

**SAFETY EVALUATION
OF FOODS DERIVED
BY
MODERN BIOTECHNOLOGY
CONCEPTS AND PRINCIPLES**

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PARIS

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ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT

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FOREWORD

Safety Evaluation of Foods Derived by Modern Biotechnology: Concepts and Principles has been prepared by the OECD Environment Directorate, in collaboration with the Directorate for Science, Technology and Industry. It is the product of work undertaken by the Group of National Experts on Safety in Biotechnology. As such, it is related to another report recently published by the OECD, *Safety Considerations for Biotechnology 1992*.

This report is intended for the use of those involved in carrying out safety evaluations of new foods or food components derived by means of modern biotechnology. It elaborates scientific principles to be considered in making such evaluations, based on a comparison with traditional foods that have a safe history of use.

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PREFACE

In 1983 the Committee for Scientific and Technology Policy created the Group of National Experts on Safety in Biotechnology (GNE). The work of the GNE led to the Recommendation of the OECD Council concerning Safety Considerations for Applications of Recombinant DNA Organisms in Industry, Agriculture and the Environment. This Council Act called, *inter alia*, for further research to improve the prediction, evaluation and monitoring of the outcome of applications of recombinant DNA organisms. *Recombinant DNA Safety Considerations*, which includes the Council Recommendations, published by the OECD in 1986, contained general safety guidelines for the use of genetically modified organisms in industry, agriculture and the environment.

In 1990, the GNE agreed that "work on food safety, with particular attention given to the elaboration of scientific principles for assessing the safety of new foods or food components produced by means of biotechnology, was of high priority and should be initiated as soon as possible". A Working Group was therefore established on food safety as related to modern biotechnology. Dr. Frank Young of the United States was elected chairman.

The Working Group participants identified a number of concepts underlying their work, issues that needed to be addressed, and approaches or processes that could be used to respond to the need expressed by the GNE. The terms of reference of the Working Group (see Annex I) were endorsed by the GNE.

Several points regarding the scope and objectives of the Working Group, as set out in the terms of reference, should be noted:

- the Working Group was not to address the safety assessment of food additives, contaminants, processing aids and packaging materials;
- it was not to address issues relating to the *environmental* safety of new foods or food components, as these issues were already addressed in OECD documents and by other working parties of the GNE; and
- the principles elaborated should focus initially on the safe use of new foods or food components of terrestrial microbial, plant or animal origin. (Organisms of aquatic origin were to be addressed in future work of the Working Group.)

Scientific principles to be considered in evaluating the safety of new foods and food components, as elaborated by the Working Group, are set out in Chapter II. As background for the discussions of the Working Group, a number of documents and publications available in OECD countries relating to the assessment of food safety were examined (see Annex II).

This report is based on material developed at several conferences and intergovernmental consultations on the subject of food safety and biotechnology. A number of

scientific meetings that addressed issues regarding the various traits, chemical composition, and properties of organisms used as food or as a source of food have also been relevant.

The terms of reference of the Working Group called for models or examples of new foods or food components to be identified, and for existing information related to their safety assessment to be collected and used to assist in developing and/or demonstrating the applicability of the proposed scientific principles and associated methods. The Working Group selected a number of novel foods or food components as examples. The case studies presented in Chapter III illustrate the application of the concepts and principles set out in Chapter II. However, they *cannot be regarded as actual evaluations or safety judgements* on the part of either the Working Group, the Group of National Experts on Safety in Biotechnology, the OECD, or any of its Member countries.

This report is intended for use by those involved in carrying out safety evaluations of new foods or food components derived by modern biotechnology. The scientific approach to such evaluations elaborated by the Working Group is based on a comparison with traditional foods that have a safe history of use. This approach is based in turn on the concept of *substantial equivalence*, which articulates procedures used in the past, albeit intuitively, for accepting new foods. The Working Group believed such an approach could also be used for the safety assessment of new foods and food components derived by other technologies.

The Working Group considered substantial equivalence to be the most practical way to address the issue of food safety at this time. This is not to imply, however, that the report is applicable to any other aspect of biotechnology safety, including environmental safety. Other OECD documents address such issues.

Chapter 1

Background

Recent years have seen tremendous advances in food biotechnology, including improvements in industrial process technology and control systems, improvements in farming systems for growing and harvesting food, genetic improvements to organisms used in the food supply, and improvements in techniques to monitor food safety and nutritional quality. It is thus expected that progress in biotechnology will play an increasingly important role in food supply.

