

History of safe use as applied to the safety assessment of novel foods and foods derived from genetically modified organisms

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Abstract

Very few traditional foods that are consumed have been subjected to systematic toxicological and nutritional assessment, yet because of their long history and customary preparation and use and absence of evidence of harm, they are generally regarded as safe to eat. This 'history of safe use' of traditional foods forms the benchmark for the comparative safety assessment of novel foods, and of foods derived from genetically modified organisms. However, the concept is hard to define, since it relates to an existing body of information which describes the safety profile of a food, rather than a precise checklist of criteria. The term should be regarded as a working concept used to assist the safety assessment of a food product. Important factors in establishing a history of safe use include: the period over which the traditional food has been consumed; the way in which it has been prepared and used and at what intake levels; its composition and the results of animal studies and observations from human exposure. This paper is aimed to assist food safety professionals in the safety evaluation and regulation of novel foods and foods derived from genetically modified organisms, by describing the practical application and use of the concept of 'history of safe use'.

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1. Introduction

Few foods have been subject to toxicological studies, however, foods generally are considered as safe to eat. An internationally accepted criterion for a safe food is a

reasonable certainty of no harm resulting from consumption (CAC, 2001). It is, however, generally recognised that, while industry and national bodies strive for production, processing and labelling systems to ensure that food is 'safe and wholesome', complete freedom from risks is an unattainable goal (FAO, 1997). Many traditional foods are considered safe even though the food may contain anti-nutrients, toxins and/or allergens. Some foods require special preparation or processing to minimize the associated

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risks. Foods are generally considered safe, provided that appropriate care is taken during development, production, processing, storage, handling and preparation. It is recognised that, in many cases, the knowledge required to manage the risks associated with traditional foods has been acquired in the course of their long history of use.

The concept of foods having a ‘history of safe use’ has appeared in regulations and in safety assessment guidance from regulatory authorities since the early 1990s. However, the term, which is widely used around the world and forms the cornerstone of the safety evaluation of novel foods, has, *per se*, been seldom defined. Canadian Guidelines on Novel Foods (Health Canada, 2003) provide one definition of ‘history of safe use’ as meaning “significant human consumption of food (over several generations and in a large, genetically diverse population) for which there exist adequate toxicological and allergenicity data to provide reasonable certainty that no harm will result from consumption of the food”. In relation to plant foods, Knudsen et al. (2005) have defined ‘history of safe use for a food’ as “the qualified presumption of safety making the food generally recognised as safe in the community”. In the absence of a consensus document, it is timely to outline the general criteria to be taken into account when describing whether an existing food or crop may be considered to have a ‘history of safe use’. Once generally agreed to have a ‘history of safe use’ the traditional food or crop may then be used as a comparator to assist in the safety evaluation of a novel or genetically modified (GM) food or to determine its regulatory status. This approach is sometimes referred to as the concept of ‘substantial equivalence’. A ‘history of safe use’ may also be applicable to the novel food itself, if that food is already traditionally consumed in countries outside the country where it is to be marketed.

The ILSI Europe Novel Foods Task Force has discussed the application and limitations of the concept of ‘history of safe use’ and has produced this paper which aims to provide a description of what is meant by this concept, in what circumstances it should be used, its participation in the process of food safety assessment and what criteria can be used to make the assertion that a food has a ‘history of safe use’. A food with a ‘history of safe use’ may be used as a comparator to focus the safety evaluation of a novel or GM food. Whether or not a food has a ‘history of safe use’ may help to determine its regulatory status when introduced into a new market within certain of the regulatory frameworks outlined in Annex 1. For example, a food that can be shown to have been used for human consumption to a significant degree in the EU prior to May 1997 is excluded from the scope of EU controls on novel foods (EU, 1997a). Food additives, flavourings, processing aids and extraction solvents are excluded from the scope of this paper.

It is hoped that this paper can be used as a guide for industrial food safety professionals to aid the development of new food products, and to assist in the safety evaluations undertaken in the regulatory approval processes.

2. Use of ‘history of safe use’ in safety assessment: concepts and basic principles

Foods are highly complex containing many different substances. It has long been recognised that whole foods cannot be tested in their own right according to the standard safety evaluation principles (WHO, 1987) used for single substances such as pharmaceuticals, food additives or food contaminants.

Traditional toxicological testing procedures are of limited use for whole foods because of their bulkiness and nutritional content, which when fed in high levels to animals may lead to nutritional imbalances. In contrast to defined chemical substances, it may be difficult to attain high enough feeding levels to establish a conventional margin of exposure relative to the predicted human intake, particularly when taking into account inter- and intra-species modifying factors. This means that an alternative approach is necessary. There is international consensus (PAG, 1983; EU, 1997b; WHO, 2000; CAC, 2003) that a novel or GM food should be rigorously analysed and compared with its traditional food comparator (if any) which is considered to be safe by virtue of an established ‘history of safe use’. This comparison will focus the need for any further testing, including the need for testing of specific components found in the novel or GM food (Howlett et al., 2003). Safety assessment is an essential part of the development of any new food product, whether or not formal regulatory approval of that product is necessary. In most countries, general food law requires that all food should be safe for consumption.

The European Commission has published guidelines concerning the information necessary to support applications for the placing on the market in the EU of novel foods and novel food ingredients (EU, 1997b). In the specific case of organisms, history of the use of the organism used as the source of novel food, including information on the past and present use of the source in other parts of the world, is described as one of the essential pieces of information required to assess the novel food for wholesomeness.

Guidance on the information necessary to support an application to market GM foods in the EU has also been published (EU, 2003a; EFSA, 2004, 2006). This guidance makes clear the important role of a traditional non-GM counterpart with a ‘history of safe use’ as a comparator in assessing the safety of a GM food.

