currently comprises eleven intergovernmental organisations.**[a]

a . *CGIAR, CBD, ICGEB, FAO, OIE, OECD, UNCTAD, UNDP, UNIDO, WHO, WTO*

AN INTRODUCTION TO OECD'S TASK FORCE

14. OECD's Task Force for the Safety of Novel Foods and Feeds is made up of individuals nominated by the governments of OECD Member countries. For the most part, they work in ministries or agencies with responsibility for ensuring the safety of products of modern biotechnology including genetically modified foods and feeds. In some OECD countries this body is the Ministry of Health; in others it is the Ministry of Agriculture. Sometimes they share this responsibility with other ministries such as environment. Other countries have specialised agencies with this responsibility. The expertise these nominated individuals have in common is principally related to their experience with food safety assessment. In addition to individuals nominated by OECD governments, other international organisations, particularly FAO and WHO, contribute to the work of the Task Force.

15. The work of the Task Force builds on the OECD's considerable experience with safety-related activities, dating back to the mid-1980s. Initially, much of the work was concentrated on the environmental and agricultural implications of field trials of genetically modified (GM) crops. This was followed by considering the implications of the scale-up of crop plants (OECD, 1993a).

16. By the end of 1990, work had been established to develop scientific principles for food safety assessment of products of modern biotechnology.

17. The main achievement of this work within OECD was *Safety Evaluation of Foods Derived by Modern Biotechnology - Concepts and Principle*s (OECD, 1993b). The main concept presented in this report is that the most practical approach to determining the relative safety of a new food is to consider whether it is *substantially equivalent* to analogous traditional foods - if such foods exist. Initially, this concept was applied to organisms of terrestrial origin; later it was concluded that, with certain caveats, the principle of substantial equivalence could also be applied to products of aquatic biotechnology (OECD, 1994).

18. It was recognised that while substantial equivalence might be determined relatively easily in some cases, in others, a product might be determined to be substantially equivalent except for the novel trait. There might also be cases where a product was so novel that the concept of substantial equivalence could not be usefully applied. The safety assessment of defined differences, and of non-substantially equivalent products, was discussed at an OECD Workshop at Oxford (OECD, 1996). At that time, the first steps were taken towards identifying strategies that could establish the safety of food produced by biotechnology when there is no acceptable counterpart for comparison and substantial equivalence cannot be applied. In considering this topic, attention was given to experiences with novel foods from non-biotechnological sources (such as irradiated foods).

19. By 1997, several OECD countries had gained experience with safety assessment of foods derived through modern biotechnology. An OECD Workshop at Aussois, France, examined the effectiveness of the application of substantial equivalence in safety assessment. The methods used in the nutritional and toxicological evaluation of new foods, particularly those methods to access protein toxicity, were also addressed. It was concluded that the determination of substantial equivalence provides equal or increased assurance of the safety of foods derived from genetically modified plants, as compared with foods derived through conventional methods (OECD, 1998).

20. The Task Force is currently focusing on further efforts to promote continued international harmonisation in the field of safety assessment of products of modern biotechnology. The main area of work at this time is the development of Consensus Documents that provide information on critical parameters of food safety and nutrition for each food crop. A number of other Task Force activities are under way - including those related to capacity-building – which are also designed to promote harmonisation.

CHAPTER I - SCIENTIFIC ISSUES

A. WHAT IS BIOTECHNOLOGY?

21. "Biotechnology" means the use of biological systems and/or living organisms (or their derivatives) to create products. Classical biotechnology includes techniques used in traditional breeding and agricultural cultivation practices. It has had a long history of use in developing native micro-organisms, plants and animals into strains for producing food (e.g. bread, wine, cheese and yoghurt). Classical biotechnology also includes the application of enzymes and micro-organisms in food processing, and the use of modified biological compounds to alter metabolism (e.g. in the production of flavouring substances).

A.1. Comparison of classical and modern biotechnology

22. "Breeding", one of the techniques of classical biotechnology, can be broadly defined as the modification of a cultivated organism's genetic material for human needs.

23. Breeding has primarily relied on the occurrence of genetic diversity in the breeding population. Genetic diversity in nature has been generated by mutations and their recombination. Throughout history, variants with the most desirable characteristics have been selected and maintained (selection breeding). For example, farmers have preserved plants that bore larger fruit and exhibited uniform seed maturation. During the last 50 years, rather than relying on naturally occurring genetic diversity, mutations have been deliberately introduced in the genetic material of plants and micro-organisms using irradiation or chemicals. This "mutation breeding" has contributed to the production of more than 1500 officially registered plant varieties, as well as strains of micro-organisms, without any apparent adverse effects on human health (Maluszynski et al., 1991). In addition, other techniques developed through tissue culture such as *in vitro* fertilisation, somaclonal variation and embryo rescue have added to traditional breeding and have increased variation for commercial use.

24. The term "modern biotechnology" refers to a particular set of techniques used to genetically modify (or "genetically engineer") organisms. These techniques include *in vitro* DNA recombination techniques, as well as direct injection of nucleic acid into cells and their organelles. In short, the introduction of genetic material from one species to another. Through the use of recombinant DNA (rDNA) techniques, modern biotechnology is changing the ways that strains of micro-organisms, plants and animals are developed and used. The characteristics of modern biotechnology include the capacity to transfer genes between completely unrelated species (and to specify which genes will be transferred) and the efficiency with which new types of plants, animals and micro-organisms (and their products) can be developed.

A.1.1. Micro-organisms

25. Traditionally, microbial strains used in food production have been developed by isolating pure strains with desirable characteristics from the environment. These strains have been improved by isolating

lines with beneficial mutations, either spontaneous or induced. Some micro-organisms (e.g. yeast) can also be hybridised or bred to combine desired characteristics; in others (e.g. bacteria), natural mechanisms of transferring DNA exist. A specific example are the koji molds used in East Asia for the production of soy sauce and miso. These are domesticated strains of the mycotoxin producing fungus *Aspergillus flavus* which ferment soybeans and have been used safely to produce food.

26. Recombinant DNA techniques allow genes to be transferred between related microbial strains that would not be able to mate successfully, such as industrial yeast strains (Nordic Council, 1991). The DNA of interest is cloned on a vector and transferred into microbial cells, where it is either integrated into the cell's chromosome or maintained separately as an extra genetic element (plasmid). rDNA techniques also allow the introduction of genes from completely different organisms, including other micro-organisms, plants or animals. This means that micro-organisms can be used for large-scale production of non-microbial products such as the recombinant enzyme, chymosin (see below).

A.1.2. Plants

27. Traditional breeding techniques have been used to develop modern crop plants from ancestors with less desirable characteristics. These techniques are still used to cross crop plants with genetically compatible species, often wild relatives, in order to obtain hybrids with improved qualities. An example of traditional breeding is the crossing of cultivated tomato with wild relatives to introduce genes for pest and disease resistance (Nordic Council, 1991). One limitation of traditional techniques is that they introduce undesirable genes along with desirable ones. To eliminate undesirable genes, and to make the progeny, hybrid plants must be back-crossed, or repeatedly mated, with the parental line. However, complete elimination of all undesired genes is not possible in traditional breeding. In addition, the genetic advances in traditional plant breeding have been relatively imprecise; they have been founded on collecting and combining uncharacterised mutations, without knowledge of their structure, primary function or interactions with other genes.

28. Modern plant breeding is not limited to methods based on crossing plants. Much of it is now carried out using plant cell culture, so that the chromosomes of individual plant cells can be manipulated *in vitro* and then regenerated into whole plants. Any genetic change to the single cell will result in a plant whose every cell has incorporated the same genetic change. Since plant cell culture techniques do not depend on eggs or pollen, plant species that would not normally exchange genes in nature can be allowed to fuse (e.g. hybrids have been produced between broccoli and cauliflower). Generally, the plant improvement objective is to transfer only one or a few traits from one species to another. High doses of gamma irradiation are used to produce breaks in the chromosomes of cells from the donor species that has the trait the breeder wishes to transfer. The irradiated cells are then fused with cells from the species into which the breeder wishes to transfer the trait. The resultant hybrid cells are regenerated into whole plants that contain all of their own chromosomes plus a small amount of DNA from the donor species. By producing thousands of these plants and screening for the new trait of interest, it is possible to achieve gene transfer between sexually incompatible species without using rDNA techniques. A drawback of this technique is that it is impossible to know the extent to which the ionising radiation has introduced unintended alterations in the genes of the introduced chromosome fragment.

29. Using rDNA techniques, plant breeders are able to transfer specific genes to plants. The DNA of interest is cloned on DNA vectors and transferred to plant cells, where it is sometimes integrated into the plant's genetic material. Plant breeders typically couple to the specific gene a selectable marker, often an antibiotic resistance gene, in order to select the transformed cells; they then regenerate whole plants from the selected transgenic cells using plant cell culture techniques. Recombinant DNA technology makes it possible for breeders to transform plants with genes from unrelated plants or from non-plant species,

including micro-organisms and animals. For example, genes encoding insecticidal toxins from the bacterium *Bacillus thuringiensis* (Bt) have been introduced into maize and potato to produce transgenic insect-resistant plants. Since rDNA techniques are used to introduce specific genes, they can reduce the need to screen progeny for desirable traits or to back-cross progeny with the parental plant line.

A.1.3. Animals

30. All modern animal breeds used in agriculture were developed through traditional selective breeding practices. Advances in embryo technology over the last 20 years have added to these techniques. The reproductive rates of certain types of livestock have increased, allowing a rapid growth in the number of rare breeds or new varieties. Identical progeny, or greater numbers of desirable individuals, can be produced using techniques such as embryo splitting. In addition, better knowledge of the genetic control of hormone levels has permitted alterations in carcass quality (such as fat to lean ratios). Increased hormone levels have also improved growth rate and milk production.

31. Compared with its use in plants and micro-organisms, the application of rDNA technology to animals is still in its infancy. No transgenic animals intended for food use have yet been commercialised or approved for commercialisation, though fish are an important exception, with genetically modified varieties of salmon close to commercialisation. rDNA techniques for animals are essentially the same as those for plants and micro-organisms, in that the DNA of interest is cloned onto DNA vectors. The standard method of DNA transfer for mammals is microinjection into embryos. The embryo is transferred to a recipient mother, where it grows into a normal animal. In a small percentage of injected embryos, the introduced DNA is integrated into the animal's genetic material. The newborn animal then contains the recombinant DNA in all its cells.

A.2. Types of modified foods entering the market

32. Numerous foods derived using modern biotechnology are now entering the market in some OECD Member countries.

A.2.1. Micro-organisms

33. Genetically modified (GM) micro-organisms are used in the production of a variety of food additives as well as food processing enzymes. For example, certain vitamins prepared from GM bacteria for use in food have been approved in Switzerland and the United Kingdom (Hemmer, 1997). In 1990, the use of a recombinant enzyme, chymosin, for cheese making was approved by the United States Food and Drug Administration (FDA). GM chymosin has now been approved in at least 17 countries (Hemmer, 1997) and is used in the majority of hard cheese production in Canada, the UK and the US (Food Biotechnology Communications Network Web Site; U.S. FDA Web Site; Vogt and Parish, 1999). Other food processing enzymes produced by GM organisms include alpha-amylase, xylanase, hemicellulase and lipase. Similarly, feed processing enzymes are now routinely used in livestock feed. The recombinant enzyme phytase, for example, is used to release phosphorus in livestock diets. Micro-organisms may also be used as sources of protein for animal feeds, or for the production of vitamins, enzymes or amino acids.

A.2.2. Plants

34. Many commercially available GM crops have been bred to enhance agricultural production. A good example is the expression of *Bacillus thuringiensis* (Bt) genes for insect resistance. Strains of Bt maize have been approved for specific uses (e.g. grain cultivation or use in food products) in Canada, Japan, Switzerland, the US and the European Union (Belgian Biosafety Web Site; Canadian Food Inspection Agency Web Site; MAFF Japan Web Site; OECD Biotech Product Database Web Site; US FDA Web Site). Strains of Bt cotton and potato have been approved in Canada, Japan and the US (Canadian Food Inspection Agency Web Site; MAFF Japan Web Site; US FDA Web Site). Crops have been engineered to resist plant viruses by expressing specific plant virus protein genes. Virus-resistant squash and potato have been approved in Canada and the US, and virus-resistant papaya and potato have been evaluated in the US. At least four genes that render plants herbicide-tolerant have been transferred into crop plants, allowing farmers to selectively kill weeds. For example, specific uses of glufosinate-tolerant maize and glyphosate-tolerant soybeans have been approved in the EU (Belgian Biosafety Web Site). In Canada and the US, approval has been given to glufosinate-tolerant canola, maize, soybean and sugar beet; bromoxynil-tolerant canola and cotton; glyphosate-tolerant canola, cotton, maize, soybean and sugar beet; and sulfonylurea-tolerant cotton and flax (US FDA Web Site).

35. An expanding area of rDNA modification of plants involves changes to product quality or to nutritional composition. Among the first rDNA whole foods approved in the UK and the US were varieties of transgenic tomato with delayed ripening (reduced softening) due to reduced polygalacturonase activity. Other delayed ripening products - including cantaloupe and tomato with various genetic modifications - have been evaluated or approved in Canada and the US. Biotechnology companies have also developed several oil-producing varieties of soybean and canola with a potentially healthier, oil composition.

36. A number of other plant products are expected to be ready for commercial marketing in the next several years. According to the US Congressional Research Service (Vogt and Parish, 1999), many of the expected market entries will be nutritionally improved products which are intended to be consumer oriented. Examples include high-stearate soybean oil, which reportedly will not require hydrogenation for margarine production; tomato with increased Vitamin C content; and delayed ripening raspberry, strawberry, banana, pineapple and cherry tomato (delayed ripening is intended to ensure longer market life).

A.2.3. Animals

37. With the exception of fish, it is expected to be a number of years before a transgenic animal is produced commercially. No transgenic animals have been approved for commercialisation, but a number of genetic modifications are under development. These are: (a) introduction of new metabolic pathways for improved nutrition; (b) alterations of proteins such as those in wool or milk; (c) modifications of animals' disease resistance; and (d) alterations of the endocrine system.

A.2.4. Animal feeds

38. Livestock feeds encompass a wide range of ingredients that include: living bacteria, yeast and other forage or silage inoculants; non-living microbial products and by-products, including enzymes, proteins, amino acids, vitamins and flavouring ingredients; and plants with novel traits and their by-products, such as soybean seed, canola meal and corn gluten.

B. WHAT ARE THE NOVEL FOOD AND FEED SAFETY ISSUES?

39. Investigating food safety, irrespective of whether or not the foods have been produced using rDNA technology, is a complex undertaking due to the many factors to be considered in determining health risks. Classical methods can be used to evaluate the toxicity of specific proteins introduced into food, but they are not suitable for assessing complex whole foods.

40. There is a widespread scientific consensus that in assessing risks, it is not the process applied in breeding but the genetic outcome and the trait it confers to the plant that matters (EUCARPIA, 1989; Editorial.Nat. biotech. 18: 239). Unexpected effects commonly occur in breeding, due to genetic interactions. These are managed by trial and error in traditional breeding practice. Large numbers of experimental plants are produced, and also favourable interactions are utilised by selecting the most favourable individuals and combinations. Materials representing unfavourable interactions are simply discarded. Only the most successful plant lines are retained for further breeding and variety development.

41. Traditional distant crosses as well as various kinds of mutations (e.g. deletions, duplications, insertions, inversions, translocations, jumping genes, even aneuploidy and polyploidy; as well as mutations in regulatory genes) often cause unintentional suppression (even loss) or enhanced expression of accompanying or other genes. If detected, such anomalies are usually discarded. Depending on the chromosomal location where the modified gene integrates, such unintentional effects may also occur with genetic modification.

42. In the past, numerous changes have been made in cultivated plants during traditional breeding with very little associated biochemical knowledge available to assist in their evaluation. A problem is that in theory, any change in the intensity of the functioning of an enzyme, irrespectively of its actual genetic cause (be it a mutation, recombination or genetic modification), may cause changes in the biochemical pathways connected to the metabolic step in question (either in its preceding or subsequent metabolic branches). This is a question of enzymatic function rather than the origin of the gene. Therefore, if a gene introduces into the plant an essentially novel metabolic function, it is reasonable to assess its possible effects more carefully than normal. Most attention in the safety assessment of GM foods has been given to the detection and prevention of potentially occurring toxic effects, allergic reactions, unfavourable changes in nutrient composition, and the issues associated with antibiotic resistance genes.

