ILSI Europe
Report Series

The Safety Assessment of Novel Foods and Concepts to Determine their Safety in Use

Expert Group Report Reviewed at a
Workshop held in November 2002

Organised by the
ILSI Europe Novel Food Task Force

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THE SAFETY ASSESSMENT OF NOVEL FOODS AND CONCEPTS TO DETERMINE THEIR SAFETY IN USE

EXPERT GROUP REPORT REVIEWED AT A WORKSHOP HELD IN NOVEMBER 2002

ORGANISED BY THE ILSI EUROPE NOVEL FOOD TASK FORCE

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EXECUTIVE SUMMARY

Approaches adopted by regulatory authorities to the safety assessment of novel foods and novel food ingredients universally acknowledge the methodological difficulties arising from their often complex nature and, in some cases, their high levels of dietary incorporation. These are characteristics which novel foods and ingredients share with their traditional counterparts but the latter have not usually been the subject of systematic safety assessments. The safety of traditional foods and ingredients is usually accepted on the basis of their history of use unless there are overt indications to the contrary. The introduction of novel foods and ingredients as a result of the increasing pace of developments in science and technology and in trade has prompted regulatory authorities to adopt a proactive approach to their safety assessment. There is a general consensus that, where possible, safety assessments should use traditional foods and ingredients as reference points and that the assessment process should focus on the differences between these and the novel foods and ingredients under assessment. Such an approach is based on the concept that there may be substantial equivalence between the novel food and a traditional counterpart whose safety is accepted. It requires a systematic comparison of the information available on the novel food and its relevant traditional counterpart, and the identification of any key additional information that may be required to permit a conclusion as to the safety of the novel food. Several schemes, usually in the form of decision trees, have been developed to assist in structuring the comparison of information and in identifying requirements for data. The objective of the present exercise, undertaken under the responsibility of the ILSI Europe Novel Food Task Force, is to suggest how such additional data might be generated within the methodological constraints imposed by the nature of the food components and their intended use, and how all of the information might subsequently be integrated to provide a focussed and scientifically valid assessment of safety.

The first step in any safety assessment comprises the collation and in-depth appraisal of information on the origin, production, composition and analysis, nutritional characteristics, history of previous human exposure and anticipated use of the material as a novel food. This exercise should constitute a formal primary evaluation and pre-test consideration phase of the safety assessment and may in some cases be sufficient to permit a conclusion as to safety. It should serve to characterise the novel food and to identify knowledge gaps and likely areas of concern. It should also provide a basis for defining the extent and objectives of any additional studies that have significance for safety assessment. Where the need for additional biological testing is identified, the primary evaluation and pre-test consideration should be used to elaborate study designs that are relevant within the limits imposed by present methodology and that are focussed on those considerations necessary for the assessment of safety. It should be recognised that the primary evaluation and pre-test consideration itself makes an important contribution to the safety assessment which in some cases will be sufficient without the need for further biological testing.

An evaluation of the nutritional characteristics of the novel food is another component of the assessment process. The novel food should be evaluated from the perspective of its likely impact on the human diet to provide assurance that its introduction into the food chain will not cause adverse effects through nutritional inadequacy or excess. The process of evaluation will identify any knowledge gaps and provide guidance as to any studies that may be necessary to complete the nutritional data set required. Where the pre-test considerations and the nutritional evaluation have identified a need for biological testing, the novel food should also be evaluated from the perspective of its impact on the diet of test animals. The inclusion of novel foods in animal test

diets at high levels may give rise to nutritional imbalances which will confound the outcome of the study. Careful thought must be given to the formulation, storage and administration of test and control animal diets if biological studies are to provide meaningful results in the context of the safety assessment of novel foods for consumption by humans.

Where biological tests are deemed necessary by the primary evaluation and pre-test consideration, the conventional toxicological testing strategy leading to the establishment of an acceptable daily intake (ADI) will most often not be appropriate. This testing strategy was developed primarily for single chemicals that can be administered at high levels relative to their anticipated human exposure. Nevertheless, existing testing methods suitably targeted on a case-by-case basis using the outcome of the primary evaluation and pre-test consideration can be used to identify levels of intake which are without toxic effect and which can contribute positively to a safety assessment.

Studies in humans should not form a routine part of the safety assessment but they can contribute to it by providing confirmation of nutritional quality and the absence of adverse effects that have been ruled out by previous considerations. Studies carried out in the general population post-launch (that is, after the satisfactory completion of a safety assessment) may be helpful in providing confirmation of anticipated patterns of use and exposure levels.

In the final step of the safety assessment process, the conventional approach used in the assessment of food chemical safety, which leads to the establishment of an ADI based on the identification of a no-effect level many times higher than anticipated human exposure, will most often not be possible or appropriate. Instead, the compositional, nutritional and toxicological characteristics defined during the primary evaluation and any subsequent additional testing undertaken should be evaluated in the light of existing and anticipated human exposure patterns in the context of normal expectations of the safety of food in general. The evaluation should be driven in focussed fashion by a specific knowledge of the characteristics of the novel food in question, using comparisons with conventional foods where appropriate. Critical examination showing the estimated intake of the novel food to be below the level indicated as without toxic or nutritional hazard by the totality of the information available will allow a presumption of reasonable certainty that no harm will result from intended uses under the anticipated conditions of consumption.

The approach outlined draws together available best practices that currently provide a high level of safety assurance in relation to the use of novel foods and ingredients. Developing technologies, for example in the fields of genomics, transcriptomics, proteomics and metabolomics, may in the future complement existing methods to provide even greater power to resolve the toxicological and nutritional characteristics of novel foods, thereby adding to the level of confidence associated with assessment of their safety.

INTRODUCTION

Guidelines have been developed by a number of regulatory authorities and others to assist those submitting products for consideration under legislation concerning novel foods (US Food and Drug Administration, 1992; Health Canada, 1994; Jonas, D.A. *et al.*, 1996; Commission of the European Communities, 1997; Australia New Zealand Food Authority, 1998). Other organisations have discussed the general principles to be employed in the assessment of such products (OECD, 1993; FAO/WHO, 1996). Assessment of safety is a central concern of all of these papers and they set out requirements for information structured in accordance with the characteristics and methods of production of the novel products and their relationship to conventional counterparts. Novel products are evaluated using the guiding principle of substantial equivalence. This is a starting point, not an end point, and it is designed to highlight the differences between the new food and its traditional counterpart if one exists. These differences then become the focus of further safety assessment, the purpose of which is to determine that the new food or derivative(s) is at least as safe as its traditional counterpart. As the degree of novelty increases so does the requirement for information but the additional information and subsequent assessment are directed to those aspects of the product which diverge from those of its traditional counterpart. Where the novel product has no relation to a traditional counterpart, extensive information including toxicology and data to establish nutritional characteristics and dietary impact may be required.

It is generally acknowledged by the authorities that substantial equivalence does not in itself constitute a traditional hazard characterisation because of the thousands of substances in the food matrix which cannot each be studied in isolation. Nevertheless, relating the requirements for information to those aspects of the product which are novel serves to focus assessment on those features for which past experience of safe use is lacking whilst at the same time drawing on the assurance of safety provided by familiarity with those features which are characteristic of traditional foods. In this way the approach provides a robust assessment process. However, beyond identifying the type of additional information that may be necessary, the various schemes presently give only limited guidance as to the extent and form it should take. Nor, beyond recommending judgement on a case-by-case basis, do they indicate a clear paradigm by which the additional information called for may be used to generate an assessment of safety. These two aspects need to be further clarified both in the interests of achieving consistency and confidence in the regulatory oversight of novel foods at the global level, and for the benefit of those making applications for the approval of novel foods.

This document addresses these aspects in relation to all types of novel foods and ingredients, extending from single chemicals and simple mixtures through complex foods and whole foods derived from both conventional and genetically modified (GM) sources. It draws on all methodologies from conventional toxicity testing to novel approaches which in themselves already provide a high level of safety assurance.

This paper was developed by an expert group of the Novel Food Task Force of the European Branch of the International Life Sciences Institute – ILSI Europe – and discussed with a wider audience at a workshop held from 20–22 November 2002, in Barcelona (see Appendix).

The draft was revised in the light of the discussions held during the workshop.

THE CONCEPT OF "SAFETY"

Assessment of the safety of any novel material proposed for use as a food or food ingredient is a necessary prerequisite for the assurance of human health. By extension, this same principle applies to the use for the first time of technologies that have the potential to alter the composition of traditional foods and food ingredients in novel ways. The primary goal of the management of risks associated with food has been defined as the protection of public health by controlling such risks as effectively as possible through the selection and implementation of appropriate measures (FAO/WHO, 1997). At the same time it has been recognised that although industry and national regulators strive for production and processing systems which ensure that all food be "safe and wholesome", complete freedom from risks is an unattainable goal. Safety and wholesomeness are related to a level of risk that society regards as reasonable in the context of, and in comparison with, other risks associated with a normal diet. In addition, for it to be fully relevant for the purposes of risk management, assessment of safety should reflect the food or ingredient as prepared and/or eaten according to its intended use. These two principles, that complete freedom from risks is an unattainable goal and that circumstances of exposure should be taken into account, lead to the premise that "safety" equates to "a reasonable certainty that no harm will result from intended uses under the anticipated conditions of consumption" (OECD, 1993).

An appropriate safety assessment programme should incorporate the following considerations:

- the analytical/compositional and nutritional characteristics of the novel food (including its fate in biological systems);
- previous history of human exposure;
- the expected applications as a novel food and the predicted exposure;
- the necessity, appropriateness and outcome of animal studies;
- the necessity, appropriateness and outcome of studies in humans; and
- the necessity and outcome of post-launch monitoring.

The programme should be seen as a coherent whole. Each of these considerations should be assessed for its contribution to the reduction of uncertainties inherent in the others and reassessed as part of an iterative process in which the totality of the information available, with each element considered in relation to the others, is taken into account.

Ultimately a judgement of safety should be made, consistent with the aim of reasonable certainty that no harm will result from intended uses under the anticipated conditions of consumption and that the novel food is at least as safe as the traditional foods it may replace.

PRIMARY EVALUATION AND PRE-TEST CONSIDERATIONS

General considerations

Application of the guiding principle of substantial equivalence and thereafter focussing progressively on the differences between novel foods and their traditional counterparts as a strategy for defining a programme of safety assessment inevitably leads to a structured, but nevertheless adaptable approach which is directed by a detailed knowledge of the nature of the novel foods concerned. The most important step in the safety assessment process is to develop a thorough understanding of the origin, production, composition, other characterising properties and intended use of the novel food. Much of this should be assembled in order to gain a sound understanding of the characteristics of the food. It will contribute to the body of information needed to evaluate its safety and will serve to identify knowledge gaps where further investigation may be needed. Where areas for further investigation are identified, a sound understanding of the characteristics of the food will help to inform the design of any studies that may need to be undertaken. The level of confidence in the degree of equivalence determined will depend on the quality of the data used in the assessment.

There are many types of novel foods, ranging from defined chemical substances through complex materials such as plant extracts and macronutrient substitutes, to whole foods from conventional and GM sources. In defining a framework for safety assessment, the EU Scientific Committee for Food, for example, has recognised six categories of novel foods, the nature of which leads to different data-set requirements (Table 1).

The extent of information needed for safety assessment should be determined on a case-by-case basis. The assessment of novel production processes very clearly starts with the determination of chemical or nutritional changes that may have been introduced by the process.