It is evident that the safety of traditional foods is an important factor in focusing the safety evaluation of novel or GM foods. Thus it is necessary to consider how the safety of traditional foods is, or has been, established before considering the safety assessment of novel or GM foods.

2.1. Traditional foods

Traditional foods have an assumed ‘history of safe use’ in the country in which they are used. In the past, human beings have developed their food cultures based on trial

and error with the available foods. Over time, they learned ways of preparation, for example, the peeling and cooking of potatoes or the soaking of lima beans, and patterns of consumption, for example, intermittent use of stimulant beverages (e.g. coffee), to limit potential negative effects, making any risks associated with these foods acceptable. Foods prepared and used in traditional ways have therefore been considered to be safe for the consuming population on the basis of long-term human experience. However, many foods contain natural toxicants, anti-nutrients or allergens that would cause concern if they were present above accepted levels or consumed by sensitive individuals (OECD, 1993; CAC, 2003).

Although traditional foods are considered to have a 'history of safe use', no food can be considered to be absolutely safe under all circumstances – individuals may tolerate the same food differently. Moreover, traditional food is considered safe within the context of its traditional use by the consuming population group and prevailing dietary, preparation and processing regimes and cultural practices. Some foods that have a 'history of safe use' in one part of the world may be deemed to be novel if introduced into another part of the world. Thus, the EU regulates as novel foods certain foods which, although new to the EU, may have a history of food use elsewhere (EU, 1997a). Various databases can be used to help to establish whether a particular product has a 'history of safe use' as a food or food source. These include national food survey reports and global, regional and national surveys of plants with food uses (e.g. FAO, 1996a; Brack Egg, 1999; Hegarty et al., 2001; IPGRI, 2004).

Traditional foods may be used as materials of reference, often known as comparators, to assist in the safety assessment of a novel or GM food. If the novel or GM food is compared with its traditional counterpart and any determined specific differences have been demonstrated not to present a hazard, it is reasonable to conclude that the food will at least be as safe as the traditional counterpart. However, this conclusion is only valid if the anticipated methods of preparation and use and consumption patterns of the novel or GM food do not differ significantly from those of the traditional counterpart. When used as a comparator, a traditional food provides a benchmark against which to assess compositional differences and differences in processing and consumption patterns for the novel or GM food. The history of use of the traditional food may also indicate certain food safety concerns (e.g. allergenicity). Thus 'history of safe use' does not necessarily equate to absolute safety, rather, it provides a benchmark indicating a level of safety that, subject perhaps to appropriate risk management procedures (e.g. labelling or cooking advice), is regarded as acceptable by consumers of the traditional food.

2.2. Novel foods

The comparative approach to focus the safety evaluation of a novel food is known as the 'concept of substantial

equivalence'. It is seen as a starting point from which to structure a programme to demonstrate any potential differences from the comparator which, if detected, can be evaluated in terms of their safety implications. Although originally introduced for GM foods (WHO, 1991; OECD, 1993) the concept is now applied for safety assessment of foods from novel sources and produced by novel processes (EU, 1997b; JECFA, 2000). ILSI Europe also proposed a classification of products based on equivalence (Jonas et al., 1996): substantially equivalent, partially equivalent, non-equivalent. Application of the concept of substantial equivalence targets toxicological and analytical testing, avoids unnecessary duplication of animal experiments and exploits the historical data. It also encourages a comprehensive/holistic approach to safety evaluation based on mechanistic insights, nutritional safety and toxicology where necessary (Dybing et al., 2002).

If the organism (plant, animal and micro-organism) used as the source of a novel food has a history of safe consumption under conditions of traditional use then any toxicological concerns about proposed new uses are reduced. However, such organisms may still be a source of potentially harmful components (toxins, allergens and anti-nutritional factors) which are not of concern in traditional use because of processing methods or consumption patterns. These compounds would have to be addressed in the safety assessment of any novel food derived from the source. 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 (Howlett et al., 2003). A distinction can be made between 'traditional' use for which limited scientific data are available, and 'established' use, supported by scientific publications. Ultimately, for all novel foods, a judgement of safety should be made. The safety assessment programme considers: analytical, compositional and nutritional data; previous history of human exposure (not only as food); expected applications and predicted exposure; necessity, appropriateness and outcome of animal and human studies and results of post-market monitoring, if conducted. The assessment of the history of human exposure will take into account the scientific rigour of the available data and its applicability to the new use and/or target groups.

To assess the safety of a novel food, the first step should be to determine what (if any) existing food(s) should be used as a comparator (or material of reference). If there is no comparator with an acceptable 'history of safe use', the novel food is not necessarily unsafe; rather it indicates that an extensive safety assessment programme is required. If a comparator exists, deemed to be traditional within the context of its use, it is compared with the novel food in order to gather the maximum of information relative to safety. The comparison includes: chemical composition; methods of production and use; intake patterns, nutritional value and target groups. In some instances the use of more

than one comparator may be appropriate to address different safety issues. These points are illustrated below.

2.2.1. Exotic products from third countries

Foods with a ‘history of safe use’ in some parts of the world may be deemed to be novel when introduced into new parts of the world (Annex 1). In these cases, ‘history of safe use’ in the traditional geographic area of use is the starting point for the safety assessment. Sometimes it is also possible to take into account other foods, traditionally consumed in the receiving country which present some degree of similarity with the novel food, to benchmark and assess specific safety issues (e.g. Ngali nuts (an exotic nut proposed for importation from Melanesia) versus other European nuts for assessing the allergenicity risk).

