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COMMISSION RECOMMENDATION 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 the preparation of initial assessment reports under Regulation (EC) No 258/97 of the European Parliament and of the Council (Text with EEA relevance) (97/618/EC)

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

Having regard to Regulation (EC) No 258/97 of the European Parliament and of the Council of 27 January 1997 concerning novel foods and novel food ingredients (1), and in particular Article 4 (4) thereof,

Whereas, in order to protect public health, it is necessary that novel foods and novel food ingredients are subject to a single safety assessment through a Community procedure before they are placed on the market within the Community;

Whereas recommendations concerning the scientific aspects of the information necessary to support an application for the placing on the market of a novel food or a novel food ingredient will facilitate the task of economic operators in preparing such an application; whereas recommendations concerning the presentation of such information and concerning the preparation of initial assessment reports by the competent food assessment bodies of the Member States will facilitate the evaluation of such applications;

Whereas the Scientific Committee for Food has made recommendations on the information necessary to support such applications, the presentation of that information and the preparation of initial assessment reports on those applications;

Whereas experience in the assessment of novel foods and novel food ingredients is at present limited; whereas therefore any recommendations in this area must be kept under constant review to take account of new scientific information and the work of the relevant international organizations;

Whereas the Member States have been consulted on this Recommendation within the framework of the Standing Committee for Foodstuffs,

HEREBY RECOMMENDS THAT:

1. When preparing applications for the placing on the market of novel foods and novel food ingredients, economic operators should follow the recommendations concerning the scientific aspects of the information necessary to support such applications set out in the Annex, Part I.

2. Economic operators should ensure that the information necessary to support applications referred to in point 1 is presented in accordance with the recommendations set out in the Annex, Part II.

3. Member States should ensure that the initial assessment reports drawn up by their competent food assessment bodies pursuant to Article 6 (2) of Regulation (EC) No 258/97 are prepared in accordance with the recommendations set out in the Annex, Part III.

Done at Brussels, 29 July 1997.

For the Commission

Martin BANGEMANN

Member of the Commission

(1) OJ L 43, 14. 2. 1997, p. 1.

ANNEX

PART I RECOMMENDATIONS CONCERNING THE SCIENTIFIC ASPECTS OF INFORMATION NECESSARY TO SUPPORT APPLICATIONS FOR THE PLACING ON THE MARKET OF NOVEL FOODS AND NOVEL FOOD INGREDIENTS

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I. INTRODUCTION

Whenever changes are made to the way in which a food is put on the market, produced or processed or uses non-traditional ingredients, the implications for consumer safety and nutritional value will require consideration. Information will be needed on any issue relating to both these aspects. At present, the issue of food safety in relation to novel foods is under consideration world-wide. The World Health Organization (WHO), the Organization for Economic Cooperation and Development (OECD), and other national and international bodies have addressed both general and specific aspects relevant to the wholesomeness of novel foods. A number of reports outline the philosophies and developments in this field (see references).

As part of the development of Regulation (EC) No 258/97 on Novel Foods and Novel Food Ingredients the European Commission has asked the Scientific Committee for Food (SCF) to develop recommendations concerning the scientific aspects of

I. the information necessary to support an application for the placing on the market of novel foods and novel food ingredients;

II. the presentation of such information;

III. the preparation of the initial assessment reports.

This report covers task I.

2. CATEGORIES OF NOVEL FOODS AND NOVEL FOOD INGREDIENTS IDENTIFIED IN REGULATION (EC) No 258/97

According to Regulation (EC) No 258/97 of the European Parliament and of the Council of 27 January 1997 concerning novel foods and novel food ingredients (1), Regulation (EC) No 258/97 will apply to the placing on the market of foods or food ingredients which have not hitherto been used for human consumption to a significant degree within the Community and which fall under the following categories:

(a) foods and food ingredients containing or consisting of genetically modified organisms within the meaning of Council Directive 90/220/EEC (2);

(b) foods and food ingredients produced from, but not containing, genetically modified organisms;

(c) foods and food ingredients with a new or intentionally modified primary molecular structure;

(d) foods and food ingredients consisting of or isolated from microorganisms, fungi or algae;

(e) foods and food ingredients consisting of or isolated from plants and food ingredients isolated from animals, except for foods and food ingredients obtained by traditional propagating and breeding practices and which have a history of safe food use;

(f) foods and food ingredients to which has been applied a production process not currently used, where that process gives rise to significant changes in the composition or structure of the foods or food ingredients which affect their nutritional value, metabolism or the level of undesirable substances.

The Regulation does not apply to: food additives falling within the scope of Council Directive 89/107/EEC (3); flavourings for use in foodstuffs falling within the scope of Council Directive 88/388/EEC (4); or extraction solvents used in the production of foodstuffs falling within the scope of Council Directive 88/344/EEC (5).

3. KEY ISSUES FOR THE ASSESSMENT OF NOVEL FOODS AND NOVEL FOOD INGREDIENTS (NF)

3.1 General considerations

Foods are usually complex mixtures of macro- and microconstituents which provide energy and nutrients and contribute to the well-being of humans. They have traditionally been regarded as natural, beneficial and necessary products whose safety and nutritional value need not be questioned. Regulatory approaches to food safety have reflected this attitude and have focused on food additives, processing aids and contaminants of natural or industrial origin. Thus, foods have not hitherto been systematically subjected to nutritional or toxicological evaluation, except in rare cases where acute toxic effects have been reported in humans (e.g. solanine, cyanogenic glycosides) or in those cases where animal studies or human experiences have suggested adverse effects from raw food materials (e.g. raw soya flour). This is not to imply that nutritional evaluation of individual foods and of whole diets has not been performed, but that such nutritional evaluations have not been used as a basis for a safety assessment of individual foods. On the other hand, food additives are not permitted in food unless they have been subjected to exhaustive toxicological evaluation.

