EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL

Scientific Steering Committee

RISK ASSESSMENT IN A RAPIDLY EVOLVING FIELD:

THE CASE OF

GENETICALLY MODIFIED PLANTS (GMP)

Scientific Opinion
of the
SCIENTIFIC STEERING COMMITTEE

Expressed on 26/27 October 2000

Risk Advancement in a rapidly evolving field: the case of Genetically Modified Plants (GMP)

1. Introduction: context of the report and opinion

The Scientific Steering Committee (SSC) is presently preparing a general opinion on how to give scientific advice on consumer protection related scientific issues that are growing quite quickly in importance, or are highly likely to do so. This growth in importance may be due to recent evidence indicating a potential adverse effect on public health or on the environment, new developments in scientific understanding in a particular area and / or escalation of a specific public concern.

In order to illustrate the difficulties encountered and its approach to cope with uncertainties - if necessary by identifying research needs to address the most important gaps in knowledge - the SSC selected one example of what is considered by a large part of the public as a growing issue, namely genetically modified plants (GMPs). The SSC is aware that this question of genetic modification is also of utmost importance for micro-organisms and has multiple societal, ethical, economical and other aspects, but its analysis is focussed on the issue of the food safety and the environmental impact of genetically modified plants (GMPs).

It is unlikely that the slow rate of introduction of new GMPs for assessment will continue. A scan of the EU data base held for the European competent authorities at the Joint Research Centre (JRC), which summarises the notifications for small scale field trials, reveals that 63 different plants have been tested in the EU so far. The range of traits varies from protection against various forms of destructive agricultural pests to the production of source material for industrial processes. A large variety of different genes can be inserted into a particular crop and tested independently. The 450 trials in the USA between 1989 and 1997 made with GM potatoes, for example, encompassed at least 32 different traits. As a consequence, the range and quality of genetic modifications in crops and numbers of new products likely to be seeking regulatory approval in the future will be far greater than those already considered and will inevitably challenge the capability of the safety assessment methods and procedures.

The present system of evaluating the risk of chemicals and foods, including GPOs, is largely based on a case by case scientific appraisal for human health and the environment. Further complexities arising through multiple-exposure to combined food constituents and their environmental impact, require increasing understanding of biological systems, their interaction and the scale of effects. Variables to be taken into account include the time scale of exposure, the significance of (repeated) low doses and threshold effects, heterogeneity in time and space, and additive consequences for health and the environment.

Scientific advances continuously generate more powerful new tools and methodologies that should be applied to the assessment of all kinds of risk to health and the environment, including those linked to GMOs, in order to cope with the complexity of the issues.

The SSC recognises that there is inevitably a problem when the demand for innovative and perhaps complex approaches to adapt safety assessments to new issues results in appreciable delays before an existing technology can be marketed.

To see the potential safety issues regarding GMP in perspectives it should be recognised that also some other techniques, e.g. chemical mutagenisis, radiation or cell fusion, produce genetic changes in plants and that an evaluation of the long-term impact of these unpredictable changes on health and environment is poorly documented. There is no scientific argument that traits from the use of these technologies should not undergo the same safety assessment as those from targeted genetic modification.

Given this series of complex interacting issues, the assessment of GMPs is considered in some detail to see whether the current approach to assessment will be adequate for the future generations of GMPs and how new methodologies could be developed to take into account the increased complexity.

2. Current assessment systems and experience to date

2.1 Assessing food, feed and environmental safety of genetically modified plants

In the EU the assessment of risk to humans, animals and the environment and any hazard following unintended consumption or exposure is based on Directive 90/220/EEC. In addition, the requirements of the Novel Foods and Novel Food Ingredients Regulation (EC 258/97) must be satisfied before a genetically modified (GM) crop (or any product derived from it) can be used for food purposes. The current principal issues considered by scientific advisory bodies in relation to the release of GM plants are:

- the potential for transfer of the introduced gene(s) to other traits or species
- the safety of the introduced gene product(s)
- the potential for the introduction of unintended secondary changes.