2.2.2. Plant extracts (or single substances isolated from plant sources)

In many cases, the plant sources from which a novel food is obtained are plants that are traditional foods or food sources with a ‘history of safe use’. In these cases the plant source becomes the comparator. Even if the plant source cannot be considered as a food in a classical sense, it may still have a ‘history of safe use’ in a different context. This is the case for many of the herbal products used in food supplements. Their use has been traditional and any information on their safety in use in a context of traditional consumption is a key element for the purpose of a food safety assessment. Even more distant from traditional food use is the case of products traditionally used as medicinal products. Some may be considered for use as food ingredients with beneficial health properties. In this case the medicinal product is the comparator.

2.2.3. Products already in use with other functionalities

Some products can have multiple e.g. technical or health functionalities in food depending on their intent and level of use. In the case of (for example) permitted additives or flavouring agents deemed to be novel foods under different

conditions of use, the comparator may be the additive or flavouring agent within the context of its current permitted use.

As indicated above, the first step in evaluating the safety of a novel food is to identify a suitable comparator with a ‘history of safe use’. Table 1 shows the comparators chosen to facilitate the safety evaluation of some novel foods in the EU. See also Annex 2.

The strategy for applying ‘history of safe use’ to the safety assessment of novel foods is, in principle, the same for all novel foods. However, for botanical preparations and micro-organisms the detailed application may be quite involved and there is a further discussion of the issue at Annex 3.

2.3. Genetically modified foods

Comparative approaches to the safety assessment of GM were first proposed by WHO and OECD in the nineties (WHO, 1991; OECD, 1993). As described above, the term ‘substantial equivalence’ was introduced by OECD (1993) and was adopted by the Codex Alimentarius Commission for the safety evaluation of foods from GM organisms (CAC, 2003). For use within Europe, the European Food Safety Authority (EFSA) has published detailed guidance for the preparation and presentation of applications for approval of GM plants and derived products under Regulation EC No. 1829/2003 (EFSA, 2004, 2006). This describes the safety assessment of GM plants and derived food and feed which is based on appropriate methods and approaches to compare the GM plant and derived products with non-GM comparators or comparators having a ‘history of safe use’. An organism (plant, animal or micro-organism) with a ‘history of safe use’ is a useful comparator for the safety assessment of a food from a GM organism (WHO, 1995). The comparative assessment is not a safety assessment in itself but is a starting point for the safety assessment (FAO, 1996b; EFSA, 2004).

To assess the safety of a GM food the first step should be to determine what (if any) traditional food with a ‘history of safe use’ is to be used as a comparator (Kuiper et al., 2004; Konig et al., 2004). Since many GM foods are obtained from plants derived from conventional food plants, the comparator(s) chosen to facilitate the safety evaluation are usually the parent (host) or other edible varieties of the same species and edible products derived therefrom. However, additional comparators may be used to address specific issues. Thus, if the host is modified to produce an oil or protein comparable to an existing food oil or protein the latter might serve as a comparator in assessing the safety of that novel component of the GM organism.

As a result of normal wide variation, there may be considerable differences in the composition of, for example, the same plant variety grown in different locations in the same year or between different varieties grown in the same location in the same year. This makes it difficult to define the

Table 1
Some novel foods and the comparators used to facilitate their safety evaluation in the EU

Novel food	Comparator(s)
High pressure pasteurised fruit preparations	Corresponding thermal pasteurised fruit preparations
Noni juice	Noni juice in the country of traditional use
Ngali nuts	Ngali nuts in the country of traditional use Nuts traditionally consumed in the EU
Chia seeds	Chia seeds in the country of traditional use
Salatrim	Claimed that no comparator exists
Phytosterols	Traditional plant sources rich in oil Phytosterols used as medicinal products in the EU
Dextran	Dextran obtained by other processes Dextran used for other purposes in the EU (e.g. as an additive or in clinical nutrition)

‘normal’ range of characteristics of a traditional crop used as a comparator for a genetically modified crop. To facilitate the harmonisation of regulatory oversight in biotechnology, the OECD has published more than 30 monographs. These give details of the ranges, means and medians of significant components in a number of food crops with a ‘history of safe use’ including potatoes (OECD, 1997), soybeans (OECD, 2000), sugar beet (OECD, 2001) and maize (OECD, 2003). Any decision reached concerning the safety of the GM food is relative to that of the comparator only when prepared, processed and used in an identical way and consumed at the same intake levels.

3. Criteria useful to determine a ‘history of safe use’

The concept of ‘history of safe use’ may be used to determine the regulatory status of a food, whether a safety evaluation is required and/or to direct any safety evaluation. Expressions such as ‘history of use’, ‘history of consumption’, ‘history of safe food use’, etc. are also frequently used in guidelines or legal texts in situations where it is unclear whether or not they were intended to be used synonymously with ‘history of safe use’. Furthermore, the absence of a ‘history of unsafety’ is often taken as supporting a ‘history of safe use’. In applying the concept of ‘history of safe use’ to facilitate the safety evaluation of a novel or GM food the relevant ‘history of safe use’ may be that of the novel food *per se* or that of an appropriate comparator.

In developing the following criteria that might be useful to determine a ‘history of safe use’ the ILSI Task Force has taken into account published material (Health Canada, 2003; Schilter et al., 2003; Knudsen et al., 2005), as well as experience gained from consideration of the EU case studies summarised in Annex 2. The Task Force emphasised that data used to describe a ‘history of safe use’ should preferably be robust and reliable (e.g. peer reviewed scientific publications, governmental documents, and scientific expert opinions) and be taken from referenced sources where possible. However, non-scientific and anecdotal evidence is also important, although is given less weight than peer reviewed data. Sometimes, this type of data will be the only information available.