If the organism which is used as the source of the novel food has a history of safe consumption under conditions of traditional use, then any toxicological concerns are reduced. Such organisms can still be a source of toxins, anti-nutrients or other potentially harmful compounds and this issue needs to be addressed in the safety assessment of any novel food derived from them. If the organism has not been used in the human food chain or to an extent to provide adequately documented assurance of safety, then the potential for toxicological concern increases and must be considered on a case-by-case basis.

In the chemical analysis of the novel food, consideration should be given both to major and minor components and to their nutritional and toxicological significance. Data should also be available to establish the microbiological and contaminant status of the food. The full range of data required will depend on the particular novel food under consideration.

The novel food should be exhaustively characterised before the start of any toxicological testing programme. This is because the material on which the toxicological testing is conducted will define the material that is ultimately approved. If the composition of the novel food or its production process changes significantly from that which was originally tested, it may be necessary to conduct some additional tests to address the differences.

There will inevitably be some variation in the quantitative and/or qualitative composition of the novel food and this will to some extent be dependent upon how the material is sourced. In the case of an extract from a natural source, there may be a large number of components which are

Table 1 – Classification of novel foods as a basis for safety assessment (Commission of the European Communities, 1997)

Class 1: Pure chemicals or simple mixtures from non-GM sources
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 subclasses can be identified: those for which the source has a history of food use; and those for which the source has no history of food use.

Class 2: Complex novel foods from non-GM sources
Complex novel foods which are, or are derived from, sources which have not been genetically modified. Intact plants, animals and microorganisms used as food as well as food components are included. Two subclasses can be identified: those for which the source has a history of food use; and those for which the source has no history of food use.

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 novel foods includes all such foods and food ingredients. Two subclasses can be identified: those for which the host plant used for the genetic modification has a history of use as food or as a source of food under comparable conditions of preparation and intake; and those for which the host plant used for the genetic modification has no history of use as food or as a source of food 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 novel foods includes all such foods and food ingredients. Two subclasses can be identified: those for which the host animal used for the genetic modification has a history of use as food or as a source of food under comparable conditions of preparation and intake; and those for which the host animal used for the genetic modification has no history of use as food or as a source of food 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 novel foods which are, or are produced using, GM microorganisms whether or not there are any living cells in the novel food as consumed. Two subclasses can be identified: those for which the host microorganism used for the genetic modification has a history of use as food or as a source of food under comparable conditions of preparation and intake; and those for which the host microorganism used for the genetic modification has no history of use as food or as a source of food under comparable conditions of preparation and intake.

Class 6: Foods produced using a novel process
This class comprises foods and food ingredients that 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 the EU regulation, the resulting product is only considered to be a novel food 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.

carried through in the processing but which represent a very small proportion of the total material. Similarly, in the case of a novel ingredient which is produced *de novo*, there may be a number of by-products which, depending on the degree of purification applied, will form a small proportion of the material. A thorough knowledge of the production process will enable relevant by-products to be identified. Extracts from natural sources may contain or have the potential to contain known toxins and anti-nutrients (e.g. lectins and trypsin inhibitors from legumes). Similarly, *de novo* syntheses may result in toxic impurities. It is important to be aware of this potential and to quantify the levels of any such constituents so that their significance for the safety of the novel food can be assessed.

Wherever possible, the information should be compared with similar information from a traditional counterpart to the novel food or the products of a similar traditional process where the process may have been the source of novelty. When no traditional counterpart exists, comparisons have to be more general and made with foods performing similar roles in the diet. An extensive review of the literature should be undertaken since it may provide valuable sources of information for these comparisons and, in some cases, on the novel food itself.

In cases where the food is intended to fulfil a particular nutritional purpose or where the food is a new source that could occupy a significant proportion of the diet, appropriate *in vitro* and *in vivo* assays are likely to be needed to support assessment of its safety in use.

However the novel food or ingredient is sourced or produced, it should comply with an initial specification which ensures that it is of consistent composition and which includes information on relevant components which may be present coincidentally as well as those of primary interest. Evaluation of this information and any testing required as a consequence will result in a final specification which defines the material which has been assessed and provides the means to ensure that the product marketed is of the quality required for safe use.

Pure chemicals or simple mixtures from non-GM sources

Pure chemicals or simple mixtures from non-GM sources might include new molecules produced through chemical means (e.g. sucrose polyesters produced through the reaction of sucrose with fatty acids) or might be isolated with or without subsequent modification from animal or plant sources (e.g. phytosterols, enzymatically modified carbohydrates, modified lipids).

The considerations prior to any toxicological testing revolve primarily around:

- the chemical/biochemical nature of the material;
- the specification of the novel food/ingredient; and
- the production process and/or the organism used as the source of the novel food/ingredient.

Chemical/biochemical nature of the material

A consideration of the nature of the material should be carried out before the start of any toxicological tests. An understanding of the chemistry, including knowledge of process technology, raw materials and potential by-products, helps in the design of any studies and ultimately their interpretation, and may also reduce the toxicological test requirements or reduce the need to use animals in any testing.

Some chemical structures may allow a degree of predictive toxicology to be applied and certainly a first step would be to identify whether or not there are any structural alerts for toxicity. Computer-based expert systems are available for some toxicity end-points e.g. mutagenicity or

sensitisation. Knowledge of an homologous series of chemicals for which toxicological information is available on some of them may be used to predict the toxicity of the novel ingredient. This approach could be used as a first screen for toxicity or be used to identify where further investigations are needed.

Knowledge of the possible metabolism of a chemical can also be useful in developing the testing strategy. For example, in the case of esters it may be possible to consider the toxicity of the component acids and alcohols. If they are regarded as safe and it can be demonstrated that the ester breaks down to its component parts rapidly within the gastro-intestinal tract, then further toxicological testing of the ester moiety will be unnecessary. Similar considerations would apply in the case of carbohydrates for which *in vitro* data indicate that they are hydrolysed to well-characterised components such as glucose or fructose, or which are fermented in the colon in the same way as conventional sources of dietary fibre.

Although a novel food/ingredient may not be chemically identical to a traditional food, there may be sufficient evidence to conclude that its chemistry and biological fate or effect is comparable to that of another food/ingredient which has a history of safe use.

Specification of the novel food/ingredient

Where pure chemicals and simple mixtures are concerned, the principal components can be specified with a high degree of precision. Information on both the maximum and the minimum levels of the principal components and, where applicable, the proportions of their isomeric forms achievable under normal production process conditions will enable the range of compositional variation to be taken into account during the safety assessment. Although "fingerprinting" technologies might be helpful, it may not be possible to identify all the minor components, even in simple mixtures of chemicals. However, it will be necessary to ensure that the presence of any component with expected toxicity, including isomeric forms where relevant, is limited to a level that is toxicologically insignificant for the product. This should be based on knowledge of how the material is produced or sourced, taking into account the potency of any toxic components and the intended use of the novel food/ingredient in the diet.

Production process and/or source organism

A critical part of the toxicological assessment of a novel food is an assessment of the process, including source organism if any, used to produce the material.

For a novel food/ingredient which is produced using a physical, chemical or enzymatic process, the process needs to be defined and a process which has a history of use within the food industry might be employed or used as a reference point. In the case of a novel synthesis, the reaction chemistry needs to be understood, so that the by-products as well as the main end-product of the reaction are identified. This has to be considered for the entire range of the reaction conditions so that any potential toxic product can be identified. Some measure of toxicological testing may then need to be conducted, first of all to address the safety of the novel ingredient and secondly to address any toxicological issues that the presence of the reaction by-products presents. If the reaction chemistry is incompletely defined, additional toxicological testing may be necessary.

In the case of ingredients obtained from a natural source, the novel ingredient would have to be separated or purified from the source. This may involve the use of physical (including solvents), mechanical or chemical processes. It would be appropriate, for example, to assess whether the nature and level of solvent remaining in the ingredient/novel food is within toxicologically acceptable limits. It is also important to assess whether or not the separation process co-extracts

and/or concentrates any undesirable or toxic components with the desired component. This relies upon having thorough knowledge of the characteristics of the source organism, an understanding of the potential toxic components associated with it and, where appropriate, setting limits as previously discussed.

There are also cases where an ingredient may be separated from the natural source and then some form of chemical processing applied, in which case the above issues need to be considered.

In all these cases it is important that the processes which are used to produce the ingredient are standardised as far as is possible and that the product complies with the specification. The significance of changes in the process that have the potential to introduce variation into the composition of the product needs to be considered and taken into account.

Complex novel foods from non-GM sources

In general, pre-test consideration of complex foods is likely to be more difficult if there are no traditional counterparts to serve as comparators. One extreme of the spectrum would be a material which previously has not been consumed in the diet. An example of this type might be a myco-protein or a single-cell protein produced by fermentation using an organism or organisms not previously considered for food use. The other extreme would be a material with a history of consumption as food but under circumstances or by populations not representative of those in which use is now proposed for a first time. An example of this type would be material derived from a plant exotic to a region where its use is proposed for the first time and where consideration should be given to the possibility of genetic differences between the population in the region of origin and that of the new market, or where subgroups may exist in the new market population which are not represented in the population of the region of origin. In principle the same considerations should be applied to the plant product itself (for example a "new" fruit) as to foods derived from it by processing. Comparability to an established food, i.e. establishing "substantial equivalence" or evidence from experience of human consumption, would provide a solid basis for an assessment. This is likely to be easier for a processed food, for example refined oil from a new plant, in which the presence of undesired compounds is less likely than, for example, in the complete fruit or vegetable. The significance of compositional differences between the novel food and any comparator should be assessed against the background of compositional variation which is normal for the comparator.

The intended use of the material will influence the type and extent of analysis, so this must be considered at the outset. If the material could make a significant quantitative and nutritional contribution to the diet, it is important that the expected level of intake is estimated (see Sections Prediction of dietary exposure to novel foods, page 19 and Assessment of safety in use, page 32), especially if particular sub-groups of the population are likely to have higher than average consumption. In most instances this will highlight the need for a thorough nutritional analysis to be completed. Because complex foods with no traditional counterparts are likely to be those for which the greatest range of testing is required, an estimate of intake will be particularly important to the process of setting test levels in toxicology and nutrition studies.

The information possibly available early in the evaluation process is likely to fall into three categories:

- information relating to the source and/or agricultural production;
- chemical composition data; and
- processing and human consumption experience.

As far as possible, published data should be evaluated, recognising that the national/regional literature may contain a wealth of information not accessible via global data banks. Other sources, including data collection on site, may also be helpful to provide facts and/or guidance for further work.

Information relating to the source and/or agricultural production

For complex materials from sources with a previous history of human consumption, data will often be available on the geographic origin, taxonomic classification and properties of different plant cultivars and on the specific conditions for growth and harvest. Information is also generally available (or should be sought) on the part of the plant consumed, the optimal degree of ripeness and sometimes also on effects on quality and safety when the plant is harvested at non-optimal times. Information may also be available on the accumulation of soil chemicals, e.g. heavy metals, and susceptibility to moulds producing mycotoxins. In some cases, data on a natural pest resistance of certain strains or cultivars could indicate the presence of natural toxins relevant for humans.

Chemical composition

Again for complex materials from sources with a previous history of human consumption, information may be readily available from existing databases on the presence and levels of macronutrients, micronutrients and anti-nutrients (e.g. OECD, 2001a; OECD, 2002a; OECD, 2002b). Specific information should be sought on the types of proteins, fats and carbohydrates in order to identify whether unusual forms are present. The variation in the composition of the novel food should be considered in the context of the range of that normally encountered in comparable traditional foods. This data will usually cover the bulk of the plant material.