The third issue highlights the wider difficulty of testing the safety of any food, whether traditional, novel or genetically-modified. Many traditional foods from other countries have been introduced into Europe without the same testing as now applied to novel foods and feeds. Inadvertent changes, i.e. other than those deliberately introduced by recombinant technology and related to the random insertion of the gene(s) (pleiotropic effect), should now be assessed in the transformed plant by generic tests, e.g. comparison of the composition of the transformed plant, to those of the host plant. This approach has proved adequate for the new crops that have been formally assessed for safety to date at a National or European level ("first generation of GMP") but so far only a

handful of structural and regulatory genes have been involved in this approach (Table 1).

Table 1: *The structural genes introduced into crops that have sought EU approval for release*

Introduced gene	Description/phenotype	Number of crop plants
	Insect resistance	
cryl1(A)b and *cry1(A)c*	truncated Bt toxin	4
	Herbicide tolerance	
pat and *bar*	glufosinate ammonium (Basta) tolerance	5
cp4 epsps and *gox*	glyphosphate (Roundup) tolerance	3
	Antibiotic resistance markers	
nptII (syn.aph(3')-II	kanamycin /neomycin resistance	5
nptIII (syn aph(3')-IIIa	amikacin tolerance	1
addA (syn.ant(3")-Ia	streptomycin/spectinomycin resistance	2
Bla	ampicillin resistance	1
	Male sterility/fertility	
Barnase and *barstar*	ribonuclease and ribonuclease inhibitor	2
	Sense/anitsense gene silencing	
Pg (partial sense)	delay in fruit softening	1
Gbss (antisense)	starch with reduced amylose content	2

The consideration of any hazards and risks posed by transgenics involving the genes listed in Table 1 drew on historical data such as the absence of detectable toxic effects of the *Bacillus thuringiensis (Btk)* toxin after 30 years of use as an insecticide as well as new data. Since these GM crops were also the first commercial products, they have been the subject of investigation by many other interested parties and, as a result, a considerable body of data exists on which to base safety assessments. Risk assessments are made on a case by case basis for each modified crop plant according to the characteristics, traits and the agricultural and environmental context of each crop.

At European level the Scientific Committees of the European Commission are in charge of carrying out Risk Assessment in the field of Consumer Health and the Environment. Until today, the above mentioned principal issues have been considered by the Scientific Committees when assessing a number of "first generation GMPs" (details are provided in annex 1) and experience has been accumulated. Two Committees have already produced guidance for applicants,

requesting authorisation of a GMP or food containing GMOs[1]. In addition to specific opinions addressing the safety of individual GMPs, also opinions of a more general nature have been issued[2].

The development of the methodology and the collection of new data on GMPs in experiments in the laboratory and from monitoring studies in the field is an ongoing process. As a result new scientific data are continually being added to the public domain, making a regular monitoring of the validity of opinions necessary.

The human safety assessment takes its starting point in the establishment of substantial equivalence. Modification of a plant, whether by conventional plant breeding or by genetic engineering, necessarily introduces changes in the composition of the plant. If the changes are minimal or of no significance from health and environmental standpoints, then the plant can be said to be "substantially equivalent" to a comparator. This does not hold true if there are significant changes.

Biological and ecological phenomena related to the environmental release of GM organisms are not readily quantifiable in many instances and the methodology underpinning environmental risk assessment is far from standardised or final. A key part of the process is the application of expert judgement , which relies on the analysis of primary data relating to the modified organism, and to reasoning by analogy coupled with a high degree of scientific understanding and a qualitative judgement which is geared to anticipating and assessing any potential harmful consequences of this new organism.

The risk assessments made and published to date by the SCP have concluded that the authorised releases of the particular modified crop plants do not present safety issues to human health or to the environment.