43. With regard to investigating the safety of GM foods, the risks associated with genetic modification are unintentional modification of the host genetic material, potentially resulting in changes in food components, including toxicants. One approach taken by regulatory bodies is to obtain data on the composition of a GM food in relation to its conventional counterpart. In principle, this provides a way to assess any new constituents introduced by the genetic modification process. It also permits an assessment of the degree of change in the amounts of the common constituents. However this does not cover new compounds for which no detection methods yet exist. Safety assessment of GM foods should take place within this general framework with “case-by-case” variations, taking into account the conventional counterpart’s often long history of safe use.

44. Specifically, safety assessment of GM foods should include the following:

- identification of the organism that has been modified and the source organism(s) of the introduced gene(s);
- identification of the primary and secondary gene products, including a description of the characteristics of the inserted gene;

- evaluation of the safety of expected novel substances in the food (i.e. proteins, carbohydrates and lipids);
- evaluation of unintended effects on food composition, including (a) assessment of changes in the concentration of nutrients or naturally occurring toxicants, (b) identification of antinutrient compounds that are significantly altered in GM foods, and (c) evaluation of the safety of compounds that show a significantly altered concentration;
- evaluation of any toxins produced directly by the modification;
- evaluation of the processed version of the food, if the food normally undergoes manufacturing or processing (Stewart, 1992);
- evaluation of food consumption issues, including: (a) identification of the potential human population consuming the GM foods and the amount they are expected to consume, and (b) assessment of any effects that may occur if intake of the modified food differs from intake of its conventional counterpart (Stewart, 1992; Anon, MAF Information Bureau); and
- assessment of the novel food's potential allergenicity.

45. Livestock feed safety is determined in order to ensure that unsafe residues are not introduced into human food products via the ingestion of GM feed by food-producing animals. Submissions must demonstrate that new genes and proteins are degraded or denatured during processing of the feed, or through digestion of the feed in the animal. If digestion is incomplete, the metabolite must be shown to be non-toxic or non-allergenic. The potential for transfer of genes to animal rumen or gut microflora is considered for both the introduced desired traits and marker genes. The nutrient composition and bioavailability of nutrients, and the introduction of toxicants or anti-nutritional factors, are also assessed.

46. In the future, the development of new analytical and *in vitro* methods of determining toxicity offers interesting possibilities for the food safety assessment of GM crops (Kuiper and Noteborn, 1996). In addition, a database of foods and their constituents, including GM foods, should be established to determine whether their composition presents a health problem. The information in the database could provide valuable reference points for assessing whether significant changes have occurred in key nutrients and toxicants. This information could be supplemented with data from specific research projects (Kok and Kuiper, 1996).

B.1. The safety of new proteins in food toxicity and allergenicity

47. A huge number of proteins are ingested in the normal diet, without adverse effects, but a small number have the potential to affect health. As proteins and peptides have a wide range of functions in organisms, different possible effects have to be considered: for example, enzymatic activity or enzyme inhibition may influence the potential to synthesise toxic compounds or cause anti-nutritive effects by binding certain nutrients, such as the binding of avidin to the vitamin biotin; and some proteins act as carrier molecules, hormones or toxins.

48. Proteins also have the potential to cause allergic reactions. Known allergens are found in milk, eggs, peanuts, tree nuts, soybean, fish, crustacea and wheat. Food allergens are typically large proteins (molecular weights of 10-70 kD). They are often glycosylated, and are relatively stable to food processing and digestion (Fuchs, 1997). Of the huge number of proteins in the human diet, few are allergens.

49. Toxicity testing may be applied to highly purified substances, such as sugar isolated from transgenic sugar beet or organic acids produced by modified micro-organisms, but it is more difficult with

whole foods. In these cases, specifications and purity criteria are important. For example, enzyme preparations can contain impurities resulting from the process of enzyme isolation.

Modern biotechnology, like classical biotechnology has the potential to introduce allergens into foods. Safety assessments of GM foods usually include an assessment of the allergenic potential of newly introduced proteins.[a] If an introduced gene comes from a food plant with a demonstrated history of dietary exposure and no known allergenic properties, there is no reason to suggest it would have an allergenic potential. However, genes obtained from allergenic sources should be treated more cautiously and subjected to appropriate testing to demonstrate that the novel protein they encode is not an allergen. No allergy risk has been established at present for the GM products that have already been approved (Bindslev-Jensen, 2000).

50. In considering the safety of new proteins in food, the possibility that a new protein may cause an allergic reaction in some individuals should be assessed. One proposed approach to assessing the allergenic potential of new proteins in foods derived from GM plants using a decision-tree approach has been published (Metcalf et al., 1996). If the gene originated from a source known to cause allergic reactions, the assessment should include *in vitro* analysis of the immuno-chemical reactivity of the newly expressed protein with IgE from the blood serum of individuals with known allergies to the source of the transferred genetic material (e.g. ELISA and RAST tests). If serum reactivity is observed, a second tier *in vivo* study should be performed (skin prick test). If this test is negative or equivocal, a food challenge test (double-blind, placebo-controlled food challenge) with patients sensitive to the allergenic source of the gene is recommended. If the source of the GM food does not suggest the presence of proteins with allergenic potential, a comparison of certain properties of known allergens with those of the newly expressed protein(s) in the food is necessary in order to assess its allergenic potential. If a protein exhibits characteristics similar to a known allergen, further evaluation is recommended.

51. Several concerns have been raised about the currently available allergenicity and toxicity testing methods. For example, the simulated gastric fluid (SGF) test, an artificial system for testing proteins' digestibility, does not mimic exactly the physiological conditions in the digestive tract. Such testing may not always provide clear evidence of the possible toxic or allergenic potential of peptides formed as breakdown products in the test system. Lack of homology of a protein's primary structure to a known allergen does not exclude the possible presence of allergenic epitopes formed by the protein's secondary or tertiary structure. Currently available *in vitro* (RAST and ELISA) and *in vivo* (skin prick and double-blind, placebo-controlled food challenge) immunological tests can only detect known allergenic proteins. These problems suggest that there is a need to improve toxicity and allergenicity testing methods, especially for digestibility tests that simulate the gastrointestinal tract more precisely. Recently software became available to predict spatial protein structures from linear amino acid sequences. This may allow for comparisons of the studied proteins with the secondary and tertiary structures of known allergens (Swiss Institute of Bioinformatics Web Site). Moreover the development of animal models to identify compounds with a potential to induce IgE immune responses is promising.

a . In a 1996 experiment, researchers inserted a gene from Brazil nut into soybean with the aim of improving nutritional value. The introduced Brazil nut protein was found at the research stage to react with sera from Brazil nut sensitive individuals. As a result, the transgenic soybean expressing a Brazil nut protein was not commercialised.

B.2. The safety of whole foods: altered expression of natural toxicants and antinutrients

52. Increases in the level of natural toxicants can occur in plant varieties bred using traditional techniques. It is possible, therefore, that GM varieties could also have altered expression of natural toxicants and antinutrients.

53. Many plants naturally produce toxicants and antinutrients, often for defence against predators. Toxicants include lectins, found in beans; erucic acid and glucosinolates, in canola; psoralen, in celery; and the glycoalkaloids solanine (potato) and tomatine (tomato). Antinutrients include chymotrypsin and trypsin protease inhibitors, which interfere with protein digestion, and the soybean component phytic acid, which binds minerals such as zinc, magnesium and phosphate. Normally, crop plants have low levels of toxicants and antinutrients following centuries of selective breeding; in some cases, toxicants are present at levels significant to human health but are inactivated by standard processing practices such as cooking. While the main concern is that genetic modification could lead to increased levels of natural toxicants, a more speculative possibility is that silent pathways for toxicant and antinutrient production could be reactivated by insertion or expression of the new genes. Similar changes in gene expression are equally theoretically possible through mutations in regulatory genes, as well as by chromosomal rearrangements induced by modern breeding paractices.

54. To address these concerns, regulators have asked plant breeders using GM techniques to verify the levels of toxicants known to be associated with the modified plants' parental line, even if present in the conventional counterpart at a low level, or inactivated. The aim is to ensure that toxicant levels are within the range of those in the safely consumed parent plant or related commercial species. Historically, such testing has not been performed systematically for plant varieties produced by traditional breeding. An exception is potato, which to a large extent is monitored by vegetable breeders for solanine levels, and oilseed rape which is tested for natural toxicants such as glucosinolates and erucic acid.

55. A related safety concern is that expression of the transgenic protein could result in the plant producing a toxicant not observed in the parent species. For example, somatic hybrids between *Solanum brevidans* and *S. tuberosum* (potato) have been observed to produce the toxicant, demissine, not found in either parental line. Laurila et al. (1996) advanced the plausible hypothesis that the hydrogenase enzyme of *S. brevidans* produced the toxicant by hydrogenating solanine, a compound that is found in *S. tuberosum* but not in *S. brevidans*. However, the appearance of dimissine is not totally surprising as it is a compound found in some species of the genus Solanum. Portions of the metabolic pathways necessary to produce this substance apparently existed in the parental species, and the mingling of the genetic material resulted in a complete pathway for production of demissine. Such a possibility has led some to propose that GM foods undergo rigorous testing, including animal feeding studies, prior to approval. Others have responded that such testing is rarely carried out on novel foods that have not been genetically modified, and that it would be impossible to conduct meaningful toxicity testing of whole foods in animals. It should be the aim of a safety assessment to include a consideration of those compounds that might be potential toxicants.

56. Traditional food safety studies are designed to assess the safety of substances such as food additives that comprise an insignificant proportion of the diet. Novel foods that make up a more substantial part of the diet pose several problems when evaluating safety by conventional methods. Classical animal feeding trials are inadequate, due to the difficulty of feeding animals adequate doses of the test food in their diet. Increased research efforts and new techniques are needed to develop alternative safety assessment techniques for whole foods, especially in the areas of immunotoxicology, gut toxicology, molecular biology and plant physiology. Nonetheless, considerable confidence exists that modern sophisticated analytical chemistry and biochemistry techniques and food safety assessment procedures can ensure that GM foods are as safe as traditional ones (Stewart, 1992; Kuiper and Noteborn, 1996).

57. One example of a testing programme for GM foods is a comprehensive project, begun in 1991, concerned with the molecular, biochemical and toxicological characterisation of transgenic insect-resistant Bt tomato. In this project it was found that modified and non-modified tomatoes had a comparable chemical composition (apart from the protein product from the newly introduced Bt genes). Levels of the naturally occurring tomato toxicant α-tomatin were similar in the modified and control tomatoes (Kuiper and Noteborn, 1996). When the transgenic tomato was tested in rats, no histopathological effects were observed in the digestive mucosa.

58. Animal feed safety assessments are designed to assess safety of substances that comprise an insignificant portion of the diet, such as additives, as well as feed materials that comprise a significant portion of the diet. For those categories of products, studies concerning the biological consequences of the use of the product in animal nutrition are relevant. Studies should be performed on target species and different categories for each target species.

B.3. The safety of whole foods: nutritional changes

59. Genetic modification of foods can alter their nutritional value, in either undesirable or beneficial ways. Food safety assessment should consider the potential for any change in nutritional composition, especially in key elements that have a significant impact on the diet, as well as the potential for any change in the bioavailability of key nutritional components.

60. A recently cited example of a potentially beneficial development is the transgenic rice containing elevated levels of vitamin A precursor and iron. This rice strain has been cited as a potential means of preventing vitamin A deficiency-related childhood deaths and blindness and reducing the frequency of children catching severe diseases such as malaria in developing countries with rice-based diets. Other potentially beneficial products include fruits and vegetables with elevated vitamin levels and oil-seed plants with different oil compositions, such as high-oleic soybean. As regards livestock feeds, canola breeders are developing a variety of canola with increased levels of the essential amino acid lysine.

61. There have also been concerns that genetic modification could affect the nutritional quality of foods by altering levels of nutrients. This could be important when specific GM food is an important source of a nutrient. Changes in levels of nutrients could theoretically arise in several ways. Insertion of genetic material could conceivably disrupt or alter the expression of normally expressed plant genes. Expression of the introduced gene – through protein synthesis - might reduce the availability of amino acids used for synthesis of normal plant compounds. Production of normal plant compounds might also be affected if the expressed protein diverted substrates from other important metabolic pathways. Finally, either the expressed protein or altered levels of other proteins might have antinutritional effects. These possible concerns are related to randomness of DNA insertion. However, changes in gene expression can also occur when traditional breeding methods are used; such changes may, in fact, be less frequent in GM plants since only a limited number of genes are transferred during the genetic modification.

62. One way nutrition-related concerns have been addressed is to measure nutrient levels in traditional plant varieties. For example, plant developers may assess whether the bioavailability of nutrients in modified varieties is within the normal range for the host species when compared with traditional varieties.

B.4. The safety of whole foods: unexpected changes in food composition relevant to human health

63. All cultivated plants contain compounds that are antinutritive, toxic, and in some cases even carcinogenic. Sometimes the concentrations of such compounds in the food plants we consume are close to

levels known to have toxic or pharmacological effects. During the long history of plants used as food, varieties have been developed that are treated and accepted as safe because they do not have obvious acute toxicity. Plant breeders may monitor substances in new varieties (e.g. solanine in potato, erucic acid and glucosinolates in canola) to ensure that concentrations in new varieties have not increased beyond acceptable levels. In other cases, processing procedures or consumption limits are needed to ensure that substances known to have toxic effects (e.g. cassava, legumes, bitter almond) are present at concentrations safe for consumption.

64. All plant breeding methods, traditional and modern, have the potential to lead to unexpected or unintended changes in concentrations of various substances in the plants. It is important that all new varieties be evaluated, in order to reduce the likelihood that unexpected changes will produce adverse health effects. In most cases of plant modification, DNA insertion takes place at random, unpredictable loci. Such random insertion may lead to unintentional changes in gene expression: first, the foreign DNA might be inserted into the coding region of a gene of the host organism, leading to a truncated or hybrid gene product whose function is altered, impaired or lost; second, it might be inserted into the regulatory region of a gene and therefore alter the gene's expression pattern; third, the foreign DNA might affect the gene of a regulatory protein thereby affecting other genes. Another issue is that plant metabolism, might be altered as an adaptation to expression of the foreign gene. None of these effects are unique to GM plants Each could also be caused by naturally "jumping genes" and natural or induced mutations, e.g. chromosomal rearrangements. All these events may lead to more or less pronounced changes in plant metabolism. Alterations in concentrations of known plant metabolites in the new variety can be monitored using existing analytical methods.

65. The concept of substantial equivalence has been used as a tool in risk assessment. This concept involves comparing the GM organism-derived plant and its conventional counterpart with respect to their phenotypic and agronomic characteristics and their food composition, taking into particular account key nutrients, antinutrients and toxicants typical of the particular plant. Agronomic and phenotypic characteristics provide an objective assessment of the plant's health, often indicating unacceptable alterations. Analyses of key substances provide increased assurance that substances important from a nutritional or health perspective are present in acceptable concentrations.

B.5. Gene transfer: potential impacts on human health (e.g. antibiotic resistance markers)

66. Horizontal gene transfer is the non-sexual or parasexual transfer of genetic material between organisms belonging to the same or different species. Though actual evidence of its occurrence or feasibility (except among bacteria and fungi) is rare, the issue is taken seriously in the safety assessment of GMOs. This issue concerns the potential transfer of genetic material from micro-organisms and plants to other organisms. There is no scientifically valid reason to treat possible gene transfer events involving genetically modified organisms differently from those involving naturally occurring organisms (Salyers, 1997). In any case, it is the gene and the trait it confers, and whether or not it brings a reproduction or selection advantage to the recipient organism that are crucial concerns when possible impacts of potential gene transfer are being considered.

67. Since selection in favour or against a gene is important in its maintenance or proliferation, genes that confer a selective advantage deserve particular attention. However, depending on the trait, selective advantage as such does not automatically imply any harmful effects. Foreign DNA is normally linked to marker genes, in order to be able to identify cells into whose genome the DNA construct has been inserted. Two categories of selection markers commonly used are genes conferring resistance to various herbicides and certain antibiotic resistance genes of bacterial origin. The marker gene commonly used in biotechnology, kanamycin resistance, does not confer resistance to antibiotics that are in (oral) therapeutic

use. Furthermore, bacterial strains resistant to the antibiotics in question (e.g. kanamycin or ampicillin) are common in the environment and in the human intestines, and large numbers of naturally resistant bacteria are acquired when ingesting fresh food (Salyers, 1997a; Smalla et al, 1997; Sci Am, March 1998).