Various foods are known to contain toxic compounds, including mutagens and carcinogens. Some chronic diseases in humans have a dietary element in their etiology. Although it is agreed that some adverse effects of the diet on health are related to the pattern of nutrient intake, the exact mechanisms involved are not known. It is possible that some ill health is due to chronic exposure to constituents of traditional foods. Until recently little attention has been given to this aspect or to the possible role of modifiers of toxic effects (e.g. anticarcinogens) naturally present in foods.

The assessment of the wholesomeness of foods including foods and food ingredients (NF) presents a number of scientific challenges. Conventional toxicological evaluation methods cannot be applied to foods, because foods present particular difficulties not encountered with the testing of food additives and contaminants in vivo and in vitro. For example, the amount of food to be incorporated in the diet for animal feeding studies without perturbing its nutritional balance makes the use of conventional safety factors inappropriate for risk assessment and management for any product intended for use as a food or a major food ingredient. Furthermore, traditional metabolic and pharmacokinetic studies are not directly applicable to complex chemical mixtures like foods. The use of mutagenicity and other in vitro tests for foods requires special techniques and cautious interpretation of the results.

Therefore, alternative approaches for the testing and assessment of the wholesomeness of foods and major food ingredients are needed. The ultimate strategy for combined nutritional-toxicological testing will extend from initial tests in vitro and in vivo studies in animal models to studies in humans if needed.

3.2 Genetically Modified Organisms (GMO)

Council Directives 90/219/EEC (6) and 90/220/EEC as amended by Commission Directive 94/15/EC (7) set out the information requirements for the safety of the contained use of genetically modified microorganisms (GMM) and the safety of the deliberate release of genetically modified organisms (GMO), respectively. The requirements in these directives are also relevant to GMO covered by Regulation (EC) No 258/97 on Novel Foods and Novel Food Ingredients and fulfil basic information requirements needed for the safety assessment of NF. The present recommendations specifically focus on those aspects relevant to human food safety issues.

3.3 Substantial equivalence

The concept of 'substantial equivalence` has been introduced by WHO and OECD with particular reference to foods produced by modern biotechnology. In the terminology of the OECD, the concept of substantial equivalence embodies the idea that existing organisms used as foods or as food sources can serve as a basis for comparison when assessing the safety of human consumption of a food or food component that has been modified or is new. 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, keeping in mind that establishment of substantial equivalence is not a safety or nutritional assessment in itself, but an approach to compare a potential new food with its conventional counterpart.

The application of the principle of substantial equivalence can be extended to the evaluation of foods from novel sources and processes. Substantially equivalent NF are thus comparable, in terms of safety, to their conventional counterpart. Substantial equivalence may be established either for the whole food or food component including the introduced 'new` change, or it might be established for the food or food component except for the specific 'new` change introduced. If a NF has not been found to be substantially equivalent to an existing food or food component, this does not imply that it is unsafe. It just indicates that such a NF should be evaluated on the basis of its unique composition and properties.

The establishment of substantial equivalence is an analytical exercise in the assessment of the relative wholesomeness of a NF compared to an existing food or food component. It contains a dynamic element, as the continuing modification of a food requires that the basis of comparison will evolve in a way that the most recent NF is compared with an appropriate former NF and not necessarily with the most traditional counterpart.

The comparison may be a simple task or be very lengthy depending upon experience with and the nature of the NF under consideration. The technical approach to establishing substantial equivalence will differ between whole animals, plants, microorganisms, chemical food ingredients and novel processes and is addressed in more detail under the different classes later in these recommendations.

3.4 Compositional analysis

Analytical studies of the composition of the NF are of crucial importance not only for the establishment of substantial equivalence but also as a prerequisite for nutritional and toxicological assessments. Methods applied have to be standardized and validated to ensure quality and consistency of the data. The analyses and data presented should be based upon sound scientific principles and should be tailored to the nature of the NF. Investigations should focus especially on the determination of the content of critical nutrients (both macro- and micronutrients) and any critical toxicants and anti-nutritional factors which might be either inherently present or process derived.

3.5 Intake

The consumption pattern may show a major change when an NF is included in the diet and thus affects human nutritional status. As it may not be possible to predict such events, a surveillance programme should accompany the marketing of an NF. Such a programme should encompass information on changes in the conditions for processing and preparation as well as effects of possible replacement of other foods or food components of dietary importance. If surveillance reveals changes in those factors which raise concerns regarding wholesomeness, a reappraisal of the acceptability of the NF would be required.

3.6 Nutritional considerations affecting toxicological testing in animals

In the overall evaluation it is of crucial importance to interprete carefully any adverse effects seen in animal studies and to distinguish between toxic effects and those due to nutritional imbalance in the experimental diet. Thus, nutritional and toxicological aspects have to be closely integrated in the assessment of NF. Thorough knowledge of the nutritional properties of the NF (e.g. energy value, protein content, and bioavailability of micronutrients) is needed as a prerequisite of the toxicological testing programme. In designing animal feeding studies, the maximum level of dietary incorporation achievable without causing nutritional imbalance should be the highest dose level, while the lowest dose level should be comparable to its anticipated role in the human diet.