2.2 Identified safety end points requiring revisiting

2.2.1 *Environmental safety*

2.2.1.1 Genetic transfer to other plants

The potential for genetic escape from any one plant to another (whether non-GM or other GM crop plants or related wild plant species) depends on a cycle of events coming together:

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[1] (a) Guidance document to facilitate notifiers in the preparation of plant GMO dossiers for consideration by the Scientific Committee on Plants (SCP/GMO/103-Final). Opinion of the SCP, 18/12/98. (b) Recommendations concerning the scientific aspects of the presentation of information necessary to support applications for placing on the market of novel foods and novel food ingredients (Scientific Committee for Food, opinion expressed on 13 December 1996) Part III: Recommendations concerning the scientific aspects of the preparation of the initial assessment reports on applications for placing on the market of novel foods and novel food ingredients (Scientific Committee on Food, opinion expressed on 13 December 1996)

[2] Opinion of the SCP on Bt-Resistance monitoring. 04/03/99

- Dispersion of pollen, containing modified genetic material, by wind or insect
- Simultaneous flowering of a recipient plant leading to successful fertilisation
- Production of viable seed
- Germination, establishment and growth of fertile hybrid plant. The competitive ability of any hybrid may be of relevance. In the absence of a selective pressure the more competitive will outgrow the others. In the presence of a selective pressure the plant that is better adapted will survive.
- Maturation to flowering of the hybrid (or recipient crop plant) and release of its pollen containing altered genetic material.

Relevant factors which will determine the likelihood of completing this sequence of events include (1) the distance that pollen disperses compared with the isolation distances required for a GMP crop and the extent of its separation from potential recipients and (2) the geographical occurrence, proximity and flowering synchrony of wild relatives with the potential for [fertile] hybridisation and the subsequent hybridisation rates.

2.2.1.2 *Accumulation of modified traits within crop plants*

There is the potential for 'gene-stacking' or the accumulation of different traits within the same plant when genetic transfer from other simultaneously flowering adjacent crops occurs or when there are residual flowering donor plants which have remained in the field from a previous crop (volunteer plants). A crop plant which has acquired the capacity to express genes, e.g. conferring tolerance to two different herbicides, would require different methods of control from that needed when either gene is expressed singly in a crop plant. This dual incorporation of genes may have crop protection consequences in the field but the significance of any transfer of genes to a wild related plant will depend on whether any selection pressure occurs in non-cropped habitats. This selection pressure may provide an environment that confers a competitive advantage to the novel plant.

The potential health implications of these processes will also need careful scrutiny.

2.2.1.3. *Potential impact on biodiversity*

The presence of, for example, a herbicide tolerant trait in a modified crop may result in a change in the pattern of herbicide use from that on the unmodified crop in terms of altered amounts or use at different times. This may impact on the diversity or structure of non-crop weed species in the field, which in turn may have an indirect impact on invertebrates associated with such weeds present in the crop. Such information is almost impossible to collect from small plot trials but requires monitoring on a biologically-meaningful scale which takes account of both the dispersion of the invertebrate species and the consequences of changes in these species for those higher up the food chain.

Preliminary information is available from limited laboratory studies on the effects of consuming GM crop plants or their expressed gene products on non-target insects. For example, in relation to insect resistant crop plants

(expressing a Bt toxin or a lectin), there is some information available from tri-trophic studies involving target insect pests and their non-target predators or parasitoids. Insects may be exposed to pollen containing the expressed products of genetic modification which may be found on both GM and non-GM food plants or the insects may themselves be pollinators collecting and storing materials. The impact on these insects or terrestrial ecology in general of changes in GM plants cannot be fully deduced from small plot trials.

In practice it has become clear that there are few assessments of the risks or details of any biological impact of existing chemical crop-protection methods. The consequences of using alternative measures to GM (e.g. the impact of conventional broad-spectrum insecticides or the use of microbial pesticides) are too poorly documented to allow a proper comparative assessment of the new GM plant on the biodiversity, e.g. of small insects in fields.

2.2.1.4. *Potential impact of insect resistant plants on insect resistance*

The constant exposure of insect pests to the expressed gene products when feeding on insect-resistant GM plants, may result in the more rapid development of resistance in target insect species compared with the use of discrete topical pesticide applications at infrequent intervals. Thus, with GM, an earlier onset of failure to control the targeted insect pest may result. Crop management options designed to slow or prevent the development of resistance include the siting of non-GM plants or "refuges" at sites adjacent to the GM crops. This approach aims to provide nearby sources of susceptible insects to mate with so that the speed of developing resistance is decreased through genetic dilution. The refuges also provide local sources of natural parasites and predators. The criteria for setting the size, structure and form of such refuges is not generally agreed and in Europe there is, as yet, little practical field experience. The recommended levels of refuge use may turn out to be large e.g. 40 % of the total crop area and detailed monitoring protocols have now been developed to detect the early emergence of resistance in field-collected insects.