Analysis of nutrients and other nutritionally significant components should include:

- protein and amino acids, including the identification of any unusual amino acids which may need more detailed study;
- fat and fatty acids, including odd numbered or unusual fatty acids;
- carbohydrate components, including those falling under the heading of fibre;
- vitamins;
- minerals;
- any anti-nutrients; and
- in the case of food sources which naturally have a relatively high content of nucleic acids, e.g., fungi, algae or bacteria, analysis of the RNA content of the product is needed. This is primarily to determine whether there is a need to control the RNA level via the production process and subsequently to ensure that the content in the final product is limited to an acceptable level (FAO/WHO UNICEF Protein Advisory Group, 1970).

In cases where the novel food is sufficiently similar to a traditional counterpart, at least for the major nutrients, but if possible for other relevant substances too, information on the composition of plants from different regions and/or (where this could significantly affect composition) with different degrees of ripeness should be obtained. Aside from the edible part of the plant, other parts (for example, leaves unavoidably co-harvested with the fruits) should also be evaluated for undesirable components if it is likely that they might enter subsequent processing steps.

The likely occurrence and presence of natural toxins and allergens and their fate during processing should be assessed, using as guidance information on substances known to be present in related plant species. Additional data of interest would relate to types and levels of relevant phytochemicals, i.e. non-nutrient components, especially any known or expected "active" materials or established anti-nutrients.

The food should be analysed for a range of extrinsic contaminants normally assessed in foods, e.g., heavy metals or pesticide residues. Depending on the source of the food and its method of production, other contaminants, such as mycotoxins, could be important. Which ones are selected for analysis will depend on a consideration of the probability that they could be present. In the case of foods from micro-organisms, analysis should be undertaken for known toxins which the production organism has the potential to produce. This is essential not just as a contribution to the safety assessment, but also as an ongoing assurance that production conditions are maintained which are not conducive to the production of such compounds.

Given that a complete analytical characterisation of any food is not feasible, appropriate fingerprinting or profiling, for example by infra-red spectroscopy (IR) or nuclear magnetic resonance (NMR) using suitably validated methods, should be considered as a means of identifying the possible presence of chemical classes of potential relevance for health. Such fingerprinting would also provide a means subsequently to validate that the article of commerce is indeed comparable to the material originally used as the basis for approval or testing.

Microbiological analysis of the food should be undertaken to ascertain that it does not carry an inherently greater degree of microbiological risk than other established foods.

Processing and human consumption experience

Information should also be available on any necessary processing without which the material would be frankly unsuitable for human consumption, for example as in the case of exhaustive washing for manioc or cooking for lima beans.

Local consumption patterns should be evaluated: a food consumed only occasionally or exclusively in combination with another material may cause problems when consumed in larger quantities or in a different context.

If the food is commonly used, the availability of existing epidemiological data should be explored. Such data may provide indications of intolerances or allergic reactions, if any exist, and there may also be information relating to consumption by specific age groups or for specific purposes. Also, collections of case reports in the region, or from local publications, can be helpful to guide further work.

Whilst experience of use in the source region can provide helpful information, it must be considered in the context of the novel use proposed.

GM plants and their products

Food crops developed through biotechnology are produced by the stable insertion of one or more well-defined genes into the genome of a plant or the targeting of specific changes in individual genes, e.g. down-regulation or gene knock-out. The genes produce one or more proteins that confer the trait of interest (e.g. insect resistance). Of the thousands of individual plants that are produced, only a few are selected, based on stringent performance standards, as the source for all the varieties eventually sold commercially.

WHO and OECD have established the safety assessment process based on the principle of "substantial equivalence" to assure that foods derived from new processes are as safe and nutritious as food produced from conventionally bred crops. This process considers two aspects: (1) the properties of the introduced trait and (2) any effects generated by the introduction or expression of the new trait in the crop or food. This is a comparative safety assessment whereby conventional foods that have a history of safe use and consumption serve as a reference point for all safety testing.

The following data should be collected systematically:

- characterisation of the new gene product, most often a protein;
- comparison of the agronomic and phenotypic characteristics of the new plant to conventionally bred plants; and
- comparison of the new food to conventional food with regard to the nutritional and biochemical composition, including the possible presence of anti-nutrients and toxins. OECD documents on the composition of conventional crops may be useful as a starting point (OECD, 2001a; OECD, 2001b; OECD, 2002a; OECD, 2002b; OECD 2002c).

Characterisation of the new trait (gene product)

The safety assessment of products derived through biotechnology requires that the DNA inserted into the plant is fully characterised and that any newly produced proteins are clearly identified. The safety aspects of the consumption of transgenic DNA have been the subject of a recent ILSI Europe Workshop. It was concluded that transgenic DNA is neither more nor less hazardous than any other form of dietary DNA, of which a large amount is consumed daily, and the possibility of a functional gene transfer via the food from a GM organism is extremely remote (Jonas, D.A. *et al.*, 2001).

It is relevant that the gene product in most GM crops is a protein and the specific proteins or other gene products that are expressed can be directly assessed for safety as defined single substances. This knowledge affects the type and extent of safety assessment performed.

To this end, each introduced protein needs to be extensively characterised to understand how it functions and to assess its similarity to proteins that are already present in foods. For example, a widely used protein that confers herbicide resistance is a member of a family of proteins naturally present in most foods, has a well-defined function and may be considered of lower concern than a previously completely unknown protein, due to its history of safe consumption. As part of the hazard identification, a comparison of the amino acid sequence of the introduced protein or proteins to known toxins and allergens should be made to assure that the protein is not a known toxin or allergen and that it is not closely related to either. Since proteins are a key component in food and are typically rapidly digested, the digestibility of the protein may provide an indication of its safety. Following hazard identification, the amount of the introduced protein is measured in key raw agricultural commodities to evaluate likely consumption levels and patterns.

The likelihood of the protein being or becoming an allergen should be considered in detail according to international standards (FAO/WHO CODEX, 2002).

Agronomic equivalence

As part of the overall safety assessment of a crop developed via genetic modification, numerous agronomic and phenotypic parameters of the crop are compared with those of the conventional counterpart to assure that there are no meaningful changes caused by the transformation process or the introduced genes or trait. The morphology, yield and other agronomic parameters are sensitive indicators of changes in the metabolism or physiology of the plant. Plants developed through biotechnology must meet stringent agronomic and performance criteria. This effectively screens for "unintended effects" in the same way as in conventional breeding practices. As in the case of conventional breeding practices, it helps to eliminate plants in which unintended effects may have occurred.

Compositional equivalence

A key focus of substantial equivalence is a comprehensive comparison between the new crop and its traditional counterpart of key nutrients, anti-nutrients, toxins and other compounds that are naturally present. For maximum rigour, GM and conventional plant varieties would need to be grown under a variety of field conditions to assess the composition under commercially representative growing conditions. The key components (e.g. protein, oil, carbohydrate, fibre, ash and moisture), the levels of the individual amino acids, fatty acids, vitamins and minerals and the levels of key toxicants, anti-nutrients and allergens should be assessed. The values for the GM crop are compared with both those of the parental control and those of other commercial varieties of that crop, the latter often available from existing databases (e.g. OECD, 2001b; OECD, 2002c), to assess whether the range of values obtained for the GM crop fall within the levels typical for conventional varieties.

GM animals and their products

The term "GM animal" is used to refer to animals modified either by a technique known as "transgenesis" (when individual genes from the same or a different species are inserted into another individual) or by the targeting of specific changes in individual genes or chromosomes within a single species ("knock-outs" or "knock-ins"). GM animals have potential use in agriculture and in medical research and therapeutics; only the former use will be considered here.

The nature of animals in agricultural systems requires broad consideration of the potential impact on the ecosystem resulting from the release or access of GM animals to the environment.

Genetic modification of farm animals may be carried out to introduce genes that confer tolerance to animal pathogens (e.g. Marek's disease in poultry, foot and mouth disease in sheep, pigs and cattle) or enhanced resistance to parasitism (e.g. trypanosomiasis).

Transgenesis has been used to introduce desirable alterations in growth rates (e.g. altered growth hormone levels in pigs, sheep and fish) or improved feed conversion ratio. GM animals with altered meat and milk composition have been created to produce, for example, leaner meat, milk with anti-microbial properties for newborn animals, or cow's milk without components that are potentially allergenic to humans. Insects are also being considered for protein production. Work is ongoing on silk moths producing silk with altered properties.

Much of this technology is still in its early stages and it is likely to be at least a decade before large animals with modified or deleted genes of commercial value have been evaluated and approved by the various regulatory bodies.

GM micro-organisms and their products

GM micro-organisms may be used both to produce foods and food ingredients, and directly themselves as foods and food ingredients. As for GM plants and animals and their products, information on their characteristics, parentage, method and nature of modification and a chemical characterisation of their metabolites and products will provide reassurance as to their safety or indicate the aspects to be the subject of further investigation or testing. Viable GM micro-organisms may be present in, or used as, foods and their safety assessment raises unique aspects in relation to genetic stability, toxicity, pathogenicity and gene transfer. Viable GM micro-organisms used in foods have been the subject of a separate ILSI Europe activity which resulted in consensus guidelines for their safety assessment (ILSI Europe, 1999). They are not discussed further here.

Foods produced using a novel process

It is the aim of the development of novel processing techniques to further improve the microbial safety and nutritional quality as well as the physico-chemical (i.e. sensory or technologically functional) properties of foods by minimizing process intensities and thus reducing energy requirements as well as waste loads (i.e. leaching of nutrients from foods) as compared to conventional thermal processing. Novel processes are also developed to meet consumer requirements, such as for more "healthy" foods, as well as to increase production and process efficiency. Novel processes for food production may encompass new types of heat processing, non-thermal preservation methods, new processes to chill, freeze or dehydrate products, and the application of new processes catalyzed by enzymes. They are used or intended to be used for the preservation or modification of foods and food constituents, to affect mass or heat transfer, and to induce or increase biosynthetic reactions. Examples of such existing or planned applications are provided in Table 2.