If the predicted usage levels and consumer intakes are likely to be high, the application of the traditionally calculated safety factors employed in safety assessment may create difficulties in designing conventional animal feeding studies with adequate dietary incorporation levels to ensure clearance for use in humans at the anticipated consumption levels. To compensate for the inability of employing reasonably adequate safety factors any subchronic or chronic animal feeding studies require supplementation by absorption and metabolism studies in animals and eventually in humans.

A holistic scientific interpretation of the overall wholesomeness assessment data on a case-by-case basis can provide the acceptable justification for the use of safety factors for NF lower than those traditionally used in safety assessment.

3.7 Toxicological requirements

In principle, the toxicological requirements for NF need to be considered on a case-by-case basis. In establishing the need for the provision of toxicological data three scenarios may be considered:

(1) substantial equivalence can be established to an accepted traditional food or food ingredient, in which case no further testing is needed;

(2) substantial equivalence can be established except for a single or few specific traits of the NF, in which case any further assessment of safety should focus specifically on these traits;

(3) neither partial nor total substantial equivalence can be established; in this case, the wholesomeness of the whole novel food or macronutrient has to be assessed using an appropriate combined nutritional-toxicological approach.

If substantial equivalence to a traditional counterpart cannot be established the wholesomeness assessment has to take into account not only knowledge of the identity, chemical structure and physico-chemical properties of the NF but also aspects such as source, composition, potential intake based on the proposed use in the general diet, the potential exposure of particularly vulnerable population groups, and the likely effects of processing. The greater the predicted dietary exposure the more extensive the required toxicological testing programme will have to be.

3.8 Implications of NF to human nutrition

The overall assessment must consider nutritional implications both at expected customary (normal) intakes and at maximum levels of consumption. This evaluation will be guided by a thorough appraisal of relevant literature, compositional analyses, comparisons to consider substantial equivalence, and, if needed, data from investigations in animal models. If an NF is expected to have an important role in the diet then appropriate human nutritional assessment data are needed. Attention should be paid to the particular physiological characteristics and metabolic requirements of groups such as infants, children, pregnant and lactating women, the elderly, and those with chronic diseases (e.g. diabetes mellitus and malabsorption).

Information will be needed on long term as well as on short term effects of eating the NF. The appropriate information should be derived by combined nutritional and safety post-market surveillance, but additionally consideration should be given to addressing these effects by specific concerns about nutritional quality (e.g. the long term effect of fat replacers on the metabolism of fat soluble vitamins).

3.9 Novel microorganisms used in food

Microorganisms may be used as producers of foods, food ingredients or food additives. Many have a long tradition of safe use in food fermentations. They may be killed in the fermented product or consumed alive with it.

By definition, microorganisms with no traditional use in food production in Europe cannot have a substantially equivalent counterpart in Europe and will therefore need to be assessed. Relevant criteria are: containment (e.g. limited to fermentor, remaining alive in food or killed during processing); potential for colonization of the mammalian gut; potential for toxigenicity as well as pathogenicity in mammals; and whether genetic engineering was applied or not. If genetic modification is employed, the considerations on potential transfer of genetic material from GMM as described in 5.VII become relevant.

The safety assessment of a GMM should consider the origin of the newly introduced material, e.g. vectors, regulatory elements, foreign genes including target and marker genes. Two cases have to be considered:

- the homologous system (self cloning), where all genetic elements involved are derived from strains within the same taxonomic species,

- the heterologous system, where the donor organism of the genetic elements belongs to a taxonomic species other than that of the recipient.

Generally, the segregational and horizontal stability of the constructs are of interest. For self-cloned organisms the concept of substantial equivalence might be applicable in most cases. In heterologous systems both the safety of the gene product in relation to its effects on the food and the effect of the new trait on the properties of the microorganism in the food and, after ingestion, in the gut need to be assessed. The implication of horizontal gene transfer in the gut should be analyzed and evaluated.

3.10 Allergenic potential

The potential occurrence of allergic reactions to novel proteins or other constituents of NF should be explored. As a general principle of assessment, the immunological reactivity of individuals who react to the traditional food counterpart should be tested in vitro and in vivo

against the NF. The latter approach may raise ethical issues which must be taken into account. If the novel protein is expressed by genes drived from a source known to be associated with food allergy, sera of people with confirmed allergies to that source can be subjected to specific immunological tests, e.g. Western Blotting or radioallergosorbent test (RAST). If in vitro tests are negative, in vivo skin prick tests or clinically supervised double blind placebo controlled challenges in these people may be performed. All studies should comply with relevant elements and ethical principles of guidelines on good clinical practice and good laboratory practice.

A number of factors can serve as indicators of the potential allergenicity of novel proteins, such as sequence epitope homology with known allergens, heat stability, sensitivity to pH, digestibility by gastrointestinal proteases, detectable amounts in plasma, and molecular weight. Additional evidence might emerge from pre-marketing human results and reports of workers' sensitizations.

New approaches are needed to assess the potential allergenicity of NF in humans. In the present state of knowledge, the allergenicity of a novel food from a GM source should include consideration of the allergenic potential of the donor and of the recipient organism.