68. In the case of antibiotic resistance genes, there is good reason to think that genetically modified strains pose much less of a threat than naturally occurring resistant bacterial strains, because the former represent old, narrow-spectrum and less mobilizable resistance genes not involved in the present problems in hospitals (Salyers, 1997b). Marker genes conferring resistance to antibiotics for therapeutic use should be avoided in viable GM micro-organisms in food. If the GM micro-organism includes marker genes, information should be provided to show that these genes do not provide a selective advantage in the gut or influence the existing microflora under either typical and extreme conditions (e.g. consumers taking medication). If the marker does provide a selective advantage in the gut, the consequences for the consumer must be defined. Genetic exchange between living bacteria by conjugation is known to occur very broadly, even across genus or family limits. Certain bacteria can also take up bare DNA from their surrounding fluid and even sometimes integrate it in their genome - a phenomenon called natural transformation. However, that occurs relatively rarely and only with DNA from the same or closely related bacterium species (Salyers, 1997a).

69. *In vivo* gene transfer of DNA from GM plants to bacteria, while hypothetically possible, is a remote possibility. This is because a number of unlikely events must occur sequentially. These events include the availability of the right kind of DNA, the type of bacteria, the ability of these bacteria to take up DNA and be transformed by that DNA and the competitiveness of the transformed bacteria. At present there is no evidence that these events occur in the bacteria normally found in human or animal digestive tracts, and the probability of transfer of antibiotic resistance traits does not present a concern. However, in evaluation, the following should be taken into account:

a) **Fate of the antibiotic resistance gene DNA**
DNA, including the genetic material encoding for the antibiotic resistance trait, is not normally exposed to the environment outside of the plant's tissue. However, once the plant cell wall and membranes have been disrupted, DNA released from the plant tissue is primarily degraded by the plant's own nucleases. In addition, DNAses and enzymes found in the digestive environment of the gastrointestinal (GI) tract degrade any remaining intact DNA into small pieces. These pieces encode little of the original information for antibiotic resistance.

b) **Uptake by bacteria**
Under idealised laboratory conditions, DNA from GM plants has been shown to transform bacteria commonly found in soil at low frequencies (de Vries, 1998). However, as noted a) above, the genetic material encoding antibiotic selection markers are normally contained in the plant cells and are not exposed to the outside environment. In fact, soil has been shown to inhibit transformation efficiencies, and the occurrence of gene transfer from plants to soil micro-organisms is considered to be so low as to be irrelevant (Nielsen, 1997; Schluter, 1995). It is known that opportunistic pathogenic micro-organisms of soil origin with various resistances to antibiotics can emerge, even in the absence of exposure to plant tissue. However, the medical implications, both human and animal, of gene transfer of antibiotic resistance genes in soil has not been documented.

In vivo gene transfer to populations of bacteria normally found in the gut is also extremely low. Neither the small pieces of DNA produced by gastrointestinal digestion of plant tissue, nor any small amounts of larger-sized DNA that may have escaped digestion, have been shown to become incorporated into, or transform, the normal flora found in the gut (Syvanen, 1999).

c) **Establishment of stable foreign DNA fragments in a bacterial cell**
Stable integration of foreign DNA into the host genetic material occurs by means of recombination. The frequency of these events occurring in either soil or gastrointestinal environments (paragraph b) is exceptionally low. The stable establishment of foreign DNA fragments within a bacterial population is dependent upon a number of events, including the relative competitiveness of any transformed bacteria with naturally occurring bacteria. It is unlikely that any transferred trait would be stably maintained, or expressed, without selective pressure (e.g. the presence of antibiotic).

d) **Successful expression of the transferred antibiotic resistance gene**
For this to occur, the regulatory segments required for gene expression must be present in an appropriate arrangement and be recognised in the new host cell.

70. The sequential occurrence of these individually rare events needed to establish *in vivo* gene transfer is highly improbable (Droege et al., 1998). Nevertheless, *in principle*, introduced genes should be restricted to those genes required to confer the desired trait, while avoiding use of marker genes that may confer resistance to therapeutically relevant antibiotics (German Central Advisory Committee for Biological Safety, 1999).

CHAPTER II - CURRENT APPROACHES AND EXPERIENCES IN THE SAFETY ASSESSMENT OF FOODS DERIVED THROUGH MODERN BIOTECHNOLOGY

A. INTERNATIONALLY ESTABLISHED SCIENTIFIC PRINCIPLES

71. The risks associated with biotechnology-derived foods are not inherently different from the risks associated with conventional ones. Those most likely to be related to consumption of GM foods concern toxic effects, allergic reactions, changes in nutrient composition, and the effects of genes resistant to antibiotics (see chapter 1).

72. Regulatory authorities world-wide already base food safety assessments on the general definition of risk analysis in the *Codex Alimentarius*. According to this definition, risk analysis has three components: risk assessment, risk management and communication of risk.

73. Experience throughout the world has led to the identification of a number of common scientific principles currently used in food safety assessment. Novel foods and food products should be as safe for the consumer as comparable conventional products. They are therefore subjected to specific safety assessments on a case-by-case basis. Risk assessment is intended to identify information on the nature and severity of any risks that may be present, allowing appropriate management methods to be defined.

74. Risk assessment is scientifically based, beginning with identification and characterisation of any potential hazards. This is followed by an assessment of human exposure to the expressed trait associated with the hazards that have been identified. In the case of GM organisms, the following are usually evaluated: the new gene, the new protein and other food components. In specific cases, additional effects may be evaluated.

A.1. The new gene

75. The origin and nature of all the genetic elements that have been introduced into the modified organism need to be identified, including structural and regulatory sequences and any remaining parts of vector sequences. The possibility of horizontal gene transfer and its consequences is also considered. If transfer of antibiotic resistance genes were to occur, the potential significance to human health would need to be considered in relation to existing levels of antibiotic-resistant micro-organisms in the human gut, or other parts of the body.

A.2. The new protein

76. Hazard identification requires knowledge of which introduced genes are expressed, the characteristics, concentration and localisation of expressed products, and the consequences of expression.

For each protein resulting from the genetic modification, the factors considered include potential toxicity and allergenicity of the expressed protein.

77. In the toxicity testing of specific proteins, current approaches are based on internationally approved acute or chronic tests in laboratory animals (rats or mice) or fast-growing domesticated species such as chickens. However no repeat dose tests with GM foods or feeds have yet been published.

78. As regards allergenicity, most authorities now base their evaluations on a decision tree (Metcalfe et al., 1996; Fuchs and Astwood, 1996) designed to assess the allergenic potential of foods derived from GM plants, which incorporates current knowledge concerning what constitutes an allergen and how allergens may be best identified. This focuses initially on the origin of the introduced gene. In the event that a gene is introduced from a known allergenic source, immunological will be required.

79. In the case of genes originating from sources not known to be allergenic, risk assessment is based on the physico-chemical properties of the newly expressed protein(s) including pH, *in vitro* digestibility and heat stability; the absence of sequence homology with known allergens; and the concentration of the newly expressed protein(s) in the final food product.

A.3. Other food components

80. The compositional analysis of a food derived from modern biotechnology may in principle provide sufficient information on composition to allow effective comparison with a conventional comparator already available in the food supply. Critical components are determined by identifying key nutrients and toxicants for the food in question. Additional components might be identified for analysis, based upon molecular and phenotypic characterisation and the nature of the genetic modification. For example, introduced proteins may also have a catalytic activity likely to modify existing metabolic processes. In this case, analysis of a broader spectrum of components may be necessary if there is an indication that the genetic modification could have an unintended effect.

A.4. Additional effects

81. Specific types of modification may introduce specific hazards. These can only be assessed on a case-by-case basis. For example, introduction of genes encoding herbicide tolerance may detoxify the herbicide in the plant, thereby generating intermediate metabolites as residues as well as the parent molecule. A risk assessment will need to consider the potential impact of such residues on food safety. The determination of maximum residue levels of the active ingredient or their metabolites following application of a herbicide is often the responsibility of the national authorities carrying out the risk assessment for pesticides.

A.5. Substantial equivalence

82. One of the concepts used to assess GM foods and feeds is that of substantial equivalence. This concept, elaborated within the OECD, has been endorsed by FAO and WHO. Determining substantial equivalence entails consideration of the trait encoded by the genetic modification; phenotypic characterisation of the new food source, compared with an appropriate comparator already in the food

supply; and compositional analysis of the new food source or the specific food product, compared with the selected comparator (FAO/WHO, 1996).

83. The OECD has agreed that safety assessment based on substantial equivalence is the most practical approach to address the safety of foods and food components derived through modern biotechnology. The concept of substantial equivalence embodies the idea "that existing organisms used as food, or as a source of food, can be used as the basis for comparison when assessing the safety of human consumption of a food or food component that has been modified or is new" (OECD, 1993b). In elaborating the concept of substantial equivalence, the OECD has noted that food safety is the reasonable certainty that no harm will result from intended uses under the anticipated conditions of consumption (OECD, 1993b).

84. In 1996, an FAO/WHO consultation endorsed the application of substantial equivalence in the safety assessment of biotechnology-derived foods (FAO/WHO, 1996). It recognised that the establishment of substantial equivalence is not a safety assessment *per se*, but that establishing the characteristics and composition of the new GM food as equivalent to those of a familiar, conventional food with a history of safe consumption implies that the new food will be no less safe than the conventional food under conditions of similar exposure, consumption patterns and processing practices. Substantial equivalence is not intended to be a measure of absolute safety; instead, it recognises that while demonstrating absolute safety is an impractical goal, it is possible to show that a GM product is no less safe than a conventional food product.

85. Three possible scenarios are envisaged as a result of a substantial equivalence evaluation (FAO/WHO, 1996):

(a) When substantial equivalence has been established for an organism or food product, it is considered to be as safe as its conventional counterpart and no further safety evaluation is needed.

(b) When substantial equivalence has been established apart from certain defined differences, further safety assessment should focus on these differences. A sequential approach should focus on the new gene product(s) and the(ir) structure, function, specificity and history of use. If a potential safety concern is indicated for the new gene product(s), further *in vitro* and/or *in vivo* studies may be appropriate.

(c) When substantial equivalence cannot be established, this does not necessarily mean that the food product is unsafe. Not all such products will require extensive safety testing. The design of any testing programme should be established on a case-by-case basis, taking into account the reference characteristics of the food or food component. The objectives should be clear, and care should be taken in experimental design. Further studies, including animal feeding trials, may be required, especially when the new food is intended to replace a significant part of the diet.

86. One important benefit of the substantial equivalence concept is that it provides flexibility that can be useful in food safety assessment. It is a tool, which helps identify any difference, intended or unintended, that might be the focus of further safety evaluation. Because it is a comparative process for evaluating safety, the determination of substantial equivalence can be performed at several points along the food chain (e.g. at the level of the harvested or unprocessed food product, individual processed fractions, or the final food product or ingredient). Although from a practical point of view (e.g. where multiple fractions from a single source will be used as different food products) substantial equivalence should

typically be determined at the level of the unprocessed food product, the flexibility of the concept permits the determination to be targeted at the most appropriate level, based upon the nature of the product.

87. Applying the substantial equivalence concept is a comparison of a GM food with an appropriate comparator which has an acceptable history of safe food use. It also requires that sufficient analytical data be available in the literature, or be generated through analysis, to allow the comparison to be made. This suggests a basic limitation of the substantial equivalence concept: dependence on a comparator, and on the information that is available or can be generated for the comparator, means safety assurance is relative to the components assessed for the particular comparator. The choice of comparator is therefore crucial to effective application of the concept of substantial equivalence to establish the safety of a GM food. An appropriate comparator must have a well documented history of use. If adverse effects have been associated with the particular food type, specific components considered to cause these effects should be described and well characterised to permit effective comparison.

88. The comparative nature of the concept suggests that determining substantial equivalence can range from cursory comparison of phenotypic characteristics to a demonstration of identity based on extensive composition data. In fact, this issue has been a key factor in criticisms of substantial equivalence as not being measurable and therefore inappropriate to safety assessment. On the other hand, the purpose of the assessment is to evaluate the impacts of both intended and unintended changes resulting from the genetic modification. Guidance on applying substantial equivalence to the safety assessment of GM foods has been developed to provide clarity in interpreting the criteria that would constitute an appropriate framework for determining substantial equivalence.

89. Considering key nutrients and toxicants in the comparison also introduces a limitation of the concept of substantial equivalence. The nature of the comparative approach with respect to nutrients limits its universality, since the relevance of nutrients in a particular crop depends on consumption patterns that may vary from one region to another. Where differences in the consumption of a particular crop exist, these must be considered in identifying the key nutrients to be assessed. This is particularly true for crops that constitute a significant portion in the diet of a particular region. The comparative approach to assessment can be applied in each region, but conclusions for one region will not automatically be valid for others if there are significant differences in consumption patterns and processing practices. A good example of a regional difference was the appearance of the nutritional disease, beriberi, which coincided with the introduction of polished rice into India and China, and the reduction in availability of B vitamins as these are present primarily in the parts removed by polishing. Another potential limitation in the application of the concept, may be the difficulty, particularly in developing countries, to assess food safety where adequate nutritional information is not available for a given population.

90. Where substantial equivalence has been established, this does not mean that a GM product is *identical* to the conventional comparator. Since the comparison does not take all components into account, substantial equivalence only provides assurance that those components most likely to be relevant to the product's safety are present in equivalent amounts.

91. Since the comparative approach links the composition of the new food to existing products with a history of safe use, the new food's impact in the diet can be predicted. Applying the concept allows everything that is the same between the GM food and the conventional food to be considered safe. Differences identified in the comparison are the focus for further scrutiny involving traditional nutritional, toxicological or immunological testing, or long-term studies, depending on the identified differences.

92. In the future, it is conceivable that there will be GM foods for which no appropriate conventional counterpart exists, or that the differences between the GM food and the counterpart will not be sufficiently characterised. The history of safe use of the comparator will therefore not be applicable in establishing the

safety of the new food under consideration. Substantial equivalence cannot be used to assess the safety of foods for which there is no comparator. In this case, although a new food is considered not to be substantially equivalent to an existing counterpart, it is not inherently unsafe. Rather, it must be directly assessed for safety using traditional safety assessment approaches. In such cases, additional testing will be required in order to determine the nutritional impact of the changes.

93. Through the development of Consensus Documents on individual crop species by the Task Force (OECD Task Force for the Safety of Novel Foods and Feeds Web Site), work continues to achieve international consensus on the specific components appropriate for comparing individual crops. Such guidance adds to the understanding of the parameters for determining substantial equivalence, although it is recognised that additional parameters may be relevant to the safety assessment. The Task Force's work also focuses on safety assessment methods that can be used with novel foods and feeds when the concept of substantial equivalence cannot be applied.

B. REGIONAL AND NATIONAL EXPERIENCE

94. The international guidance developed by the OECD and FAO/WHO has been practically applied to the safety assessment of GM food products in several countries. To facilitate such assessments, guidance documents embracing the substantial equivalence concept have been published. The majority of these documents address the safety assessment of GM plants and have interpreted substantial equivalence consistently. Internationally, these guidance documents have been used in the assessment of a significant number of GM plant products during the five years, demonstrating that the concept of substantial equivalence is a rational scientific approach that has been applied effectively to the assessment of those novel foods which have been approved for commercial use. However, there are clearly differences in the application of substantial equivalence in different Member countries, and other stakeholders, which need to be resolved.

95. There are also regional and national differences in the levels of risk that are considered acceptable. The results of risk assessment studies have been taken into account differently in different OECD countries, as reflected in specific provisions of their regional and national legislation.

96. These differences have resulted in different risk management decisions and approaches. For example, some countries require an explicit approval decision, while in others this is voluntary. In addition, some countries prohibit the production, import, sale, and deliberate release of GM foods containing genes that might confer antibiotic resistance to micro-organisms if such genes have been introduced through genetic modification for food production.