These processes, termed invisible processing or minimal (*schonend*, gentle) processing, can be applied individually or as combination processes – the "hurdle" concept. They have reached different levels of development worldwide, ranging from existing industrial processes (e.g. high pressure processing – see Commission of the European Communities, 2001) to processes still under scientific debate (i.e. oscillating magnetic fields) (Busta, F., 2000, Barbosa-Canovas, G.V. *et al.,* 1998, Mertens, B. *et al.,* 1997, Gould, G.W., 1995, Anon, 2001, Hendricks, M. *et al.,* 2002). Key problems arising from assessment of existing and emerging novel technologies and from experience with proposals submitted for novel food legislation include the following:

- it is the goal of novel technologies not merely to mimic existing technologies but to be superior to them and to improve the safety and quality of our food supply. The aim is not only to achieve substantial equivalence with existing products but to exceed the compositional quality achieved by conventional technologies. The aim is to achieve fresh-food quality; thus the points of reference to be selected for comparison will be difficult to identify. Discussion is required as to whether or not substantial equivalency can be regarded as having been achieved in those cases where overall nutritional quality of products processed by novel processing techniques is better but different from those processed by conventional methods. Any such discussion should take into account the possible need for measures to ensure that individual concentrations of beneficial nutrients or other food constituents do not approach nutritional stress/toxic levels;

Table 2 – Examples of existing and intended applications of novel processing techniques

Application	Types of foods considered	Processes
preservation/ decontamination (e.g. shelf-life extension)	whole foods macro-ingredients micro-ingredients micro-organisms ready to eat meals packaging materials	high hydrostatic pressure pressure assisted freezing high intensity electric field pulses high voltage arc discharge electric resistance (ohmic) heating ultrasonics high intensity pulsed light
modification (e.g. gelatinization)	whole foods macro-ingredients micro-ingredients	high hydrostatic pressure high intensity electric field pulses
stress induction (e.g. increase in biosynthetic activities)	whole foods micro-organisms cell cultures algae	high hydrostatic pressure high intensity electric field pulses
mass transfer modification (e.g. extraction, expression)	whole foods micro-organisms cell cultures algae raw materials for macro- or micro-ingredients food process wastes	high hydrostatic pressure high intensity electric field pulses ultrasonics

- assessment of the novel process technologies reveals that generation of allergens or toxins are not key issues but their sufficient and effective inactivation needs considerable attention. Other process safety indicators need to be identified and/or developed (e.g. free radical formation, generation of electrolytic products);
- the processing of foods usually involves a number of unit operations (20 to 25 on average). Quantification of the impact of novel processes within the entire food processing chain and the product is required;
- studies on inactivation kinetics of microorganisms by novel process technologies clearly indicate that the log linear inactivation kinetics (as applied for conventional thermal processing) needs to be re-evaluated;
- in cases where specific constituents of novel food sources are being used (e.g. an oil from a GM oilseed) the safety of other constituents of those sources (e.g. proteins from the same oilseed) must be ensured when these constituents are subjected to conventional or novel process technologies.

To allow an adequate appraisal of the impact of a novel process on the safety and wholesomeness of foods or food constituents, sufficiently detailed information must be available to permit a clear distinction between novel and existing processes for a given food or food ingredient. Such information may include the principle of the process and its mode of action, the process intensity (e.g. processing time, pressure and process/product temperature, or time, electrical energy input and temperature, inlet and outlet temperature), the packaging material used during processing and the scale and the history of the process used. Since higher process intensities are usually beneficial for microbial safety but often detrimental for product quality, precise process optimisations are necessary to achieve product safety and organoleptic (e.g. colour, flavour) and nutritional quality. Further information required is whether combination processes have been applied (novel/conventional or novel/novel) to process a given food. If the process has been applied to packaged products, the type and thickness of the packaging material and the kind of packaging (e.g. vacuum, modified atmosphere with inert gases) is also required (Ozen, B. F. *et al.*, 2001). Post-processing information such as proposed shelf life and required storage conditions and – since process-induced changes of foods or food constituents may occur during storage – data from storage tests are needed. Processing knowledge must also include an assessment of any organic and inorganic residues or contaminants derived from machinery or equipment or from chemical, physical or biological aids used in the novel process.

To ensure the reliability of evidence regarding substantial equivalence of foodstuffs derived by novel processes, the meaningful selection and accurate description of the conventionally processed point of reference is essential.

The critical aspects of the novel process are those which ensure that the final product has been processed within the good manufacturing practice requirements and that the final product consistently and reproducibly meets adequate microbial safety needs as well as defined compositional and quality criteria.

Detailed information must also be available to allow an assessment of 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. Since specific impacts of the process can also be product specific, case-by-case evaluation is required.

Prediction of dietary exposure to novel foods

The estimation of the likely level of consumption of a novel food is important in the overall assessment of the safety of the food in the context of its expected use. It is also an important consideration in defining the extent of, and in setting test levels in, toxicological, nutritional and clinical studies and account should be taken of the range and pattern of intakes for the general population as well as specific sub-groups. The key objectives in predicting dietary exposure to novel foods should be:

- to anticipate potential nutritional implications;
- to establish whether there is previous or existing consumer exposure to the food or its components from other sources;
- to estimate the mean and upper intake levels, which will help to decide whether feeding studies are indicated and, if so, to set appropriate testing levels for both animal and human studies;
- to identify specific groups of consumers, such as children, the elderly, or people suffering from or at risk for certain diseases, which may merit closer evaluation of safety;

- to establish whether the consumption of a novel food that is present in a wide range of complementary products may lead to a high overall intake despite a low content in individual products;
- to establish whether the consumption of the novel food will lead to an intake of certain components significantly increased over background levels (e.g. a plant extract consumed in purified form versus conventional consumption of plants).

A key factor in assessing the safety in use of a food is to relate the results of safety studies to the expected future consumption. The contribution of the prediction of dietary exposure to the safety assessment of novel foods and ingredients is covered in more detail in Section Assessment of safety in use, page 32.

Outcome of the primary evaluation and pre-test considerations

Pre-test considerations are an integral part of the safety assessment of novel foods and processes. A critical analysis of information on origin, production, composition and other characterising properties, intended use and anticipated exposure is at least as valuable in a predictive sense as studies in biological, *in vivo* systems. It provides guidance on whether there is a need for further data and/or studies and, if so, on the form the data and/or studies should take. The following general principles are relevant in this regard:

- the elements of pre-test evaluation should comprise analytical, historical, exposure and biochemical/metabolic considerations;
- for specific novel foods, case-by-case approaches are appropriate, particularly in view of the nature of the different categories of novel foods involved;
- pre-test considerations provide the basis for comparisons of novel foods with existing foods they may replace;
- based on the outcome of pre-test considerations of purified compounds, no further testing might be necessary;
- if thorough analysis shows that the composition of a complex novel food is within the range of acceptable natural variation of existing foods, there should be no further safety concern;
- for foods subjected to novel processes there may be a need for additional indicators of safety. It may be worthwhile to generate more data to enable an evaluation of the effects of novel processes on groups or categories of foods since this may obviate the need to evaluate individual foods produced by novel processes on a case-by-case basis.

NUTRITIONAL CONSIDERATIONS

Nutritional aspects require consideration in order to:

- evaluate the nutritional impact and/or efficacy for the consumer of the novel food; and
- determine appropriate diets for use in experimental safety evaluation.

A thorough chemical analysis (Section Primary evaluation and pre-test considerations, page 8) of the novel food will provide significant information on its likely nutritional characteristics. For many foods this information may be sufficient to allow an assessment of the expected nutritional impact. However, in cases where the food is intended to fulfil a particular nutritional purpose, or where the food is a new source which could occupy a significant proportion of the diet, a more thorough nutritional evaluation may be indicated to support the intended use of the novel food.

On the basis of the nutrient analysis outlined in Section Chemical composition, page 13, the important nutritional features of the food can be identified and/or confirmed. Not only will this analysis pinpoint the likely nutritional impact of the product and allow comparison with traditional counterparts, but it will also provide essential information for use in the formulation of suitable diets for subsequent nutrition and toxicology studies, should these be deemed necessary.

Nutrition studies in support of the intended use of the novel food

If the food is expected to fulfil a specific nutritional purpose, or when its consumption may be expected to have a nutritional impact on the diet, there will often be a need to carry out bioassays to confirm the nutritional quality with regard to the parameters of interest. For example, a new source of fibre may affect the availability of minerals in the food, or even from other sources in the diet, and this would require investigation. Protein quality, not just quantity, will need to be established where a new food is likely to make a significant contribution to the diet. In cases where the food is intended to have a low digestibility with respect to a particular nutrient, this would need to be confirmed by an appropriate bioassay. At the simplest level, there may be sufficient published information on similar foods to reach a conclusion without the need for practical investigations, but in other cases data may be generated through *in vitro* or *in vivo* assays. The extent and need for such assays will depend on the specific properties of the food and its intended use.

Performance studies in farm animals such as dairy cows, beef cattle, pigs and poultry are used to confirm the compositional data which show, for example, that the grain from GM crops is nutritionally equivalent to feed from conventional crops. Because of their commercial significance, the nutritional requirements of farm animals are particularly well understood and, as a consequence, these studies are sensitive to unexpected effects associated with the consumption of the GM crop. Furthermore, such studies can provide additional confirmation of the safety of the introduced trait (protein), the nutritional/compositional equivalence of the whole food, and the outcome of feeding studies in laboratory rodents.

In some cases, the use of farm animals or other species may be indicated for the purpose of specific nutritional investigations. For example, the pig has been used in digestibility studies as a model for humans and the growing (i.e. broiler) chicken has been used in well-established bioassay procedures to determine amino acid availability and/or general nutritional performance.

In some cases, the nutritional evaluation may extend to human volunteer studies to confirm the nutritional adequacy of the foods for humans (see Section Human studies, page 30).

Nutritional considerations during toxicological testing

In contrast to most food additives and contaminants, novel foods potentially represent a substantial part of the human diet. For the safety assessments of novel foods (e.g. whole novel foods and macronutrients) therefore, more sophisticated approaches must be employed since, among other things, it is generally impossible to derive large safety factors between the highest possible test levels and expected intakes. One of the primary aims when designing an animal study to test the safety of a novel food or ingredient is to achieve a concentration of the novel food or ingredient in the diet which, at the highest level used in the study, does not cause nutritional imbalance or metabolic overload. Thus, the diets used in these studies require special attention, particularly to ensure nutritional equivalence between the control and all the test diets used.

The successful preparation of laboratory animal diets for the toxicological testing of a novel food depends on having as complete a picture as possible of the nutritional content and quality of the food. The bioavailability of various nutrients will vary between different foods and, in the case of novel foods, is likely to be unknown. *In vitro* and *in vivo* assays to determine digestibility and nutrient bioavailability can be employed on a case-by-case basis to provide specific data on the novel food. For example, mineral availability is an important piece of information which can be used in diet formulation to ensure comparability of major minerals across all test and control diets, thereby enabling the avoidance of mineral-related conditions such as nephrocalcinosis in rats. Other nutrients, such as amino acids and fats, might be bound thereby limiting bioavailability, but the need for bioassays has to be decided case by case.

Definitions and types of diets used in animal studies

In the following discussion, four different types of animal diets are considered:

- diets based on natural ingredients such as cereals, soya and other, mainly agricultural, ingredients; these include the commercially produced, standard laboratory animal diets ('chow') and individually formulated and specially prepared diets of this type which may be considered for the testing of novel foods;
- purified diets, sometimes referred to as semi-synthetic diets;
- chemically defined (synthetic) diets; and
- human-type diets.

Because natural-ingredient diets are formulated with agricultural products and by-products, they are relatively inexpensive, nutritionally acceptable and palatable to most animals. These diets have typically been used for rodent feeding studies with GM crops, though formulation is a complex process.

Purified diets on the other hand are formulated with a more refined and restricted number of ingredients, for which a detailed chemical analysis is often available. Purified diets are most often preferred when whole food and macronutrients are tested because it is easy to manipulate ingredients in this type of diet and higher test levels are potentially achievable than with natural ingredient diets.

The third type is the chemically defined diet, made from the elemental constituents such as amino acids, specific sugars and fatty acids etc. This type of diet is very expensive and difficult to prepare and is therefore used only in extremely specialised instances where it is important to change one variable against a background of consistency (National Research Council, 1995).

A human-type diet, representing a balanced human meal, is a further possibility for an experimental animal diet. This diet, which can be useful for the testing of novel processes, will have to be adapted, qualitatively and quantitatively, to the nutritional requirements of the test animal, but background experience with such diets is limited.