3.11 Assessment of marker genes

Marker genes are used as 'tags` to identify and to select those cells of plants or microorganisms which have been transformed successfully by genetic modification. Normally they are not supposed to play a role of their own in the final product or NF. The marker genes, presently used most frequently in plants, are those conferring resistance to antibiotics or increased tolerance to herbicides. Others confer heavy metal tolerance or phenotypic and biochemical selection. The requirements for evaluating the safety of marker genes are basically similar to those applicable to the safety evaluation of any other foreign genes.

The assessment in plants needs to consider:

- the marker gene itself and the product it encodes,

- the methods for analyzing and quantifying the marker gene and its expression products in the food,

- the potential toxicological and/or nutritional effects related to the function of the marker gene,

- the potential for horizontal gene transfer to gut microorganisms.

The use of marker genes in microorganisms, especially those genes conferring antibiotic resistance, has to be assessed in relation to the host organism, the biological containment established by the genetic construct, the possibility of colonization of the human gut by these GMO, and the relationship between the efficacy of antimicrobials and the acquired resistance.

It can be foreseen that a list of approved marker genes can be developed based upon an evaluation of their primary effects on the host organism. Their secondary effects on the host will depend on, among other factors, the insertion site in the host DNA and will need an assessment on a case-by-case basis, although there is no reason to suppose that the potential for secondary effects is greater for marker genes than for any other inserted genes.

4. SCIENTIFIC CLASSIFICATION OF NOVEL FOODS FOR THE ASSESSMENT OF WHOLESOMENESS

Foods and food ingredients which fall within the scope of Regulation (EC) No 258/97 on Novel Foods and Food Ingredients are very diverse (see Section 2). To facilitate safety and nutritional evaluation, six classes of NF have been identified. These differ in complexity and in the issues that need to be addressed.

For the purpose of these recommendations, the term 'plants` covers also seaweed. The term 'animals` includes fish and shellfish, and the term 'microorganism` encompasses bacteria, fungi

(including yeasts), and micro-algae (viruses and plasmids are outside the scope of these guidelines).

Class 1 Pure chemicals or simple mixtures from non-GM sources

This class comprises foods and food components that are single chemically defined substances or mixtures of these which are not obtained from plants, animals or microorganisms that have been genetically modified. Two sub-classes can be identified:

1.1 the source of the NF has a history of food use in the Community;

1.2 the source of the NF has no history of food use in the Community.

Class 2 Complex NF from non-GM source

This class comprises complex NF which are not, or are derived from sources which have not, been genetically modified. Intact plants, animals and microorganisms used as foods as well as food components (e.g. complex carbohydrates, fats, proteins or those substances collectively described as dietary fibre) are included. Two sub-classes can be identified:

2.1 the source of the NF has a history of food use in the Community;

2.2 the source of the NF has no history of food use in the Community.

Class 3 GM plants and their products

GM plants can be consumed directly as unprocessed foods or after having been processed into foods and food ingredients including pure chemicals. This class of NF includes all such foods and food ingredients. Two sub-classes can be identified:

3.1 the host plant used for the genetic modification has a history of use as food or as a source of food in the Community under comparable conditions of preparation and intake;

3.2 the host plant used for the genetic modification has no history of use as food or as a source of food in the Community under comparable conditions of preparation and intake.

Class 4 GM animals and their products

GM animals can be consumed directly as unprocessed foods or after having been processed into foods and food ingredients including pure chemicals. Products directly produced by GM animals (e.g. eggs, milk) can be consumed either processed or unprocessed. This class of NF includes all such foods and food ingredients. Two sub-classes can be identified:

4.1 the host animal used for the genetic modification has a history of use as food or as a source of food in the Community under comparable conditions of preparation and intake;

4.2 the host animal used for the genetic modification has no history of use as food or as a source of food in the Community under comparable conditions of preparation and intake.

Class 5 GM microorganisms and their products

Living GM microorganisms may be used in food production or in the production of food ingredients. This class includes all NF which are, or are produced using, GM microorganisms whether or not there are any living cells in the NF as consumed: Two sub-classes can be identified:

5.1 the host microorganism used for the genetic modification has a history of use as food or as a source of food in the Community under comparable conditions of preparation and intake;

5.2 the host microorganism used for the genetic modification has no history of use as food or as a source of food in the Community under comparable conditions of preparation and intake.

Class 6 Foods produced using a novel process

This class comprises foods and food ingredients which have been subjected to a process not currently used in food production. Novel processes for food production may encompass for example new types of heat processing, non-thermal preservation methods, new processes to chill or freeze products, to dehydrate products, and the application of new processes catalyzed by enzymes. According to the scope of Regulation (EC) No 258/97, the resulting product is only considered to be an NF, if the process results in changes in the chemical composition or structure of the food or food ingredient, which affect its nutritional value, metabolism or level of undesirable substances.

The association between the described classes and the categorization in Regulation (EC) No 258/97 on Novel Foods and Novel Food Ingredients is outlined in Table I.

5. IDENTIFICATION OF ESSENTIAL INFORMATION FOR ASSESSMENT OF WHOLESOMENESS

In this section structured schemes are provided to identify the types of information that are likely to be required to establish the safety of particular classes of NF. It is recognized that no formalistic approach can cover adequately all NF, and these schemes are therefore provided for guidance only. If other information is available or relevant for the assessment, it should be submitted. However, if it is proposed to omit certain information from a dossier requested in any of the schemes, the scientific justification for this should be given. The results of any investigations relevant to safety assessment which have been carried out must be reported.

In the assessment of NF the focus is the novelty per se. Chemical or microbiological contaminants of NF not specifically related to the novelty are not addressed in these recommendations. Similarly, the presence of microbial toxins and microbial or viral infective agents is not considered unless this is a consequence of the novelty.