The novel food or comparator (and, if appropriate, its source) should be fully characterised. This includes a precise biological identification (e.g. taxonomy, phenotype, and genotype) using appropriate methodologies. The origin, geographical distribution and genetic diversity of the food source should be described. The composition of the food or foods should be determined based on randomly selected and statistically valid samples. Typically, compositional data for complex foods should include: proximate analysis (moisture, protein fat and ash); amino acid and fatty acid profiles; vitamin, mineral and trace mineral composition; key nutrients; chemical hazards (e.g. toxicants, anti-nutrients, allergens, mycotoxins and heavy metals);

organisms (e.g. bacteria) and bioactive components (e.g. phyto-oestrogens/androgens). For purified ingredients, focus should be given to chemical identity and potential impurities arising from manufacture. Special attention should be given to compounds that may have implications for the health of any groups of the general population (e.g. infants, children, elderly, pregnant women, etc.).

Evidence of previous human consumption of the novel food or comparator should be documented. This should demonstrate significant human consumption, ideally over a period of several generations by a diverse population covering a range of genetic backgrounds and age groups. It is not sufficient to include only evidence of short-term consumption or consumption by a particular sub-group of the population or limited consumption, e.g. as a medicine.

Details should be given of the way in which the novel food or comparator is used including details of preparation and processing. If the food source is processed into several products, details of these should be given. In general, the safety of lightly processed foods is indicative of the safety of more highly processed products produced from them. However, the possibility that further processing may introduce potential hazards into foods previously considered to be safe cannot be ignored (e.g. roasting peanuts increases allergenicity potential). Therefore, details of preparation and processing might include any fermentation, soaking, peeling or preparation steps for the food (including the temperature used during cooking, time of cooking, and possible toxic or allergenic substances formed or removed during the processing or cooking). Any specific processing designed for particular uses should be described. Special attention should also be given to methods of preparation that reduce adverse effects e.g. by reducing levels of toxic, allergenic or antinutritional substances or by improving digestibility.

Details should be given of the purpose for which the novel food or comparator is used and of intakes. Details of the purpose for which the comparator is used might include whether it is used as an ingredient, staple food or medicine, or in a particular nutritional application. Intake/exposure data should include: serving size, daily intake, frequency of consumption, and period of use (number of years of consumption of the product). Magnitude of usage is also important (i.e. whether it is consumed by whole populations, specific subsets, target groups, etc.) as is the number of people exposed. Again, sensitive groups in the population consuming the material of reference (e.g. young, old, pregnant, immuno-compromised persons, those receiving medication, etc.) should be identified. Known limitations on use should also be given. These might include: cultural practices; specific processing designed for specific populations or specific uses; known adverse reactions or regulatory limits. Evidence of non-food exposure (e.g. environmental exposure or use as a medicine) is also useful.

Evidence should be provided of safety and of any health concerns from diverse human experience. Evidence of

adverse effects might come from intentional and non-intentional exposure routes, known cautions, any consequences of unintended or accidental exposure without such precautions. Possible adverse effects may also be observed in the country of origin (where exposure is likely to have been the longest) or in those with high exposure (for example if the product has been used for medicinal purposes, even if exposure may not have been prolonged or the exposure group not large). As described above, possible adverse effects may also be indicated by the methods traditionally used to prepare the comparator such as soaking or cooking to eliminate antinutritional factors or from epidemiological data or from clinical trials. Information should be presented concerning all potential hazards. Depending on the nature of the food this may include:

- Toxicology data including details of known natural toxicants.
- Nutritional data including details of known natural antinutritional factors.
- Allergenicity.
- Pathogenicity (for micro-organisms).
- Known health compromising contaminants (nature and level of, for example, mycotoxins, heavy metals or residues of agrochemicals).
- Bioactive substances (e.g. phytoestrogens/androgens).
- Metabolic and/or gastrointestinal effects in humans.

History of safe use: key issues

History:

Correct identification
 Biology (origin, genetic diversity)
 Length of use
 Geographic/demographic distribution of use
 Details of use
 Evidence of adverse effects
 Reliability of data

Safe:

Composition (especially toxic, allergenic, metabolic, nutritional and antinutritional components as well as health compromising compounds)

In silico tests (e.g. structural homology to known allergens or known toxins)

In vitro tests (e.g. serum screening, digestibility tests)

Animal studies (toxicology and nutrition studies)

Experience from human exposure

Clinical studies

Epidemiological evidence

Use:

Type/purpose (e.g. as a food, ingredient, supplement or pharmaceutical)

Preparation and processing

Known precautions

Pattern of consumption (occasional, regular or co-administration)

Intake (level, populations exposed, mean/ extremes)

4. Conclusions

The OECD states that “a long history of use is a reassuring and practical starting point” for evaluating the safety of a novel food (OECD, 1999).

The ‘history of safe use’ of a food is the body of knowledge accumulated from the use and experience of that food within its cultural context and conditions of use, which describes its established safety profile. This profile also describes known limitations and restrictions for sensitive populations, e.g. known anti-nutrients, toxicants, and allergens. Too much caffeine for pregnant women, raffinose in legumes and cyanide in cassava are examples of known problems associated with particular foods with established procedures (e.g. avoidance, processing) to limit their consequences. Allergens in peanuts are a problem for a significant number of people and, in some, the reaction is potentially fatal. In this case, the potential risk is managed by avoidance, or labelling to enable those at risk to avoid peanut-containing products.

This document has described general criteria to consider when collecting together evidence to provide support, or to describe, a ‘history of safe use’ either of a novel food *per se* or of a comparator used to facilitate the safety evaluation of a novel or GM food. The description of a ‘history of safe use’ is not a safety assessment in itself, but can help with data to support the safety of a new product and highlight knowledge gaps or concerns.