Diet formulation

When using a purified diet or natural-ingredient diet to test the safety of a novel food it is inadvisable to mix the novel food directly into a diet of standard composition. Depending on the composition of the novel food, such an approach would be very likely to result in overload and/or imbalance of individual nutrients (protein, minerals and vitamins) and overload or dilution of essential micro- and macronutrients. Depending on the nature and amount of the novel food, the content of at least some ingredients in the diet will require adjustment in order to maintain the nutritional balance within and between diets.

In order to make this manipulation of the diet, the detailed nutrient composition of the novel food or novel food ingredient must be known. This information should also include anti-nutritional factors if they are likely to be associated with the source of the novel food or ingredient, and include information regarding components that might arise from the production process. The need and extent for such information should be decided on a case-by-case basis.

If possible not only the composition but also the bioavailability of the components in the novel food or novel food ingredient must be taken into account. For example, certain minerals and lipids can be very tightly bound to the novel food matrix thus reducing their bioavailability, or the presence of the novel food in the diet can affect the bioavailability of other nutrients in the test diet. If low availability is suspected, bioavailability studies on the significant nutrients might be necessary. The diet formulation should be adjusted according to detailed information on the bioavailability of these nutrients.

If a novel food or ingredient contains a component, for example a mineral, in a relatively high concentration, a high amount of this novel food or ingredient included in the diet can result in an unphysiological, nutritional or possibly toxic effect. These effects can be predicted from compositional analysis, preliminary studies and literature, allowing these factors to be taken into account in diet formulation. Such features may determine the maximum amount of the novel food which can be incorporated into the diets.

Most of the above nutritional considerations arise in relation to the incorporation of whole novel foods and novel macronutrients that contribute significantly to the bulk of the diet of laboratory animals. Adding novel micronutrients to the animals' diet will not normally present the same kind of considerations if they are added on top of the diet up to a maximum of 5% of the feed. However, in each case it must be considered whether even these small percentages can be added to a mixed diet without risk, as those levels in some cases may still cause physiological, nutritional or toxicological imbalance.

The most important influence on food consumption is the energy content of the diet. Animals adjust their food intake according to the energy density of the diet in an attempt to maintain an energy intake compatible with their physiological requirements, though this process is only partially successful (Edwards, D.G. *et al.*, 1985a, Edwards, D.G. *et al.*, 1985b). Therefore, the energy contents of the test and control diets need to be given special attention to avoid differences which would cause different food intakes between groups. This is especially so when ingredients with a high energy concentration, such as fats, are being tested, or when ingredients with deliberately or naturally low energy contents are involved, such as fat substitutes. If reduced food intake resulting in intakes of nutrients which are suboptimal is to be expected, diets must be formulated to avoid this.

Ideally the test article should have the same physical form, e.g. particle size, as the other ingredients. Otherwise, inhomogeneity may occur during the mixing, transport and storage of the feed and, in addition, may enable the animal to separate the test substance from the other feed constituents (National Research Council, 1995).

Control diets

The use of appropriate control groups is of fundamental importance. This refers to the traditional comparator of the novel food, or a comparator as closely related to it as possible, as well as to nutritional equivalence between control and test diet. When a whole food is tested, e.g. a rice variety which is substantially equivalent except for a certain trait to a conventional rice, it is recommended that a control group be included and fed the comparable conventional rice variety. Adjustments to the type and amount of ingredients in the diets when adding a novel food or ingredient must be determined on a case-by-case basis. The optimal situation is that the diet including the novel food will be nutritionally equivalent and have the same composition regarding micro- and macronutrients and energy values as the diet given to the control group. This ideal situation seldom occurs, however, and when it does, differences in the bioavailability of the seemingly identical compounds can make the diets nutritionally different. One other obstacle when trying to assure the same composition of nutrients in all diets in a study is that the novel food or ingredient can contain components (special kinds of carbohydrates, amino acids, lipids or contaminants) which do not appear in a normal animal test diet. The best way to handle this is to have an equal overall amount of macronutrients in the control and test diets, to ensure the appropriate supply of essential nutrients (e.g. amino acids) and to pay special attention to the potential action of these components when evaluating the effects observed. If the control diet has been subject to major compositional changes in order to make it nutritionally equivalent to the test diet, it may be appropriate to include a second control group fed a normal rodent diet. This will facilitate the differentiation between adaptive nutritional and potential toxic effects.

Recommended approach

Purified diets may be preferred when testing novel foods and novel food ingredients as it is easier to manipulate ingredients in these diets. Also, they are palatable to most animal species. Diets based on natural ingredients may constitute a more complex task with regard to formulation, but they are often included as a more complex option in the testing of novel foods. To aid in the formulation of complex diets where multiple adjustments are involved, use of suitable commercially available computer programmes should be considered.

In the testing of a novel food it is desirable to obtain the highest concentration possible of the test compound in the feed. In addition, the maximum test level of the novel food should exceed the anticipated exposure of humans. In the case of a protein-rich test material, it is often possible at the highest test level to substitute all dietary protein with novel protein. However, consideration

should be given when substituting all protein, and in other cases fat and carbohydrate, to the introduction of nutritional effects that could inadvertently be interpreted as toxicological effects. For instance, if all dietary protein is to be replaced by the novel food, its amino acid profile must be determined and a potential deficiency of essential amino acids must be corrected by selective supplementation or by including an additional control group.

Before embarking on toxicology studies, it is advisable to confirm that the nutritional quality of the diets to be used and the palatability and nutritional comparability of the range of diets to be tested are satisfactory by conducting a short feeding trial. The criteria by which this should be judged should be those indicative of adequate nutrition, i.e., food intake, growth, food utilisation and clinical signs, unless there are specific reasons to include other criteria. In most cases, a 14-day or 28-day preliminary study will be appropriate before running additional animal studies with repeated doses. If the test diet is not palatable with the selected concentration of the novel food or ingredient, alternative methods of dosing (e.g. oral gavage) or masking of taste could be considered. As a last resort, a change of animal species could be necessary. Such preliminary studies will thus be of considerable value in setting appropriate test levels and diet formulations for subsequent studies to determine the safety of the novel food.

In animal studies it is normal to feed the animals *ad libitum*. However, this could, depending on the diet formulation, result in overfeeding, leading to obesity and decline in survival of the animals in long-term studies (Keenan, K.P. *et al.*, 1996). Special attention should be given to the diets from this point of view, particularly to the levels of energy and fat, and to ensuring that they are balanced with regard to other key nutrients. Another way, which, although laborious, results in slower growth and healthier animals, is to restrict and control the amount of food consumed by the test animals. However, this practice of restricted feeding has not yet been incorporated in any international study guidelines. Hazard identification by methods of animal-based toxicology has been further addressed under the project "Food Safety in Europe: Risk Assessment of Chemicals in Food and Diet" (FOSIE) (Barlow, S.M. *et al.*, 2002).

Although the primary aim of a feeding study may be to evaluate potential toxicological effects, observations concerning confounding nutritional effects are an important part of the understanding of any unwanted biological effects of the novel food and should be adequately documented.

Quality assurance

Before starting the diet formulation process, it is necessary to prepare appropriate protocols and standard operating procedures consistent with good laboratory practices according to generally acknowledged standards covering the whole process. These protocols should cover the raw materials to be used and criteria for their acceptance (e.g. analysis), procedures for preparing the diets including any pre-mixes, quality control of the diets and criteria for acceptance, packaging, diet storage and shelf life.

TOXICOLOGY

General considerations

Systematic consideration of the origin and compositional characteristics of a novel food and the likely patterns of consumer exposure to it may allow judgements about its safety to be made either by analogy with traditional foods or through a pre-existing knowledge of the toxicological and nutritional properties of the components (including traits) defined as novel. But safety assessment may also involve a consideration of foods or food components or their circumstances of use for which there is no previous experience. Also, in cases where there is previous experience to draw on, analysis of the information available for primary evaluation and pre-test considerations (Section Primary evaluation and pre-test considerations, page 8) or considerations arising during nutritional evaluation (Section Nutritional considerations, page 21) may indicate knowledge gaps or potential toxicological or nutritional concerns. Where this is the case, laboratory studies to investigate both toxicological and nutritional aspects may be called for. Many previous authors have pointed out (WHO, 1987; FAO/WHO, 1991; Health Canada, 1994; Knudsen, I. *et al.,* 1995; Munro, I.C. *et al.,* 1996) that conventional animal testing methods cannot always easily be applied to foods or products intended to be used as major constituents of foods. Moreover, it has also been pointed out that the use of mutagenicity and other *in vitro* tests for complex foods requires special techniques and cautious interpretation (Commission of the European Communities, 1997).

While the use of studies on laboratory animals has a key role in the assessment of the safety of novel foods, their strengths and limitations and the particular nature of novel foods as compared to substances commonly subjected to toxicological studies necessitate special considerations in relation to study design. Use of a knowledge of the novel food's characteristics, composition, production methods and circumstances of use is required to inform the choice of appropriate tests and the interpretation of their results.

Toxicological studies have historically been developed for assessing discrete chemical substances. They have been based on single compound evaluation and their strategy is one designed firstly to establish overt toxicity so that the nature of any hazard associated with the compound could be identified, and secondly to establish the level of exposure below which that toxicity does not occur (the no observed adverse effect level or NOAEL). In contrast, the strategy underlying judgements about the safety of foods and food ingredients is generally to establish the absence of toxicity at any reasonably attainable level of exposure. In considering the use of toxicology testing in the safety assessment of novel foods, it is important to keep this difference in strategic approach in mind. The objective of any toxicology testing programme for a novel food should be to contribute to the assessment of the reasonable certainty that no harm will result from its intended uses, on a comparable basis with judgements about the safety of the foods it will replace.

Within this objective, with due attention to the considerations outlined in this section and a comprehensive prior knowledge of the history, compositional, biochemical and nutritional characteristics, intended use and likely exposure level (Sections Primary evaluation and pre-test considerations, page 8 and Nutritional considerations, page 21), traditional toxicological testing methods can provide a sound basis for the assessment of novel foods. A publication undertaken under the responsibility of the ILSI Europe Task Force on Novel Foods has previously elaborated an approach based on such considerations (Jonas, D.A. *et al.,* 1996).

In some instances it may be possible to focus animal studies on discrete components which are known to represent the only significant difference between the novel food and its traditional counterpart. In others, it may be necessary to subject the whole food to toxicological study. For the safety assessment of GM-derived novel foods, consideration of both the isolated new gene product and the whole food material is advisable in order to identify potential unintended consequences of the gene insertion on the host organism. In any case, the objective of the toxicological studies is not to provide the sole basis of the safety assessment with, as an outcome, the derivation of a numerically expressed acceptable daily intake. Rather, they are intended to complement the information available on the nature, composition, expected use and exposure of the novel food to provide a weight of evidence sufficient to conclude with reasonable certainty that no harm will result from intended uses under the anticipated conditions of consumption (see Section Assessment of safety in use, page 32).

Where whole foods or ingredients are the subject of testing, the test article should be representative of the product intended for marketing and consideration should be given to how it will be prepared for consumption. Otherwise, the data obtained may not be wholly applicable for the safety assessment of the product as it will be consumed.

Recommended types of studies

It is not possible to formulate general rules specifying a definitive list of studies, either for single defined substances or for whole foods. In deciding which studies are necessary and appropriate for particular novel foods, the guiding principles should be that the studies address aspects of toxicity not addressed elsewhere by the information already available and that they are capable of doing so in an unambiguous fashion. If they are not designed and undertaken with clear and achievable objectives in mind, it is unlikely that they will contribute positively to the safety assessment.