97. Other factors that could lead to differences in legislation include the wish to ensure that production and use of GM organisms are consistent with concerns for ethical behaviour and social justice, that they conform to the principle of sustainable development, and that they not have detrimental effects on health and the environment.

98. In order to expand on these topics, several Member countries have contributed descriptions of their national experiences with the safety assessment of GM foods for this report (see Annex 1).

CHAPTER III - CURRENT NEEDS AND FUTURE CHALLENGES

A. INTRODUCTION

99. Recent developments in applying modern biotechnology to food and feed production have attracted considerable attention and generated much concern among the public. The introduction of novel food characteristics that differ significantly from the conventional could increase this concern in the future. It is important, therefore, to ensure that mechanisms are in place to keep the public informed about the safety assessment procedures that exist for novel foods.

100. A related challenge is the varying needs and expectations of consumers in different parts of the world regarding food quantities and quality, nutritional values and cultural distinctions. Such factors need to be taken into account in considering issues related to food production methods, trade, and recent developments such as improvements in the nutritional qualities of crops, functional foods, or nutraceuticals.

101. Although a large volume of information exists on the effects of consuming various foods and feeds, in order to fully assess the equivalence of a novel food or feed to their conventional counterparts, it is necessary to establish “baseline” information on the composition of conventional foods and feeds (i.e., the constituents of foods and feeds). The Task Force has begun the process of accumulating an information base, useful to regulators, through its Consensus Documents. It is anticipated that information from new techniques, such as proteomics and metabolic profiling, will expand that information base in the future.

102. Given the current scale of consumption of GM foods, with some 40 million hectares of GM crops cultivated in 1999 (worth an estimated USD 2.1-2.3 billion (ISAAA, 1999), it is important for the Task Force to identify the types of products likely to be developed in the future and consider whether current safety assessment techniques will be sufficient. It is essential that safety assessment techniques keep pace with the type of foods being developed.

103. This chapter examines a number of current needs, particularly that of harmonising data requirements or approaches in order to improve the safety assessment of novel foods and feeds. It also addresses several challenges related to the safety of the “next generation” of GM products.

104. Consumer groups and the governments of several OECD countries have called for the establishment of a post-market surveillance mechanism for products that have been approved as novel foods, following a safety assessment. Some parties advocate that this mechanism should follow up and reinforce the initial risk assessment, as an integral part of the risk analysis process; others recognise the many technical challenges involved in implementing such a mechanism and therefore favour proceeding in a step-wise manner, beginning with a feasibility study.

105. As more countries develop pre-market approval systems for novel foods, it will become increasingly important to reach a consensus on safety assessment approaches internationally. To assist in this process, the Task Force has been developing Consensus Documents on crops including soybean and oilseed rape. The intention is to identify the key components that need to be analysed as part of the safety assessment of GM crops. Such an approach will increase the uniformity of data packages and facilitate international harmonisation of data requirements for approval of GM foods. Another need is to ensure that

all countries globally have the capacity to assess the safety of novel foods and feeds. The Task Force has recognised the need for capacity-building as a priority activity.

B. THE ADEQUACY OF EXISTING ASSESSMENT METHODS

106. GM foods are assessed for safety before being placed on the market. The previous two chapters have discussed the current safety assessment approaches in detail. These approaches are used routinely by regulatory authorities world-wide. Nevertheless, some criticisms, which have been discussed in detail at OECD and FAO/WHO expert meetings (OECD, 1996; FAO/WHO, 1996),[a] related to the adequacy of current approaches include the following:

- Some countries believe that procedures for establishing substantial equivalence are based on the determination of gross composition. This kind of evaluation might fail to detect possible toxic metabolites which have accumulated, if the introduction of transgenic material has silenced an existing plant gene and disrupted a metabolic pathway. We acknowledge that this kind of effect is not unique to novel foods. It can just as easily occur using conventional breeding techniques for crop development. New approaches such as differential display techniques, or the development of proteomics, may (when validated for use in safety assessment) further the development of the concept of substantial equivalence. In Chapter II of this report, the concept of substantial equivalence is described in detail.
- Some countries believe that issues concerning long-term tests should be re-evaluated, and the problem of a specially formulated test and control diet should be examined.
- Some countries believe that it is questionable whether the use of proteins extracted from sources other than the GM organism under examination is adequate for developing toxicity tests. Proteins expressed in a different host undergo different post- translational modification and may not have the same biological and physical properties. However, for those inserted genes posing special risk concerns because they express toxins (e.g. pesticidal proteins), some countries require specific data to allow analysis of any potential structural and functional differences.
- Tests aimed at evaluating endocrine and exocrine functions are not included in the pre- market safety assessment. It would be useful to have these tests available for use in those cases where the novel gene products are similar to chemicals known to have endocrine and exocrine functions.
- Tests normally used to assess toxicity include *in vitro* digestibility of the protein which is used to compare the properties of the novel gene product to the characteristics of known proteins. This test is not intended to detect any potential toxicity in the very young, the elderly, and that segment of the population which is unable to produce stomach acid. Test methods should be designed to evaluate

a . The first meeting of the Codex Ad Hoc Intergovernmental Task Force on Foods derived from biotechnology, in Chiba, Japan, on 14-17 March 2000, agreed to develop a set of broad general principles for risk analysis of foods derived from biotechnology. This Task Force also agreed to develop specific guidance on risk assessment of foods derived from biotechnology. Both tasks are due to be completed by 2003. The report of this meeting is available at: http://.codexalimentarius.net.

potential risks for those subjects when the gene product is similar to a chemical that is implicated in having unique toxicity when not digested.

107. A question frequently asked about food safety with regard to newly introduced traits concerns the effect of long-term exposure to new proteins. Chronic toxicity testing is used to address long-term exposure to synthetic chemicals. However, for proteins (as opposed to other chemicals) there is a certain predictable metabolic fate in the human or animal gut similar to that for conventional dietary proteins. One method used to address this metabolic prediction is the *in vitro* digestibility assay, which indicates the likelihood that a protein will have characteristics that would be unusual in dietary proteins. It is assumed that all proteins will act like dietary proteins and break down under digestive conditions into their constituent amino acids. If a protein is shown to be resistant to typical digestive fluids, there may be added exposure to the intact protein or to large pieces of the protein. This digestive resistance would lead to a different analysis than if the protein were broken down as expected. However, there is still no consensus on resistant proteins being a significantly different risk if none of the other toxicity tests yields adverse results. This question may be partly resolved when we know more about the quantity and quality of our current dietary exposure to proteins resistant to digestive enzymes. A more detailed discussion of the use of toxicology studies in the safety assessment of GM foods can be found at the Food Standards Agency UK web site.

108. The following paragraphs address the issue of testing whole foods, *in lieu* of testing the gene products of concern.

109. Animal studies are a major element of the safety assessment of many compounds, including pesticides, pharmaceuticals, industrial chemicals and food additives. In most cases, the test substance is well characterised, of known purity, and of no nutritional value. Human exposure is generally low. It is relatively straightforward to feed such compounds to animals at a range of doses (some several orders of magnitude above expected human exposure levels) in order to identify any potential adverse effects of importance to humans. Thus, it is possible in most cases to determine levels of exposure at which adverse effects are not present and so establish safe upper limits through applying appropriate safety factors.

110. However, foods are complex mixtures of compounds characterised by wide variations in composition and nutritional value. Due to their bulk and effect on satiety, they can usually be fed to animals only at low multiples of the amounts that might be present in the human diet. Another factor to be considered in conducting animal studies on foods, in order to avoid introducing adverse effects not directly related to the material itself, is the nutritional value and balance of the diets used. Identifying potentially adverse effects and relating these conclusively to an individual characteristic of the food can be extremely difficult.

111. Animal tests are an important tool in specific circumstances, but the need for them should be decided on a case-by-case basis. There is no scientific justification for insisting that all GM foods be subject to long-term feeding studies, as in the vast majority of cases these studies would be unlikely to produce meaningful information. Another consideration, in determining the need for animal studies, is whether it is appropriate to subject experimental animals to such a study if it is unlikely to produce meaningful information. Potential application of new techniques such as proteomics to complement existing safety assessment tools should continue under review, as should development of improved animal models that could mimic some features of the induction/elicitation of food allergy in humans or express preliminary signs of a novel protein's possible unintended effects. Until validated tests become available for reliable evaluation/prediction of a novel protein's allergenicity, the record of reported allergic reactions (which could be part of post-marketing surveillance) in relation to actual intake of the novel food would be a useful tool to guarantee complete safety for consumers.

112. Very few foods consumed today have been the subject of toxicological studies. Safety assessment of the many thousands of food products launched each year is generally based on the assumption that if individual ingredients already have an extensive history of consumption, a new combination of these ingredients will be equally safe. Many existing foods, however, would be likely to show adverse effects if consumed at high enough doses. When a novel food is compared with a conventional counterpart, the intention is to determine whether the new food is as safe as the counterpart. Since it is well documented that conventional soybean has the potential to affect endocrine functions, for example, GM soybean with an equivalent composition would have the same potential.

113. Toxicological examination of whole foods for dietary safety assessment may seem an ideal response to concerns about new traits introduced by modern biotechnology, especially in view of the sensitivity of the compositional analyses now used and the wide variation in food plants' identified nutrient levels. However, an important factor to be considered is that whole food testing rarely gives a margin of safety to the introduced substance being tested. The whole food may have a very low concentration of expressed protein for the new trait. Actual toxicity, if any, may be very difficult to discern in a whole food test, given the sensitivity limitations imposed by the number of test animals used, the low amounts of substance tested in the whole food, and the possibility that any adverse effect may be a rare occurrence. In addition, if the whole food is found by testing to be safe, it is difficult to extrapolate these results to other food plants that may have the same trait but at higher protein expression levels.

114. Unlike traditional toxicology methods used to assess the safety of conventional synthetic chemicals (e.g. pesticides) in isolation, whole food testing is limited to the amount of test substance (i.e. the new trait) expressed in the food. This can lead to complications during the whole food assessment, as illustrated by several products seen to date including the Flavr Savr™ tomato and Bt maize. Care must be taken to ensure that the laboratory animal is provided an appropriate diet. The fact that the non-modified tomato test substance itself may have a toxicological endpoint in the test animal also limits the sensitivity of the intended test. Tomato is not normally a part of the rodent's diet and may have its own toxicity for the animal. Unless appropriate control treatments with tomato are included in the study design, or a clearly different toxicological endpoint for the added trait is known beforehand, complications in interpretation may occur. The adverse effects seen when Flavr Savr™ tomato paste was used in rodent studies, due to dosing volume issues and inappropriate diet composition, are examples of this difficulty.

C. ALLERGENICITY

115. Since virtually all food allergens are proteins, food allergy is a major concern with regard to new proteins in food plants. The analysis is somewhat different for proteins coming from sources that have already had dietary exposure. In that case, the protein can be screened for reactivity to the sera of sensitive humans with some assurance that reactivity could indicate potential to induce food allergy. There are currently no validated animal models of food allergy that could be used to assess a protein's potential to become a food allergen if it has had no previous dietary exposure. Without a valid animal model, the allergenicity analysis for new dietary proteins consists of a comparative approach with known allergens. Nevertheless, some animal models are under development.

116. The current analysis for potential allergenicity to new proteins includes two main features: an amino acid similarity comparison with known toxins and allergens, and the results of *in vitro* digestion assays with the protein along with other biochemical characteristics of the protein. There are limitations on the amino acid similarity comparisons. The level of similarity between a suspect protein and a known allergen that would signal a significant food allergy is unclear. One approach has been proposed that the standard for comparison be eight contiguous amino acids; an eight contiguous amino acid sequence is believed to be the smallest epitope that can be recognised by an antibody. However, discontinuous epitopes

are also known to be recognised by antibodies. Regions of similarity with a suspect protein that are inside a protein's three-dimensional structure, and not exposed, are difficult to interpret. To date, no eight contiguous amino acid similarity have been found in the allergen database of any of the proteins thus far introduced into new foods.

D. NEW PRODUCTS AND FUTURE DEVELOPMENTS

D.1. Developments in modern biotechnology

117. Modern biotechnology is evolving rapidly. It is expected that new methods being developed will help address some of the concerns about the current "generation" of GM products. For example, questions raised with regard to the introduction of genes encoding antibiotic resistance have led to the development of alternative strategies. Many other mechanisms for selecting transformed plants now exist. Where antibiotic resistance markers are used, mechanisms exist to remove them from the transformed food plant.

118. One of the issues concerning the safety assessment of GM foods is whether gene insertion would affect vital metabolic pathways in the host organisms which could have adverse implications for human health. This situation is no different to the one encountered with classical breeding methods. Learning from the success of yeast artificial chromosomes, the development of plant artificial chromosomes (PAC) promises to be a powerful candidate for the next generation vector in plant transformation. PAC would allow the introduced genetic material to be precisely defined, and to be introduced and stably maintained within the plant without disrupting any existing genetic elements.

119. Mechanisms for introducing hybrid sterility already exist. These and other transformations that reduce compatibility, or the ability to compete in the wild, will help ensure that any potential problems associated with the transfer of introduced genes to non-transformed crops of the same type will be minimised.

120. Improvement of agricultural crops through modern biotechnology has primarily focused on the identification and isolation of genes that control important *agronomic* traits of food plants (first generation of GM plants). Food crops have been modified through insertion of new traits or the inhibition of existing gene functions, resulting in plants with improved herbicide tolerance or pest resistance. Evidence from field trials indicates that, in addition to introducing further improvements in agronomic properties, future genetic modification of plants will be focused on the improvement of food quality characteristics and on industrial and medicinal applications. In the future, it is likely that products will be developed that are not substantially equivalent to conventional counterparts. The OECD has already recognised the challenges presented in assessing the safety of such products (OECD, 1996).

D.2. Agronomic applications

121. All of the crops that have currently been genetically modified to increase their resistance to attack by specific insects, notably the European corn borer, produce a single crystalline protein derived from the bacterium *B. thuringiensis*. To increase efficacy, broaden activity and delay the development of insect resistance, strategies have been developed to introduce a number of different genes into crops. This may be done through conventional crosses between two GM plants, or through using a GM plant as the parent line for further transformation events, and is sometimes referred to as pyramiding genes or gene stacking. Genes coding for proteinase inhibitors, α-amylase inhibitors, lectins, chitinases or cytolytic endotoxins have all been successfully examined for their ability to increase the insect resistance of a wide variety of

crop plants. To date, these resistance factors have been used individually; in the future, they may be used in various combinations (including with the *Bacillus* protein) to produce transgenic plants with resistance to a far greater range of insect pests than at present.

122. Improving the capacity of crop plants to cope with specific environmental stress conditions is an important goal, given the need to bring marginal land into production. For instance, plants have been developed with the increased availability of phosphorus in animal feeds, through insertion of genes coding for phytase (alfalfa), or for phosphate transport proteins (*Arabidopsis*, tomato, potato). Aluminium tolerance has been increased in tobacco, papaya, rice and corn through insertion of genes coding for citrate synthases. Further research is focused on isolating, characterising and expressing multiple genes that help crops cope with drought, salt, or heat/cold stress conditions.

D.3. Food quality and public health

123. Detoxification of mycotoxins (fumonisin) by maize plants has been demonstrated through inserting genes from micro-organisms able to metabolise mycotoxins, while insertion of cowpea trypsin inhibitor in tobacco showed efficacy against mycotoxin-producing strains of *Aspergillus* and *Fusarium.* Identification of genes responsible for producing vitamins, carotenoids and many other bioactive compounds has provided the means to modify the content of these compounds in plants. Soybean and lupin have been modified to express higher concentrations of essential amino acids, potato and sugar beet to express higher content of starch and novel carbohydrates, soybean and sunflower to express higher oleic acid content; tomato has been modified with enhanced levels of beta carotene and lycopene, and rice with higher Vitamin A precursors and iron content.

124. In the future, it may be possible to remove or reduce the allergenic potential of foods to which sections of the population develop an allergic response. Some of these applications could be useful in combating diseases like childhood blindness and anaemia, as well as those resulting from protein deficiencies in developing countries. The development of foods with health protection or health promotion claims attracts considerable attention, but many issues such as identification of biosynthetic pathways and their regulation, characterisation of nutritional and toxic ranges of the modified food, still need to be elucidated.