Many aspects are considered when assessing the history of safe use of a food. The data must be considered as a whole. There is no particular information which may be of greater importance than another; therefore it is not possible to provide a decision tree. In addition, a checklist approach is not recommended since the whole of the information must be considered together, and this history of safe use does not rely simply on specific criteria (such as the number of years of use).

The first steps in assessing the safety of a novel and/or GM food for which there is no ‘history of safe use’ for the product *per se* are consideration of the following:

- Identify the material(s) of reference or comparator(s).
- Establish ‘history of safe use’ and all other relevant data on previous use of the comparator(s).
- Identify the differences between the novel or GM food and the comparator.
- Assess the safety concerns linked to these differences.

Most of the traditional foods consumed benefit from an assumption of ‘history of safe use’, even if their safety in use, as in the vast majority of cases, has not been formally evaluated, and nor is that required. A description of the history of safe (or traditional) use is also helpful to assess the safety of any new product development whether or not regulatory approval is required. The degree of information available depends among others on the novelty, and so this accumulation of information and a comprehensive description of the history of use can aid in determining the novelty of a particular new crop, food product or derived ingredient.

In the case of a traditional food considered novel in the country where it is to be introduced, a thorough description of its history of use, with a good description of its safety profile (taking into account the criteria listed) is valuable information. This could highlight the requirement for, and extent of, additional safety testing.

When making comparisons of the novel food with a traditional counterpart, one should make sure that the comparator is appropriate by having a generally agreed ‘history of safe use’ (with known limitations) and is thus an acceptable benchmark upon which to base the comparison. This also means that the product as consumed must be compared with its counterpart as consumed. In the case of GM foods, the comparison is initially made at the crop level (raw agricultural commodity) and after crop processing. The way that raw material is processed and prepared for consumption (e.g. as an oil), must also be taken into account and considered in relation to ‘history of safe use’. This involves both qualitative and quantitative considerations.

If the ‘history of safe use’ of a novel food or the comparator used as a benchmark to assess the safety of a novel or GM food can be sufficiently described, limitations identified, and the intended conditions of use are the same, then few further safety data should be required. If the novel or GM food is taken out of the cultural, processing, and intended use context of the novel food or comparator, which provides its acceptable ‘history of safe use’, then more safety data/evaluation may be required.

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Annex 1. ‘History of safe use’ in a regulatory context

In addition to its use in the safety evaluation of new foods or food ingredients, the concept of ‘history of safe use’ is also used in their regulation in various parts of the world as illustrated in the following paragraphs.

1.1. European Union

New foods and food ingredients are considered novel if they were not used for human consumption to a significant degree within the European Community before 15th May 1997. Such foods and food ingredients have to comply with Regulation (EC) No. 258/97 concerning novel foods and novel food ingredients (EU, 1997a). This Regulation (as amended) applies to foods and food ingredients which have not hitherto been used for human consumption to a significant degree in the Community *and* which fall under the following categories:

- foods and food ingredients with a new or intentionally modified primary molecular structure;
- foods and food ingredients consisting of, or isolated from, micro-organisms, fungi or algae;
- foods and food ingredients consisting of or isolated from plants, or food ingredients isolated from animals, except for foods and food ingredients obtained by traditional propagating or breeding practices, and having a *history of safe food use*; or
- foods and food ingredients to which has been applied a production process not currently used, where that process gives rise to significant changes in the composition or structure of the food or food ingredient, which affect their nutritional value, metabolism or level of undesirable substances.

The concept of ‘history of safe use’ is used both implicitly in the overarching preamble to the description of the regulated categories and explicitly in the exemption for certain plant and animal products. However, whilst in the former case, a history of food use (albeit in the Community) is sufficient to take a product outside the scope of the regulation, in the latter case a history of *safe* food use is required.

The basic criteria for the authorisation of novel foods under Regulation (EC) No. 258/97 are that they must not:

- present a danger for the consumer;
- mislead the consumer; or
- differ from foods or food ingredients that they are intended to replace to an extent that their normal consumption would be nutritionally disadvantageous for the consumer.

The Regulation requires pre-marketing *approval* for most, but not all, novel foods. For those that on the basis of the scientific evidence available and generally recognised or on the basis of an opinion delivered by one of the competent bodies are substantially equivalent to existing foods or food ingredients as regards their composition, nutritional value, metabolism, intended use and level of undesirable substances contained, and that:

- are foods and food ingredients consisting of or isolated from micro-organisms, fungi or algae; or
- are foods or food ingredients that consist of or are isolated from plants, or food ingredients isolated from animals, except for foods and food ingredients obtained by traditional propagating or breeding practices, and having a *history of safe food use*,

a simplified *notification* procedure can be used.

In the EU, genetically modified organisms used as food, food containing or consisting of genetically modified organisms, and food produced from or containing ingredients produced from genetically modified organisms are regulated under Regulation (EC) No. 1829/2003 (EU, 2003a) as are comparable materials used as animal feed. The Regulation requires that a genetically modified food must not:

- have adverse effects on human health or the environment;
- mislead the consumer; or
- differ from the food which it is intended to replace to such an extent that its normal consumption would be nutritionally disadvantageous for the consumer.

In Regulation (EC) No. 1829/2003, the term ‘history of safe use’ is only found under the definition of a ‘conventional counterpart’. A ‘conventional counterpart’ is defined as meaning “a similar food or feed produced without the help of genetic modification and for which there is a well-established history of safe use”. Where a GM food (or feed) differs from its conventional counterpart as regards one of the following characteristics or properties:

- composition;
- nutritional value or nutritional effects;
- intended use of the food; or
- implications for the health of certain sections of the population,

then labelling is required to mention those characteristics as specified in the authorisation.