2.2.1.5. *Potential transfer of genetic material to soil microbes*

There is the potential to transfer genetic material to soil microbes which degrade modified-plant material. The extent of any such gene transfer and its significance has to be assessed taking account of the considerable variation in the background status of soil microbes. Thus antibiotic resistance transfer may occur but this needs to be related to the extent of pre-existing antibiotic resistance within the soil's microbial system. The fitness of the transformed species needs to be considered.

2.2.2. *Feed and food safety.*

2.2.2.1. *Substantial equivalence*

The concept of substantial equivalence is a useful framework to identify significant similarities and differences between genetically modified foods and a suitable comparator that has a history of safe use. The establishment of substantial equivalence should as a starting point guide the safety evaluation

(WHO/FAO Expert Consultation 2000). An operational definition is needed. At present, there is no agreed definition of "substantial equivalence" and the Scientific Committees apply the concept of "substantial equivalence" on a case by case basis. However, the SSC proposes that this issue should be the focus of a future opinion. Against the changing background composition of plants developed and cultivated by both, classical or modern techniques, the level of detail required for the comparative analysis of the composition depends on the genetic modification methods and the type of modification.

The routine analytical procedures currently in use still need to be standardised in terms of sampling and extraction procedures, validation of profiling methods and in bio-informatics (see annex 2). Currently applied methods do not provide certainty to detect all new non-targeted toxic plant constituents or an increase of the amount of unidentified existing toxic constituents and, therefore, the methods need to be expanded. Toxicants might accumulate if the processes of introducing the transgenic material, both by gene technology and by modern conventional plant breeding, were to alter an existing metabolic pathway or introduce a new one.

The most promising of the new tools that may transform risk-assessment are derived from the very same technology which gives rise to GM-plants. At present, cDNA microarray technology is being used in a wide range of applications, including risk assessment. Although proteomic and metabolomic techniques are still less well developed, they will offer greater opportunities to risk assessment (see also annex 2).

2.2.2.2 *Digestibility and toxicological testing*

One of the issues which have triggered the safety assessment of novel food products is the capability of the digestive tract to digest both the transgene DNA itself and the protein encoded by the transgene. There is a need to evaluate the fate and subsequent toxicological, hormonal, allergic and metabolic effects of the precursors as well as the products of digestion. There are arguments that the currently used tests of gastric and intestinal protein resistance to gastric and intestinal hydrolysis represent a “best case” situation and do not reflect the digestive capacity of the very young and those with pancreatic and severe gastric disorders. The fact that a protein is digested does not preclude for some eventual pharmacological/toxicological properties of derived peptides. Such properties have been observed for conventional foods and thus should be anticipated in all foods, whether they are derived from GM protein or from non-GM protein.

The capacity of the intestinal secretion to hydrolyse, the modified DNA requires that the modified DNA-section of plants is being evaluated to see whether this section can be taken up by intestinal micro-organisms and incorporated into their DNA. Whilst transfer of DNA to micro-organisms can occur, specific selection pressure is necessary to favour the altered micro-organism. If so, then the implication of this DNA transfer needs to be assessed in terms of potential impact on intestinal flora/host interactions. The significance of any functional DNA fraction being taken up by the body also

needs to be evaluated. So far no functional DNA fractions have been discovered.

The difficulty in extracting sufficient GM protein from a transgenic plant for testing, has led to an “accepted” practice of making tests on the protein from the same gene expressed in a different host, usually a bacterium. It is well known, however, that a protein expressed in a different host can undergo different post-translational modification and may not possess the same biological and physical properties. Extrapolating from the tested behaviour of an isolated protein produced in a bacterium to predicting the behaviour of the same protein when it is an integral part of the transgenic plant can be accepted only if the chemical identity (including conformational identity) of the two proteins has been demonstrated.