D.4. Medicinal applications

125. Modified plants incorporating antigenic proteins of human pathogens may soon be used as oral vaccines. Raw potato, containing antigens of either hepatitis B virus or cholera toxin, are being tested in humans for oral immunisation. Altered forms of monoclonal antibodies against oral and gut pathogens can be produced by plants: for example, the expression of the Norwalk virus capsid protein, resulting in protection against viral gastroenteritis. Certain fruits, like banana, may serve as attractive carriers for edible vaccines. Production of therapeutic proteins in plants is promising, but clinical efficacy, differences in glycosylation patterns, allergenicity and stability need to be carefully studied. If such modified plants are intended for medical purposes, they must be assessed in the same manner as other medicinal products.

D.5. Industrial applications

126. Growing plants for other purposes than to provide food is not new. Crop plants may be grown to produce, for example, textiles or fuel. Through genetic modification, some new or expanding uses of crop plants for industrial purposes are possible. Crops grown for high production of seeds, like canola, corn,

cereals and rice, are suitable for chemical production since much of the product can be formed in the plant seed and is then readily harvested and stable during storage.

127. Use of products from GM plants for industrial applications can provide more cost-effective routes to high-value pharmaceuticals or a source of sustainable feedstock for the chemical industry. The oleic acid content of soybean has been increased, rendering this crop suitable for production of fatty acid polymers (estolides), components of hydraulic fluids. Oleic acid may also be converted into epoxy or acetylenic derivatives, components of paints and coatings. Canola genetically modified to produce a detergent (high lauric acid) for industrial use has completed field trials, and other varieties have been modified in order to produce biodegradable plastics based on polyhydroxybutyrate. GM maize is already used for commercial production of beta-glucuronidase (GUS) and chicken egg white avidin. Aprotinin for the pharmaceuticals industry made from GM maize is on the market.

D.6. Challenges posed by the "new generation" of GM products

128. Safety testing strategies for the "new generation" of GM products need to be designed according to the nature of the crop's modification or its intended use, especially if this is for medicinal purposes. In such cases, applying the principle of substantial equivalence is likely to lead to the conclusion that the new product cannot be considered comparable to its counterpart since profound alterations in the food crop's composition may have taken place.

129. In the case of genes coding for proteins to enhance the plant's ability to resist pests, information may need to be generated on the specific biological action of the protein. For example, it may be necessary to understand how the protein binds to receptors in the insect and how it mediates its toxic effect. Animal testing may be necessary to look for toxicity in mammals. For non-proteinaceous "pesticides," depending on their characteristics, it may be necessary to test for the potential of the substance to cause immunotoxic or endocrine effects, or the ability to disrupt digestive function. Generating such information may involve either whole food or single test substance testing. Because it is possible that introduced substances may interact with one another in gene stacking situations, it may be necessary to test for potentiation or antagonism.

130. A similar approach should be taken to assess the safety and functionality of foods that have been altered in their content of components with added nutritional value. Specific nutritional and toxicological studies must be designed in order to determine the *safety* and *beneficial* dose ranges of the new food ingredient or food. However, the scientific basis for demonstrating the safety and functionality of bioactive compounds is still fragile, and more research is needed to underpin health and other claims for food components. Many traits that may be of interest from the nutritional point of view are controlled by *multiple* genes involved in regulating biochemical pathways that are imperfectly understood. New molecular techniques such as micro-array DNA/RNA technology will be of great value in elucidating complex genetic control mechanisms in food plants, and in studies of interactions between bioactive food components and humans or animals.

131. The development of non-food crops presents a number of risk management challenges, associated in particular with cross-pollination. It will be important to consider food safety implications as part of the approval process for such crops. The use of by-products from such crops as animal feed is an additional issue that would need to be addressed before such crops could be approved for commercial cultivation.

132. To identify unintended effects due to the genetic modification, a systematic analytical comparison is made between the agronomic properties and composition of the GM organism and those of

its parent or other direct comparator, grown under conditions that are as identical as possible. Compositional analysis is normally on *single* components like macro- and micronutrients and plant-specific antinutrients or toxicants. Animal experimentation with complex foods to assess unintended effects can have severe drawbacks. It may not be possible to devise suitable diets containing substantial amounts of the test material without incurring nutritional imbalances, low sensitivity and small safety margins.

133. The process of assessing novel (including GM) foods needs to be sufficiently comprehensive to be able to address concerns regarding the safety of such foods now and in the future. New technological advances therefore need to be incorporated into the assessment procedure as soon as they are considered reliable enough to yield meaningful results. Various novel techniques were considered at the OECD workshop held in Aussois in 1997.

134. Detection of unintended effects at a higher integration level than single compound/component analysis can be carried out through (a) DNA sequence and gene expression analysis (genomics), (b) protein expression analysis (proteomics) and (c) secondary metabolite profiling (metabolomics). A combination of these techniques could provide detailed information on the nature and extent of potential changes in the metabolism of GM food plants, which may or may not be of toxicological concern. Results from these analyses would guide further toxicological studies, if necessary.

135. The Aussois workshop considered whether techniques such as micro-arrays and proteomics were robust enough to use in the routine safety assessment of novel (including GM) foods. Although it was felt that such techniques could potentially be very useful in helping to characterise even more precisely than at present any differences between GM and non-GM crops, they were still in their infancy. Much more development work would be needed before they could be utilised in the regulatory framework. The workshop concluded that current assessments of GM foods are thorough, and that they utilise reliable techniques to keep risk to a minimum, but that techniques which built on and refined the current substantial equivalent assessment would be welcome once validated. It was felt that these techniques show sufficient promise to be worth investigating further in the context of crops.

D.7. Genetically modified animal feeds

136. This document has focused primarily on the safety assessment of GM foods for human consumption. However, issues related to the use of animal feeds are also of importance. For example, GM soyabean or maize (with agronomic properties) have been authorised as animal feeds.

137. In addition there are already certain additives used in animal feeds derived from GM micro-organisms such as vitamins or amnoacids. The application of biotechnology in animal nutrition may deliver the following benefits:

- Improvement in the efficiency of feed conversion
- Optimal livestock performance
- Improvement in the nutritional properties of feed

E. THE FEASIBILITY OF USING POST-MARKET SURVEILLANCE TO ASSESS IMPACTS ON HUMAN HEALTH

138. To protect the consumer and animal health, it is accepted that novel foods and feeds should be fully assessed for safety before being placed on the market. If the assessment identifies safety concerns, the

product will not be approved for commercial use. Some member countries, therefore, see no scientific justification for the use of post-market surveillance.

139. On the other hand, others see the surveillance of potential adverse -or beneficial - effects of novel foods as a logical follow-up to the initial scientific risk assessment. They argue that post-market surveillance ought be required, serving to reinforce the initial pre-market risk assessment, as the results of the latter mean that a product's safety has been established only on the basis of the current state of available scientific knowledge. This could, in fact, apply to any pre-market safety assessment process. Nevertheless, it is recognised that drawing clear conclusions from epidemiology studies, particularly in relation to food components, is sometimes difficult.

140. A key requirement for post-market surveillance systems is that a clear hypothesis for testing be identified. While such a hypothesis may be available in the future concerning some novel foods, particularly those considered not to be substantially equivalent, it may not be available in all cases. However, it should be noted that post-market surveillance is one of the only methods, up to now, that can be used to demonstrate the absence of any possible long-term or unintended effect potentially due to consumption of a novel food.

141. Establishing a system for surveillance of the potential health effects of exposure to novel foods requires monitoring the patterns of consumption of novel foods in the population (and of health effects in both "exposed" and "non-exposed" individuals or populations) so that risk estimates can be derived. For such a monitoring system to be useful there needs to be a range of exposures; otherwise, any variation in health outcomes would be unexplainable by that exposure. Variations in exposure could be apparent over time (temporal trends), space (geographical trends) or both.

142. Some have suggested that insofar as modified crops used in food are also used in feed, it might be possible to draw conclusions from a post-marketing surveillance mechanism in farm animals, where the same type of feed is usually distributed to a large number of animals at the same growth stage. Exposed or non-exposed animal populations are easy to establish. However, as with post-market surveillance with human foods, the feasibility of such an approach has not been evaluated.

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

144. Besides monitoring for longer-term (chronic) effects, monitoring for acute effects needs to be considered. Possible health effects would include allergic reactions (including urticaria), gastrointestinal disturbances, skin rashes, etc. One possibility would be to monitor trends at allergy clinics, for example when a new food is launched on the market. However, this is an imprecise approach: it would be subject to possible referral biases, delays in referral, and other factors complicating interpretation. An example of a referral bias was the outcome of Bt microbial sprays in British Colombia, Canada. There was a large public concern at the prospect of public spaces being sprayed for the control of the gypsy moth. Before any Bt spraying was initiated, the agency in charge of the program flew over and sprayed water as part of a program to determine exposure. After the spraying of the water there was a significant increase in the reports of health effects probably due to the referral bias following increased public scrutiny. Such increased bias needs to be taken into account when such public monitoring programs are being designed. Another approach might be to monitor consultations with local medical practitioners. Any effect of

exposure to a novel food on consultation patterns/rates would need to be detected against background variations in consultations. Interpretation (without further study) would be limited, since exposure data on individuals would not be available. However, acute changes from the usual pattern of consultations (e.g. for allergic problems) following widespread introduction of a new food would provide a valuable indicator of the need for further study of a possible adverse health outcome.

145. Other epidemiological study designs might also be adopted, but there are problems associated with them as well. Ideally, it would be desirable to carry out long-term (cohort) studies on individuals, although such studies would be costly. They would need to be very large, and would be subject to difficulties in ensuring compliance.

146. Consideration could also be given to carrying out case-control studies when a particular outcome (in relation to a novel food) is suspected. Such a study would be "reactive" rather than constituting true "surveillance". Unless only very recent exposures were considered, it seems unlikely that an accurate picture of past exposure could be obtained in the case of widely used food ingredients (such as GM soybean products). However, this approach might be suitable for specific brand name products where there is a reasonable expectation of observing differences between people who have purchased the product, compared with those who have not.

147. The possibility of establishing a post-market health surveillance system has been examined in the UK. Recognising the many difficulties involved in developing such a system, an initial feasibility study to look at available data and the usefulness of the data has been proposed. Work is currently being commissioned; when completed in 18 months, it will be subject to peer review.[b] In France, planning is well under way to establish a traceability system for GM crops intended for use as food or feed, in order to facilitate labelling requirements. Post-market surveillance can also be performed on a case-by-case basis if it is found (through risk assessment) to be needed. The first step in implementing this type of surveillance would be to track GM crops used in food. Traceability procedures could provide this information.

148. If feasibility studies indicate that post-market surveillance is practical, methods and details concerning data collection should be determined. Common basic strategies should be harmonised internationally in order to minimise efforts and the use of resources, while maximising the reliability of the final results. This is an issue that the Task Force for the Safety of Novel Foods and Feeds may wish to keep under review.

F. COMMUNICATION WITH THE PUBLIC ON APPROACHES TO SAFETY ASSESSMENT

149. It is widely recognised that more could - and should - be done to make information concerning the safety assessment of novel foods available to the public. This has become more important with increased consumer interest in the safety of GM foods. OECD countries and intergovernmental organisations are looking for new ways to share their experiences. They are promoting information dissemination and sound understanding of the safety issue on the part of consumers.

150. A number of countries have adopted measures concerned with sharing information on the safety assessment of GM foods with the public. These include:

b . A full discussion of the issues involved can be found at: http://www.foodstandards.gov.uk/maff/archive/food/novel/elliott.htm.

- inviting public comments on reports containing safety evaluations by scientific assessment bodies;
- disclosure of data used in safety assessments to support applications; and
- publication of results of meetings of safety assessment bodies.

151. Regulatory authorities are actively involving, and consulting with, the public with regard to food safety and regulation. Some authorities have a policy of full disclosure of information contained in applications (except for confidential commercial information).

152. The Internet is increasingly used to make information on safety assessment and approval procedures available to the public. It is a good source of information on crops and other foods that have been approved. Some countries are exploring the potential of the Internet to make details of applications more widely available to make the assessment process as open transparent and inclusive as possible.

153. OECD's BioTrack Online site (OECD, Web Site) is a valuable source of information on regulatory developments in Member countries. It includes: information on responsible ministries or agencies; details of laws, regulations or guidelines. There are also two important databases: one on products that have been commercialised, and the other on field trials of GM crops that have taken place in OECD countries.

154. Food labelling is a valuable source of information for many consumers. Labels contain important information on ingredients. If consumers wish, they can seek more detailed information from the manufacturer or retailer. Given the small size of many labels, there are constraints on the amount of information they can provide, therefore food labelling would not be a practical way of communicating to the public information on approaches to food safety assessment. Ways to make information electronically available to consumers using new technology, including in-store terminals and bar code readers, are being investigated by a number of retail organisations. Such an approach would enable consumers to access the types of information they consider most important and could also provide consumers with more detailed information, such as safety assessment approaches.[c]

155. Other approaches adopted with considerable success in some countries include appointing consumer representatives to committees responsible for safety assessments. Consensus conferences have been tried with varying success.

c. Discussions aimed at agreeing whether and how to implement a general international standard for labelling GM foods are being taken forward through the Codex Committee on Food Labelling.

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ANNEX 1:

NATIONAL EXPERIENCES CONTRIBUTED BY MEMBER COUNTRIES

AUSTRALIA

A. The current situation

Australia established a food standard for regulating genetically modified (GM) foods in July 1998. This food standard is a joint standard with New Zealand. The food standard makes it mandatory for GM foods to undergo a comprehensive safety assessment before they may be sold. The food safety assessments are undertaken by the Australia New Zealand Food Authority (ANZFA), an independent statutory authority responsible for developing and reviewing food standards in Australia and New Zealand. To date, ANZFA has completed food safety assessments and recommended approval of glyphosate-tolerant soybeans and *Bt*-cotton. Food safety assessments for 17 other GM crops, the majority of which have been modified to be herbicide and/or resistance to insect pests, are currently underway and are due to be completed by mid to late 2000.

B. Principles used in safety assessment

ANZFA uses an open and transparent assessment process. All data submitted in support of an application (except commercial-in-confidence data) is available to of the public. ANZFA also undertakes two rounds of public consultation during its assessment of applications. This ensures that the public may comment on, and contribute relevant information to, the safety assessment reports before they are finalised.

ANZFA's safety assessment process for GM foods is based on concepts and principles that have been developed through the expert consultation processes of the OECD and the WHO/FAO. Guidelines,[1] explaining ANZFA's safety assessment process, are published on its web site.[2]

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

i. safety assessments use scientific, risk-based methods;
ii. safety assessments are conducted on a case-by-case basis;
iii. both the intended and unintended effects of the genetic modification are considered;
iv. where appropriate, comparisons are made to conventionally produced foods.

C. Issues considered in the safety assessment of GM foods

In assessing the safety of a GM food, ANZFA considers the following issues:

(i) Nature and Stability of the genetic modification

A full description and molecular characterisation of the genetic modification is considered necessary for identifying the relevant parameters requiring assessment in the new food. Information is therefore required on the gene transfer method, the origin and function of any novel genetic material, and a molecular characterisation of the inserted genetic material. Data demonstrating that the novel genetic material has been stably integrated in the host genome and that the phenotype is stably maintained over several generations is also required.

(ii) General safety issues

The general safety issues are divided into three areas - history of use, nature of any novel protein and the potential for transfer of novel genetic material to gut micro-organisms.

The history and extent of use of the conventional unmodified food is an indication of its wholesomeness and safety and thus it can be used as a benchmark for comparison with the modified food variety. Factors considered include the levels of nutrients, anti-nutrients, natural toxicants and ability to support typical growth and well being.

The nature of the novel proteins present in the GM food are analysed to determine their expression levels and patterns and to determine whether the expressed protein has been modified in any unexpected way.

The impact on human health from potential transfer of novel genetic material, including antibiotic resistance genes, to cells, including micro-organisms, in the human digestive tract is also considered. ANZFA considers the overall risk of gene transfer affecting the therapeutic use of antibiotics in humans to be so low as to be effectively zero. Nevertheless, this issue is addressed on a case-by-case basis in all safety assessments.

(iii) Toxicological issues

Toxicological concerns include the levels of naturally-occurring toxins as well as the potential toxicity of any novel proteins. The levels of naturally-occurring allergenic proteins as well as the potential allergenicity of any novel proteins are also considered.