1.2. Australia and New Zealand

As described in Standard Novel Food A-19 (FSANZ, 1999), the first step in the evaluation of a novel food to be introduced onto the market is to establish its novelty, and the second step is to establish its safety. The document defines a novel food as a non-traditional food for which there is insufficient knowledge in the broad community to enable safe use in the form or context in which it is presented, taking into account:

- the composition or structure of the product;
- levels of undesirable substances in the product;
- known potential for adverse effects in humans;
- traditional preparation and cooking methods; or
- patterns and levels of consumption of the product.

Thus a non-traditional food for which there is sufficient knowledge to enable safe use (i.e. a *history of safe food use*) would be regarded as not novel.

1.3. Canada

A novel food is defined in Amendment (Schedule No. 948) to the Food and Drug Regulations (Health Canada, 1999) as:

- a substance, including a micro-organism, that does not have a ‘history of safe use’ as a food;
- a food that has been manufactured, prepared, preserved or packaged by a process that has not been previously applied to that food, and causes the food to undergo a major change;
- a food that is derived from a plant, animal or microorganism that has been genetically modified such that:
 - (a) the plant, animal or microorganism exhibits characteristics that were not previously observed in that plant, animal or microorganism;
 - (b) the plant, animal or microorganism no longer exhibits characteristics that were previously observed in that plant, animal or microorganism; or
 - (c) one or more characteristics of the plant, animal or microorganism no longer fall within the anticipated range for that plant, animal or microorganism.

1.4. United States of America

In the United States of America, foods or food ingredients may be given GRAS status, i.e. generally recognised as safe (FDA, 1997). General recognition of safety may be based only on the views of experts qualified by scientific training and experience to evaluate the safety of substances directly or indirectly added to food. The basis of such views may be either (1) scientific procedures or (2) in the case of a substance used in food prior to January 1, 1958, through experience based on common use in food. General recognition of safety requires common knowledge about the

substance throughout the scientific community knowledgeable about the safety of substances directly or indirectly added to food. A “common use in food” has been defined as a “substantial history of consumption of a substance for food use by a significant number of consumers” (FDA, 1997). An ingredient not in common use in food prior to January 1, 1958, may achieve general recognition of safety only through scientific procedures but not necessarily by the Food and Drug Administration.

Annex 2. Examples of applications in which ‘history of safe use’ has been used

The importance of the concept of ‘history of safe use in the safety evaluation of novel or GM foods/food ingredients is illustrated by the following examples which are summaries of reports of evaluations by various advisory bodies to the European Commission.

2.1. Novel foods

2.1.1. Food itself

Ngali nuts: Ngali nuts are produced by the commonly cultivated Nangai tree (*Canarium indicum* Linné) native to the Pacific, and are exported to Japan, Hawaii and Australia as gourmet products. The EU’s Scientific Committee for Food (SCF) was asked, within the context of an application for approval under Regulation (EC) No. 258/97, to assess the safety from a consumer’s health point of view of ngali nuts as a novel food. Although it had been estimated that the consumption of ngali nuts in Western Melanesia was equivalent to 70g/day/person and that ngali nuts therefore had a ‘history of safe use’ in the region, the SCF was unable to draw any conclusions concerning safety from a consumer’s health point of view (SCF, 2000a). The SCF concluded that: the information submitted for safety assessment was considered incomplete with regard to analytical procedures employed for determining the nutritional composition of ngali nuts and the extent of natural variation of the data submitted; that adequate toxicological data were not available and that the possible allergenicity of ngali nuts had not been investigated.

Noni juice: In 2002, the SCF reviewed the safety from a consumer’s health point of view of an exotic fruit juice based on noni (*Morinda citrifolia* L.). Noni fruit had been consumed previously in Polynesia and South East Asia and the juice had been marketed since 1996 in the USA and other countries. The SCF concluded (SCF, 2002a) that the noni juice was acceptable at the observed level of intake of 30ml/person/day. In reaching its conclusion the SCF noted that the noni juice had been marketed for several years in a number of countries and that few untoward reactions had been reported. The SCF also concluded that there were no indications of adverse effects from laboratory studies on subacute and subchronic toxicity, genotoxicity and allergenicity. This conclusion of safe use is limited to noni juice as other noni-derived products (e.g. jam, dried

whole fruit, spray dried juice, etc.) would require a separate application for approval under Regulation (EC) No. 258/97. Moreover, the approval of noni juice is specific to the applicant as competitors’ noni juice cannot be marketed unless evidence of substantial equivalence to the approved juice is demonstrated.

Chia: The food safety of chia (*Salvia hispanica* L.) was reviewed by an EFSA Panel in 2005 (EFSA, 2005a) following a request for approval of the whole and ground seed as a novel ingredient in soft grain bread that would provide another possible food source of $n - 3$ polyunsaturated fatty acids. The seeds have a long history of consumption in South America and chia was a major part of the diet in pre-Columbian populations. Historically the seeds were roasted, ground and mixed with water to form porridge or soaked in water and flavoured with fruit juice to form a drink. There was limited evidence of recent food use of chia seed.

An initial assessment by the UK competent authority (ACNFP, 2004) concluded that consumption, as an ingredient in the narrow range of foods proposed, was not dangerous or misleading to the consumer. However, the ACNFP was concerned about the proposed strategy to limit potential allergenicity risks. Some EU Member States agreed with the initial assessment report, others did not. Therefore, the EFSA Panel was asked for its opinion on whether the authorisation of chia as a food ingredient for bread was likely to have an effect on public health and to focus on the concerns of a scientific nature raised by Member States. In particular the Panel was asked to address the question of whether the safety of chia could be established without additional toxicological studies.