2.2.2.3. *Immune and hormonal status*

The difficulty of achieving the higher test concentration of a transgene in the diets of test animals required for toxicological testing has already been noted. In addition to these standard toxicological requirements, more subtle effects or those which may have a relatively long gestation need to be considered. One such issue is that of allergenicity. Existing assessments *include* comparing the similarity of the transgenic protein with known allergens (i.e. whether the sequence homology is or is not the same as any known allergens). "Allergens homology" is clearly not a sufficient criterion to assess the allergic potential of a new protein and even less of a whole novel food derived from GM plants. A fortiori the absence of homology in not an evidence of non-allergenicity. Even if such an approach may be considered as relevant, it is necessary to improve data bases, and to develop algorithms and software to compare structures and not only sequences. Assessment now includes an evaluation of the physical/chemical properties of the newly inserted proteins (i.e. degradation, glycosylation and the level and site of expression). Risk assessment strategies for potential allergenicity are not “fool-proof” and studies on structure/function relationships of allergenic proteins are needed together with the further development and validation of animal models (WHO/FAO report 2000).

A second set of issues – to give a further example - relates to intestinal secretions and hormonal changes, i.e. endocrine and exocrine functions that only got limited consideration in the current guidelines for the assessment of GM plants. Although not particularly relevant to those crops already approved for release, these issues might become of greater concern in the future. Many of the genes now being considered for introduction to provide insect resistance depend for their action on disrupting the digestive function of the pest (Table 2). It is therefore important to exclude the possibility that some of the enzyme inhibitors and lectins being considered may produce similar effects in mammals. In addition, if absorbed, these components could have effects on many aspects of metabolism, including the immune and hormonal systems.

Table 2: Insect resistance genes transferred to crop species

α-Amylase inhibitors	*Lectins*
Bean	Snowdrop lectin - GNA
Cereal	Pea lectin
Protease inhibitors	Wheat germ agglutinin - WGA
Soybean (serine protease)	Jacalin
Barley (trypsin)	Rice lectin
Squash (trypsin)	*Others*
Cowpea (trypsin)	Bean chitinase
Mustard (serine protease)	Tobacco peroxidase
Rice (cysteine protease)	Tomato chitinase
Potato (protease inhibitors I and II)	Tryptophan decarboxylase
Soybean (Kunitz trypsin inhibitor)	*Animal genes*
Tomato (protease inhibitors I and II)	Various enzyme inhibitors

Taken from Schuler et al *TIBTECH 16 168-175 (1998)*

2.2.2.4 Long term nutritional impact

The ability to modify substantially the composition of plants means that there are potential benefits as well as risks to the nutritional well-being of the population. The recent development of transgenic rice with β-carotene and additional iron is one example of a potential benefit for populations showing a deficiency. Care is needed however, when evaluating transgenic plants to be used for animal and/or human consumption to ensure that the nutritional quality of the crop is maintained or even enhanced rather than reduced during the practical procedures involving the selection of the most suitable transgene.. If transgenic crops become an appreciable part of the diet then the long-term impact of nutritional changes in the amount, bio-availability or precise structure of any macro- or micro-nutrient could have a substantial impact on the health of the population. For example, changes in individual fatty acids especially the saturated and poly-unsaturated fatty acids such as the n_{-3} fatty acids, could have important effects not only on cardiovascular diseases but perhaps also on brain development and function and the immunological status. Subtle changes in the bio-availability of minerals and vitamins, e.g. of zinc or selenium or folic acid could also be of health importance.

At present, petitions for the introduction of novel foods, including GM-foods, require an exposure assessment under worst-case conditions where there are any changes in the nutritional composition of the food. Non GM fat-replacers, phytosterol -containing margarines, have already been examined for their impact on nutrient intake and absorption. Modelling the effects of multiple changes in the nutrient content of several GM products that may be present in foods as ingredients is needed. These should be based on existing national food consumption databases and food ingredient databases and require appropriate consideration of regional differences and differences between population groups in probabilistic analyses.

2.2.2.5 Post-marketing surveillance

With regard to environmental impact, post-marketing surveillance is known to be essential. It should be evaluated to what extent post-marketing tracing and surveillance allow the assessment of the impact of the GM-products (foods and feeds) on health and environment. The difficulty with post-market surveillance is that it is crude in relation to human and animal health and can, as some environmental groups have highlighted, come too late to allow the elimination of the problem. It would be appropriate to develop practicable post-marketing surveillance approaches applicable to GM-products. These methodologies should allow the tracing of illegal presence of non-food and non-feed GM plants in the food and feed chain.