Where a repeat dose animal feeding study is deemed necessary, a 90-day subchronic study in a rodent species is likely to be the minimum reasonable duration, and may often be the sufficient duration necessary, to provide data adequate for use in evaluating safety or to determine whether further studies are needed. The scope of the study should normally include the full range of parameters appropriate to an adequate protocol. The inclusion of additional, targeted parameters and the need for further studies (second species, reproduction or carcinogenicity studies, use of specific animal models) may be indicated depending on prior knowledge, the level of concern and biological effects anticipated from pre-test considerations and/or the results of initial animal testing.

In practice, toxicokinetic and genotoxicity studies will be possible only for defined chemicals or simple mixtures, or where foods from GM sources have a limited number of introduced new traits. In general, the testing of whole food extracts in genotoxicity studies is inappropriate as it is likely to result in artefacts making interpretation difficult. Indications from prior knowledge may, however, suggest isolated components of complex foods which it may be appropriate to investigate in these studies. For complex foods, some assurance of the absence of a potential for genotoxicity may be gained by appropriate investigations of bone marrow or peripheral lymphocytes undertaken as additional elements of repeat feeding studies in rodents.

Setting of test levels

As a general rule, to have relevance for the assessment of safety, test levels should be higher than the equivalent anticipated human consumption. Given that foods are normally consumed in much higher quantities than, for example, many food additives, test levels will usually be limited by nutritional and physiological factors, as well as by practical considerations specific to individual novel foods (see Section Nutritional considerations during toxicological testing, page 22).

In the case of novel foods expected to be consumed in small quantities or ingredients added to foods at low levels, high margins between test levels and expected human intakes can be achieved, but only if physiological limitations allow. In the case of GM plants and their products where the novel element may be identifiable in terms of one or more new traits (Section Chacterisation of the new trait (gene product), page 15), it may be possible to isolate and test the new gene product at levels which are multiples of the likely human exposure. However, for most foods and food ingredients, including macronutrient substitutes, large margins between test levels and the expected consumption by humans are unachievable. Consequently, the approach of setting test levels in toxicology studies with the objective of achieving some pre-determined large multiple of expected consumption is often not feasible.

For novel foods expected to have a high intake in humans, maximum test levels should be set at the highest amount that can be introduced into the animal diet without causing nutritional imbalance. It is therefore important to estimate the likely maximum human intake in order to ensure that toxicology studies are conducted using appropriate test levels. The intake predictions should take account of potentially sensitive population sub-groups, including children, nursing mothers and the elderly. The prediction of dietary exposure is dealt with in greater detail in Section Assessment of safety in use, page 32.

While in some cases a single test level may be sufficient, toxicity studies should preferably include at least a second test level (e.g. equivalent to the expected maximal human consumption). This approach will enhance the predictive value of the study and it may help in the interpretation of the relevance of any effects observed.

Interpretation of data obtained from animal studies

While experience gained in the identification and classification of toxicological findings remains valuable, the strategies underlying such methods, the eventual use made of the data they generate and the relevance of the toxicological end-points need careful re-evaluation in the context of their application to the assessment of a material intended for use as a novel food.

Commonly in toxicological testing, the highest concentration of the test compound in the diet should result in an observable toxic effect. However, this testing strategy normally would not be used when testing a novel food. In most cases when testing a novel food, it is not the toxicity of the food that is determined but the level of physiological and nutritional tolerance to the novel food item. The effect, for example, of an excess of a mineral contained in the novel food or ingredient must be separated from toxic effects caused by the novel food itself. In the case of pure chemicals or simple mixtures intended for use at low levels (for example as micronutrients) traditional testing methods may at first sight seem entirely appropriate. Nevertheless, in interpreting findings it will be important to be able to distinguish between, and to adequately document, adaptive and otherwise acceptable physiological effects, nutritional effects and frank toxicity.

Unlike in conventional toxicity testing, which aims at a wide safety margin between the test level of the compound that induces adverse effects in animals and human exposure, the safety assessment of novel foods is fundamentally based on a comparative approach. This also applies to animal feeding studies. The aim is to determine whether the novel food is as safe as its appropriate traditional comparator, i.e. whether or not it induces specific unwanted effects if fed at an equivalent amount. If a traditional comparator does not exist, the food items or ingredients that the novel food may replace in the human diet should be used as comparators. The totality of the information collected during primary evaluation and pre-test considerations (see Section Primary evaluation and pre-test considerations, page 8) and from toxicological testing (which in such a case will be particularly comprehensive) will serve as a basis for the judgement of whether the consumption of the novel food under the intended conditions of use can be expected to be safe for humans. In such a case, human studies may be required to further support the conclusion of safety (see Section Human studies, page 30). These considerations are of particular importance for whole foods that are intended for consumption in large quantities and where the margin between expected human and maximally feasible test animal exposure is therefore low.

In the main, methods for obtaining toxicological information have been developed for assessing risks associated with single defined chemicals with moderate to low effect levels in terms of dose per unit body-weight. The safety assessment of food chemicals conventionally applies uncertainty factors to data from tests in experimental animals to derive Acceptable Daily Intakes (ADIs). These factors are used to compensate for uncertainties in the process of extrapolating the results in experimental animals to humans. In the case of food chemicals that have low exposures, the factors are usually of the order of 100. This provides a ten-fold factor for inter-species differences in sensitivity and a ten-fold factor for intra-species differences in sensitivity. Because of the limitations discussed in this section, the same approach may theoretically be feasible only for novel food ingredients whose intended use is expected to result in low levels of intake. However, the approach is considered inappropriate in the context of the safety assessment of novel foods and novel macro-ingredients. Unlike conventional food chemicals (e.g. food additives), novel food components are more likely to induce nutritional or physiological adaptive changes that are self-limiting with regard to their use, rather than actual toxicity. Other authors have pointed out (Renwick, A.G., 1993; Renwick, A.G., 1995; Munro, I.C. *et al.*, 1996; WHO, 1987) that, where additional information is available which reduces the uncertainties in extrapolation, it may be appropriate to apply smaller safety factors to animal-derived data.

In principle, therefore, consideration of the results of animal studies in the light of additional information relating to a novel food's characteristics, composition, fate in biological systems and circumstances of use will:

- reduce the uncertainties deriving from the weaknesses inherent in present methodologies for safety testing as applied to macro-ingredients and/or complex ingredients; and
- provide reassurance in the light of margins of exposure below those conventionally associated with the assessment of chemicals consumed in small amounts.

HUMAN STUDIES

Studies in humans are not a routine part of the safety assessment of novel foods and should not replace other aspects of the safety assessment or be used to investigate prior indications of toxicity. Their inclusion should always be determined on a case-by-case basis and supported by a sound scientific justification. For many novel foods such studies will be unnecessary, but in specific cases they will provide confirmation of safety.

Studies in human volunteers can be undertaken only when the assessment of pre-test considerations and animal studies (if appropriate) indicates that no adverse health effects are to be expected. Human studies should be conducted in line with the principles of good clinical practice and with prior ethical approval in accordance with the Helsinki declaration (World Medical Association, 2002).

Possible reasons for conducting studies in humans include:

- confirmation of the safety of foods, previously assessed through animal studies, where the expected human exposure is high and the margin between the animal exposure studied and human exposure may be low;
- confirmation of the absence of any adverse reactions, including intolerance reactions or subjective responses, which may not be predicted from animal studies;
- demonstration of the nutritional quality of the food for human subjects in cases where the food may occupy a significant portion of the diet for some population groups;
- confirmation of the safety and suitability of the food for specific population sub-groups; and
- the study of specific end-points suggested by other studies or considerations.

Human studies on efficacy may also provide ancillary information about safety (see Section Intended effect of the food, page 31).

Study design considerations

When, on a case-by-case basis, clinical studies are considered, the choice of test levels to which subjects are to be exposed should take account of expected consumption estimates. The levels tested should include one that is equal to or exceeds the maximum predicted intake and the test diet should reflect as closely as possible the circumstances under which the novel food or ingredient is intended to be used.

In all cases, an appropriate control diet must be included which should be based on the normal human diet. Depending on the study design, the administration of the test and control diets may be to separate groups of subjects or, in the case of cross-over designs, to all subjects in a sequence.

The overall study design, for example cross-over or parallel, the number of subjects per group, the study duration and the frequencies of measurement of key parameters, should be appropriate for the purpose and based on sound statistical principles.

Careful consideration should be given to the choice of parameters to be measured during human studies, including anthropometric measurements and clinical analyses. The measurements selected must be appropriate to the aims of the study and the interpretation of the outcome.

For some novel foods it will be appropriate to include or base studies on particular population sub-groups. The selection of the subjects will depend on the intended use of the novel food, whether it is intended to be used only by part of the population, is aimed at a particular sub-group, or might affect particular sub-groups differently from the general population. This aspect is a separate consideration from that of extreme consumption, which should be handled through the choice of suitable test levels should this need to be considered.

Confirmation of safety

Studies to confirm safety in humans are typically of relatively short duration and the parameters measured would generally include blood analysis, urine analysis, anthropometric measurements and recording of subjective assessment by the supervisors and subjects themselves – preferably blinded to reduce the possibility of bias. In addition, there may be specific measurements related to the properties of the novel food or which have been indicated by previous investigations. However, which measurements are included will depend on individual protocols.

Such studies should normally be considered for novel foods that have no traditional counterpart or have little or no history of previous consumption, where evidence of safety is based on a programme of laboratory and animal tests. The interpretation of the data generated in humans should take account of normal ranges and treatment-related trends for the relevant parameters. Blood chemistry, haematology and urine analysis will be especially important in this respect, but other general reactions to the food will form part of the data evaluation.

These studies are primarily intended to confirm the safety of the food as indicated by other data, including the results of earlier test programmes in animals. Rarely, they may detect potentially toxic responses which may not have been predicted by animal tests, or they may be used to confirm that an animal-specific response does not occur in humans.

Potential allergenicity and other, idiosyncratic reactions

In order to assess the risk that known atopic individuals might react to the novel food, sera from atopic individuals are increasingly being used as an *in vitro* screen for cross-reactivity with other allergens. The testing of known atopics could add valuable information on an at-risk group, though ethical considerations may preclude this. Studies on atopics should be considered only when other evidence indicates the absence of allergenicity. Detailed monitoring of a small number of subjects is recommended in such cases.

Where no particular concern is indicated for any specific population group, the occurrence of non-immunologically based idiosyncratic reactions may still become apparent post-launch and post-launch monitoring (Section Test marketing and post-launch monitoring, page 35) provides a mechanism for assessing this.

Nutritional quality

Novel foods that are expected to occupy a significant portion of the diet in place of other foods, or that are otherwise suspected on the basis of pre-test considerations of having potentially significant nutritional impact, should have their nutritional quality confirmed in human studies. Such studies should focus on the main attribute of the novel food (for example its protein, fat or carbohydrate component) and any new considerations arising from its consumption (for example, micro-nutrient availability).

Intended effect of the food

Where novel foods are developed to possess particular nutritional properties or to exert physiological effects, human studies will be needed to confirm the intended effects. Such studies on efficacy, while not a requirement for safety assessment, may also provide ancillary evidence of the safety of the food at its intended level of use. In interpreting them in the context of safety, however, consideration needs to be given to aspects of study design and execution (for example, statistical power, retention of archived samples) which may not be optimised for the study of safety-related end-points.