The Panel concluded that whilst no adverse effects had been reported from the previous human exposure to chia in pre-Columbian civilisations, information on the history of use of chia in modern society was not sufficient to establish a ‘history of safe use’. The nutritional information provided did not, in itself cause a concern for the Panel regarding use of chia in multi-grain bread at levels of up to 5%. However, the Panel was unable to undertake a full nutritional assessment as the compositional and bioavailability data were limited and did not take into account the effects of storage and processing. There were also concerns over the possible allergenicity of chia, cross-reactivity of chia with common food allergens and the potential sensitizing activity of chia proteins. The presence of constituents that might exert anti-nutritional or toxic effects were not excluded. The Panel concluded that it was not possible to perform a safety assessment of chia based on the limited toxicological information provided and, consequently, that additional studies were required.

2.1.2. Change of use (extract, increased concentration of certain components)

Salatrim: The SCF has reviewed the safety from the point of view of consumer health of salatrim – a family of reduced calorie fat replacers as a novel food. Salatrim

were accorded the status ‘generally recognised as safe’ (GRAS) in the US in 1994 and products containing them were being marketed in a number of other countries at the time that an application was made in the EU for approval under Regulation (EC) No. 258/97. Salatrimms comprise a family of structured triacylglycerol derivatives; predominantly mixtures of long chain fatty acids (principally stearic acid) and short chain fatty acids (acetic, propionic and butyric acids) all esterified with glycerol.

It was claimed that there were no traditional counterparts for salatrimms and that approval was required. In reaching its decision, the SCF (2001) took into account that salatrimms were produced using interesterification technology widely used (with a ‘history of safe use’) in the edible oils and fats industry. The long chain fatty acids used in the manufacture of salatrimms derive from hydrogenated edible oils and the short chain fatty acids derive from triacetin, tripropionin and tributyrin. The short chain fatty acids are normal products of colonic bacterial fermentation and the levels of other materials in salatrimms occur at same levels as in the fats and oils used as source materials and having a ‘history of safe use’.

The SCF noted the absence of a chronic toxicity study and of developmental toxicological studies and a paucity of information on effects of consumption by children. However, the SCF also indicated that salatrimms contained no structural alerts for mutagenicity or carcinogenicity, were non-genotoxic and easily hydrolysed in the gastrointestinal tract, and that animal feeding studies showed no significant toxic effects. Furthermore, there were no concerns over reproductive or developmental toxicology since the structured triglycerides present were not known to cause such effects and animal-feeding studies had shown no toxic lesions in the reproductive organs. The SCF concluded that the use of salatrimms was acceptable in bakery and confectionery products except in foods aimed at children and that any extension of use would require a new assessment.

Phytosterols: The past five years has seen the introduction into the EU market of a number of phytosterol-based products which have the ability to reduce consumers’ serum cholesterol levels. One of the earliest of these, a mixture of phytosterol esters, was reviewed by the SCF in 2000 (SCF, 2000b) following an application for approval as a Novel Food under Regulation (EC) No. 258/97 of phytosterol esters in yellow fat spreads. Plant sterol esters in plant oil-based products had been given GRAS status in the USA in 1997. They also had a history of use in pharmaceutical preparations with a good safety profile.

Phytosterols are extracted from edible oils and esterified with sunflower oil fatty acids. They occur naturally in food as free alcohol, esterified with long chain fatty acids or conjugated as glucosides. The majority of plant oils contain up to 0.5% phytosterols although some germ oils contain up to 4%. Typically, reduced and low fat spreads contain 0.3–0.4% phytosterols. The application

proposed a use in yellow fat spreads of up to 12% or 8% on average.

Although naturally present in foods (and there by presumed to have a history of food use), the use of phytosterols in yellow fat spreads was considered to be novel because of the significant (8- to 12-fold) increase in consumption that would occur from their use. The SCF concluded that, based on extensive toxicological testing, no safety concerns were apparent and the use of phytosterol esters in yellow fat spreads at a maximum level corresponding to 8% free phytosterols is safe for human health. The SCF noted that ingestion of 20 g/day of products containing 8% free phytosterols reduced plasma β -carotene levels by 20% and was concerned that this effect should be communicated to consumers. The Committee also considered that the very small number of people with inborn error of phytosterol metabolism should be made aware of the presence of higher levels of phytosterols in these products and that patients on cholesterol-lowering medication should consume the product under medical supervision.

With a number of phytosterol ester-containing products approved as novel foods and an appropriate risk management strategy (labelling to prevent consumption of phytosterol-containing products by non-target consumers) in place, the number of companies selling the products has increased as manufacturers of plant sterols seek to notify their products as ‘substantially equivalent’ to previously approved products. The UK Competent Authority gave a positive opinion on two such notifications in 2004 (ACNFP, 2004).

Dextran: The SCF reviewed the safety from the consumers’ health point of view of bacterial dextrans as novel food ingredients in 2000 (SCF, 2000c). It was intended that dextran would be used at levels of up to 5% in bakery products. Dextrans have a prior history of limited food use in the EU, e.g. in clinical nutrition, in fructose syrup, in fermented products and as an additive in products such as candies and ice cream. Use in fructose syrup and in clinical nutrition products was reviewed by the UK ACNFP in 1990 and 1993, respectively, and found to be of no safety concern (ACNFP, 1990, 1993). There was also a long history of use of dextran as a blood extender.

The SCF concluded that dextran produced by the process described in the application and added to bakery products at levels below 5% does not constitute a safety concern from the point of view of consumer health. In reaching this conclusion the Committee noted that the production organisms were already used in food processing without restriction and that dextran is highly digestible, presented no toxicological concerns and was unlikely to give rise to an allergic reaction after oral intake.