The identification of essential information for assessment is guided by the division into six classes described in chapter 4. After allocating an NF to a class or sub-class, the attached Table II can be used to determine which of the structured schemes I-XIII should be consulted to provide the information required to support its safety and nutritional evaluation.

In the following, the information requested in each particular structured scheme is specified in more detail:

I. Specification of the NF

Specification of the origin and the composition of the NF is needed to ensure the identity of the product tested/evaluated and the product to be marketed. In the design of the specification, parameters most relevant to characterize the product from a safety and nutritional point of view should be considered.

Such parameters include species and taxon, as well as chemical composition relating particularly to nutritional properties and possible antinutritional/toxicological concerns. Taxonomic identity should be established according to referenced and internationally accepted principles and deviation from such principles should be explained.

Information on the availability of specified reference material should be submitted.

II. Effect of the production process applied to the NF

In principle, this scheme applies to all NF which have been processed during production. The description of the technical details has to be sufficiently detailed (i) to permit a distinction between novel and existing processes, and (ii) to predict whether the potential of the process to introduce physical, chemical and/or biological changes in the food might have an impact on essential nutritional, toxicological and microbiological parameters of the final product.

The assessment of new technologies needs to address any organic and inorganic residues or contaminants derived from apparatus and equipments or from chemical, physical or biological aids used in the novel process. Critical aspects of the production process in relation to NF are

those which ensure that the final products of the described process comply with the specifications given under scheme I.

Hygienic parameters are not included in the assessment of NFs but are covered by Directive 93/43/EEC (8).

The assessment will focus on the food product resulting from the novel process on a case-by-case basis. The ultimate aim of assessment will be the evaluation of the process in a wider sense without the need for actually testing and assessing each conceivable food/process combination. This implies a broader strategy in which representatives of relevant food classes, processed by the novel food process, should be compared either to untreated counterparts or to counterparts which have been processed in a related traditional manner.

III. History of the organism used as the source of the NF

The novelty of food plants, food animals or food microorganisms in relation to these guidelines is defined by their novelty in the European food supply. If species/taxons of plants, animals or microorganisms have had no generally recognised use in the diet of any of the Community countries according to national dietary records, the species/taxon is considered new, and a full description is needed to assess its future role in the European food supply. This should include information on the past and present use of the plant, animal or microorganism and its products in the food supply in other parts of the world. Such information should also include:

- past and present methods to obtain raw materials and food, e.g. by raising, harvesting, slaughtering, and capture,

- procedures for fermentation and preparation,

- description of transport and storage conditions, and

- its traditional role in the diet at locations outside the Community.

IV. Effect of the genetic modification on the properties of the host organism

The information gathered through this scheme focuses on the effects of the genetic modification on the properties of the GMO compared to the host organism. It differentiates between intended and unintended effects. In the latter case, special attention should be given to any nutritional, toxicological, and microbiological impact on the foods.

GM plants

The principles for evaluating GM plants and their products are similar to those valid for non-GM plants and their products. The safety evaluation of a GM plant may be a simpler task than the evaluation of a novel non-GM plant, if the non-modified organism is a traditional food plant and the alteration has occurred by means of a precisely defined process of genetic modification. In this case, the safety assessment can focus on the results of the genetic modification.

Where the genetic modification results in a new phenotype, the compositional consequences of this modification should be defined and tested. If, for example, a genetically modified plant is so designed as to express a naturally occurring insecticide, encoded by a gene derived from another organism, and has therefore become resistant to certain insect pests, then the toxicological profile of the introduced insecticidal component needs to be determined. The safety of this modification of the chemical composition can be evaluated by standard toxicological procedures; it should include an assessment of the potential allergenicity. In addition, secondary effects (positional effects) have to be taken into consideration. These effects of the insertional event, e.g. the insertional mutation itself or a genomic rearrangement will influence the overall outcome of the genetic modification. A knowledge of the normal toxin production in the plant and the effect on it of various growth and culturing conditions to which the GM plant is subjected, as well as knowledge whether the new gene product appears in the final food, is essential. The same reasoning applies to nutritionally important components especially in food plants.

Essential steps of the safety evaluation are therefore:

- characterization of the parent food organism,

- characterization at the molecular level of the nature of the genetic modification including insertional position, copy number and biochemical expression level,

- establishment, as far as possible, of substantial equivalence between the parent food organism and its new derivative through chemical and phenotypic analysis,

- if substantial equivalence cannot be established, conventional safety studies on specific chemicals occurring in the food due to the phenotypic changes involving either the new product of the new gene or the safety of inherent natural toxins now present in altered amounts. The potential allergenicity of the new components also needs to be addressed.

GM animals

The general principles established for the safety evaluation of GM plants apply also to GM animals. The safety assessment will initially address the establishment of substantial equivalence between the parent organism and the GM organism focussing on primary and secondary effects of the genetic modification process. For example if the modification is directed towards changing the globulins in cow's milk to a more 'human` type, the new globulins have to be assessed. Another example may be a fish genetically modified to produce an antifreeze protein. The safety of this chemical modification can be evaluated by conventional toxicological strategies and should also include an assessment of the allergenicity aspects.