Micro-organisms

Examples of traditional food biotechnology include the use of yeasts in the brewing and baking industries, and the use of bacteria and moulds and their components in the dairy industry for making cheese and yoghurt. Moulds and bacteria are also used for the fermentation of plants or plant products (for example, miso). Purified enzymes from micro-organisms are used extensively in making products such as high-fructose corn syrup and certain types of hydrolysed or predigested protein products.

In many such products, the micro-organisms function in the production process and the food product does not contain viable cells. In others, such as yoghurt, microbial cultures remain viable and are consumed. Such traditional applications have a long history of safe use, and many have formally been affirmed as safe by various national and international food safety evaluations. Key considerations have included non-pathogenicity and non-toxicity of the organism and its products.

Modern biotechnologies are being used increasingly to improve food micro-organisms for the enhanced production of essential components or products, as well as the improvement of nutritional value, flavour, texture, and the shelf life of fermented foods.

Plants

Plants are consumed directly as whole food, or are processed into many types of foods. Many plants have a long history of use as foods. Undoubtedly, the plants selected were the ones that appeared healthy, grew vigorously, and gave higher yields. Edible portions had desirable taste, smell and appearance. Selection might have included an evaluation of safety, although it was not formally recognised. In any case, there is little historical record or documentation of the process by which the safety of food plants was

maintained, or of involvement of national food authorities. Now that new biotechnology has vastly increased the variety of new traits that can be introduced into plants, the impact of plant biotechnology on food safety is receiving attention.

Early farmers selected and preserved plant variants that had desirable food or agronomic attributes, such as larger fruit or uniform dormancy and maturation times for seeds. Such properties are deleterious to wild plants and so would not have been developed without the efforts of early "breeders". Practices of early farmers led eventually to the development of desirable clones, land races, and varieties of major food crops, with predictable reproducible agronomic characteristics yielding foods with uniform properties. As the agronomic properties of individual crops were made more uniform, production methods could be designed to obtain optimum yields.

With the relatively recent advent of directed plant breeding for improvement of agricultural crops, the objectives of plant breeders became: *i*) to increase yield, *ii*) to improve quality, and *iii*) to reduce production costs by, for example, identifying traits which could increase resistance to pests and diseases.

Although it may not have been a major objective, plant breeders have been effective in conserving the nutritional quality of plants developed for food. Routinely, they have selected plants with desirable qualities and rejected undesirable plants by destroying them in the breeding plots.

Preferences of the humans consuming the crop have contributed to the food characteristics of plant varieties ultimately developed. For example, varieties of potatoes and beans are quite different in different areas of South America, where their selection has been influenced by the taste preferences of native peoples. As another example, the milling and baking quality of flour is checked during the variety development process since wheat is often developed for particular baking products.

In the case of certain crops, breeders have deliberately attempted to improve nutritional value. Often, as for example in the case of high-lysine corn or high-vitamin C tomato, other factors have prevented these varieties from becoming widely accepted. The best-tasting, most nutritious variety will not succeed as a commercial crop unless it also gives high yield. Difficulty in processing, susceptibility to pests or diseases, an undesirable flavour or colour, or simply difficulty in getting the plants to market will also limit the adoption of a new variety.

Public acceptance of a high-nutrient variety is not based on nutrient content alone. Carrot and sweet potato varieties that have a bright orange colour are more acceptable to humans than those that do not. They also have a higher content of the pigment that supplies vitamin A precursor in the human diet. The ascorbic acid (vitamin C) content of tomatoes has been extensively examined, and varieties with higher content developed. However, since the fruit of these tomatoes is more yellow-orange than red, they have not been as acceptable to consumers.

The nutritional value of fruit or vegetable crops can be quite variable, and may be difficult to assess definitively. The composition of plant foods, particularly fruits and vegetables, is transient because the edible portion undergoes rapid biochemical changes during the ripening process. For example, in red tomatoes the content of ascorbic acid is low in green fruit, increases rapidly as the fruit ripens, and then drops off with time. Ascorbic acid content also varies in ripe tomatoes with their position on the vine, since higher light intensity increases the amount. Moreover, field-grown tomato plants produce fruit of higher vitamin C content than those grown in glasshouses. In view of these

considerations, the significance of a genetically induced change in the level of a nutrient, such as ascorbic acid in modified tomatoes, would be difficult to assess. The significance of a genetically induced change in the level of a particular nutrient would also depend on the position of the food in the total diet.