2.1.3. Products of novel processes

High pressure processing: In 2001, certain fruit preparations that have been processed using high pressure processing were approved for food use in the EU (2001). Before this date high pressure had not been used for fruit processing in

the EU to a significant extent and the products were deemed to be novel. Approval followed initial evaluation of an application under Regulation (EC) No. 258/97 by the French Competent Authority and endorsement of the favourable opinion by other Member States.

High pressure is used as an alternative to heat pasteurisation of fruit preparations and heat pasteurised fruit preparations have a ‘history of safe use’ in the EU and elsewhere in the world. No differences of safety significance were seen between the composition of high pressure and heat pasteurised fruit preparations. Although the sensitivity of viruses and micro-organisms to heat and high pressure vary, any potential food safety risks can be managed (for both processes) through the application of a suitable Hazard Analysis Critical Control Point (HACCP) plan.

2.2. Genetically modified (GM) foods

2.2.1. GM maize

In 2002, the SCF reviewed the safety from a consumer point of view of maize grain and derived products from a GM maize tolerant to the herbicide glyphosate. The conditions of use of the food or food ingredients were those that applied to conventional maize food products. In its report (SCF, 2002b) the Committee took into account that maize, the source of the new food, had a long ‘history of safe use’. It is one of the few major crops indigenous to the Western Hemisphere and is grown in nearly all areas of the world including the EU. The genetic modification results from the introduction of a 5-enolpyruvyl-shikimate-3-phosphate synthase (EPSPS) gene from maize that has been modified to allow it to function in the presence of glyphosate. Toxicological and allergenic considerations focussed on the modified EPSPS protein that is expressed in transformed maize grains.

The SCF was satisfied that on the basis of data presented, substantial equivalence apart from its glyphosate-tolerance trait had been established for the GM maize line with non-transgenic and near-isogenic comparator plants in regard to phenotypic characteristics, growth criteria and yield. The data on chemical composition of GM maize line and two derived transgenic hybrid lines allowed the SCF to conclude that the GM maize lines were substantially equivalent to non-transgenic controls and other commercial maize varieties. The nutritional profile of GM maize was unchanged by the genetic modification from that of conventional maize lines.

As a result of its considerations, the SCF concluded that from the point of view of consumer health, this glyphosate tolerant maize line and derived products were as safe as maize and derived products from conventional varieties.

Annex 3. Application of ‘history of safe use’ to botanicals and microorganisms

The principle of the concept of ‘history of safe use’ is identical for all foods although, in the case of botanical

preparations and microorganisms the details are more complex. These two examples are discussed in more detail below.

3.1. Botanical preparations

Botanicals and botanical preparations may be derived from conventional primary food sources (soy extracts with isoflavones, tomato extracts with lycopene) or secondary sources (garlic oil, green tea extracts). Others may have no significant use as food ingredients but are derived from sources used in herbal medicinal products in various regions of the world (Gingko, etc.). The history of use (food or medical application) provides valuable information concerning safety (Schilter et al., 2003; Kroes and Walker, 2004). Products commonly eaten are presumed safe unless a significant risk has been identified. Absence of evidence of toxicity, however, is not necessarily evidence of absence of toxicity under the proposed conditions of usage (e.g. long-term use of herbal preparations). Therefore, epidemiological evidence and clinical reports should be considered where available. However, the availability of this type of information may often be limited to acute toxicity as it is usually difficult to obtain adequate chronic toxicological data from historical sources.

In some instances the desired components of a botanical source with a ‘history of safe use’ may be concentrated or extracted for use as a food ingredient (e.g. polyphenols from grape-seeds). Although the source materials (grape-seeds or green tea) have a ‘history of safe use’ this should be interpreted with caution when assessing the safety of the polyphenol preparation and any requirements for toxicity testing. Methods of preparation should be carefully considered; processes differing from the traditional methods (e.g. solvent extracts compared to water infusions typically used for herbal teas) may have the potential to result in a different compositional profile and concentrate undesirable components. In particular, the safety assessment should take into account anticipated dietary intakes with use of the new source compared with dietary intakes from the traditional use of the new source and total dietary intakes.

3.2. Microorganisms

Microorganisms used in or as food should be safe for their intended use. The safety assessment of microorganisms is of value also in assessing the safety of their products such as enzymes. However, microorganisms pose several unique problems including their chemical complexity and genetic instability. Nevertheless, the concept of ‘history of safe use’ can be used to assist in the safety evaluation of microorganisms.

The term ‘familiarity’ has also been used by the European Commission (EU, 2003b) in association with suggested approaches to describe the safety of microorganisms used in foods. This is being followed up by the

European Food Safety Authority to provide a background on which to determine if a 'Qualified Presumption of Safety', or QPS status can be given to certain microorganisms (EFSA, 2005b). Familiarity (acknowledged to be a confusing term) can be described as a body of information already available on the microorganism. It encompasses practical experience of the use of the organism, including its history of use for particular purposes and any body of the literature on the biology of the taxonomic unit for which QPS status is sought. This body of knowledge must be sufficient (determined by a weight of evidence approach) to provide adequate assurance that any potential to produce adverse effects in humans, livestock or the wider environment is understood and predictable.

A decision tree approach to the safety assessment of microorganisms intended for use as sources of microbial enzyme preparations has been outlined by Pariza and Johnson (2001) and is widely used. Thoroughly characterised non-pathogenic, non-toxic microbial strains, particularly those with a 'history of safe use' in food enzyme manufacture are logical candidates for generating a safe strain lineage. The non-pathogenicity of commonly used probiotic micro-organisms has been described in Borriello et al. (2003).

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