GM microorganisms

In compliance with the provisions set out for GM plants and GM animals, the parent microorganism, which is the subject of genetic modification has a priori to be recognized either as a microorganism with a tradition in food fermentation in the Community, as a non-pathogenic, biologically advantageous human intestinal commensal, or as a traditionally used production organism for foods, including food additives and technical aids, to simplify the evaluation procedure. In other cases, not only the genetic modification but also the parent microorganism needs to be assessed as being novel.

V. Genetic stability of the GMO used as NF source

The question of genetic stability relates to the structural and local maintenance of the introduced genetic material and to the gene expression in the GMO.

VI. Specificity of expression of novel genetic material

This scheme relates to the factors involved in regulation of gene expression, for instance organ/tissue specificity, conditions of repression and activation.

VII. Transfer of genetic material from GMO

Based on current knowledge, considerations of gene transfer from GMO in the human gut focus on microorganisms. Horizontal gene transfer among microorganisms is well established and has therefore to be considered in food safety assessments. One aspect of biological containment is the possible transfer of genetic material from GM microorganisms to the human gut microflora. There are different possibilities for addressing this aspect in an experimental setting, e.g. animal or in vitro gut models.

In assessing the food safety consequences of gene transfer, the nature of the gene and its product, the frequency of the transfer, and the level of expression in transformed gut microorganisms should be taken into account. Transfer of genes from plants to microorganisms is a theoretical possibility; the consequences of such an event should be considered.

VIII. Ability of the GMM to survive in and colonise the human gut

The genetic modification might facilitate survival during passage through the intestines and colonization of the human gut. Antagonistic and synergistic effects on the composition of the intestinal flora may occur and have an influence on human health. Therefore, experimental data are required on the respective properties of the GMO.

For living GMM in food, attention should particularly focus on their capability to survive in and colonize the gastrointestinal tract and to maintain their genomic stability. For this assessment in vitro and in vivo gut models mimicking the human situation as closely as possible may be needed. Aspects relating to pathogenicity and gastrointestinal immunity need special consideration.

IX. Anticipated intake/extent of use of the NF

Projections of anticipated intakes are needed to evaluate the dietary and nutritional significance of NF. This assessment will naturally draw upon information on the nature of the NF and its anticipated uses based upon its properties e.g. as a fat replacer.

X. Information from previous human exposure to the NF or its source

Documentation on previous use of the NF source in the Community or the NF source and/or the NF in other parts of the world is important to establish a baseline for assessment. However, history of food use outside the Community is not of itself a guarantee that the NF can be safely consumed in the Community. The information should deal with such aspects, where traditional handling and preparation of the plant, animal or microorganism prevent misuse or adverse short and long term health effects, for example those due to inherent antinutritional/toxic factors. In many cases, necessary precautions are reflected in the corresponding regional and cultural habits.

XI. Nutritional information on the NF

The overall assessment should, as indicated above, include a systematic review of the NF's composition, preparation and role which it is expected to have in the diet. Such an assessment with a review of relevant published material would enable an appraisal of substantial equivalence to a traditional food or food component.

If substantial equivalence cannot be established, appropriate preliminary assessments should be made in animal models to establish some aspects of nutritional quality but full nutritional assessment needs to be done in human subjects. Such studies should be based on well defined hypotheses with clear nutritional and metabolic outcomes relevant to the NF, to its dietary context, and to the anticipated consumer group.

Nutritional consequences should be assessed at normal and maximum levels of consumption, and the nutrient compositional data should take into account the effects of storage, further processing and cooking. The effect of antinutritional factors (e.g. inhibiting mineral absorption or bioavailability) on the nutritional value of the whole diet should also be assessed.

The numbers involved in study groups should ensure that the study has adequate statistical power. All studies should comply with relevant elements and ethical principles of guidelines on good clinical practice and good laboratory practice.

In some circumstances it is envisaged that plans should be provided for post-market surveillance for possible long term effects of the NF.

XII. Microbiological information on the NF

In addition to toxicological and nutritional safety, wholesomeness of an NF embraces microbiological safety. Generally, the intentionally used source organism for the NF has to be recognised as a non-pathogenic, non-toxigenic microorganism of known genetic stability which does not affect the desirable properties of the normal intestinal flora. The examination of an NF should include a characterization of the microorganisms present and the analysis of their metabolites.

XIII. Toxicological information on the NF

This scheme covers the set of toxicological information needed to assess the NF. The range of scenarios can extend from foods for which substantial equivalence can be established to foods for which substantial equivalence cannot be established and which, therefore, require an appropriate nutritional-toxicological testing program.

If substantial equivalence to a traditional counterpart cannot be established, the safety assessment based on a case-by-case evaluation must consider the following elements:

- consideration of the possible toxicity of the analytically identified individual chemical components,

- toxicity studies in vitro and in vivo including mutagenicity studies, reproduction and teratogenicity studies as well as long term feeding studies, following a tiered approach on a case-by-case basis,

- studies on potential allergenicity.

In the case of novel microconstituents and isolated novel food components, which differ by identifiable characteristics from traditional foods, or of defined novel products obtained from genetically modified organisms, it is possible to restrict testing to only those products or substances rather than the whole NF. In some cases, the testing of the novel property would have only marginal nutritional implications for laboratory animals so that the traditional toxicological approach can be applied for establishing safety.

Most of the defined chemical substances can probably be tested for their safety similarly to food additives by utilizing conventional methods of safety evaluation as described in the SCF Report No 10. This implies the use of conventional toxicological testing procedures applied in a tiered sequence. This would involve initial mutagenicity studies and an appropriate feeding study in a rodent species with an exhaustive investigation of all relevant toxicological parameters. Furthermore, if warranted by structural or exposure considerations, additional investigations should be undertaken covering all the usual toxicological endpoints including metabolism, toxicokinetics, chronic toxicity/carcinogenicity, reproductive function, teratogenicity, and possibly neurotoxicity and immunotoxicity.