3. Some future developments

The focus of debate on GM crops has been their safety in respect to food use and the consequences for the environment. Relatively little attention has been paid to broader questions of risk assessment. Programmes designed to detect gene transfer to other non-transgenic crops and related wild species and the spread of resistance to the Btk toxin amongst target insects are underway.

However the SSC considers the impact of new GM crops grown for industrial rather than food/feed purposes is likely to become of great importance. Plants have long been used as bioreactors, able to produce high value naturally-occurring chemicals, predominately for pharmaceutical or cosmetic use.

Recombinant technology has greatly expanded the options for the production of high-value products, particularly peptide and protein based therapeutics. Transgenic constructs exist which are able to express antibodies, to produce proteins for vaccines and various signalling peptides.

At the other end of the scale, low-cost source material for industrial processes can now be produced in bulk and economically and will be able to replace, in part, such feedstock derived from non-renewable sources. So far bulk production has focused on the use of oilseed rape in which the oil produced has been modified by changing the expression of key-enzymes. One of the first GM plants to be approved for release in the USA (1993) was an oilseed rape modified to produce high concentrations of lauric acid for use in the detergent industry. Table 3 shows this and some other transgenic rape crops designed for industrial purposes which have reached the stage of field trials. It is also necessary to assess the likely toxic impact on the environment, animals and man of the chemicals in transgenic plants being primarily produced for industrial use.

Table 3: *Transgenic rape crops producing oils modified for industrial purposes*

Seeds modified to produce:	Industrial products
Stearic acid (40%)	Margarine, cocoa butter substitute
Lauric acid (40-60%)	Detergents
Oleic acid (80%)	Food, lubricants, ink
Petroselinic acid	Polymers, detergents
Jojoba wax	Cosmetics, lubricants
Myristic acid (40%)	Detergents, soap
Erucic acid (~90%)	Polymers, cosmetics, ink
Ricinoleic acid	Lubricants, plasticisers, pharmaceuticals
Polyhydroxybutyrate	Biodegradable plastics

Taken from Murphy et al *TIBTECH 14 206-213 (1996)*

The only economically significant route for the disposal of the seed meal remaining after the extraction of oil from oilseed plants is as animal feed. At present feed compounders or those farmers who mix feed on the farm treat all batches of oilseed meals as equivalent. This may no longer be possible without a safety assessment of the feed if seed meal derived from GM rape used for industrial chemical production or pharmaceutical production become commonplace. The reason is that that the same seed meal (from rapeseed) may have rather different characteristics, making parts of it unsuitable for feed.

Feed producers will need to source accurately their raw ingredients to ensure that their composition is not modified in such a way that they present a risk for animals (or for humans consuming derived products.) It is doubted whether it will be possible to keep all GM foods completely separated given the huge range of current developments. The shared need for productive land will also act to bring food and industrial plants into close proximity. The SSC recognises that a variety of management strategies might be needed to limit the entry of by-products of industrial crops into the human food and animal feed chains. If complete separation of GMPs is required because of consumer demands or for other needs, then the animal feed industry would require a complete transformation of agricultural practice. The animal feed trade, like the food industry, is a global enterprise that sources its ingredients from all over the world. In the absence of any risk management strategy, traditional routes for the disposal of some novel crop by-products may have to be reconsidered.

The issue of cross-fertilisation between GM and non-GM varieties has already been dealt with. The SSC considers that the accidental transfer of transgenes from existing GM crops currently cleared for food use is not thought to pose any risk for human health or the environment and to have few long-term implications for hybrid crops such as maize where seeds are not retained for planting. However, the picture changes when considering transgenes for industrial use. If crops, intended for industrial or medicinal purposes are grown alongside other varieties, whether GM or conventional, intended for the food chain the expression in food crops of an accidentally acquired gene coding for

the production of a non-food compound could have serious health effects. New technologies may provide the best means for reducing this risk at present. For genetically modified crops and fruits containing pharmaceutically active substances (nutraceuticals) a complete separation from the human, livestock and wildlife food chains needs to be guarantied.