Many plants are known to produce compounds toxic to other species. Acutely toxic poisonous plants, such as some fungi and ornamental plants, are not consumed. A number of plants consumed by humans are acutely toxic in the raw state, but are accepted as food because processing methods alter or eliminate their toxicity. For example, the cassava root is quite toxic, but proper processing converts it into a nutritious and widely consumed food. Soybeans and lima beans, among other crops, also require proper processing. Thus the mere presence of a toxicant in a plant variety does not necessarily eliminate its use.

In other plants that contain toxicants affecting humans, such as potato and tomato, plant breeders have succeeded in reducing the level of these toxicants in food varieties. Over time, there have been few reported examples of plant breeding inadvertently leading to increases in toxicants. Varieties with an increased toxicant level have been quickly removed from agricultural use. In some countries new varieties have been monitored for levels of a particular toxicant, but systematic food safety assessment has not generally been conducted. The impact of plant biotechnology on food safety is now receiving wider attention. At the same time, there is increasing general recognition of the relevance of plant breeding's historical record.

Toxicant levels might become important, particularly when traits are introduced for resistance to pests and diseases, simply because a compound inducing resistance to another organism might possibly affect humans. The molecular basis for the resistance mechanisms is just beginning to be understood by plant scientists, and may be a target for biotechnology approaches to enhance resistance. Some mechanisms appear to be quite general, while others have adverse effects on a specific pest or pathogen. Knowledge of the mechanisms should, in the future, provide a valuable tool for the plant breeder and should facilitate evaluations of safety.

Animals

The development of new strains of domestic mammals and birds for food has had a long history, and extensive procedures are in place to improve yield and assure the health of these animals. In general, foods from new strains of mammals and birds that appear to be in good health have proven to be as safe as the animal breeds from which they were derived. No endogenously produced toxicants are known to come from such domestic animals.

In recent years, breeding technologies have been developed that permit increased numbers of desirable individuals through techniques such as embryo splitting. In addition, improved knowledge of the genetic control of hormonal levels has permitted the alteration of carcass quality, for example of fat to lean ratios, which has resulted in consumer-desired lean meats. Increased hormone levels have also enhanced the rate of growth, as well as milk production. There is no evidence of adverse effects to humans from the use of such technologies.

Chapter II

Food Safety and Biotechnology: Concepts and Principles

The consideration of the safety of foods and food components derived from biotechnology involves several *continua*: from older to newer biotechnology; from traditional techniques to the latest techniques based on molecular and cellular biology; from simple to complex products; from a well-known history of exposure and safety of use to areas of less knowledge of the trait in different organisms; from whole organisms to specific chemical compounds or substances; and from simple to complex assessment approaches. For a rational and practical approach to ensuring safe use, these *continua* can be separated into manageable pieces, facilitating the description of the concepts or principles of safety. Accordingly, scientific principles and procedures should be applied in a flexible fashion, taking into account the knowledge of: the characteristics of the newly introduced trait(s); potential dietary exposure; the preparation and processing of the foods or food components; nutritional considerations; and toxicological aspects.

Concepts of food safety

The safety of food for human consumption is based on the concept that there should be a reasonable certainty that no harm will result from intended uses under the anticipated conditions of consumption. Historically, foods prepared and used in traditional ways have been considered to be safe on the basis of long-term experience, even though they may have contained natural toxicants or anti-nutritional substances. In principle, food has been presumed to be safe unless a significant hazard was identified.

Modern biotechnology broadens the scope of the genetic changes that can be made in food organisms, and broadens the scope of possible sources of foods. This does not inherently lead to foods that are less safe than those developed by conventional techniques. Therefore, evaluation of foods and food components obtained from organisms developed by the application of the newer techniques does not necessitate a fundamental change in established principles, nor does it require a different standard of safety.

Moreover, the precision inherent in the use of certain molecular techniques for developing organisms for use as food should enable direct and focused assessment of safety where such assessment is desired. Knowledge obtained using these methods might also be used to approach safety assessment of new foods or food components from organisms developed by traditional methods.

Safety considerations and substantial equivalence

For foods and food components from organisms developed by the application of modern biotechnology, the most practical approach to the determination of safety is to consider whether they are *substantially equivalent* to analogous conventional food product(s), if such exist. Account should be taken of the processing that the food may undergo, as well as the intended use and the exposure. *Exposure* includes such parameters as the amount of food or food component(s) in the diet, the pattern of dietary consumption, and the characteristics of the consuming population(s). This approach provides a basis for an evaluation of food safety and nutritional quality.