In an evaluation of the potential toxicity of the novel protein there is consideration of any known toxins in the organism which was the source of the novel genetic material, as well as the similarity of the novel protein to any known toxins. The results of any animal toxicity tests and the likely human exposure to the novel protein are also considered.

There are two issues with regard to potential allergenicity which are considered. Firstly, whether an allergen has been transferred during the genetic modification which may cause foods previously considered non-allergenic to become allergenic. Secondly, whether the expression of a novel protein in a food will lead to the development of a new allergy in certain individuals. The former is more easily addressed than the latter because, if an allergen is already known, it is possible, using human sera or human

skin tests, to test for its presence in the modified food. There are no reliable tests or animal models, however, which enable the prediction of the allergenic potential of novel proteins. Instead, potential allergenicity can only be indicated by examination of the novel protein, to determine whether it has any of the characteristics common to allergens. If the novel protein does not possess these characteristics, it can usually be concluded that the novel protein is unlikely to be allergenic.

(iv) Nutritional issues

In assessing the safety of a GM food, a key factor is the need to establish that the food is nutritionally adequate and will support typical growth and well-being. In most cases, this can be achieved through an understanding of the genetic modification and its consequences together with an extensive compositional analysis of the food. Where, on the basis of available data, there is still concern or doubt in this regard, ANZFA considers that carefully designed feeding studies in animals may provide further reassurance that the food is nutritionally adequate. Such studies may be considered necessary where the compositional analysis indicates significant differences in a number of important components or nutrients or where there is concern that the bioavailability of key nutrients may be compromised by the nature of the genetic changes to the food. Ordinarily, however, ANZFA does not consider animal feeding studies to be essential for determining the safety of a GM food.

D. Public concerns in relation to GM food

ANZFA regularly consults with the public on the issue of GM foods. The comments received from these consultations reflect:

- a considerable lack of understanding among the general Australian public of the nature of the technology;
- an unease in relation to the safety of GM foods;
- strong demands for consumer choice;
- the need for more communication about the technology by Government and by the agri-food industry.

E. References

1) Guidelines for the Safety Assessment of Foods to be included in Standard A18 – Food Produced using Gene Technology.

2) http://www.anzfa.gov.au

CANADA

Canadian regulatory framework for biotechnology products

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 realised 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 favourable climate for investment, development, innovation and the adoption of sustainable Canadian biotechnology products and processes.

Departmental/Agency responsibilities

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, fertilisers and veterinary biologics. For genetically modified crop plants, the CFIA assesses the potential risk of adverse environmental effects; authorises 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 micro-organisms used in bioremediation, waste disposal, mineral leaching or enhanced oil recovery.

Canadian regulatory process

A. Foods

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.[1] These Guidelines are based upon the Organisation for Economic Co-operation and Development (OECD) approach of substantial equivalence.[2] 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 characterisation 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 straightforward. 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 through the sequence until a conclusion can be reached as to whether or not the modified 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.

B. Feeds

In Canada, Novel Feeds are regulated by the federal Feeds Act and Regulations. The Regulations were amended in 1997 to specifically address feed products of biotechnology, or Novel Feeds. All Novel Feeds are evaluated in terms of safety and efficacy prior to their use.

The term Novel Feeds encompasses a wide range of ingredients that include: viable microbial products such as direct-fed bacteria, yeast, and forage/silage inoculants; non-viable microbial products and by-products such as fermentation products including enzymes, biomass proteins, amino acids, vitamins,

and flavouring ingredients; and plants with novel traits and their by-products such as soybean seeds, canola meal, and corn gluten. Products of traditional breeding, mutagenesis, as well as recombinant nucleic acid techniques, trigger the requirement for pre-market review in Canada.

A guiding principle in Novel Feed safety assessments has been substantial equivalence. With regards to livestock feed, substantial equivalence can be viewed as the equivalence of the Novel Feed in terms of its specific use and safety to animals, humans and the environment, in comparison to that of the same species that is in use and generally considered safe in Canada, based on valid scientific rationale. A comparison is made of the microbial, molecular, and compositional aspects of the Novel Feed to those of its traditional counterparts. Once substantial equivalence to an existing feed product can be established, additional safety testing may not be required. Where similarity or degree of equivalence cannot be established, a more extensive feed safety assessment is necessary.

Assessments are carried out on a case-by-case basis. Typical assessments include a complete identification of the product and how it is processed, a description of the host and donor organisms, a characterisation of the modification and the introduced novel trait, and an assessment of the final modified feed. An essential part of the process used in the feed safety assessment is to ensure that unsafe residues are not introduced into human food products by the animal ingesting Novel Feeds. The submission must demonstrate that the new gene and proteins are degraded or denatured during the processing of the feed or digestion of the feed in the animal. If incomplete digestion occurs, the metabolite must be shown to be nontoxic or non-allergenic. The potential for transfer of genes to animal rumen or gut microflora for both the introduced desired traits and marker genes is considered. Nutrient composition and bioavailability, the introduction of toxicants or anti-nutritional factors are also assessed.

Canadian experience (foods and feeds)

Since 1994, forty-three genetically modified plant products for human food use have completed the regulatory process in Canada. Similarly, seven micro-organisms and thirty-five genetically modified plants have been approved for feed usage. The majority of these products are crop plants, e.g. corn, canola, soybean, and potato that have been genetically modified to improve agronomic traits such as crop yield, hardiness, and uniformity; insect and virus resistance; and herbicide tolerance. Tomatoes that express delayed ripening characteristics have also been approved. A few of the products reviewed have been modified to result in an intentional compositional change (e.g. canola oil with increased levels of lauric acid).

Over the past six years, genetically modified plants have been part of the Canadian food supply. This is significant when considering that corn and soybean are ingredients in many processed food products. There have been no reports of adverse health effects in the population due to the consumption of these products. Similarly, there have been no reports of adverse health effects in animals due to the inclusion of genetically modified plants and /or micro-organisms in their diets.

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.

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.

References

Foods

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

2) Organisation for Economic Co-operation and Development. Safety Evaluation of Foods Derived by Modern Biotechnology: Concepts and Principles, OECD: Paris, 1993.

Feeds

1) Regulatory Directive, Dir 95-03, Guidelines for the Assessment of Livestock Feed From Plants with Novel Traits, April 1995, Canadian Food Inspection Agency.

2) Draft Guidelines for the Safety Assessment of Novel Feeds: Microbial Products, November 1996, Canadian Food Inspection Agency.

3) Canadian Feeds Regulations, SOR/83-593, 1983.

For additional information:

Health Canada's web site: http://www.hc-sc.gc.ca/food-aliment

Canadian Food Inspection Agency's web site: http://www.cfia-acia.agr.ca

Expert Scientific Panel: http://www.rsc.ca/english/index.html

Canadian Biotechnology Advisory Committee: http://www.cbac.gc.ca

GERMANY

Regulatory framework

Before the European Union Regulation on Novel Foods (Regulation No 258/97) [1] came into force, the placing on the market of genetically modified organisms (GMOs) and derived products intended for food use required an authorisation according to the European Communities Directive 90/220/EEC [2]. The safety assessment was carried out taking into account any aspects of toxic or other harmful effects arising from the genetic modification on human health and the environment (Directive 94/15/EC [3], Annex II B Part D and Directive 97/35/EC [4]). According to these requirements, insect tolerant maize, glyphosate tolerant soybeans and rapeseed were considered as safe as their conventional counterparts for human consumption.

Since the coming into force of Regulation (EC) No 258/97 (Novel Foods Regulation) on 15 May 1997, the food safety assessment has been carried out according to the Commission Recommendation 97/618/EC [5] of 29 July 1997. These recommendations describe the scientific aspects and the presentation of information necessary to support notifications for the placing on the market of novel foods and serve as a guideline for the competent authorities for the preparation of the initial assessment reports. This includes the evaluation of the genetically modified organism focusing on those aspects relevant to human food safety issues.

Responsible bodies

Two federal institutes share the responsibility for the safety assessment of foods derived from genetically modified organisms (GMOs) according to the Regulation (EC) No 258/97. The Robert Koch Institute (RKI) provides in co-operation with the Federal Institute for Health Protection of Consumers and Veterinary Medicine (BgVV) the initial assessment reports or comments to initial assessment reports delivered by competent authorities of other European Union member states as far as foods containing or consisting of GMOs but do not contain them. The BgVV has the lead in preparing initial safety assessment reports and comments for those foods which are derived from GMOs but do not contain them. The Robert Koch Institute is responsible for the environmental risk assessment of the GMOs whereas the BgVV is responsible for the assessment of food safety. For any other categories of novel foods within the scope of Regulation (EC) No 258/97 is the BgVV the competent authority to deliver initial safety assessment reports or comments. The BgVV is also the German competent authority for the delivery of statements on the substantial equivalence of novel foods which can be used as a basis to notify substantial equivalent novel foods to the European Commission according to Regulation (EC) No 258/97.

The BgVV receives advice from a Scientific Advisory Committee. Members of the committee are scientists from academia, industry, federal and state institutions as well as consumer associations which have expertise in the fields of molecular biology, toxicology, allergology, nutritional sciences, food chemistry and technology, microbiology and veterinary medicine.

Activities

Requirements for the safety assessment of new proteins derived from genetic modifications in plants were elaborated by a Working Group on the Evaluation of Food Safety of the German Research Council (DFG) in 1997. They were presented at the OECD Workshop on the Toxicological and Nutritional Testing of Novel Foods in Aussois, France, on March 5-8, 1997.[6]

In November 1997, an International Symposium on "The Novel Foods Regulation in the European Union - Integrity of the Process of Safety Evaluation" was held in Berlin. Proceedings of this Symposium were published in 1998.[7]

A brochure on foods and genetic engineering was published in 1998 for the information of the consumer, particularly about the safety assessment of these novel foods.[8]

Funded by the European Commission and the German Ministry of Health, a study on the feasibility of a post-market monitoring system for foods derived from genetically modified organisms is being carried out.

As the Novel Foods Regulation requires the labelling of foods derived from genetically modified organisms if these are no longer equivalent to conventional counterparts, it was necessary to enable the responsible bodies to control compliance with this requirement. In Germany a working group was established in 1994 to develop and standardise methods for the detection of genetic modifications in novel foods. The first detection methods were published in 1998.[9] Further efforts are focusing on the development of methods to quantify food ingredients derived from genetically modified organisms.

References:

1) Regulation (EC) No 258/97 of the European Parliament and of the Council of 27 January 1997 concerning novel foods and novel food ingredients, Official Journal of the European Communities No. L 043, 14/02/1997, p. 0001-0007.

2) Council Directive of 23 April 1990 on deliberate release into the environment of genetically modified organisms (90/220/EEC), Official Journal of the European Communities No. L 117, 08/05/1990, p. 0015-0027.

3) Commission Directive 94/15/EC of 15 April 1994 adapting to technical progress for the first time Council Directive 90/220/EEC on the deliberate release into the environment of genetically modified organisms, Official Journal of the European Communities No. L 103, 22/04/1994, p. 0020-0027.

4) Commission Directive 97/35/EC of 18 June 1997 adapting to technical progress for the second time Council Directive 90/220/EEC on the deliberate release into the environment of genetically modified organisms, Official Journal of the European Communities No. L 169, 27/06/1997, p. 0072-0073.

5) Commission Recommendation 97/618/EC of 29 July 1997 concerning the scientific aspects and the presentation of information necessary to support applications for the placing on the market of novel foods and novel food ingredients and preparation of initial assessment reports under Regulation (EC) No. 258/97 of the European Parliament and of the Council, Official Journal of the European Communities No. L 253, 16/09/1997, p. 0001-0036.

6) Pöting, A. in: Report of the OECD Workshop on the Toxicological and Nutritional Testing of Novel Foods, Aussois, France, 5-8 March 1997.

7) BgVV Federal Institute for Health Protection of Consumers and Veterinary Medicine (Ed.) (1998) Proceedings of the International Symposium on Novel Foods Regulation in the European Union – Integrity of the Process of Safety Evaluation, November 18-20, 1997, Berlin.

8) Schauzu, M. et al. (1998) Lebensmittel und Gentechnik – Eine Verbraucherinformation, BgVV-Informationsschrift.

9) Zagon, J. et al. (Eds.) (1998) Methods for the Detection of Genetic Modifications in Transgenic Organisms, BgVV-Hefte 06/1998.

KOREA

The Korea Food and Drug Administration (KFDA) is responsible for the safety assessment and management of foods in Korea.

The KFDA established "Guidelines regarding safety assessment for genetically modified foods and food additives" on August 20, 1999 (KFDA Notification 1999-46). The objectives of these guidelines are to establish safety assessment requirements and procedures for genetically modified foods and food additives. Foods and food additives developed through recombinant DNA techniques may be commercially distributed after the Commissioner's confirm which such foods and food additives do not pose any health risks to humans.

Application scope of these guidelines is divided into two groups, the foods with recombinant or without recombinant itself; the former includes agricultural products produced through recombinant DNA techniques and progeny cultivar thereof, and the latter include food additives derived from recombinants.

The guidelines also include the procedures for application and requirements. The documents for application are regarding the purpose and methodology of using recombinants, host, vector and inserted DNA. Not only these information, the information of recombinants are needed. The information includes newly added traits due to recombinant manipulations (products of genes), toxicities (excluding allergenicity), metabolic pathways (reaction possibility due to unique ingredients included in host), difference from the host (data on nutrients and anti-nutrients, and data on changes in ingredients which become toxic due to changes in contents), and allergenicity.

To evaluate the safety of genetically modified foods, KFDA operates a special expert committee on safety evaluation of these foods which are composed of experts from KFDA, universities, research institutes, and consumer's unions.

KFDA is considering to change the statues of these guidelines to systematic mandatory regulation based upon the Food Sanitation Act in Korea.

IRELAND

The novel foods regulation of the European Parliament and of the Council

As a member of the European Union, the placing of genetically modified food on the market in Ireland is governed by Regulation (EC) No 258/97 of the European Parliament and of the Council of 27 January 1997 concerning novel foods and novel food ingredients. This Regulation came into force in all Member States on May 15 1997 and provides that novel foods and novel food ingredients (including genetically modified food) must undergo a safety assessment and be officially approved/authorised before being placed on the European market. It also contains provisions in certain instances for the labelling of novel foods and novel food ingredients.

Applicants seeking market approval for their product in the European Union are required to supply a detailed dossier of information. In line with the Commission's Recommendation 97/618/EC of July 29, 1997 key issues to be contained in the dossier include compositional analysis, toxicological requirements, implications of the novel food to human nutrition, allergenic potential and assessment of marker genes.

The assessment of applications in Ireland

The Department of Health and Children is currently the competent authority and assessment body for this Regulation in Ireland. However, it is planned to designate the Food Safety Authority of Ireland as the competent authority and the assessment body for this Regulation in the coming months. The Food Safety Authority of Ireland Act (FSAI) was enacted in July 1998 and the Authority was formally established in January 1999. The principal function of the Authority is to take all reasonable steps to ensure that food produced, distributed or marketed in the State meets the highest standards of food safety and hygiene reasonably available and in particular to ensure that such food complies with food legislation and where appropriate with standards or codes of good practice.

At present, the GMO and Novel Foods Sub-Committee of the Food Safety Authority of Ireland assesses applications made under this Regulation. To date, no application has been made to the Irish competent authority (i.e. the Department of Health and Children) so the experience in the assessment of novel foods is at present very limited. However, this Department has received applications that have been submitted to the competent authorities of other EU Member States and the GMO and Novel Foods Sub-Committee has commented on these applications.

Coordination of a national position

A number of Ministries has responsibility for various aspects of biotechnology. In order to co-ordinate the overall Government position, an inter-departmental working group on GMOs, chaired by the Department of Enterprise, Trade and Employment, has been established. The Group is comprised of senior officials from the Department of Enterprise, Trade and Employment; the Department of Health and Children; the Department of Agriculture, Food and Rural Development; the Department of the Environment and Local Government; the Department of Education and Science; the Food Safety Authority

of Ireland and the Environmental Protection Agency. The Group is due to report in the coming months. This report will include a number of recommendations for the future.

JAPAN

Governmental research activities were launched in 1986 to assure the safety of food ingredients derived from genetically modified micro-organisms. They not only built a compendium of the existing research and development works but also identified the potential problems and the areas where government actions were required.

A Sub-Committee on Biotechnology was established in 1989 within the National Food Safety Council, which advises the Minister of Health and Welfare on technical matters. The Sub-Committee published in 1991 three documents shown below.