4. Overall conclusions

4.1 General

The SSC highlights the rapidly increasing complexity of the changes in plants arising from the insertion of a variety of genes and a variety of combinations of genes. Current evaluation methods regarding human and animal health and the environment, suffer from different limitations when dealing with the variety of issues which might emerge from the development and introduction of new GMPs.

The SSC also wants to underline that a similar situation already exists today for other methods of modern plant breeding. For example, chemical mutagenisis, radiation or cell fusion produce random genetic changes in plants and an evaluation of the long-term impact of these unpredictable changes on health and environment is poorly documented. That means that no benchmarks or standards presently are established for contents of inherent nutrients and toxicants in ordinary food and feed plant products by which to make an initial acceptance through substantial equivalence for GM plant products. It is therefore questionable whether such traits could be used as comparators for substantial equivalence assessment of GMPs.

Considerable effort is needed in research and technological developments to elaborate appropriate systems and methods for improving the evaluation, namely of the long term impact of GM and other technologies in plant breeding.

4.2 Methods

The example of GMPs was originally chosen because there is intense industrial and scientific interest in the development of new GMPs but extreme public concern about the safety. Many of these concerns relate to complex scientific issues and potential effects, which are assumed to appear in the long term and perhaps in an unexpected and indirect manner. This concern is difficult to allay; it is evident that also the speed and range of technological innovation, including gene technology, requires the continuous upgrading of assessment methods. The same scientific knowledge that feeds innovation also provides benefits to the evaluation of the safety of the products of same technologies but also of other food and non-food products and technologies.

The development of regular assessment schemes, based on sound protocols and a clarification of "substantial equivalency" is essential. For specific gene constructs this needs to begin in parallel with the development of any new gene technology or construct.

As in other cases, post marketing surveillance is no substitute for proper pre-marketing evaluation. Both approaches are needed in an integrated manner to encompass the effects of gene interactions and the long-term impact of their extensive use, e.g. in GMPs.

Post marketing surveillance systems need to be developed further with appropriate monitoring systems for the potential human and environmental effects of GMPs.

4.3 Procedures

Delays in starting the safety and environmental assessment of GMPs should be limited by requiring notification to regulatory bodies of all industrial and publicly funded GM-developments intended for release. Without such a system, there could be a three to four year delay in approving a new crop, i.e. the time needed to develop or standardise new and appropriate assessment methods to establish the safety of the products of this new technology. Commercial confidentiality needs to be safeguarded.

4.4 Dealing with scientific uncertainty in an area of public concern

In view of the public concern triggered by the perceived and existing uncertainty regarding long term and indirect effects of newly applied technologies, the outcome of any risk assessment needs to be put into an appropriate context for communicating with the public as well as the scientific and industrial community. This will require a new approach.

*Risk communication needs to play a central role in ensuring that all stakeholders, i.e. in GMP the public, the industry and scientific community, **are jointly** aware and convinced of the care being taken with the assessment procedure.*

The involvement of all stakeholders is necessary, who needs assurance that scientific risk assessment is carried out by independent scientists operating in the general interest.

Annex 1

Details on the work on GMOs already carried out by the Scientific Committees of the European Commission

By the end of June 2000, the EC Scientific Committee on Plants (SCP) had evaluated 20 submitted dossiers on 7 different modified crop types (maize, oilseed rape, beet, cotton, tomato, potato and chicory) with a limited number of traits. Fifteen opinions have been published (14 favourable and 1 unfavourable). These opinions have primarily been given in the context of Directive 90/220/EEC which requires an assessment to be carried out before a product containing or consisting of genetically modified organisms (GMOs) can be placed on the market. The aim of each assessment is to evaluate the risks to human health and the environment arising from the release of the GMO. For genetically modified plants, these must be based on the information outlined in Annex II B to Directive 90/220/EEC and take into account the proposed uses of the products. However, as no equivalent regulation currently exists on Novel Feeds and Novel Feed Ingredients the Scientific Committee on Plants also evaluates the risks arising from these uses in co-operation with the Scientific Committee for Animal Nutrition (SCAN).