The concept of substantial equivalence embodies the idea that existing organisms used as food, or as a source of food, can be used as the basis for comparison when assessing the safety of human consumption of a food or food component that has been modified or is new.

If one considers a modified traditional food about which there is extensive knowledge on the range of possible toxicants, critical nutrients or other relevant characteristics, the new product can be compared with the old in simple ways. These ways can include, *inter alia*, appropriate traditionally performed analytical measurements (for example, alkaloid levels in potatoes, cucurbitin in vegetable squash cultivars, and psoralens in celery) or crop-specific markers, for comparative purposes. The situation becomes more complex as the origins/composition/exposure experience decreases, or if the new products lack similarity to old established products or, in fact, have no conventional counterpart.

A demonstration of substantial equivalence takes into consideration a number of factors, such as:

- knowledge of the composition and characteristics of the traditional or parental product or organism;
- knowledge of the characteristics of the new component(s) or trait(s) derived, as appropriate, from information concerning: the component(s) or trait(s) as expressed in the precursor(s) or parental organism(s); transformation techniques (as related to understanding the characteristics of the product) including the vector(s) and any marker genes used; possible secondary effects of the modification; and the characterisation of the component(s) or trait(s) as expressed in the new organism; and
- knowledge of the new product/organism with the new component(s) or trait(s), including the characteristics and composition [*i.e.* the amount of the component(s) or the range(s) of expression(s) of the new trait(s)] as compared with the conventional counterpart(s) (*i.e.* the existing food or food component).

Based on a consideration of the factors in the paragraph above, knowledge that a new food or food component(s) was derived from organism(s) whose newly introduced traits have been well-characterised, together with a conclusion that there is reasonable certainty of no harm as compared with its conventional or traditional counterpart, means that a new food or food component(s) can be considered substantially equivalent.

Set out below are the *principles for the application of substantial equivalence* to the assessment of foods from organisms developed by the application of biotechnology:

- If the new or modified food or food component is determined to be substantially equivalent to an existing food, then further safety or nutritional concerns are expected to be insignificant;
- Such foods, once substantial equivalence has been established, are treated in the same manner as their analogous conventional counterparts;
- Where new foods or classes of new foods, or food components are less well-known, the concept of substantial equivalence is more difficult to apply; such new foods or food components are evaluated taking into account the experience gained in the evaluations of similar materials (for example, whole foods or food components such as proteins, fats or carbohydrates);
- Where a product is determined not to be substantially equivalent, the identified differences should be the focus of further evaluations;
- Where there is no basis for comparison of a new food or food component, that is, where no counterpart or similar materials have been previously consumed as food, then the new food or food component should be evaluated on the basis of its own composition and properties.

As an example of the application of substantial equivalence, potatoes have long been part of the human diet. The presence of viral coat proteins in the potato are due to natural viral infections; consequently, these proteins have a long history of human consumption. Coat proteins have never been associated with a toxicity problem and are not considered a food safety issue. Consequently, a potato in which the coat protein of one of these viruses is expressed after the gene has been introduced would be considered substantially equivalent to the infected potatoes that have a long history of safe use and consumption provided the amounts expressed were not grossly different from those occurring following natural infection. This analogy applies only to viral coat proteins in the portions of the plant traditionally consumed, taking into account the characteristics of the new trait and possible untoward effects of the modification on alkaloid levels and key nutrient starches, as well as the extent of consumption.

Some specific examples of additional considerations which it may be necessary to take into account when applying the concept of substantial equivalence are indicated in the following paragraphs.

The intended use(s) and degree of exposure must also be considered in assessing safety. This includes the effect(s) of the level of the food or food component in the diet, the pattern of dietary consumption, and the characteristics of the consuming populations (*i.e.* infants, the elderly, the immunocompromised, etc.).

The consideration of safety may include the need to evaluate possible effects occurring through cooking or other processing. For example, trypsin inhibitors from certain leguminous plants, such as the cowpea trypsin inhibitor, have a long history of safe consumption when properly cooked. However, if the cowpea trypsin inhibitor is expressed in other plants, the safety question relates to whether the normal use of these plants as food involves cooking sufficient for its inactivation.

In special cases, depending on the product consumed, the consideration of safety may also include the need to evaluate the potential for, and human health implications of, transfer of the new genetic material. For example, the use of some antibiotic resistance markers in micro-organisms should be carefully considered since transfer to the microflora of the human gut could, if demonstrated, possibly have human health implications.