- *Basic Principles on Safety Assurance for Foods and Food Additives Produced by Biotechnology*
- *Guidelines for Manufacturing Foods and Food Additives by Application of Recombinant DNA Techniques*
- *Guidelines for Safety Assessment of Foods and Food Additives Produced by Recombinant DNA Techniques*

In 1993, a governmental research group was established to prepare guidelines for the safety evaluation of recombinant-DNA seed plants. In January 1996, the report of this research group resulted in the enlargement of the scope of the aforementioned Ministerial Guidelines to include seed plants.

As of December 1999, 29 foods and six ingredients have been evaluated and recognised as safe by the Ministry of Health and Welfare. The safety evaluations of genetically modified foods are being operated on a voluntary basis at this stage.

A revision of the current safety assessment scheme has been started with a view to making it mandatory to the effect that foods whose safety has not been evaluated will not be allowed to be marketed. This will be implemented as of April 2001. This planned revision is expected to increase the transparency of the safety evaluation procedures (see footnote) and to increased consumer confidence.

Ministry of Agriculture, Forestry, and Fisheries created in 1996 *Guidelines for Safety Assessment of Feed Produced by the Recombinant DNA Technique*. As of March 2000, 27 feeds have been recognised as safe by Ministry of Agriculture, Forestry, and Fisheries.

Footnote

Criteria for the safety assessment procedure (as regard food safety);

- Similarities between the newly developed food and conventional food
- Purposes and usage of recombinants
- Host
- Vector

- Gene and Gene products
  - Donor
  - Method of gene insertion
  - Structure
  - Properties
  - Purity
  - Stability
  - Number of inserted gene copies
  - Position, timing and amount of gene expression
  - Safety on antibiotic-resistant marker genes
  - Presence or absence of exogenous open reading frames and the possibility of their transcription and expression
- Recombinants
  - New properties acquired by the recombinant DNA techniques
  - Allergenicity of recombinant products
  - Toxicity of recombinant products
  - Effect of recombinant products on metabolic pathways
  - Difference from the host
  - Survival and proliferation in the external environments
  - Restrictive conditions on survival and proliferation abilities of recombinants
  - Inactivation method of recombinants
  - Approval and usage as food in other countries
  - Methods of preparation, breeding and cultivation
  - Methods of seed production and management

THE NETHERLANDS

In the early nineties in the Netherlands, the Food and Nutrition Council and the Health Council both issued advisory reports on Biotechnology and product safety. These were the basis for the national legislation on novel foods and novel food ingredients as a part of the food law. Now the Health Council Committee on the safety assessment of novel foods advises, under the terms of the European Novel Foods Directive 258/97, the Dutch Minister of Public health, Welfare and Sport and the State Secretary for Agriculture, Nature management and Fisheries. Genetically modified foods are an important category that has been assessed in the years since the Directive was implemented. So far there have been dossiers on genetically modified maize and soybean with the agronomically relevant traits of herbicide resistance and resistance to plague insects. The gene constructs that were used for this are well known, as well as the proteins that are produced by them. The Netherlands Committee pays special attention to secondary plant metabolites as indicators for possible side effects of genetic modification as long as techniques like genomics and proteomics are not yet applicable. The Committee is gradually developing and refining its evaluation tools in this relatively new field of risk assessment. Alongside the further refinement of analytical, nutritional and toxicological tests there should be proportional attention for the relevance of possible outcomes in terms of consumer safety and health effects. A public version of the advisory reports of the Committee are made available at the web site of the Health Council at www.gr.nl.

NORWAY

Regulatory framework

Norwegian legislation on GM foods is divided between the Norwegian Ministry of Environment and the Norwegian Ministry of Health and Social Affairs.

The Gene Technology Act of 1993, laid down by the Norwegian Ministry of Environment, relates to the production and use of genetically modified organisms, including the use of such organisms as foods and feeds. The purpose of the Act is to ensure that the production and use of genetically modified organisms take place in an ethically and socially justified way, in accordance with the principle of sustainable development and without detrimental effects on health and the environment. No application for use of genetically modified organisms as food or feed has as yet been approved for marketing under this Act, although several are at time under consideration. Since autumn 1997, three GM edible plants have been banned from being marketed because of the presence of antibiotic resistance genes used as marker genes.

As part of the EEA-agreement (European Economic Area) between EFTA (European Free-Trade Area and the EU, Norway has implemented the Directive 90/220(EEC on the deliberate release into the environment of genetically modified organisms).

The Food Control Act, laid down by the Norwegian Ministry of Health and Social Affairs, includes a regulation on approval of GM foods, which entered into force 1 January 1999 (Regulation of 18 June 1998 amending the general regulations of 8 July 1983 No. 1252 on the production and sale etc. of foodstuffs). The Norwegian Food Control Authority (SNT) is the competent authority for administrating the regulation. The regulation includes novel foods and all types of GM foods except genetically modified organisms. The purpose of the regulation is to ensure that novel food and GM food is evaluated for human consumption prior to marketing. No GM food has as yet been approved for marketing under this regulation, although processed products from three different types of GM maize are at time under consideration. A Norwegian regulation is being developed for the purpose of banning the production, import and sale of GM foods containing genes coding for resistance to antibiotics when such genes have been introduced by means of genetically modification. Similar regulation for GM feedstuffs is also under development.

Risk assessment

Prior to approval of a GM food in Norway, a risk assessment has to be conducted based on a case-by-case evaluation of each individual GM food. The health risk assessments of each GM food are performed by the National Institute of Public Health and the National Council on Nutrition and Physical Activity. Principle questions as to the health risk in GM food are treated in SNT's Scientific Committee.

The health risk assessment is performed according to SNT's guidelines for health risk assessment of novel food. The guidelines are mainly based on recommendations from the European Union (Commission Recommendation 97/618/EEC of 29 July 1997).

SNT is keeping the criteria for health risk assessment under continuous review, taking into account any new scientific information. Particular attention is given to possible measures of unintended effects of the genetic modification, for instance through a broader measure of the concept «substantial equivalence» and the development of methodology on feeding tests.

SPAIN

Where food safety is concerned, Spain, as a Member State of the European Union, applies Directive 90/220/EEC on the deliberate release into the environment of genetically modified organisms (GMOs) and Regulation (EC) No 258/97 concerning novel foods and novel food ingredients.

In order to consider notifications of the deliberate release and placing on the market of such products, Spain has enacted a law setting up the National Biosafety Commission (CNB). The said Commission studies, revises and oversees files before granting consent. It is responsible, more especially, for assessing the safety of transgenic products.

Where novel foods are concerned, products are evaluated prior to being placed on the market, that evaluation taking account of such aspects as allergenicity, new components, the presence of possibly toxic products, etc.

Moreover, foodstuffs, novel foods and food ingredients deriving from genetically modified organisms, which are intended for human consumption, have to be labelled in accordance with the various EC Regulations.

UNITED KINGDOM

The UK has had a system for assessing the safety of all novel foods for a number of years. The first novel food, mycoprotein, was cleared in 1983. The UK Government receives advice from the Advisory Committee on Novel Foods and Processes (ACNFP). The ACNFP has considerable experience in assessing the safety of novel foods, including those produced using genetic modification, having been considering these issues for over ten years.

When assessing a novel food, the ACNFP bases its safety assessment on the concept of substantial equivalence. Similarities and more importantly, differences between the novel food and the existing food are identified and examined carefully. The Committee then decides whether the novel food can be considered equivalent to, and therefore as safe as, the existing food.

There are a wide range of foods and food ingredients encompassed within the term “GM food”. The information needed to support an application for approval of an individual GM food needs to address the specific safety issues relevant to that particular food. For this reason it is not possible to set out a checklist of information that needs to be submitted in all cases. Prior to the development of EC legislation in this area, the ACNFP developed a series of decision trees that use structured series of questions to identify the information requirements of a particular novel food. Based on this experience, the European

Community developed its own decision trees, which form the basis of the guidance which lays down how safety assessments of novel foods should be conducted.

Issues considered during the safety assessment of individual GM foods

Foods are complex mixtures of compounds, which have a wide variation in their composition and nutritional value. They can only be fed to animals at low multiples of the amounts that might be present in the human diet. Identifying potential adverse effects and relating these to the food and not other factors can therefore be extremely difficult for a number of reasons. It has to be considered, therefore, whether subjecting animals to experimentation is likely to give rise to meaningful information. If the ACNFP is not satisfied that the data submitted answers any concerns, then they request further information. This can include data from animal tests. Each case is decided on its merits. The ACNFP has published a paper on the toxicological issues relevant to the safety assessment of novel foods on its web site.

There is a remote possibility that levels of a previously unknown toxin, allergen or antinutrient might be elevated as an unintended consequence of a genetic modification and not be detected by the compositional analyses. Modern molecular approaches could be used to enhance the ability to compare the whole genome of the parent organism with that of the GM derivative, to give further reassurance that no unintended effects had occurred as a result of the genetic modification. The ACNFP recently reviewed the available technology. It felt that, in the future, it may be possible to use genomic, proteomic and/or metabolic profiling approaches to further increase the robustness of the substantial equivalence principle as a safety evaluation tool, but at present such approaches are not sufficiently developed for routine use in this way.

In assessing the safety of a GM food or food ingredient, the ACNFP considers a number of issues:

i) toxicity of the inserted genes

All foods consumed raw or only lightly processed will contain genetic material which is readily digested in the human gastrointestinal tract. The inserted genes will be digested in the same way as the genes already present in the organism. Therefore, it is highly unlikely that consumption of the inserted gene itself would have any implications for health. Nevertheless this issue is carefully considered in the case of each application.

ii) toxicity of the products of the inserted genes

If a novel protein is present in the derived food products, this can be extracted and its toxicity investigated using conventional toxicity tests. Any novel protein is likely to be digested in the same way as the many conventional proteins already present in that food. Nevertheless, the safety assessment of all GM foods includes an evaluation of the toxicity of any protein products of the inserted genes. Nothing is assumed or taken for granted.

iii) allergenicity of the products of the inserted genes

The safety assessment of GM foods includes a consideration of potential allergenicity. Many foods derived from GM organisms undergo considerable processing before consumption, which might destroy any novel proteins. If intact novel proteins are present, their allergenic potential needs to be

assessed. This includes a consideration of the allergenicity of the host organism, as well as that of any organisms used as sources of the inserted genes, together with that of any taxonomically related species. Foods containing genes from plants known to be associated with serious allergenicity are not allowed onto the market if there is any likelihood that public health will be adversely affected.

Reliable and predictive tests for potential allergenicty are not available at present, and research to develop such tests is currently being carried out. As an additional safeguard, consideration is always given to the need for some form of post market monitoring or surveillance to be carried out as a condition of the approval. Such arrangements were put in place when (non GM) lupin flour was approved in the UK to enter the food supply in 1997.

iv) transfer of genes encoding antibiotic resistance

If such genes are present in the final food products, any safety implications that they might raise are thoroughly evaluated. The ACNFP considered this issue in detail in 1994 and 1996. Their conclusions are that GM micro-organisms consumed in a viable form should not contain antibiotic resistance marker genes. All other GM foods need to be assessed on an individual basis, taking into consideration the likelihood of transfer of the gene, its subsequent maintenance and expression in micro-organisms found in the human gut, and the clinical use and importance of the antibiotics for which resistance is encoded. In addition to possible transfer to gut micro-organisms, it is also important to consider the likely levels of exposure and the possibility of transfer into bacteria present in the mouth and in the respiratory tract as a result of exposure via pollen and other airborne sources, such as dusts generated by dry milling.

It is also known that some ampicillin resistance genes have undergone point mutations, which resulted in extension of the range of antibiotics that could be inactivated by the products of the resistance gene to include a number of clinically important cephalosporins. If such point mutations occurred in antibiotic resistance genes used as selective markers, which subsequently transferred into gut micro-organisms, this could have implications for the clinical treatment of serious infections including meningococcal meningitis or any other disease.

Using this precautionary approach, the ACNFP has recommended rejection of three applications submitted to it. These cases involved a maize containing an ampicillin resistance marker gene, and two GM cottonseeds containing a gene conferring resistance to streptomycin and spectinomycin. It was considered that there was a very small, though finite risk of transfer of resistance to micro-organisms in the intestinal tract of animals fed unprocessed plant material (processing destroys the antibiotic resistance gene), and that this could compromise clinical therapy in man. Other factors, such as clinical and veterinary use of antibiotics and their use as growth promoters in animal feed, are likely to have a much greater effect on the occurrence of resistance in the wider environment than possible transfer from GM plants. Nevertheless, the ACNFP believes that it is right to be cautious about their use in genetic modification.

v) Nutrition

Any nutritional consequences of the consumption of the GM food need to be considered, both in terms of possible changes in the levels of nutrients in the food itself and in terms of the effects on the overall diet of replacing a conventional food with the GM one. It has been recognised for a long time that whereas each individual change may not be significant on its own, cumulative effects on nutrient intake may be significant. However this is equally applicable to changes in food products arising from conventional plant breeding. A recent joint meeting of ACNFP and the UK Committee on the Medical

Aspects of Nutrition Policy has recommended building on current diet and nutrition data collection systems to monitor this issue.

vi) GM micro-organisms

The safety assessment of all GM micro-organisms is conducted using experience and background acquired in the assessment of the safety of non-GM micro-organisms. This assessment takes into account whether or not the final food will contain viable micro-organisms, and includes a full characterisation of the inserted DNA, including the sources from which it was obtained, plus a history of human exposure to the host organism and any associated health effects. Information is always required on the vector used in the modification and to demonstrate that the new genes are inserted in a stable way. If the GM micro-organism is consumed in a viable form, information on its behaviour and lack of pathogenicity is also carefully assessed.

vii) GM plants

The assessment of the safety of foods derived from GM plants is carried out in comparison with the non-GM counterparts that they would replace. In doing this, the natural variation in the composition of plants and in the foods derived from plants, due to climatic and other environmental factors is taken into account as far as is possible. Information is therefore assessed on the composition (major nutrients, including vitamins and other beneficial components) and agronomic behaviour (growth patterns, flowering time and yield, both with and without application of herbicides in the case of herbicide-tolerant GM plants) of GM plants grown at several sites. This information is evaluated in comparison with that obtained on non-GM plants grown at the same time. These data are needed to demonstrate that the GM plant falls within the natural variation seen for the non-GM counterpart, except for any intended effects of the modification. The assessment also considers the nature of the genetic modification and includes a detailed characterisation of the inserted genetic material. The approach taken to date has been based on a case-by-case evaluation of each individual GM food, so that any unintentional effects of the particular modification can be assessed. The ACNFP is not prepared at this stage to consider any blanket clearance of particular gene sequences.

Various novel techniques were considered in November 1999 at a UK Advisory Committee on Novel Foods and Processes (ANCFP) seminar (Food Standards Agency UK Web Site).

Finally, in a new measure designed to increase the openness of the regulatory system, Regulations have been introduced in the UK which require companies submitting novel food applications to the UK to permit the routine disclosure for public comment of all non-confidential information that they provide in support of an application. Criteria are laid down for deciding what information can legitimately be claimed to be confidential. The intention is to keep this to a minimum. The data to be released will be made available electronically on the ACNFP webpage at www.foodstandards.gov.uk/maff/archive/food/foodnov.htm. It will offer anyone who is interested, including members of the public, the opportunity to submit comments that the ACNFP can take into account as part of their deliberations. The ACNFP's draft conclusions will also be offered for comment before being finalised.

Food Standards Agency of the United Kingdom Web Site,
http://www.foodstandards.gov.uk/maff/archive/food/novel/toxrev.htm.

UNITED STATES

FOODS DERIVED FROM GENETICALLY ENGINEERED PLANTS – FDA'S EXPERIENCE

I. Introduction

In 1992, the Food and Drug Administration (FDA) published in the *Federal Register* (57 F.R. 22984, May 29, 1992) a policy statement regarding foods derived from new plant varieties. The policy statement explains how foods and animal feeds derived from new plant varieties, including those produced by the new methods of recombinant DNA (rDNA) techniques, are regulated under the existing framework of the Federal Food, Drug, and Cosmetic Act (the Act). The policy also provides guidance to industry that describes a standard of care for ensuring the safety and wholesomeness of foods developed by rDNA technology. The guidance addresses safety issues with respect to the food crop that is being modified, the potential for any introduced genetic material to encode harmful substances, the safety of intentionally introduced substances such as proteins, fatty acids, and carbohydrates, and the assessment of endogenous toxicants and important nutrients in the modified plant. The guidance also discusses regulatory issues such as when an introduced substance is not generally recognised as safe and would require premarket approval as a food additive, and when special labelling would be required under the Act.