ASSESSMENT OF SAFETY IN USE

General considerations

The assessment of safety in use, i.e., that the expected use of the food and its expected level of intake is without appreciable risk, will be based upon a thorough knowledge of the composition of the food, evidence from any nutritional, toxicological and human studies, the expected use of the food and its expected consumption. This includes any adverse nutritional impact on the diet.

The traditional approach applied to food chemicals whereby an acceptable daily intake (ADI) is set is inappropriate for most novel foods.

Only in cases where the novel food is a discrete compound intended to be consumed at a low level of intake might it be possible to apply a large safety factor between the highest level producing no adverse effect in toxicology studies and the acceptable human intake. Even then, test levels may be limited by nutritional or physiological effects, which are not toxicity as such, making it impossible to apply a large safety factor.

Complex novel foods present a much more difficult case where divergence from the traditional ADI approach is even more marked. Thus, even in cases where extensive toxicology has been performed, the physical and physiological limitations on the level tested and the possible high intake of the food make the ADI approach inappropriate. Rather, the totality of the data available should be used to arrive at a conclusion as to whether the food may be safely consumed.

After successful completion of the primary evaluation and pre-test considerations and any toxicology or human studies considered necessary, the results must be related to the likely consumption of the novel food when it has been placed on the market. The way in which intake may be estimated and the facility with which it may be related to the safety data will depend on the nature of the novel food.

It is difficult to generalise because both the maximum test levels and the consumption of the novel food will be affected by its characteristics and its expected use, but in many cases a reasonable margin of safety can be expected between the maximum level which does not cause harm in tests (the "highest identifiable safe level") and the estimated daily intake (EDI) expressed per unit of body-weight.

Intake prediction

The prediction of intake depends first of all on the nature of the novel food. The main examples of types of novel foods are:

- whole foods which are consumed as such;
- food ingredients which are expected to be used as major ingredients in a variety of products; and
- ingredients intended to be used at low levels in foods.

The nature of the food or food ingredient and whether it is a replacement for, or an alternative to an existing food, determines how it will be used and in what food product categories. This information can be combined with available data on food consumption, for example from governmental and commercial national food surveys, to arrive at an estimate of expected average intake (Kroes, R. *et al.*, 2002). The accuracy of the estimates will depend on the quality of the data available.

Food ingredients that have an exact existing counterpart and that have upper limits of use related to their technological properties will be relatively easy to assess. Based on the knowledge of which food products are expected to include them, coupled with predictions of market penetration and a knowledge of individuals' consumption habits, intakes can be calculated using published food consumption data which include data on consumption of the food categories of relevance. For foods that will have a limited range of uses or that are limited by the nature of their consumption, intake levels can be predicted relatively easily compared with those that will have a wide range of applications.

In the case of novel foods for which there are no existing equivalents, it is necessary to determine which new food products will be created and which existing products they may replace in the diet. Information on consumption of the existing foods being replaced, the expected degree of replacement (as with, for example, a meat substitute) and the expected market penetration will be required. Survey data, as in the previous example, will be essential to estimate the expected average consumption.

The intended outcome of the process of intake prediction is to arrive at an Estimated Daily Intake (EDI) for the novel food. The EDI should not just be determined to reflect average consumption, but it should also take account of extreme consumers and, where relevant, specific sub-groups. As a rule of thumb, the 90th or 95th percentile of consumption should be estimated. This should be done in a way that relates directly to product presentation, portion sizes, indications of consumption frequencies and duration of exposure which might reasonably be expected rather than by using arbitrary multiples of the average.

The key to achieving a sound assessment of safety in use is to ensure that the prediction of intake is as accurate as possible. Where an estimate of intake has been generated at an early stage in the assessment process, for example to determine test levels used in toxicology studies, it is important that it be reviewed to ensure that it reflects expected, and possibly modified, product uses as the food approaches the market.

Novel foods with traditional counterparts

In cases where the novel food has a clearly identifiable traditional counterpart, e.g. a new version of a crop, a new source of an existing food or macro-ingredient or an existing food produced by a new process, it can be possible to determine the safety of the food by comparing its detailed composition with that of the traditional counterpart. As well as analysis, other safety data may be available to add reassurance to the comparison. Such data are likely to focus on specific differences between the novel food and the traditional counterpart, e.g. in GM crops.

If the specific differences between the novel food and its traditional counterpart have been demonstrated not to present a hazard, and the composition is otherwise equivalent to its traditional counterpart, it is reasonable to conclude that the food will be at least as safe as the traditional counterpart which it may replace.

Novel foods intended to be used at low levels

Novel foods intended to be used at low levels, such as phytochemicals and other plant extracts, form a group which possibly lends itself to a traditional risk assessment. Even if they are not totally compatible with traditional toxicological approaches because of nutritional or physiological limitations, it is probable that intake levels can be predicted with a reasonably high degree of accuracy. This is because the majority of foods in this sub-group are likely to be used as nutritional supplements or have defined levels of use if used as ingredients in compound foods.

The safety data available on these types of novel foods can be related with reasonable accuracy to the expected intake. It is quite possible that use of the novel food will result in an intake additional to an existing background intake from the diet. If so, the background intake must be taken into account in the comparison with the safety data or form part of the totality of evidence if that approach to safety assessment is employed.

It is possible that this sub-group of novel foods can be assessed against a reasonably high safety margin between available safety data and expected consumption.

Complex foods with no traditional counterpart

This sub-group is likely to cover a wide range of novel foods which will vary in complexity, purpose and expected level of consumption.

It is expected that a complex novel food being considered for placing on the market will not have exhibited any toxic effects in studies undertaken to determine safety. Therefore, the main objective must be to judge the highest levels established in toxicology or, sometimes, human studies which do not demonstrate any adverse effects against the EDI of the food when released onto the market.

TEST MARKETING AND POST-LAUNCH MONITORING

After a satisfactory assessment of safety in use has been conducted (see Section Assessment of safety in use, page 32), where appropriate including suitable human studies, novel foods are likely to progress to test marketing. This provides an opportunity to gather additional information from consumers. It is likely to be useful in identifying problems only if they are significant but an absence of any complaints will add to the overall assurance of safety.

Test marketing in a wider geographical area poses greater difficulties in detecting reactions to the food. Collaboration with local health authorities can be helpful in providing alerts in respect of any increases in complaints which could be related to the novel food in question.

In the case of medicines, a system of post-marketing surveillance (PMS) is in place for the monitoring of the known and unknown side-effects. Post-launch monitoring (PLM) has been used as the term for the monitoring of foods in the marketplace. There are a number of important differences between the marketing of medicines and that of foods which warrant this distinction. Access to medicines is carefully controlled through use of prescriptions and availability through pharmacies or hospitals, whereas novel foods are widely available without prescription through retail outlets. Therefore, in terms of monitoring adverse events, the main sources of information in PMS for medicines are primarily through physicians and pharmacists, whereas in PLM for foods it is through direct contact between the consumer and the marketing company by use of, for example, telephone customer care lines.

PLM cannot serve as a tool to replace appropriate pre-market risk assessment and management steps as described in the previous sections. PLM is neither a mandatory nor a routine element of safety assessment.

In general, post-launch monitoring provides a means to confirm that the actual intake levels are within the anticipated range and that there are no unexpected effects when a large population with a diverse genetic make-up and including people with illnesses is exposed for potentially long periods of time.

Data collected in the marketplace under real-life conditions can help to confirm the validity of the initial risk assessment and to correct the assumptions used in the process. Since in many cases the assumptions regarding exposure will only be estimates, often corrected to avoid the likelihood of risk due to underestimation of exposure, a refinement of the pre-market assumptions is desirable both for the manufacturer and the competent authorities. However, it should be noted that in the vast majority of situations there will be no indication that adverse health effects are to be expected. In the majority of cases the post-launch learning will help to avoid unjustified restrictions.

Regulatory agencies (e.g. European Commission, ANZFA) are starting to include post-marketing studies in their guidelines as an additional end-point to address in the safety assessment. They do not define specifically what is required but in general the idea is to confirm the pre-market assumptions, such as those concerning data on consumption and the absence of unexpected health effects.

As usually applied, PLM may be used to address three questions:

- is use as predicted or recommended?
- are expected effects as predicted?
- does the use of the product result in unanticipated effects?

Is use as predicted or recommended?

Most manufacturers monitor the introduction of new food products into the marketplace as a standard procedure. Marketplace surveys can be commissioned to check that consumers' usage patterns are consistent with marketing expectations, for example, to establish which consumers are using the product and to estimate how much they are using. These data provide information on what the households buy, when they buy it and what demographic group the purchaser belongs to. Registered households are classified into demographic groups (for example, age of primary shopper, size of household, socio-economic group based on occupation, presence of children and geographical region).

This technique is non-invasive and, because panel members are not aware of which purchases are being monitored, it can provide information on real purchase patterns and supplies a link between purchase data and consumer type. It also allows a detailed estimate of intake, albeit at the household level. The information output can be used to answer questions both about absolute quantities of product sold and about trends.

Are expected effects as predicted?

The studies conducted as part of the initial safety assessment both in animals and in humans should be used to establish whether there are any potential adverse effects of the novel food. Any such effects would then be considered as part of the safety assessment in which predicted consumption figures are used. Consumer usage patterns from the market research data will provide a valuable means to confirm the validity of the assumptions of the initial safety assessment.

Does the use of the product result in unanticipated effects?

As a rule, the manufacturers of a novel food and the companies applying it in their products will observe the situation on the market after introduction for any negative consumer response. In some cases this will be part of the routine observation of consumer responses. In other cases targeted programmes will be arranged to collect such information actively and to follow consumer complaints for their relevance for the product tested. For this purpose the marketing companies will utilise the tools that they have in place and, although these are not usually specifically designed to provide data for safety assessments, they may be useful for the purpose. For example, the protocols of the telephone customer care lines which are often in place for monitoring consumer comments and complaints can be modified to provide data for this purpose. Although in general it may be difficult categorically to establish the absence of any effects, or indeed whether any effects reported are truly associated with consumption of the product, such information can provide some reassurance on the absence of acute effects.

FUTURE DIRECTIONS

Although experience gained to date indicates that questions arising during the safety assessment of novel foods can be handled satisfactorily by current techniques, the suitability of today's methodologies for new generations of products is under discussion. Research alternatives are at an early stage of development and will require validation to demonstrate their relevance, adequacy, feasibility and potential to discriminate components of biological significance against the background of normal biological variation.

As in any scientific field, there is a constant need to develop safety assessment to the highest practicable standard, consistent with the development of new approaches and knowledge. It is important to appraise new models and procedures since they may be useful in increasing the level of safety assurance or in preventing an excessively precautionary approach to future, more complex products. Where new methodologies can be seen to offer sensitivity or predictive value which increases the power of safety assessment they should be developed, validated and used for that purpose but the fact that they are available should not in itself lead to a requirement that they be used.

Existing methodologies and procedures and new strategies for the assessment of risks from food-borne hazards have recently been examined by the European project 'Food Safety in Europe (FOSIE): Risk Assessment of Chemicals in Food and Diet'. The key issues identified have been summarised in a series of critical reviews of the use of animal-based methods (Barlow, S.M. *et al.,* 2002); *in vitro* methods (Eisenbrand, G. *et al.,* 2002); approaches to dose-response, mechanisms and extrapolation (Dybing, E. *et al.,* 2002); mathematical modelling and quantitative methods (Edler, L. *et al.,* 2002); exposure assessment (Kroes, R. *et al.,* 2002); and epidemiology (van den Brandt, P. *et al.,* 2002). Emerging issues and research needs have also been addressed. Overall, it is recognized that the assessment of traditional and novel foods requires practical and workable approaches that take into account the unique nature and chemical complexity of food.