Novel macroconstituents, or NF which are not substantially equivalent to traditional counterparts, will require a testing programme depending on the toxicological concerns raised. In general, this programme should include at least a 90 day feeding study in a rodent species, whereby special attention is paid to the choice of doses and the avoidance of problems of nutritional imbalance. These constraints may require a different way of conducting toxicological studies and interpreting their results (see 3.6).

The potential for mutagenicity needs investigation. Any in vitro mutagenicity studies will need to cover the usual major endpoints. Special technical problems may be encountered in testing novel macroconstituents in in vitro mutagenicity test systems, particularly because of effects of the NF or its constituents on the growth medium, the test cells or the test organisms, unrelated to mutagenicity. There may be cases where feeding studies in a second species and an investigation of effects on the composition of the intestinal flora are needed. Also chronic toxicity/carcinogenicity studies may be necessary. The allergenic potential needs also to be investigated.

6. REVIEW OF RECOMMENDATIONS

The area of novel foods is developing rapidly. The science and technology are making enormous advances and many countries and international organisations are elaborating procedures and guidelines for the safety assessment of novel foods. The SCF will review these recommendations in the light of experience gained in their application and new scientific developments in the field.

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8. GLOSSARY

This glossary is intended to explain the way in which various terms are used by the SCF in its recommendations rather than to provide precise scientific definitions.

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PART II RECOMMENDATIONS CONCERNING THE SCIENTIFIC ASPECTS OF THE PRESENTATION OF INFORMATION NECESSARY TO SUPPORT APPLICATIONS FOR THE PLACING ON THE MARKET OF NOVEL FOODS AND NOVEL FOOD INGREDIENTS

INTRODUCTION

In Part 1 of the SCF Recommendations on the Assessment of Novel Foods recommendations concerning the scientific aspects of information necessary to support applications for the placing on the market of novel foods and novel food ingredients (NF) have been presented. In this part recommendations concerning the scientific aspects of the presentation of such information are summarized. Such a uniform structure of applications will facilitate their scientific evaluation.

GENERAL SCHEME

It has been emphasised in the first part of the recommendations that no formalistic approach can adequately cover all NF. Thus, the schemes developed are not to be considered as a rigid checklist but are provided for guidance only. Nevertheless, the underlying philosophy and the major principles of the recommendations should be reflected in an application for placing NF on the market. The following box illustrates the logic flow.

>START OF GRAPHIC>

General description of the NF including technical data and categorization according to Regulation (EC) No 258/97

/

Allocation of the NF to one of the SCF classes/sub-classes

/

Identification of essential information requirements

/

Consultation of structured schemes (decision trees) and provision of data required

/

Evaluation and conclusion by the applicant>END OF GRAPHIC>

The information package submitted by the applicant should be presented in the order and under the headings described below:

1. Administrative data

This section should include information on the name and address of the applicant, of the manufacturer of the NF and of the person responsible for the dossier.

2. General description

In order to ensure that the food or food ingredient intended to be placed on the market falls within the scope of Regulation (EC) No 258/97 on novel foods and novel food ingredients, data should be provided to enable a categorization according to Article 1 (2) of Regulation (EC) No 258/97.

To facilitate the assessment procedure the SCF has reclassified the diverse categories defined by the legislation according to their similarities in terms of safety considerations. Six major classes and corresponding sub-classes are defined in chapter 4 of the SCF Recommendations on the Assessment of Novel Food, Part I (later referred to as Part I). The NF should be allocated to one of these classes/sub-classes (see also Table I, Part I); the scientific justification for this allocation should be given.

3. Identification of essential information requirements

Table II, Part I should be used to determine which of Schemes I-XIII are essential to provide data permitting a safety and nutritional evaluation of the NF.

4. Consultation of structured schemes (decision trees)

The structured Schemes I-XIII elaborated in Part I should be consulted regarding the data to be assembled. The schemes lead through a decision-tree-like set of questions and will assist in deciding whether the data available to the applicant are sufficient or if further information has to be sought and reappraised.

The logic of the schemes should be followed in the dossier. For each box the information leading to either 'yes` or 'no` should be provided in detail. If it is proposed to omit certain information requested in any of the schemes, the scientific justification should be given. If other information is available or considered to be relevant for the assessment, it should be submitted.

5. Evaluation and conclusion by the applicant

Conclusions drawn by the applicant after having evaluated the total information assembled should be presented covering the key issues relevant to the NF (see chapter 3 of Part I).

6. Summary by the applicant

A summary has to be provided that is suitable for further circulation to the Member States as foreseen in Article 6 (2) of Regulation (EC) No 258/97.

PART III RECOMMENDATIONS CONCERNING THE SCIENTIFIC ASPECTS OF THE PREPARATION OF THE INITIAL ASSESSMENT REPORTS ON APPLICATIONS FOR THE PLACING ON THE MARKET OF NOVEL FOODS AND NOVEL FOOD INGREDIENTS

INTRODUCTION

Regulation (EC) No 258/97 on novel foods and novel food ingredients stipulates in Article 4 that a person responsible for placing such a product on the Community market submit a request for this action to the Member State in which the product is to be marketed for the first time. According to the provisions of Article 6 the Member State must then prepare an initial assessment report.