II. The first genetically engineered food

The first food derived from a crop modified through rDNA techniques to come before FDA was the Flavr Savr™ tomato developed by Calgene, Inc. (Calgene) of Davis, California. To develop this tomato, Calgene used rDNA techniques to introduce an antisense polygalacturonase (PG) gene into the tomato genome. The PG gene, normally present in tomatoes, encodes the enzyme PG, which is associated with the breakdown of pectin (a constituent of the tomato cell wall) and the resulting softening of ripe tomatoes. The antisense PG encodes an RNA that suppresses the production of the PG enzyme. The result is a tomato that softens more slowly and, thus, can remain on the vine longer for enhanced flavour development. In developing the Flavr Savr™ tomato, Calgene used the kanamycin resistance marker gene that encodes the enzyme aminoglycoside-3'-phosphotransferase II (APH(3')II, also known as neomycin phophotransferase, nptII), as a selectable marker.

Calgene asked FDA to evaluate the Flavr Savr™ tomato under the most stringent procedures available for foods to ensure public confidence in their product. Thus, in addition to evaluating the firm's safety and nutritional assessment of the tomato, Calgene requested that FDA approve use of the APH(3')II enzyme, the only new substance in the Flavr Savr™ tomato, as a food additive.

Overall, FDA evaluated the data and information provided by Calgene to determine whether Flavr Savr™ tomatoes have been significantly altered when compared to varieties of tomatoes with a safe history of use. Based on the safety and nutritional assessment described in the 1992 policy statement and the modifications of the Flavr Savr™ tomato, FDA evaluated the following information for the new tomato variety: the source, identity, function, and stability of genetic material introduced into Flavr Savr™ tomatoes; analytical studies on the composition of Flavr Savr™ tomatoes; and the safety of APH(3')II. FDA also evaluated the environmental safety of the use of the kanamycin resistance gene as part of its review of the food additive petition for APH(3')II.

Based on the analysis of the information that Calgene submitted concerning the Flavr Savr™ tomato, FDA concluded that the new variety had not been significantly altered in regard to safety when compared to varieties of tomatoes with a safe history of use. FDA also concluded that APH(3')II was safe for consumption when present in tomatoes as a result of use as a selectable marker and promulgated a regulation to that effect (21 CFR 173.130 and 573.170). With respect to labelling, the agency concluded that the correct common or usual name for the Flavr Savr™ tomato is "tomato" because the new tomato is not significantly different from the range of commercial varieties referred to by that name.

Prior to its decisions, however, FDA convened a public meeting of its Food Advisory Committee (FAC), a committee composed of experts from outside the FDA, and discussed its policy as well as its evaluation of the safety of the Flavr Savr™ tomato that had taken approximately four years. The FAC agreed that the policy represented appropriate oversight of foods derived from genetically engineered plants and that all safety questions have been answered for the Flavr Savr™ tomato. The FAC further advised FDA that based on the nature of the products that were approaching the market, it would be appropriate to institute a process that involves a more judicious review procedure that is customised to address the specific changes in the food product.

III. Consultation procedures

Following the Flavr Savr™ decision, FDA has not found that it is necessary to conduct a comprehensive scientific review for each food derived from a bioengineered plant. Rather, consistent with its 1992 policy, FDA has been advising industry that it is prudent practice for developers of new varieties to consult with the agency on safety and regulatory questions before marketing their products. To facilitate these consultations, FDA developed procedures through which developers can consult with the agency, and through which these consultations can be brought to closure.

Briefly, the consultation procedures are as follows (the procedures can be found at http://vm.cfsan.fda.gov/~lrd/consulpr.html). Developers initiate consultations with FDA early in the product development phase. When the developer has accumulated the data that it believes are adequate to ensure that its product is safe and complies with the relevant provisions of the Act, the developer submits to FDA, information regarding the safety and nutritional assessment that has been conducted for evaluation by agency scientists, and if necessary, meet with agency scientists to discuss the scientific data in more detail.

The goal of FDA's evaluation of the data provided by developers during the consultation process is to ensure that human food and animal feed safety issues or other regulatory issues (e.g., food additive issues, labelling) are resolved prior to commercial distribution. During the consultation process, FDA does not conduct a comprehensive scientific review of data generated by the developer. Instead, FDA considers, based on agency scientists' evaluation of the submitted data and other available information, whether any unresolved issues exist regarding the food derived from the new plant variety that would necessitate legal action by the agency if the product were introduced into commerce. Examples of unresolved issues may include, but are not limited to, significantly increased levels of plant toxicants or antinutrients, reduction of important nutrients, the presence of new allergens, or the presence in the food of an unapproved food additive. FDA considers a consultation to be completed when all safety and regulatory issues are resolved.

The safety and nutritional assessment summary submitted to FDA typically includes:

- The purpose or intended technical effect of the modification on the plant, together with a description of the various applications or uses of the bioengineered food, including animal feed uses.

- Information on the molecular/genetic characterisation of the modification including the identities, sources and functions of introduced genetic material as well as stability of the insert.
- Information on the expression products encoded by the introduced genetic material, including an estimate of the concentration of any expression product in the bioengineered plant or food derived from the plant.
- Information regarding any known or suspected allergenicity and toxicity of expression products and the basis for concluding that foods containing the expression products can be safely consumed. This would generally include an assessment of the introduced protein for properties attributed to food allergens such as resistance to digestion, acid and heat degradation, as well as comparing the amino acid sequence of the introduced protein to sequences of known allergens for any similarities that may be indicative of allergenic potential.
- Information comparing the composition or characteristics of the bioengineered food to that of food derived from the parental variety or other commonly consumed varieties with special emphasis on important nutrients, and toxicants that occur naturally in the food. Depending on crop, typical parameters measured include protein, fat, carbohydrate, moisture, ash, amino acids, fatty acids, vitamins, calcium, phosphorus, selected trace minerals, acid detergent fiber, and acid detergent fiber. Examples of antinutrients measured include phytic acid (canola, corn, soybean), erucic acid, glucosinolates (canola), gossypol, cycloprepenoid fatty acids (cottonseed), lectins, phophatides, stachyose, raffinose, trypsin inhibitors (soybean).
- For those foods that are known to cause allergy, submissions to FDA have included data on whether the endogenous allergens have been altered by the genetic modification.
- Some submissions have included the results of comparisons of wholesomeness feeding studies with foods derived from genetically engineered plants and the non-modified counterparts.

In November, 1994, FDA presented the consultation procedures to a joint meeting of its Food, and Veterinary Medicine Advisory Committees using seven products that came before the agency following the Flavr Savr™ tomato. These included three new tomato varieties that have been genetically engineered for delayed-ripening, two pest-resistant crops (a virus-resistant squash, and a Colorado potato beetle-resistant potato), and two herbicide-tolerant crops (a bromoxynil-tolerant cotton, and a glyphosate-tolerant soybean) The joint committee agreed with FDA that the consultation procedures represent appropriate oversight for the type of products that were coming before the agency.

To date, FDA has completed 45 consultations on foods derived from genetically engineered plants. Most of these plants from which the foods have been derived have been modified for agronomic properties although some were modified for processing characteristics or modified oil compositions. A complete list of the completed consultations can be found at http://vm.cfsan.fda.gov/~lrd/biocon.html on the World Wide Web. The products are grouped by the year in which the consultations were completed. The name of the developer, the trait introduced into the variety, as well as the source and identity of the introduced gene responsible for the trait are also given.

IV. Other activities

1. Conference on Allergenicity

On April 18-19, 1996, FDA, the Environmental Protection Agency (EPA), and the Department of Agriculture (USDA) hosted a "Conference on Scientific Issues Related to Potential Allergenicity in Transgenic Food Crops". The goal of the Conference was to foster a dialogue among scientists on food allergy and on whether foods derived from genetically engineered plants have an altered potential to induce food allergy. The conference assessed current information regarding what makes a protein a food allergen and what means are available to assess allergenic potential of proteins.

Topics that were discussed include plant breeding and biotechnology, allergenic foods, exposure and allergenic response, T cell and B cell antigenic determinants, *in vitro* and *in vivo* diagnostics, and animal models. The scientists noted that methods are available to assess allergenic potential for proteins that are derived from sources to which consumers have reacted and for which serum is available, but it may be useful to establish a serum bank. They also noted that while there are no direct methods to assess potential allergenicity of proteins from sources that are not known to produce food allergy some assurance can be provided that a new protein is unlikely to cause an allergic reaction by evaluating its similarity with characteristics of known food allergens (i.e. whether the new protein has a similar protein sequence, is resistance to enzymatic and acid degradation, is heat stable, and is of the appropriate molecular size).

FDA has gained valuable information from this conference and has used this information in its assessment of the potential allergenicity of proteins newly introduced into food as a result of genetic engineering of plants. In addition, using information from the conference and other published information, FDA is in the process of preparing a draft guidance to industry on the assessment of newly introduced proteins into foods for potential allergenicity.

2. Draft Guidance regarding Use of Antibiotic Resistance Marker Genes as Selectable Markers

Since FDA's decision regarding the use of the kanamycin resistance (*kan*^{r}) gene product, aminoglycoside 3'-phosphotransferase II (APH(3')II, also known as neomycin phosphotransferase II or nptII) in the development of transgenic tomato, cotton, and oilseed rape, the agency continued to receive inquiries regarding the safety and regulatory status of antibiotic resistance marker genes. Therefore, FDA sought to develop sound scientific principles regarding the safety of the use of antibiotic resistance marker genes in the development of transgenic plants for food use and to provide sound scientific guidance to crop developers regarding the safe use of antibiotic resistance marker genes. Towards this end, FDA undertook several consultations with outside experts between November, 1996 and February, 1997. The purpose of the consultations was to determine whether circumstances exist under which FDA should recommend that a given antibiotic resistance gene not be used in crops intended for food use, and if so, to delineate the nature of those circumstances.

Based on these consultations, in September, 1998, FDA issued a draft guidance to industry regarding the use of antibiotic resistance markers in genetically engineered plants. This draft guidance as well as the report of the consultations on which the guidance was based can be found at http://vm.cfsan.fda.gov/~dms/opa-armg.html on the World Wide Web.

3. Public Meetings

FDA recently concluded a series of three public meetings (November 18 and 30, and December 13, 1999, see http://www.fda.gov/oc/biotech/default.htm) on issues related to foods and animal feeds derived from plants developed using bioengineering techniques. The purpose of these public meetings was for the agency to share its current approach and experience over the past 5 years regarding safety evaluation and labelling of food products derived from bioengineered plant varieties, to solicit views on whether FDA's policies or procedures should be modified, and to gather information to be used to assess the most appropriate means of providing information to the public about bioengineered products in the food supply.

Some of the specific questions FDA asked on scientific and safety issues included:

- Has FDA's consultation process achieved its intended purpose? Based on experience to date, should this regulatory approach ''sunset," continue in its current state, be made mandatory, or otherwise be revised?
- What newly emerging scientific information related to the safety of foods derived from bioengineered plants is there, if any? Are there specific tests which, if conducted on such foods, would provide increased assurance of safety for man or animals consuming these foods?
- What types of food products derived from bioengineered plants are planned for the future? Will these foods raise food safety issues that would require different approaches to safety testing and agency oversight? If so, what are those approaches?

On labelling and public information issues, FDA asked the following questions:

- Should FDA's policy requiring labelling for significant changes, including changes in nutrients or the introduction of allergens, be maintained or modified? Should FDA maintain or revise its policy that the name of the new food be changed when the common or usual name for the traditional counterpart no longer applies? Have these policies regarding the labelling of these foods served the public?
- Should additional information be made available to the public about foods derived from bioengineered plants? If so, what information? Who should be responsible for communicating such information?
- How should additional information be made available to the public: e.g., on the Internet, through food information phone lines, on food labels, or by other means?

These meetings afforded consumers, industry, and academia an opportunity to provide focused comment on these issues. FDA accepted written comments on these issues through January 13, 2000. FDA will evaluated information it has received from the three meetings as well as comments, and determine if the agency needs to alter or refine its existing policies and procedures.

CURRENT NATIONAL EXPERIENCE - ENVIRONMENTAL PROTECTION AGENCY

The USEPA has evaluated several types of pest resistance traits that appear in food. One type are those traits that fall under the proposed jurisdiction of the pesticide laws (FIFRA and FFDCA) and have been registered as plant-pesticides. The other types are those traits that occur in food plants as a result of traditional methods of plant breeding and have been proposed as excluded from registration requirements.

For the second type of traits a specific evaluation for food and feed safety was required in order to propose an exemption from the pesticide registration requirements.

The companies that registered the plant-pesticides have submitted to EPA toxicology tests and biochemical analyses to assess potential toxicity and food allergenicity hazards prior to making a determination on food safety for the introduced traits. The traits registered to date have been for the most part protein toxins derived from *Bacillus thuringiensis*. The tests performed on these proteins include an acute oral toxicity test at high doses and *in vitro* digestibility tests with simulated gastric and intestinal fluids. All these tests are done with purified preparations of the protein. Other biochemical tests such as the protein's stability to acid and heat in typical food processing are also often done as part of the assessment for food allergenicity. Since the exact amino acid sequence is known or can be deduced from the introduced nucleic acid sequence, the proteins are also compared to known protein sequence databases for similarities to known toxins and allergens. This comparison is done sequentially, eight amino acid residues at a time, for areas of homology between the introduced protein and known protein toxins or allergens. Protein expression data for the introduced trait is often generated to assess insect resistance management issues but also the likely dietary exposure. The totality of this information, including what EPA has seen to date for toxicity and exposure to the proteins in their natural bacterial host which have often been registered as microbial pesticides, is used to judge the likely hazards and risks for the proteins expressed in plants. To date EPA has chosen to grant a food tolerance (i.e., maximum residue level) exemption to these bacterial proteins based on their low toxicity. The DNA associated with the introduced traits as well as certain plant pathogenic viral traits have also received food tolerance exemptions base on their safety as a part of the current food supply. The rationale for exempting the latter traits is similar to that used to examine pesticidal traits naturally occurring in food plants which follows.

The second type of experience relates to pest resistance traits in plants that EPA evaluated when choosing to exclude certain traits from registration requirements. Technically, these pest resistance traits are "pesticides" under the legal definition of FIFRA. EPA has chosen to exempt these pest resistance traits from the requirements for pesticide registration when they are found in sexually compatible plant species. This sexual compatibility standard is a convenient means of describing the resistance traits currently found in the commercial cultivars and introduced through traditional breeding. The pest resistance traits found in food plants have a certain type of safety evaluation due to their long history of dietary exposure without adverse effects. In many ways this dietary history is a more rigorous appraisal of food safety due to the longer exposure in humans and domestic animals. However, it does not lend itself to the traditional food safety evaluation done for other agricultural chemicals based on the results of toxicology tests with high doses of purified compounds in homogenous laboratory animal populations.

An examination of compounds expressed by food plants that have been implicated in incidents of food intoxication reveal several groups that may be related to pest resistance traits. These traits include disease recognition proteins that induce a resistance phenomenon termed the hypersensitive response which probably have little toxicological concern. It also probably includes glycoalkaloids, cyanogenic glycosides, glucosinolates, lectins or enzyme inhibitors found in various food plants that appear to be related to disease resistance or could be insect- active toxins or feeding deterrents. That foods such as potatoes, tomatoes, cassava, mustards and soybeans have demonstrable levels of plant toxins and have been consumed for long periods by human populations without significant adverse effects is testimony to the safety of the food supply. That altered levels of these toxin traits can be incidentally introduced into traditional food plants, even in current breeding practices with wild plant relatives, attests to the effectiveness of the safety screening now used and provides a sound foundation for the further safety assessment done for plants developed through the new technologies. The safe consumption of foods derived from plants containing these compounds often relate to specific efforts to reduce toxin levels through food processing or selective breeding for cultivars with reduced toxin levels.

ANNEX 2: LIST OF PARTICIPANTS IN THE TASK FORCE FOR THE SAFETY OF NOVEL FOODS AND FEEDS

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