New technologies and methodologies are being evaluated to determine, *inter alia*, their utility for increasing the sensitivity of food toxicology, allergy prediction, nutritional impact and overall safety assessment. Computer-based bioinformatics and fingerprinting techniques have the potential to increase the predictive power of pre-test considerations and the development of specific animal models (for example using transgenic animals), the identification of relevant biomarkers and the improvement of immunotoxicity testing and techniques for the short-term assessment of proliferative lesions offer the possibility of increased targeting in toxicology. Further development and refinement of databases on dietary intake by humans will allow more precise estimates of exposure and thereby decrease the uncertainties in the final phase of the safety assessment process.

The success of large-scale genome-sequencing programmes such as the Human Genome Project has stimulated the development of new technologies that are finding increasingly wide application and facilitate a non-targeted approach permitting the simultaneous measurement, characterisation and, if required, comparison of large numbers of biological variables at one time. In this regard the developing methodologies of genomics, transcript profiling, proteomics and metabolomics (collectively GPTM or 'omics') offer interesting potential (ECETOC, 2001).

Developments in omics, once validated, may lead to the identification of biomarkers that will help to further refine and enhance the information provided by compositional and toxicological studies. They may also be helpful in the identification of susceptible sub-groups in the human population during the pre-market phase of safety assessment. In these ways they may provide the means to target studies more precisely to parameters particularly relevant for the novel food under investigation.

Because of the resultant large number of observable changes (many of which are not individually biologically significant), the extensive use of bioinformatics is required to interpret the data. Even with a targeted approach, the current lack of reference data could lead to misinterpretation or over-interpretation and subsequent misplaced safety concern. Therefore a great deal of collaborative work is currently in progress internationally to determine how to develop and apply these methodologies in a meaningful and proportionate way, particularly recognizing intrinsic variability in the context of many food constituents. In Europe a consortium of laboratories is currently evaluating the above approaches under the auspices of a project supported by the EU Fifth Framework Programme (GMOCARE, QLK1-1999-00765).

In principle, with sufficient knowledge from pre-test considerations it is possible to map out a pathway for the safety assessment for any particular novel food and to identify which data gaps, if any, need be resolved by toxicity studies and which by further studies on composition or exposure and intake. Although some generalisations are possible in relation to classes of novel foods, each novel food has its own defining characteristics and with the present state of knowledge the shortest and most productive pathway to safety assessment must be to consider requirements on a case-by-case basis.

As more experience is gained with the safety assessment of novel foods it may be possible to establish more generic guidance. However, it is likely that the qualitative and quantitative differences between categories of novel foods and the applicability of toxicity testing methodologies to them will dictate broad differences in requirements and outcomes on a class-by-class basis. In order to identify the extent to which generic guidance might be developed, it would be valuable to use the existing and developing case-history database to elaborate a class-by-class comparison of the requirements for each of the four stages (hazard identification, hazard characterisation, exposure assessment and risk characterisation) which constitute the formal process of conventional risk assessment. Such a comparison would provide the basis for future debate about the applicability of a unified approach to the safety assessment of novel foods.

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REFERENCE LIST

Anon (2001) High intensity electric field pulses. *Trends Food Sci.Technol*. 12:89-112.

Australia New Zealand Food Authority (1998) Guidelines for the safety assessment of foods to be included in Standard A 18 – Food produced using gene technology.

Barbosa-Canovas, G.V., Pothakamury, U.R., Pafou, E., Swanson, B.G. (1998) *Nonthermal preservation of foods*. Marcel Dekker inc. New York.

Barlow, S.M., Greig, J.B., Bridges, J.W., Carere, A., Carpy, A.J., Galli, C.L., Kleiner, J., Knudsen, I., Koeter, H.B., Levy, L.S., Madsen, C., Mayer, S., Narbonne, J.F., Pfannkuch, F., Prodanchuk, M.G., Smith, M.R., Steinberg, P. (2002) Hazard identification by methods of animal-based toxicology. *Food Chem Toxicol* 40:145-191.

Busta, F. (2000) Quantification of destruction kinetics for microbial inactivation by alternative food processing technologies. *Food Sci* 65 (8) (suppl.): 1S-108S.

Commission of the European Communities (1997) 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. L253:1-36.

Commission of the European Communities (2001) Decision of 23.05.2001 on authorising the placing on the market of pasteurised fruit-based preparations produced using high-pressure pasteurisation as a novel food ingredient under Regulation (EC) N° 258/97 of the European Parliament and of the Council.

Dybing, E., Doe, J., Groten, J., Kleiner, J., O'Brien, J., Renwick, A.G., Schlatter, J., Steinberg, P., Tritscher, A., Walker, R., Younes, M. (2002) Hazard characterisation of chemicals in food and diet. Dose response, mechanisms and extrapolation issues. *Food Chem Toxicol* 40:237-282.

ECETOC (2001) Genomics, Transcripts profiling, Proteomics and Metabolomics (GTPM) an introduction. Document 42.

Edler, L., Poirier, K., Dourson, M., Kleiner, J., Mileson, B., Nordmann, H., Renwick, A., Slob, W., Walton, K., Wurtzen, G. (2002) Mathematical modelling and quantitative methods. *Food Chem Toxicol* 40:283-326.

Edwards, D.G., Porter, P.D., Dean, Jill. (1985a) The responses of rats to various combinations of energy and protein I: Diets made from purified ingredients. *Lab.Anim* 19: 328-335.

Edwards, D.G., Dean, Jill. (1985b) The responses of rats to various combinations of energy and protein II: Diets made from natural ingredients. *Lab.Anim* 19: 336-343.

Eisenbrand, G., Pool-Zobel, B., Baker, V., Balls, M., Blaauboer, B.J., Boobis, A., Carere, A., Kevekordes, S., Lhuguenot, J.C., Pieters, R., Kleiner, J. (2002) Methods of *in vitro* toxicology. *Food Chem Toxicol* 40:193-236.

FAO/WHO (1991) Strategies for assessing the safety of foods produced by biotechnology.

FAO/WHO (1996) Biotechnology and food safety. *FAO Food and Nutrition Paper* 61.

FAO/WHO (1997) Risk management and food safety. *FAO Food and Nutrition Paper* 65.

FAO/WHO CODEX (2002) Report of the Third Session of the CODEX Ad Hoc Intergovernmental Task Force on Foods Derived from Biotechnology, Proposed draft annex on the Assessment of Possible Allergenicity.62-74.

FAO/WHO UNICEF Protein Advisory Group (1970) PAG Statement N°4 on Single Cell Protein.

GMOCARE QLK1-1999-00765. New methodologies for assessing the potential of unintended effects in genetically modified food crops. www.entransfood.com/RTDprojects/GMOCARE/default.htm

Gould, G.W. (1995) *New methods of food preservation*. Blackie Academic & Professional, London.

Health Canada (1994) Guidelines for the safety assessment of novel foods.

Hendricks, M., Knorr, D. (2002) *Ultra high pressure processing of foods*. Kluywer, New York, NY.

ILSI Europe (1999) Safety assessment of viable genetically modified micro-organisms used in food. International Life Sciences Institute Press, Washington, DC.

Jonas, D.A., Antignac, E., Antoine, J.M., Classen, H.G., Huggett, A., Knudsen, I., Mahler, J., Ockhuizen, T., Smith, M., Teuber, M., Walker, R., De Vogel, P. (1996) The safety assessment of novel foods. Guidelines prepared by ILSI Europe Novel Food Task Force. *Food Chem.Toxicol*. 34:931-940.

Jonas, D.A., Elmadfa, I., Engel, K.H., Heller, K.J., Kozianowski, G., Konig, A., Muller, D., Narbonne, J.F., Wackernagel, W., Kleiner, J. (2001) Safety considerations of DNA in food. *Ann.Nutr.Metab* 45:235-254.

Keenan, K.P., Laroque P., Ballam, G.C., Soper, K.A., Dixit, R., Mattson, B.A., Adams, S.P., Coleman, J.B. (1996) The effects of diet, *ad libitum* overfeeding, and moderate dietary restriction on the rodent bioassay: the uncontrolled variable in safety assessment. *Toxicol Pathol*. 24:757-768.

Knudsen, I., Ovesen, L. (1995) Assessment of novel foods: a call for a new and broader GRAS concept. *Regul.Toxicol.Pharmacol*. 21:365-369.

Kroes, R., Muller, D., Lambe, J., Lowik, M.R., van Klaveren, J., Kleiner, J., Massey, R., Mayer, S., Urieta, I., Verger, P., Visconti, A. (2002) Assessment of intake from the diet. *Food Chem.Toxicol*. 40:327-385.

Mertens, B., Knorr, D. (1997) Developments of nonthermal processes for food preservation. *Food Technol*. 46(5):124-133.

Munro, I.C., McGirr, L.G., Nestmann, E.R., Kille, J.W. (1996) Alternative approaches to the safety assessment of macronutrient substitutes. *Regul.Toxicol.Pharmacol.* 23:S6-14.

National Research Council (1995) Nutrient requirements of laboratory animals.

OECD (1993) Safety evaluation of foods derived by modern biotechnology: concepts and principles.

OECD (2001a) Consensus document on compositional considerations for new varieties of soybean: key food and feed nutrients and anti-nutrients. 2.

OECD (2001b) Consensus document on key nutrients and key toxicants in low erucic acid rapeseed (canola). 1.

OECD (2002a) Consensus document on compositional considerations for new varieties of potatoes: key food and feed nutrients, anti-nutrients and toxicants. 4.

OECD (2002b) Consensus document on compositional considerations for new varieties of sugar beet: key food and feed nutrients and anti-nutrients. 3.

OECD (2002c) Consensus document on compositional considerations for new varieties of maize (Zea mays): key food and feed nutrients, anti-nutrients and secondary plant metabolites. 6.

Ozen, B.F., Floros, J.D. (2001) Effects of emerging food processing techniques on the packaging materials. *Trends Food Sci.Technol*. 12:60-67.

Renwick, A.G. (1993) Data-derived safety factors for the evaluation of food additives and environmental contaminants. *Food Addit.Contam* 10:275-305.

Renwick, A.G. (1995) The use of an additional safety or uncertainty factor for nature of toxicity in the estimation of acceptable daily intake and tolerable daily intake values. *Regul.Toxicol.Pharmacol.* 22:250-261.

US Food and Drug Administration (1992) Foods derived from new plant varieties. Federal Register 57 (104) 22984.

van den Brandt, P., Voorrips, L., Hertz-Picciotto, I., Shuker, D., Boeing, H., Speijers, G., Guittard, C., Kleiner, J., Knowles, M., Wolk, A., Goldbohm, A. (2002) The contribution of epidemiology. *Food Chem Toxicol* 40:387-424.

WHO (1987) Principles for the safety assessment of food additives and contaminants in food. *Environmental Health Criteria* 70.

World Medical Association (2002) Helsinki Declaration concerning ethical principles for medical research involving human subjects; first adopted Helsinki, June 1964 and last amended Washington 2002. www.wma.net/e/policy/b3.htm

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