In the light of experience so gained from assessing submitted dossiers, the SCP published guidance[3] for the benefit of notifiers to assist them in their preparation of dossiers for the risk assessment of plant GMOs and requested comments and observations from interested parties. A separate detailed opinion was published on proposals to monitor for the development or appearance of resistance to Bt in target pests of maize[4].

Likewise the Scientific Committee on Food (SCF) has issued guidelines on safety assessment of novel foods[5]. So far no GM-food products have been assessed by SCF according to the Regulation on Novel Foods and Novel Food Ingredient (EC 258/97), since the detailed assessments so far have been performed by the member states.

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3 Guidance document to facilitate notifiers in the preparation of plant GMO dossiers for consideration by the Scientific Committee on Plants (SCP/GMO/103 - Final. Opinion expressed by SCP on 18 December 1998.

4 Opinion of the SCP on Bt-Resistance monitoring. Opinion expressed on 4 March 1999.

5 Guidelines for …. SCF, ….

Annex 2:

Examples for newly developed and forthcoming profiling methods and bio-informatics

1. Apart from the expected routine genomic analysis of the DNA insert into the host plant, there should be an assessment of transcriptomes. Differential display methods can detect differences in mRNA induced by other genes as well as the transcribed gene. However, current methodology is considered to be labour intensive and largely dependent on individual skill (Kok *et al,* 1998).

2. **Metabolome profiling** techniques should lead to a clear documentation of amplified or suppressed metabolism and diminish uncertainty regarding unexpected and unintended effects. Analyses of metabolic pathways should be mandatory not only when an introduced gene is known to code for an enzyme involved in the production of plant secondary metabolites (e.g., the *epsps* gene) but also whenever on a theoretical basis the formation or change in concentration of non-target compounds cannot be excluded and more generally when there are significant modifications in different metabolic fluxes. A new induced pathway may well divert substrate from other metabolically significant pathways. For such analysis all up-to-date separation, identification and quantification techniques will be needed on a case-by-case basis. Such chemical fingerprinting requires careful statistical fingerprints of, preferably, isogenic controls and an extended range of commercial varieties in order to interpret the biological relevance of any significant differences detected (Kuiper, 2000). These techniques are already being developed further and compared with functional genomics and proteomics in a EU funded Project "GMO-Care" (N° QLK1-1999-007 of the 5th Framework Programme).

3. Any modification of a biological system (microorganism, plant, animal) due to the modulation of gene expression or the introduction of a gene (e.g. GMP), but also to the incidence of many other factors (physiological state, nutrition, pathology, environmental conditions) results in a modification of the metabolome, i.e. the quantity but also the nature of products of the functional proteome. A global assessment of food material (GMPs) characteristics, but also of the interaction of that food with an animal model, i.e. modifications of the animal metabolic status (metabolome) that can be interpreted subsequently in terms of toxicity, can be obtained using spectral analysis (NMR, mass spectra) as fingerprinting instead of structural analysis technique. “Biological signatures” that correspond to general canonical relationships between food fingerprints on one hand, and metabolic fingerprints obtained on animal models fed with GMPs on the other hand can be established that may provide some insights in a potential metabolic disruption that cannot be detected by transcriptome and proteome analysis due to their reduced intrinsic measurement range but also to the non-linear relationships between the different metabolic clusters.

4. **Proteome Assessment**. Proteomics applied to detect differences in total protein expression would allay concern about whether the transcribed gene had led to different protein structures because of additional post-transcriptional changes, e.g. by the addition of carbohydrate units by virtue of these processes occurring in a new plant host. There are currently significant technical problems to overcome since proteins may constantly change their secondary, tertiary and quaternary

structures according to their surrounding molecular environment but also undergo post traductional modifications, thus profoundly influencing their electrophoretic behaviour and molecular mass (Kuiper 2000). However, two dimensional gel electrophoresis and peptide mass fingerprinting techniques are now available to assess these developments.

5. **Proteomic interactions**. A novel method for assessing the likelihood of proteomic interactions by two-hybrid analysis has been proposed. This research method could potentially allow an assessment of the impact of post-transcriptional changes and whether a novel transgenic protein has an unexpected interaction with one of the host plant proteins.

References

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