Part I of the SCF Recommendations on the Assessment of Novel Foods presents recommendations concerning the scientific aspects of information necessary to support applications for the placing on the market of novel foods and novel food ingredients (NF). Part II summarises recommendations concerning the scientific aspects of the presentation of such information.

Some experience in assessing the safety of novel foods has been gained by applying the procedures of various national and international bodies and authorities. For practical purposes it is necessary to achieve comparability between assessments by different national authorities and also uniformity in the reports of their scientific appraisals. Details of the requirements for particular types of NF are provided in Part I and elsewhere, e.g. with regard to products produced by genetic modifications (1), or other novel sources of protein (2). Specific recommendations for safety testing have not been made for each class of NF and it is not possible to do so in the current state of knowledge. The use of a case-by-case approach ensures that novel risks are adequately addressed. Part III is intended to provide guidance for this task and therefore contains recommendations concerning the scientific aspects of the preparation of the initial assessment reports by the competent authorities of the Member States.

STRUCTURE OF THE INITIAL ASSESSMENT REPORT

The general considerations underlying the assessment of NF have been set out in Part I, e.g. Section 3.1. Initial assessment reports are confined to the human food safety of NF. Their preparation should proceed in the following three phases:

1. Check of the completeness of the application and its presentation in accordance with Part II;

2. Appraisal of appropriateness of interpretations and evaluations by the applicant of the data submitted;

3. Assessment of the data submitted, executive summary, conclusions and recommendations.

1. Check of the completeness of the application and its presentation in accordance with Part II

The initial assessment report must provide a statement that the submission contains the appropriate administrative and technical details presented in the order laid down in Part II, sections 1 and 2, as well as the information set out in Part I, sections 5 and 5.1. If the data submitted differ from those requested in Part II or are not presented in the order required, the applicant's explanation should be reviewed.

2. Appraisal of appropriateness of interpretations and evaluations by the applicant on the data submitted

The adequacy of the data and of the arguments relating to their interpretation and evaluation by the applicant should be assessed and an opinion provided. In the event of disagreements in

the interpretations and evaluations between the national assessing authorities and the applicants the pertinent reasons should be fully described in the assessment report.

2.1 Substantial equivalence

For assessment purposes the comparison of the final product with one having an acceptable standard of safety furnishes an important element. Therefore, the initial assessment report should include the competent authority's opinion regarding the applicant's claims concerning substantial equivalence.

2.1.1 Substantial equivalence to a traditional counterpart is claimed

For guidance the relevant discussion in Part I, section 3.3 should be consulted. If substantial equivalence to a traditional counterpart has been established, the NF can be regarded as wholesome and as toxicologically and nutritionally acceptable for use in the overall diet in a manner comparable to its counterpart or as replacement of its counterpart. When judging the comparability of the NF to its counter part, the limits of known and measurable natural diversity of any conventional counterpart should be taken into account.

2.1.2 Substantial equivalence except for one or more defined traits is claimed

If substantial equivalence except for one or more defined traits has been established, the assessment should focus on these traits. These should be evaluated on a case-by-case basis and may in certain cases require data, matching those needed for the safety evaluation of food additives.

2.1.3 Substantial equivalence is not claimed

If substantial equivalence to a traditional food or food ingredient is not claimed, the NF will require extensive testing details of which are outlined in Part I.

2.2 Special considerations

For foods that are substantially equivalent to existing foods no further data need to be evaluated. Other NF require further consideration. This may be targeted at specific defined traits or at the whole NF. The information provided in the application will need to be assessed in the light of the origin, method of production and complexity of the NF, and its role in the diet of the population at large and particular sub-groups.

2.2.1 Nutritional assessment

Special attention should be paid to the expected consumption level of the NF and its potential nutritional impact (see Part I, e.g. sections 3.8 and 5.XI). It should be checked, for example, that the effects of the consumption of the NF on the total dietary intakes of nutrients, for which PRI's (population reference intakes) or an 'acceptable range of intakes` have been established, have been assessed within specific population groups.

The competent authority should evaluate the documentation on animal models and human metabolic studies, including clinical observations. Long term as well as short term effects of the NF on human nutrition have to be considered. Attention should be paid to the occurrence of unexpected adverse interferences with other dietary constituents and to changes in relevant biomarkers.

2.2.2 Assessment of novel microorganisms for food use

For NF which are or which contain live microorganisms, scrutiny by the authority should confirm, that the application contains adequate data on their safety in use. Even with microorganisms the data submitted should allow them to be categorised according to the principle of substantial equivalence (see also Part I).

2.2.3 Assessment of toxicity and allergenicity

The evaluation will need to address - as appropriate - data on toxicity and allergenicity regarding defined traits of the NF or the entire NF. The information necessary to assess the wholesomeness of NF has been discussed in Part I, e.g. sections 3.7, 3.10 and 5.XIII. The application should be scrutinized for the adequacy of the data presented and an opinion on the data should be formulated.

2.2.4 Novel Processes

Products of novel processes should be evaluated on the basis of the concept of substantial equivalence (see also Part I and II).

3. Assessment of the data submitted, executive summary, conclusions and recommendations

The assessment report should include an opinion on the adequacy and completeness of the data provided. The competent authority should prepare an executive summary. The assessment report should be accompanied by a statement on its conclusions and recommendations including any conditions for marketing. In addition, benefits claimed by the applicant as well as pitfalls should be described and discussed briefly.

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